

Outer Hair Cells Amplify the Fluid Traveling Wave by Changing Organ-of-Corti area in the Short-Wave Region

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Abstract. There are two kinds of cochlear amplification: “non-propagating amplification” that is widespread but doesn’t couple to the traveling wave, and “traveling-wave amplification” (TWA) that enables wide-band outer hair cell (OHC) motility to produce sharply tuned amplification. TWA has been thought to be produced by an “OHCs-push-on-the-basilar-membrane” mechanism. Here it is hypothesized that in the traveling-wave short-wave region, OHC motility causes longitudinal cortilymph flow in the organ-of-Corti (OoC) tunnels, producing OoC area changes that drive scala media fluid motion and amplify the traveling wave.

INTRODUCTION

Cochlear amplification has been thought to be produced by outer hair cell (OHC) somatic motility acting on the basilar membrane (BM) at the right phase to add energy cycle-by-cycle to the traveling wave. However, this “OHCs-push-on-the-BM” hypothesis has several obstacles: OHCs do not directly contact the BM, OHCs have no anchor for their push on the BM, and how OHC contractions are properly timed to add energy to the traveling wave is unknown. Adding to the conundrum, the motions of many organ-of-Corti (OoC) structures, e.g., the reticular lamina (RL), are amplified at frequencies that are far from frequencies amplified on the BM. These issues are addressed by dividing cochlear amplification into two types, and by a new method for traveling-wave amplification.

Traveling-wave properties and two types of amplification. Although the traveling wave is often talked about as if it were mainly on the BM, the energy of the traveling wave is carried by motion of the fluids in scala tympani, scala media and scala vestibuli (ST, SM and SV) [1]. BM motion is produced by the pressure difference across the cochlear partition (SV-SM). Traveling-wave pressure has been measured in the scalae [2-4] but fluid motion in the scalae has not been measured (although the motions of the structures abutting the scalae provide measures of the motions in the adjacent fluids). Starting at the cochlear base, the traveling wave propagates apically with a speed that decreases as it approaches CF; near the stapes the wavelength is long, but near a tone’s best-frequency (BF) region the wavelength is much shorter. These are denoted the long-wave and short-wave regions [5].

The long- and short-wave regions demarcate the approximate locations of the two types of cochlear amplification: “traveling-wave amplification” and “non-propagating amplification” (Fig. 1). Traveling-wave amplification is manifest by increases in BM motion and by increases in traveling-wave pressure. A crucial aspect of traveling-wave amplification is that increases (and decreases from two-tone suppression (2TS)) are carried apically

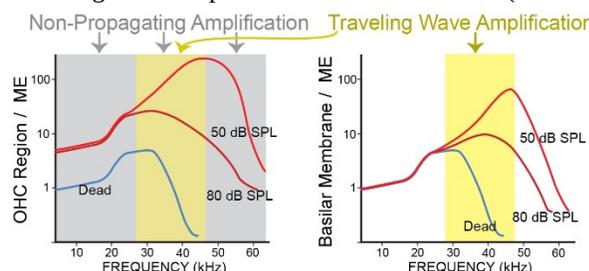


FIGURE 1. Frequency regions that show traveling-wave amplification (yellow) and non-propagating amplification (gray) on outer-hair-cell (OHC) region motion (left) and basilar-membrane (BM) motion (right). Lines are smoothed versions of mouse data from [6]. Both amplifications are present in the center of the left panel.

by the traveling wave so that amplification (or 2TS) produced in each OoC cross-section *accumulates* as the traveling wave moves forward (e.g., [7,8]). In contrast, non-propagating amplification is present everywhere that the traveling wave amplitude is enough to substantially deflect OHC stereocilia and cause OHC contractions/elongations, but it is local and not coupled to the traveling wave. This conclusion is supported by 2TS of non-propagating amplification having an effect only locally [9,10]. Also, solutions that block OHC motility and

The Shape of Noise to Come: Signal vs. Noise Amplification in the Active Cochlea

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Abstract. According to the dominant view, the mammalian cochlea spatially amplifies signals by actively pumping energy into the traveling wave. That is, signals are amplified as they propagate through a region where the medium's resistance is effectively negative. While signal amplification has been extensively studied in active cochlear models, the same cannot be said for amplification of internal noise. According to transmission-line theory, signals are amplified more than internal noise in regions where the net resistance is negative. Here we generalize this finding by showing that a distributed system composed of cascaded “noisy” amplifiers boosts signals more rapidly than the internal noise; the larger the amplifier gain the larger the signal-to-noise ratio (SNR) of the amplified signal. We further show that this mechanism is present in existing active cochlear models: the cochlear amplifier increases the SNR of cochlear responses, and thus enhances cochlear sensitivity. When considering also that the cochlear amplifier narrows the bandwidth of the “cochlear filters”, activation of the cochlear amplifiers dramatically increases the SNR (by about one order of magnitude in our simulations) from the tail to the peak of the traveling wave. We further demonstrate that the tapered ear-horn-like cochlear geometry significantly improves the SNR of basilar-membrane responses.

INTRODUCTION

Long before cochlear models included an active amplifier, K.K.N. Chang [1] analyzed the noise factor—a measure of degradation of signal-to-noise ratio (SNR)—in transmission lines including both positive and negative resistances. He concluded that:

“For a transmission line with both positive and negative distributed resistances as well as distributed random noise sources, low-noise amplification can be achieved via the line provided that (1) the line is operated at sufficiently high gain, (2) the line is well matched at both the input and the output, and (3) the net negative resistance and/or the net negative conductance is large; i.e., that gain per unit length is large. These conditions, which have been deduced from a quantitative analysis, are the necessary ones for low noise amplification.”

In particular, the analysis of Cheng reveals that active transmission lines with net negative damping (and small scattering) spatially amplify the signal more rapidly than they amplify internal incoherent noise sources. Strikingly, theoretical work points out that the mammalian cochlea fulfills the three conditions for low-noise amplification identified by Chang [2, 3, 4, 5, 6]. That is, existing active cochlear models are expected to spatially amplify signals more than the intracochlear noise.

Additionally, a common noise reduction technique consists of band-pass filtering signals to remove noise outside the frequency range of interest. The cochlear amplifier narrows the bandwidth of the so-called “cochlear filters”, and therefore the cochlear frequency-selective amplification is expected to boost the signal-to-noise ratio (SNR) of cochlear responses, thereby improving cochlear sensitivity. Furthermore, we previously proposed that the earhorn-shaped geometry of the cochlea helps maintain the signal intensity as this propagates along the cochlea. Based on this observation, we conjectured that the tapered geometry produces a significant improvement of SNR relative to the fictitious “rectangular” cochlea often depicted in models [7].

In a nutshell, physical intuition suggests that the cochlea is well-equipped with active (cochlear amplification) and passive (geometrical) mechanisms to minimize signal degradation by internal noise. Here, we test this conjecture using active cochlear models. As a first step, we analyze how distributed (“cascaded”) amplification improves the SNR of the amplified signal.

The dramatically dispersive character of the traveling wave

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Abstract. Using optical coherence tomography (OCT) vibrometry we studied wave propagation by recording at multiple longitudinal positions in the gerbil and guinea pig cochlea. Our aims are to (1) fully portray the unusual dispersive character of the wave; (2) derive from these properties the underlying physics of the wave and the way it is regulated by physiological processes; (3) challenge cochlear modelers to report and analyze wave propagation in their models. In the current study we report two unexpected features of the spatial profiles of sound-evoked vibrations of the basilar membrane. The profiles of low-frequency components show very little systematic phase accumulation, whereas the slow waves near the best frequency often exhibit abrupt, place-fixed transitions in propagation velocity.

INTRODUCTION

The advent of OCT vibrometry has shaken up the field of cochlear mechanics. It does not require the use of reflectors and allows for vibration measurements across many different intracochlear positions. In contrast, the bulk of pre-OCT data consisted of single-point basilar membrane (BM) recordings. Consequently, decades of modeling efforts have concentrated on reproducing single-point BM data. Likewise, the conceptual framework of most models has been “BM centered”, e.g. seeking to determine “BM impedance”, or describing how “outer hair cells move the BM”, etc. The complex micromechanics unveiled by OCT vibrometry expose the severe shortcomings of both the predictive power of existing cochlear models and the underlying conceptual framework. For instance, vibrations many octaves below the characteristic frequency display physiologically vulnerable nonlinearities and complex motion patterns (“hotspots”), contradicting the basic tenets of all BM-centered models. Amidst the (healthy) confusion, it is reassuring to find an unchallenged tenet of cochlear mechanics: the traveling wave.

Apart from the ability to look beyond the BM, OCT vibrometry has also facilitated the study of traveling waves in the cochlea, because the choice of recording locations is no longer restricted by the need to place reflective microbeads on the structures of interest.

In the current study we exploit this freedom of choice to obtain accurate, densely spaced longitudinal profiles of the traveling wave in the base of the gerbil cochlea. In our opinion, it is important to have such an accurate, quantitative characterization of cochlear waves. Despite many decades of theoretical analyses, the physics of these waves is still obscure. From previous experimental work [e.g. 1,2] we already know that the cochlear traveling wave is highly dispersive, i.e., that at a given location the propagation properties are dependent on frequency. A systematic quantitative description of wave propagation and its dependence on frequency, however, is still lacking.

METHODS

Sound-evoked vibrations were recorded from the basilar membrane of deeply anesthetized gerbils. The bulla was opened and the cochlear partition was viewed through the intact round window membrane. Images (B scans) and vibration measurements (M scans) were obtained using a Thorlabs Telesto III Optical Coherence Tomography (OCT) system at a sample rate of 111.6 kHz. The optical wavelength was 1300 nm and the effective lateral and axial resolution were ~ 10 μm and ~ 6 μm , respectively. For detailed methods, see [3]. The acoustic stimuli were irregularly spaced tone complexes (zwuis, [4]). Vibration responses were analyzed in the Fourier domain by extracting the stimulus-related spectral components and subjecting them to a Rayleigh test [5]. Only components

Perturbing the Cochlea

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Abstract. Cochlear mechanics can be studied by perturbing physiological and mechanical components of the organ of Corti (OC) and observing the outcomes. We have combined OCT-based *in vivo* vibrometry at the base of the gerbil cochlea with pharmacological perturbation of different components of the amplifier, including transiently abolishing the endocochlear potential (EP) with intravenous furosemide and inhibition of somatic electromotility by introducing sodium salicylate into the perilymphatic space. Vibrations in healthy cochleae were measured before and for several hours after the pharmacological perturbations to characterize the loss and recovery of the active process. DPOAEs were monitored and, for the furosemide experiments, EP and local cochlear microphonic observations were available from a previous set of experiments in our lab. For both salicylate and furosemide perturbations, outer hair cell sub-best-frequency (BF) nonlinearity recovered before the BF peak. In the salicylate studies intra-OC changes in the motion occurred as the cochlea recovered. In the furosemide experiments, the recovery of the BF peak occurred many minutes after EP recovery. Normal transduction currents have been shown to be necessary to maintain stereocilia morphology and loss of EP might transiently damage hair cell stereocilia, leading to the delayed recovery of functional amplification of the BF peak. We explored this hypothesis with histological studies of bundle morphology following furosemide. These observations have not yielded clear-cut results – bundle morphology usually appeared normal, although important changes might have occurred at more subtle levels. In sum, the constellation of factors that together give rise to cochlear amplification include EP, electromotility and transducer nonlinearity, and as-yet unidentified factors that must be properly aligned to give rise to a functioning whole.

INTRODUCTION

The endocochlear potential, the $\sim +80$ mV potential in scala media, is essential for normal cochlear amplification. In previous studies on furosemide, we reversibly eliminated the EP by an intravenous (IV) injection of furosemide in gerbil and measured the basal local cochlear microphonic (LCM) [1], the vibrations of the OC complex (OCC) [2], and distortion product otoacoustic emissions (DPOAEs). The EP recovered over ~ 40 minutes while vibrations, LCM and DPOAEs recovered later, ~ 2 hours post injection. Vibration was measured using optical coherence tomography (OCT). The axis of OCT measurement had both longitudinal and transverse components, and the measured motion was a combination of these [3].

In a second set of experiments, we transiently blocked OHC electromotility by introducing millimolar sodium salicylate into the scala tympani using a trans-round window membrane application, and monitored DPOAEs and OCC vibration. In the salicylate experiments we expanded the OCT vibration methodology employed in the furosemide study by constructing areal maps of the motion by taking a series of one-dimensional vibration measurements across the nearly radial field of view. The axis of OCT measurement was similar in the salicylate and furosemide experiments.

Following both furosemide and salicylate treatment, vibration amplitudes were diminished with basilar membrane (BM) vibrations resembling those of a passive cochlea, showing linear growth and a loss of the best frequency (BF) peak. The OHC region, some $60 \mu\text{m}$ deeper in the cochlear partition also showed decreased amplitudes and a loss of the BF peak, but in contrast to the BM, its vibrations retained broad-band nonlinearity at frequencies below BF following both furosemide and salicylate. Recovery of the BF peak occurred in both studies over hours, taking longer following salicylate.

Vélez-Ortega *et al.* found that normal transduction currents are necessary to maintain stereocilia morphology [4]. We hypothesized that the loss of EP following IV furosemide will thus damage hair cell stereocilia and may in part explain the delayed recovery (after EP recovery) of cochlear amplification. In the new results presented here, we investigate the effect of IV injection of furosemide on the morphology of the OHC bundles by *ex vivo* imaging of the OHC bundles using scanning electron microscopy (SEM). Other new results presented here are *in vivo* areal maps of the vibration of the OCC during recovery from furosemide, to compare to our previously reported vibration maps following salicylate. All experiments were performed in young adult gerbils.

Human Cochlear Partition Anatomy and Motion Using Optical Coherence Tomography

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Abstract. It has long been assumed that the motion of the cochlear partition (CP) is similar for all mammals. This “classic view” has been inferred from basal-turn measurements in laboratory animals (e.g., mouse, rat, gerbil, guinea pig, chinchilla, cat). However, our recent findings reveal the human CP anatomy and motion to be substantially different from the classic view, challenging the assumption that cochlear mechanics is universal among mammals. Inconsistent with the classic view, the human CP has a soft tissue structure between the bony osseous spiral lamina and inner pillar cells – the CP “bridge” – that has only recently been anatomically delineated. Laser Doppler vibrometry of the basal human cochlea showed the entire CP to be moving, with the osseous spiral lamina and bridge moving nearly as much as the BM, as opposed to solely the BM region as in the classic view. To better understand the implications of this new finding, we imaged the anatomy and measured the motion of the CP and organ of Corti structures with optical coherence tomography (OCT) in a ~13 h post-mortem fresh human specimen. This approach allows measurements of the intact cochlea through the round-window membrane. We present OCT images that detail the human CP and allow identification of structures within the organ of Corti. OCT vibrometry of CP structures enables us to measure motion of the BM, bridge, and osseous spiral lamina driven by air-conducted sound, as with previous methods; additionally, motion of structures such as the limbus, pillar cells, outer hair cells, supporting cells, reticular lamina, and tectorial membrane can now be measured. These preliminary measurements advance our understanding of the unique architecture and motion of CP structures in the human organ of Corti and how they may shape the sensory input at the inner hair cells.

INTRODUCTION

The cochlea has a complex structure that comprises two fluid-filled compartments separated by the cochlear partition (**CP**), which is responsible for the amplification of mechanical vibrations and subsequent transduction to neural signals. The CP contains the cochlear sensory tissue, the organ of Corti (**OoC**), which is bounded by the basilar membrane (**BM**) and tectorial membrane (**TM**), as well as the bony osseous spiral lamina (**OSL**). The introduction of sound produces a displacement of the BM leading ultimately to the firing of auditory nerve fibers. The sensitivity and frequency response of hearing are dependent upon the anatomy and mechanical properties of structures within the CP, which have been previously thought to be conserved among mammalian species. This generalized “classic view” of cochlear physiology has been widely accepted because radial motion measurements recorded in the cochlear base of several laboratory animals have been shown to be similar (1, 2).

Recent studies, however, have indicated several key differences between the anatomy and motion of the human CP and the classic view at the base of the cochlea (3). In laboratory animals (such as mice, gerbils, guinea pigs, chinchillas, and cats), the BM is attached to the short and relatively static OSL. In the classic view of cochlear mechanics, motion of the CP facing scala tympani is restricted to the BM which moves as a simple beam with maximum motion near the BM center (near the three rows of outer hair cells). However, in the human CP, the OSL is long and flexible, and we have identified a highly mobile soft-tissue structure, termed the “bridge” (absent in the classic view) between the OSL and inner pillar cells. Moreover, in human the TM attaches to the mobile limbus above the bridge instead of the classic view’s fixed OSL. Measurements using laser Doppler vibrometry (**LDV**) in human temporal bones have demonstrated that BM motion only accounts for <50% of CP volume velocity and the OSL and bridge have significant mobility, with peak motion near the BM-bridge connection (near the inner hair cells). These divergences in cochlear structure and movement may contribute to differences in cochlear mechanics, such as some of the sharper cochlear tuning which has been observed in humans compared to laboratory animals (4-6).

Differential Transverse Motion of Outer Hair Cells Measured in Gerbil High-Frequency Region

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Abstract. The great sensitivity and frequency selectivity of mammalian hearing originates in the mechanical properties of the cochlea. Cochlear motions in response to sound are amplified using metabolic energy. The motor element of this cochlear amplification is the outer hair cell (OHC), that expands and contracts lengthwise in response to a change in receptor potential at audio frequencies. How thousands of OHCs, acting through the local cytoarchitecture, work to achieve cochlear amplification is not fully understood. The properties of individual OHCs measured in micro-chamber environments are low-pass with a corner frequency of, at most, a few kHz. OHC corner frequencies within the cochlea have been estimated to be ~3kHz. Since in-vivo cochlear motion measurements show amplified frequency responses that extend up to many tens of kHz, but OHCs have corner frequencies of a few kHz, it has been suggested that OHCs are not active at the highest frequencies. How to reconcile these measurements has been a challenge. To address this, we made transverse cochlear motion measurements using a high-resolution optical-coherence-tomography (OCT) system at approximately the two ends of the OHC axial length: at the OHC bottom near the OHC-Deiter-Cell junction and at the OHC top near the reticular lamina. From these in-vivo measurements near the 45 kHz best frequency (BF) region of the gerbil cochlea, we determined the transverse differential response of OHCs. To remove phase from the traveling wave, we normalized the differential response by the motion at the OHC-Deiter-Cell junction. The normalized OHC differential response showed an almost exactly ½-cycle OHC top-to-bottom phase difference at frequencies up to 30 kHz, which is ½-octave below the BF (above this frequency the traveling wave is amplified). As frequency increased above 30 kHz, the phase difference decreased from ½ cycle, until near BF there was very little phase difference. From the lowest frequencies to BF the OHCs had substantial motion. Thus, OHCs continued to be active at frequencies up to BF of 45 kHz, more than an order of magnitude above their low-pass corner frequency.

INTRODUCTION

It well-established that outer-hair cells (OHC) have piezo-electric like electromotile properties¹ thought to generate forces up to 80 kHz² and pump power into cochlea over the wide frequency range found in high-frequency mammals such as mice³. Most measurements demonstrating OHC electro-motility have been from isolated OHCs in micro-chamber like environments. These measurements indicate a resistance-capacitance (RC) time constant “problem” that would limit electromotility to a few kHz^{4,5}. Theoretical work indicates that OHCs must be analyzed with appropriate loading for them to do work at high frequencies^{6,7}. Recent in vivo measurements from the gerbil ~25 kHz best frequency (BF) region suggests that the OHC current-to-voltage conversion is low-pass with a corner frequency of about 3 kHz^{8,9}. This raises questions about the ability of OHCs to do work on the basilar membrane (BM) and reticular lamina (RL) at the highest frequencies in vivo. These gerbil studies did not report measurements from which OHC top-to-bottom differential motion could be determined. Measurements in the 9 kHz region of the mouse found nearly out-of-phase OHC top-to-bottom differential motion that, based on motion from harmonic distortion, extended to 20 kHz¹⁰.

We made measurement from the gerbil ~45 kHz BF region, with an approach that is more transverse to the organ of Corti (OoC) than previously reported measurements. This approach allowed transverse measurements at

Advective mass transport along the cochlear coil

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Abstract. Mammalian auditory epithelium (the organ of Corti) stands out among different inner-ear epithelia in that it has large extracellular fluid spaces such as the tunnel of Corti, the Nuel's space, the outer tunnel, and the spacing between the outer hair cells. We tested the hypothesis that advective flow facilitates mass transport in the cochlear fluids, using computational simulations of cochlear fluid dynamics and *ex vivo* experiments to investigate mass transport in extracellular fluid spaces of the cochlea. Three model simulations were performed in series—cochlear mechanics, nonlinear fluid dynamics, and mass transport. In nonlinear fluid dynamics, we incorporated the convection terms for more accurate computation of drift flow. For mass transport, both diffusion and advection were considered. For experiments, we measured vibrations of excised cochlear turns using optical coherence tomography. The excised OoC was subjected to acoustic and electrical stimulations.

INTRODUCTION

The organ of Corti (OoC), the sensory epithelium in the mammalian cochlea, includes substantial extracellular spaces such as the tunnel of Corti, outer tunnel, and Nuel's space. Fluid in these spaces is interconnected by spacings between the columns of outer pillar cells and outer hair cells. Only mammalian species has such a large fraction of extracellular fluid volume within the auditory epithelium. Chemical and electrical properties of this Corti fluid are similar to yet distinct from the lymph in the scala tympani [1, 2]. The role of Corti fluid has hardly been studied perhaps because it was difficult to access in the past.

The OoC transmits basilar membrane vibrations to the hair bundles. For such kinematics, a rigid OoC is beneficial to convey vibration signals without compromising vibrations. On the other hand, the OoC is deformed by active outer hair cells. Outer hair cells contract or elongate in response to change in their transmembrane potential [3]. This electro-motility is required for cochlear amplification [4-6]. Investigations have been performed to explain how electro-motility amplifies OoC vibrations, both experimentally [7-13] and theoretically [14-24]. Recent observations showed apparent outer-hair-cell motility well below the characteristic frequency of measurement location [13, 25-29]. This led to diverse interpretations. Some believe that cochlear amplification is not local—outer-hair-cell energy accumulates over the length of the cochlea for amplification [25, 26], while others maintained that cochlear amplification is locally achieved [12, 28]. Another explanation was that outer-hair-cell motility is relevant to encoding the envelope of sound signals [30].

One way to summarize recent observations is to describe them as a substantial change in OoC cross-sectional area well below CF. Interestingly, these observations when combined with classical observations on cochlear traveling waves (wavelength longer than transvers dimensions and propagation speed on the order of m/s) form an

Nonlinearity and Energetics of Active Cochlear Models

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Abstract. The outer hair cell (OHC) of the mammalian cochlea is the nexus of the active processes giving rise to the nonlinear, biologically vulnerable, acoustic response. We present a model for the behavior of the OHC in view of its mechanical and electrical properties, and the external loading of the cell. Because of the low-pass electrical membrane impedance and rate dependent processes, there is a continuing debate on the mechanism of the amplification process at high frequencies. We will focus on the electrical-to-mechanical energy conversion at the cellular level, and show how we must consider the external mechanical loading of the cell to interpret the power transfer. In addition, we show that simple models can be used to fit *in vitro* data from experiments, but subtle model changes in the parameters change the predictions of power deposition by the OHCs.

INTRODUCTION

The outer hair cell (OHC) of the mammalian cochlea is the mediator of active and nonlinear processes necessary for healthy hearing. The mechano-electric-transducer (MET) channels of the OHC stereocilia are mechanically gated ion channels which present a nonlinear deformation dependent conductance to the resting voltage difference between the scala media and OHC intracellular voltage. Prestin-related somatic motility of the OHC is thought to either power a cycle-by-cycle conversion of electrical to mechanical power or be implicated in an automatic gain control algorithm. In the present paper, we will investigate the constitutive behavior of the OHC and the implications of this behavior for cycle-by-cycle power conversion.

The discovery of the electromotile response of outer hair cells (OHCs) by Brownell [5] has spawned research into determining the precise nature by which the OHCs participate in the hearing process. To this end, many experimental and theoretical studies have been undertaken to quantify the transduction process. OHCs exhibit voltage and stress dependent capacitance [4, 13, 17, 20], voltage dependent stiffness [12], and voltage dependent length changes [3, 5, 21]. There is contradicting evidence as to the ability of OHCs to contribute effective cycle-by-cycle forcing at high frequencies. Some *in vitro* (e.g., [8]) and *in vivo* [10] experiments indicate that OHC-mediated electromotility extends to 100 kHz, while *in vitro* experiments indicate that rate dependence could limit high frequency forcing (e.g., [9, 22]). In the present study, we focus on fitting models to the *in vitro* experiments and testing the predictions of the mathematical models along the lines of recent work [19, 22].

OHC MECHANICS

The OHC is a fluid-filled cell of nearly cylindrical shape *in situ* and when carefully extracted from the organ of Corti [2, 15]. Its outer cell wall consists of highly dense prestin molecules packed into the plasma membrane mechanically connected in parallel to a cortical lattice. As has been documented for isotropic and anisotropic nonlinear constitutive modeling of OHCs [6, 14, 15], assuming isovolumetric expansion and contraction of the cell due to the enclosed fluid, the radial strain can be related to the axial strain, and the stress-strain relations can be written in terms of the axial force on the cell and axial displacement of the cell [1] along with a dependence on the transmembrane potential. Under equilibrium conditions at constant temperature, the Gibb's free energy function of the coupled electro-mechanical system, which depends on the load applied to the electromotile element and the transmembrane potential, can be used to represent the thermodynamics state of the OHC [6, 7, 19]. In Fig. 1, a schematic of the various components of a

Micro-mechanical motion of the guinea-pig organ of Corti

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Abstract. One-dimensional measurements of sound-evoked motion were made by applying optical coherence tomography to the high frequency, basal turn of the cochlea in deeply anesthetized guinea-pigs. Wideband acoustic stimuli were used to evoke nanometer-scale vibrations of the basilar membrane (BM) and organ of Corti (OoC). Both macro- and micro-mechanical aspects of the responses were analysed, where macro-mechanical refers to ‘motions observed on the BM’, and micro-mechanical covers the motions of other structures ‘relative to those observed on the BM’. Both macro- and micro-mechanical motions exhibited compressive nonlinearity across wide dynamic ranges (typically from ~30 to >80 dB SPL near a site’s characteristic frequency or CF). Only the macro-mechanical motion was sharply tuned, however – the micro-mechanical motion, which included a transverse ‘squeezing’ type of OoC deformation, was low-pass filtered (well below CF), and *not* sharply tuned in its own right. The micro-mechanical motion was also delayed, accumulating ~0.5 cycles of phase-shift with respect to the macro-mechanics between 0 Hz and CF. Outer hair cell (OHC) and Deiters cell (DC) length changes were also analysed: OHC length changes exceeded macro-mechanical movements by factors of ~2-4 at low frequencies, but decreased in (relative) magnitude with increasing frequency as the CF was approached. At low frequencies, OHCs became longer and shorter when the BM moved towards the scala tympani and scala vestibuli, respectively. At frequencies closer to CF, however, this phase relationship reversed, in accordance with the ~0.5 cycles of phase-accumulation in the micro-mechanics. These observations are discussed with respect to previous findings, including a recent theoretical study that considered frequency-dependent changes in the mode-shape of a wave propagating along a simple physical waveguide [1].

INTRODUCTION

Recent experimental studies (e.g., [2–8]) have provided new insights into the way that healthy mammalian cochleae respond to sound stimuli, advancing the field of cochlear mechanics far beyond the level of the BM’s classically studied macro-mechanics [9–11] (see Table 1 for abbreviations). These studies use novel optical techniques to probe the sound-evoked vibrations of light-scattering structures deep inside the cochlear partition, without the need to physically open the cochlea itself. Here we apply one such technique to study the spatial distributions of sound-evoked vibrations across the width and depth of the cochlear partition in the basal turn of the guinea-pig cochlea. We focus on the differential motions that occur between anatomical structures within single ‘radial/transverse’ cross-sections, i.e. motions that relate directly to the micro-mechanics of the OoC.

TABLE 1. Abbreviations.

BM	Basilar membrane	OoC	Organ of Corti
DC	Deiters’ cell	RL	Reticular lamina
IHC	Inner hair cell	SM	Scala media
ME	Middle-ear	SPL	Sound pressure level
OCT	Optical coherence tomography	ST	Scala tympani
OHC	Outer hair cell	TM	Tectorial membrane

Modeling the Fine Structure of Ear Canal Pressure and Cochlear Microphonics in Response to a Pure Tone

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Abstract. Experimental measurements of the ear canal pressure (ECP) and cochlear microphonics at the round window (RWCM) in response to a pure tone exhibit quasi-periodic ripples in the amplitude. This fine structure, which is hypothesized to be due to a linear reflection mechanism caused by inhomogeneities in the properties of the cochlear partition, can be used to provide noninvasive information about cochlear function. In this work, a previously developed model of the gerbil cochlea is used to study the generation of the fine structure on the ECP and RWCM. The model includes cochlear roughness due to inhomogeneities in the properties of outer hair cells (OHCs) and a longitudinal cable model to represent the propagation of electrical currents in the cochlear ducts. The fine structure predicted in both ECP and RWCM is in line with experimental measurements in other species. Model simulations are used to derive the reflection components of the ECP and RWCM by taking the difference between predictions with a model with roughness and a smooth model. Results from simulations are analyzed to determine the cochlear regions that contribute to the RWCM fine structure.

INTRODUCTION

The cochlear microphonics (CM) is an extracellular potential generated due to the electrical response of OHCs [1]. It can be measured either at the round window (which will be called RWCM) or near the BM in the scala tympani (which will be called local CM or LCM). Charaziak et al. [2] recently demonstrated that, in chinchillas, the RWCM exhibits spectral ripples similar to what is observed in the ear canal pressure. Three different components of different latencies were identified. Both the short and the long latency components are generated by basal OHCs, either from direct stimulation by the forward traveling wave, or from the stimulation by the reverse wave that arises from coherent reflection near the peak of the forward wave [3]. However, Charaziak et al. demonstrated what the RWCM may also include contributions from a mid-latency component directly generated by OHCs located near the peak of the traveling wave. The presence of this mid-latency component suggests that the function of non-basal OHCs may be monitored by measuring the CM at the round window. In this work, a previously developed physiologically-motivated model of the cochlea [4, 5] is used to simulate the spectral ripples in the ear canal pressure (ECP) and RWCM and to identify the spatial regions that contribute to these spectral ripples.

PHYSIOLOGICALLY MOTIVATED MODEL OF THE COCHLEA WITH COCHLEAR ROUGHNESS AND LONGITUDINAL CABLES

We have recently developed and calibrated a physiologically-motivated model of the gerbil cochlea [4]. The model was calibrated based on both mechanical measurements (scala tympani (ST) fluid pressure) and electrical measurements (LCM) at a basal location (23.5 kHz best place). In this model, electrical longitudinal cables are included in the scalae of the cochlea to represent the spread of electrical currents within the ducts [6]; as shown in [4], these cables are essential in order to predict similar characteristics for the LCM as in measurements.

As in our recent work which focused on the generation of stimulus frequency otoacoustic emissions (SFOAEs) [5], the model includes roughness by adding small random perturbations in the value of the OHC electromechanical coupling coefficient, ϵ_3 , which relates the electromotile force to the transmembrane potential. The size (standard deviation) of these random perturbations, ΔR , was adjusted to 0.3% to predict similar RWCM spectral ripples as in the experiments from Ref. [2] (peak to notch level differences of about 25 dB, with deep notches). Application of roughness in BM stiffness or in conductance of MET channel was also considered, but it did not have significantly change model predictions.

Fluid focusing contributes to the BM vibration amplification by boosting the pressure

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Abstract. Two hydrodynamic effects are introduced in the standard transmission-line formalism, the focusing of the pressure and fluid velocity fields near the basilar membrane and the viscous damping at the fluid-basilar membrane interface, which significantly affect the cochlear response in the short-wave region. In this region, in which the wavelength is shorter than the cochlear duct height, only a layer of fluid of order of the wavelength is effectively involved in the traveling wave. This has been interpreted [8] as a reduced fluid contribution to the system inertia in the peak region, which is a viewpoint common to the 3-D FEM solutions. In this paper we propose an alternative approach, from a slightly different physical viewpoint. Invoking the fluid flux conservation along the traveling wave propagation direction, we can derive a rigorous propagation equation for the pressure integrated along the vertical axis. Consequently, the relation between the average pressure and the local pressure [4] at the fluid-BM interface can be written. The local pressure is amplified by a factor dependent on the local wavenumber with respect to the average pressure, a phenomenon we refer to as “fluid focusing”, which plays a relevant role in the BM total amplification gain. This interpretation of the hydrodynamic boost to the pressure provides a physical justification to the strategy [10] of fitting the BM admittance with a polynomial containing both a conjugated pole and a zero. In the short-wave region, the sharp gradients of the velocity field yield a second important effect, a damping force on the BM motion, proportional to the local wavenumber, which stabilizes active models and shifts the peak of the response towards the base, with respect to the resonant place. This way, the peaked BM response is not that of a proper resonance, corresponding to a sharp maximum of the admittance, but rather a focusing-driven growth toward the resonant place, which is “aborted” before reaching it by the sharply increasing viscous losses. The large values of the wavenumber that ensure strong focusing are ultimately fueled, against viscosity, by the nonlinear OHC mechanism, hence the otherwise puzzling observation of a wide nonlinear gain dynamics with almost level-independent admittance.

INTRODUCTION

It is well-known that the WKB 1-d transmission line cochlear models require non-trivial parameter tuning to give accurate predictions in the short-wave region, where the wavelength of the traveling wave (TW) is shorter than the cochlear duct height H , and 2-d, 3-d fluid effect must be included in the model [4]. The main effects are the focusing of the TW in a thin fluid layer close to the basilar membrane (BM) and the strong viscous damping of the BM motion associated with the sharp gradients of the velocity field in the BM-fluid interface region [6]. In the short-wave region,

My 50 years of cochlear modeling

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Abstract. The goal of this presentation is multi-fold: The primary goal is to discuss my present understanding of cochlear function. A secondary goal to review the history of my work in modeling the cochlea and the role of four close friends: Egbert de Boer, Steve Neely, Paul Fahey and George Zweig.

Regarding my present understanding of how the cochlea works, including experimental data on cochlear function, the tympanic membrane, middle ear, basilar and tectorial membranes, inner and outer hair cells, auditory nerve, and the cochlear amplifier. These views have been greatly sharpened by looking back and piecing this complex puzzle together. A great deal of progress has been made in the last 50 years.

Conclusions: My recent review of neural tuning curve data from 1985, using nonlinear (NL) distortion product generation, has revealed a deeper understanding of cochlear function. The most important, and surprising result, is that the cochlea is much more linear in its filtering properties than I previously assumed. When the suppressor frequency f_s is at least 1/2 octave lower than the characteristic frequency f_{cf} , we call this “low-side” suppression. This BM linearity is seen for “low-side” suppressors below 65 [dB-SPL]Fahey and Allen²³. Above 65 [dB] the suppression dominates with a slope greater than 1 [dB/dB]. The obvious explanation is that the threshold of excitation of the inner hair cells and of suppression threshold of the outer hair cells, which control the NL suppression, are the same. This is unexpected result, because low-side suppression on the basilar membrane has a 20-30 [dB] higher threshold^{20,24}.

This implies that low-side suppression and loudness recruitment (the reduced loudness of low-intensity sounds in the hearing-impaired ear) are closely related (i.e., are likely the same phenomena). The ramifications of this observation seem important as they will impact the diagnosis of cochlear hearing loss, and the fitting of hearing aids. In other words, two-tone suppression acts like an automatic gain control, elevating the loudness threshold, with very little distortion. This unexpected conclusion, about the linear nature of the cochlear response for low-side suppressors, is surprising.

INTRODUCTION

The path to new friends: After obtaining my MS in Electrical Engineering from the Univ. Penn on modeling the electrical thawing of frozen dog kidney (1968), and PhD on modeling a 1 [m] × 1 [cm] 18 kC° plasma arc-jet (1970). By 1971 I joined AT&T Bell Labs and in 1975 I was transferred to the *Acoustics Research Department* in Murray Hill NJ.

I was soon introduced to visiting scholar Egbert de Boer, who was widely known for his significant wide-range of hearing-science contributions. Egbert soon informed me that I would start modeling the cochlea (inner ear). I took the “hint” from both him and my highly knowledgeable supervisor David Berkley, who had published on this topic. I was immediately in the able hands of Mohan Sondhi who greatly upgraded my otherwise meager understanding of the necessary mathematics. Several papers followed^{6,12,19,31–33}.

Researching the inner ear: Bell Lab’s Acoustics Research Department was mostly involved in automatic speech recognition (ASR) and various acoustic applications (speaker phone and electret microphones), but historically there was always one person doing hearing research, and I quickly morphed into that lucky soul. At Bell Labs, limits were only determined by one’s imagination.

The next major event in my life was the arrival of Steven Neely from Cal Tech, who was assigned to work with me, and work we did. This turned into a life-long seminal friendship, with many important joint publications. Within a few years (circa 1982) I was setting up a lab at Columbia University in the Black Building (168th St, NYC), to record from the auditory nerve of the cat. For this work University of Scranton physicist Paul Fahey joined in, resulting in another life-long friendship/collaboration, along with, in our view, several key publications on how the nonlinear cochlea processes sound.

Cochlear modeling was soon followed by modeling the middle ear. This interest led to a PhD relationship with Sunil Puria, also from Columbia University. Today Sunil is one of the leading, if not the number-one expert, on middle ear science. Throughout this time up to the 2020 MoH meeting (Canada), I was in a continuous fun conversations with de Boer, although we almost never agreed. These years have been carefully documented due to the extensive work of Chris Shera, who designed the MoH website, with all the MoH publications freely available.

Around 1982-83, AT&T began the highly successful development of multi-band wide dynamic range hearing aids, which within five years was sold to the ReSound Corporation^{8,10}. ReSound is one of the few remaining large hearing aid companies in a highly competitive industry. My role at ReSound molded my future in many ways, largely due to its founder, and another very close friend, Stanford’s ENT Dr. Rodney Perkins, and also via another equally special friend, Mead Killion the founder of Etymotic Research.

Following the amazing experience with ReSound, I returned to Bell Labs research to continued my research on modeling the middle ear and cochlea, and quantifying auditory speech decoding features^{16,26,27}. The publications that best document these novel views are AF-92¹⁴ and FA-85²³.

How exceptional is the ear?

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Abstract. Many studies and reviews commonly refer to how “remarkable” and “exceptional” the ear is. Here we compile some of the key arguments raised in this regard. Several salient examples include: ▷ Ear is encased in hardest bone in body ▷ Ear contains most vascularized tissue in body ▷ Ear has highest resting potential in body ▷ Ear has a unique “fingerprint”? ▷ Displacement of eardrum at the threshold of hearing is $\sim 1/100$ of the diameter of a hydrogen atom ▷ Ear can detect signals below thermal noise floor and ▷ Ear is highly nonlinear (or highly linear, depending upon who you ask). For each, we provide biophysical arguments and references that allow their justification to be more critically assessed, aiming to assign a degree of validity. While of general interest to researchers and clinicians in the field, we also aim to frame these arguments so to draw attention and create enthusiasm towards the area of auditory neuroscience.

BACKGROUND

For many hearing scientists, it is usually not overly difficult to give a successful talk to a general audience. Most people *hear*, so it is natural to make a connection point to audience members. Especially older ones, who are finding hearing (typically in noisy environments) increasingly difficult. For audiences comprised of scientists and engineers, the task is even easier, as one approach is to impress upon the audience the “remarkable” [1, 2] functionality of the mammalian cochlea as a biological detector of sound. That is, the ear exhibits numerous characteristics that from a biomechanical point of view are, given limiting constraints (e.g., thermal noise, operating range of neural responses, fluid mechanics), impressive.

Consider for example that hearing intrinsically spans a very broad of spatial dimensions. The length scales (in meters) of the following hearing-related structures and phenomena span 16 orders of magnitude:

- ◇ 10^{-12} m = displacement of the eardrum in response to sound at the threshold of hearing [3]
- ◇ 10^{-9} = thermal-noise agitation of hair-cell bundles [4]
- ◇ 10^{-8} = step size of a myosin motor
- ◇ 10^{-7} = displacement of the eardrum in response to damage-inducing sounds
- ◇ 10^{-5} = width of a hair cell
- ◇ 10^{-2} = length of the cochlea
- ◇ 10^0 = “our” size
- ◇ 10^{-2} to 10^4 = the acoustic world we commonly perceive

On one hand, one might find it difficult to argue that this is not in fact remarkable. But on the other, there is nothing really special about hearing per se in terms of spatial scales of sensing. One could carry the argument to vision, claiming the spatial scale spanned there is 10^{26} (e.g., small: wavelength of visible light $0.5 \mu\text{m}$, retinal cone diameter of $1 \mu\text{m}$, large: distance between Earth and the far-away-but readily-visible star system Eta Carinae, $\approx 10^{20}$ m). An extra order of magnitude of magnitudes greater. So perhaps the ear is not so remarkable after all....

CLAIMS OF REMARKABLENESS

Nonetheless, numerous assertions regarding the ear are commonly mentioned. To set the stage, we state several here, without reference, justification, nor claims to veracity/refutation:

Sound-Evoked Vibrations at the Apex of the Chinchilla Cochlea

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Abstract. Despite tremendous advances in the field of cochlear mechanics, the apex remains one of the least understood of the cochlear regions, particularly in laboratory animals whose low-frequency hearing shares similarities with humans. Direct measurements of sound-evoked vibrations of the organ of Corti at the apex were until recently fraught with technical difficulties and experimental artifacts due in part to the necessity of opening the otic capsule to allow such measurements. With the advent of optical coherence tomography (OCT) machines, some of those difficulties have been overcome. Recently published results showed that at the apex of the guinea pig cochlea, nonlinear vibration amplitudes as a function of frequency display low-pass characteristics, which differs from the band-pass behavior commonly seen in basal responses. Here we present an overview of apical recordings performed using an OCT system in the cochlea of the chinchilla, an animal with a frequency hearing range similar to humans'. Just as with apical recordings in the guinea pig, the vibration pattern in responses to single tones in the chinchilla apex exhibits low-pass characteristics at a site having a cutoff frequency of around 500 Hz.

INTRODUCTION

The development and application of new technologies, such as optical coherence tomography (OCT), to the field of cochlear mechanics has improved our understanding of the functioning of the cochlea [e.g., 1-6]. In many situations, measurement of vibrations in the organ of Corti (OoC) can be performed in intact cochleae using OCT and thus diminishing the effects of experimental artifacts. Whereas basilar membrane (BM) responses at the base of the cochlea exhibit a band-pass shape, mechanical responses at the apex of the guinea pig and gerbil show a low-pass profile.

Here we try to extend our knowledge of apical cochlear mechanics by recording sound-evoked responses in chinchillas, an animal with low-frequency hearing similar to humans' [7]. OoC recordings were performed in intact cochleae using a Spectral Domain OCT and vibrometry at a region with a characteristic frequency (CF) of around 500 Hz. Non-linear responses to acoustic stimuli were measured at various locations along the optical axis of the beam inside the OoC. Displacement amplitudes as a function of stimulus frequency reveal a low-pass characteristic with a cutoff frequency of 400-600 Hz, i.e., near CF.

OCT-based Method for the Combined Measurement of Structural Vibration and Fluid Pressure

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Abstract. Simultaneous measurement of both vibration and pressure inside the cochlea *in vivo* would enable combined tracking of slow as well as fast-wave propagation. Such a measurement method could provide new information on the backward propagation of otoacoustic emissions. Thus far, the *in vivo* measurements of the organ of Corti vibrations using Optical Coherence Tomography (OCT) and measurement of pressure in the scalae using optical microphone have been reported only separately and involving different sensors. In this article, a method for integrated pressure and vibration measurements using OCT is described. The microphone consists of a micro-scale cavity, with a thin diaphragm made from an optical adhesive attached to the cavity similar to Olson's [1] optical microphone. However, the key difference in this new method is that there is no optical fiber for the electrical recording of the pressure. Instead, the vibrations of the microphone diaphragm are detected along with the vibrations of any multi-layer structure, such as the organ of Corti, simultaneously using OCT. A calibration chart of velocity per pressure for the microphone is used to convert the OCT-measured microphone diaphragm velocity into pressure recordings. The demonstration of this method in an air-filled vibroacoustic microchannel and application to eardrum impedance measurement is reported. The eardrum impedance measured in a GRAS ear simulator agrees well with the measured human ear drum impedance from literature.

INTRODUCTION

Certain vibroacoustic applications benefit from or require measuring the vibration of a structure and the acoustic pressure in an associated fluid in the vicinity. While it is reasonable to use multiple devices to detect vibration and pressure separately in larger applications, microscale applications generally cannot afford the space requirements, or the uncertainties brought about by multiple sensors. The performance of these applications could be limited by discrepancies caused in the measurements using multiple sensors due to calibration errors or differences in sensitivities of the sensors.

These challenges are further extended in microscale channels like the hearing organ cochlea, where suitable commercial sensors may not be available [2]. Sound entering the cochlea causes the propagation of a fluid borne compression wave and a structurally coupled travelling wave [3]. The coupled travelling wave excites the microstructures within the cochlea and travels much slower than the compression wave. While the nature of the forward propagation of the waves inside the cochlea is reasonably understood [4], it is unclear whether the compression wave or the travelling wave is responsible for the reverse propagation of signals generated inside the cochlea. Understanding the reverse propagation of waves is essential to understanding otoacoustic emissions, which are sounds generated from the cochlea and important for auditory diagnoses. Pressure transducers like those developed by Olson [1] have been vital in providing information about fluid pressure in live rodent cochlea. There have also

Spatial Buildup of Cochlear Compression Revisited

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Abstract. In 2013 we published an experimental study (Versteegh and Van der Heijden, doi.org/10.1007/s10162-013-0393-0) that introduced a traveling-wave perspective of cochlear nonlinearity, the so-called spatial buildup of compression and suppression. We recorded basilar membrane (BM) motion in the base of the gerbil cochlea, and obtained experimental evidence for the spatial buildup by independently varying the frequencies of the suppressor and the probe. The study concluded that the nonlinear response at any point in the cochlea can only be properly understood in terms of a spatial buildup of compression. Traveling waves start out as linear responses to the stapes drive and gradually accumulate compressive nonlinearity after entering their peak region, $\sim 1/2$ octave short of their best place. Likewise, the nonlinear effects of intensity on vibration phase can only be understood in terms of local changes in propagation velocity of the wave. Once viewed through this lens, a large body of published data on the effects of compression and suppression, often featuring complex patterns and seemingly contradicting trends, was shown to fit in a unifying framework. Despite the emphasis on spatial buildup, the data underling the 2013 study were obtained from single BM locations, due to the need for reflective microbeads with laser Doppler vibrometry. The spatial aspect was only explored by proxy, i.e., by varying the stimulus frequency and exploiting the tonotopy of the cochlear response (“scaling”). Optical coherence tomography (OCT) vibrometry has liberated us from this limitation, and in the current work we actually traced the spatial buildup of compression. In the BM and OHC region of the 13-24-kHz region of the gerbil cochlea, we recorded responses to equal-amplitude tone pairs centered at 15 kHz, spaced by 20 Hz. The resulting beating pattern affords a dynamic way of obtaining I/O curves. Spectral analysis of the responses yielded an accurate quantitative description of the compressive growth. We observed that the amount of compression (the difference in gain between the peak and dip episodes of the beat) increased gradually and systematically along the course of the slowly propagating wave, which confirms the spatial buildup claimed in our 2013 study. With increasing instantaneous intensity, the spatial rate of compression increased systematically over the nonlinear region. Overall, the conclusions of the 2013 study were confirmed, emphasizing the tight relation between cochlear compression and the wave character of cochlear vibrations.

INTRODUCTION

In the mammalian ear, the huge (>100-dB) dynamic range of audible sounds is compressed to less than 40 dB to fit the much smaller dynamic range of inner hair cell transduction. The exact mechanisms underlying this mechanical sensitivity control are unknown, but outer hair cells play a crucial role. The nature of cochlear compression is very complex, and capturing this complexity in terms of a limited number of unifying principles may be a first step toward understanding the physiological mechanisms. The main characteristics of cochlear compression at the level of the basilar membrane (BM) are:

- 1) It is very fast but not instantaneous. [1]
- 2) In essence it is a *multiband* gain control, meaning that sensitivity is independently regulated in different frequency bands [2,3].
- 3) At high intensities the independence of frequency bands breaks down asymmetrically. Low-frequency components start suppressing the sensitivity to sounds at much higher frequencies (upward spread of masking [4]).
- 4) At a given BM location the degree of compression, expressed as the slope in dB/dB of I/O functions, is strongly frequency dependent. Components more than $\sim 1/2$ octave below the best frequency (BF) show linear (1-dB/dB) growth. With increasing frequency the slopes become increasingly more compressive (< 1dB/dB), and this trend continues beyond the BF [3,5].

The Timing of the Cochlear Wave Propagation: A Comparative Study on How Computational Models Reproduce the Phase Response of Excitation Patterns

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Abstract. It is believed that the phase of the cochlear wave propagation might play a crucial role in binaural perception and sound localization by generating cochlear disparities. Experimental data demonstrate that, while a tone is being played, an excitation pattern is formed extending from the base to the apex of the cochlea. The phase of the excitation pattern decays along the cochlear length until the slope of the phase curve (i.e. group delay) reaches its maximum at a location with the characteristic frequency (CF) that matches the frequency of the input tone. Thereafter, the phase stays almost constant (group delay equals zero) until the apex. Computational models have been aiming to simulate the cochlear responses and thereby illuminate the underlying electromechanics of the human inner ear. These computational models can be divided, according to their topology, into two groups: Parallel filterbanks that model the cochlea as several independent filters versus cascade filterbanks (including transmission lines) that assume that the filters are coupled in series. Due to their modeling principles, cascade filterbanks intrinsically include the longitudinal traveling wave propagation whereas the parallel filterbank models lack this feature by default since there is no longitudinal relation between the filter stages in these models. The objective of this study was to verify if cascade filterbanks are actually more successful in simulating the phase responses than parallel filterbanks. The excitation patterns generated by seven cochlear models (four parallel filterbanks, two cascade filterbanks and a transmission-line model) in response to 4 and 9 kHz tones were estimated using an impulse, and the results were compared with corresponding experimental data recorded at comparable lengths in living mammalian cochleae. The accuracy of the model predictions was reported in mean absolute error (MAE) relative to the experimental data. The results show that cascade filterbank models are remarkably more successful with CARFAC and VERHULST models predicting the experimental data most closely. However, DRNL model (a parallel filterbank) also produces outcomes that are comparable in accuracy with those generated by cascade filterbank models. Further investigations showed that this specific parallel filterbank model externally incorporated correct phase delays in the impulse responses of its filter stages. The results indicate that if parallel filterbanks incorporate the phase delays in their impulse responses according to the proposed method, they could successfully simulate the timing of the longitudinal wave propagation along the cochlea within the same accuracy range as cascade filterbank models do.

INTRODUCTION

The human auditory system is capable of distinguishing sounds with a just-noticeable frequency resolution of 1/230 octave, approximately $\pm 3\text{Hz}$ at 1 kHz. (Patterson and Moore, 1986; Glasberg and Moore, 1990). This remarkable frequency sensitivity is believed to arise in the early stages of the auditory system, from the biomechanics of the cochlea. When a mammalian cochlea is subject to a sound pressure field, a displacement wave (i.e. traveling wave) is formed along the cochlear structures propagating from base to apex. The envelope of the traveling wave (i.e. excitation pattern) peaks at a certain location depending on the frequency of the input sound (von Békésy, 1960; Ruggero et al., 1997). Consequently, every location on the cochlea is attributed to a certain frequency, known as the characteristic frequency (CF) (von Békésy, 1960; Greenwood, 1990). This location-frequency selectivity of the cochlea is believed

Cochlear Wave Propagation and Dynamics in the Human Base and Apex

Model-Based Estimates from Noninvasive Measurements

Samiya A Alkhairy^{a)}

(Dated: 4 April 2022)

Abstract.

We estimate wavenumbers and impedances in the human cochlea using noninvasive measurements to better understand cochlear wave propagation and dynamics. The wavenumber and impedance encode information regarding how the cochlea works including wavelengths, gain and dissipation, and amplification and absorption. They provide a window into the cochlear amplifier and effective dynamic representations of the Organ of Corti.

Motivated by our interest in understanding how the cochlea works, we develop methods to estimate mechanistic variables (wavenumber and impedance), using noninvasive response characteristics (such as the quality factors of psychophysical tuning curves or group delays of stimulus frequency otoacoustic emissions) and an existing analytic shortwave model of the mammalian cochlea. The model is valid at low stimulus levels and was derived using a physical-phenomenological approach, and tested using a variety of datasets from multiple locations and species.

The model's small number of parameters and simple closed-form expressions enable us to develop methods for estimating mechanistic variables from noninvasive response characteristics. Developing these methods involves (1) deriving expressions for model constants, which parameterize the model expressions for wavenumber and impedance, in terms of characteristics of response variables - e.g. bandwidths and group delays of pressure across the Organ of Corti; followed by (2) deriving expressions for the model constants in terms of noninvasive response characteristics. Using these derived expressions we provide general methods for estimating the wavenumber and impedance from noninvasive response characteristics.

We then use these expressions along with reported values for quality factors from psychophysical tuning curves measured in humans. Our resultant estimates for human wavenumbers and impedances show that the minimum wavelength (which occurs at the peak of the traveling wave) is smaller in base than the apex. The Organ of Corti is stiffness dominated rather than mass dominated, and there is negative damping prior to the peak followed by positive damping, indicating a region of amplification followed by a region of absorption. The stiffness, and positive and negative damping are greater in the base than the apex.

Future work involves studying the closed-form expressions for wavenumber and impedance for qualitative mechanistic interpretations across mammalian species as well as studying derived mechanisms such as power flux into the traveling wave and features of the cochlear amplifier. The methods introduced here for estimating mechanistic variables from characteristics of invasive or noninvasive responses enable us to derive such estimates across species and locations where the responses are describable by sharp filters. In addition to studying cochlear wave propagation and dynamics, the model properties (such as the ability to determine model constants based on desired response characteristics) make it particularly appropriate for auditory filter design.

MOTIVATION AND OBJECTIVES

The cochlea has fascinating signal processing features which motivates our interest in understanding how it works. For instance, stapes vibration results in traveling waves that propagate along the length of the cochlea and are subject to dispersion and amplification. Relative to the stapes stimulus, the response at each location along the length of the cochlea relative to the stapes stimulus peaks at a particular frequency. Such features are of particular interest to auditory physicists as well as those interested in bio-mimetic design, which motivates our goal of determining what underlies these interesting features.

For box representations of the cochlea, information regarding how it works is entirely encoded in two mechanistic variables: differential pressure wavenumber, and the organ of Corti effective impedance. The wavenumber and impedance are a window into properties such as effective stiffness, positive and negative damping or amplifier profile, incremental wavelengths, gain and decay, phase and group velocities, travel times, and dispersivity. These two mechanistic variables therefore provide us with a better understanding of what underlies cochlear features of high gain and place-based wavelet analyzers. Of further interest, are comparisons between how the cochlea works in different species or at different locations.

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Comparison of Synchronized Spontaneous Otoacoustic Emission Dynamics in Human Data and Cochlear Mechanics Simulation: Effects of Roughness

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Abstract. The synchronized spontaneous (SS) otoacoustic emission (OAE) refers to the long-lasting oscillation evoked by clicks after transient-evoked OAEs (TEOAEs) attenuate. This research aims to study the SSOAE spectro-temporal dynamics by comparing human data and simulation. The simulation of SSOAE is based on a computer model of cochlear mechanics. In the model, the roughness of the basilar membrane (BM) can be adjusted and its effects on SSOAE patterns are observed. It is noted that the change in roughness level (5%, 10%, 15%, and 20%) affects the likelihood distribution between single-frequency, two-frequency, and a band-of-frequencies components. There is a general trend that band-of-frequencies occur more as the roughness level increases. The simulation result shows that, unlike the roughness level of 5% and 10%, roughness levels of 15% and 20% can generate SOAE oscillation below 2 kHz. Signal patterns of simulation are similar to what is observed in human SSOAE data, and thus support the standing wave theory of SOAE.

INTRODUCTION

OAEs can be regarded as a tool to assess power-amplifying function in the cochlea [1]. Among different types of OAEs, the synchronized spontaneous (SS) otoacoustic emission (OAE) refers to the long-lasting oscillation evoked by a series of clicks. As the name suggests, SSOAEs are closely related to spontaneous OAEs (SOAEs) but can be synchronously triggered by external stimuli. SSOAEs are present at isolated frequencies and typically decay slowly with time on the order of several hundred milliseconds [2]. There have been past studies on the theory of SOAE and stimulus-frequency otoacoustic emissions (SFOAE) generation using computer simulation. One of the studies tested the prediction of the multiple-reflection theory of SOAE generation using state-space equations for humans and concluded that instabilities across a wide bandwidth of frequencies arise when a smooth spatial variation of BM impedance is disturbed [3]. In a recent work [4], cochlear roughness was added to test the ability of their developed model to simulate SFOAE, and the link between fine structure and standing wave resonance of SFOAEs were further examined. The model was poised close to but below the limit of linear stability, so that it did not emit SOAEs. Then, the model was compared with and without roughness. Given that the afore-mentioned studies were focused on the effect of roughness on SFOAE generation, in this research, we aim to explore the roughness effect on SSOAE generation using a computer model of cochlear mechanics [5] and compare the simulation results with human data.

In particular, we study the SSOAEs spectro-temporal dynamics. In the model, the roughness of the basilar membrane (BM) can be adjusted and its effects on SSOAE patterns are observed. We shall describe how the roughness level affects the number of SSOAE spectral components and their temporal tendencies (decaying or sustaining) in simulation. The paper is organized as follows. In the method section, SSOAE human data collection is described and the related signal processing procedures are introduced. The result section consists of the comparison of simulation and human data in terms of SSOAE components and signal tendency. Discussions are given in the last section.

Understanding Bone Conduction In The Human Cochlea With Optical Coherence Tomography Vibrometry

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Abstract. To date, bone conduction (BC) has been extensively investigated using laser doppler vibrometry (LDV), intracochlear pressure measurements (ICP) and lumped element models (LEM). However, these techniques can disrupt the cochlear homeostasis, or are only applicable extracochlear. In this study, we used Optical Coherence Tomography (OCT) to overcome these limitations by in-depth, longitudinal, and contactless imaging of the human cochlear hook region through the round window membrane. Hereby, we were able to visualize the vestibular and tympanic plate of the osseous spiral lamina, basilar membrane, spiral limbus, Reissner's membrane epithelium, stapes anterior crus and head, scala tympani and scala vestibuli. Using OCT vibrometry, BC mechanisms are investigated in combination with subjective loudness balancing tests (LB), equalizing a 60 dB HL AC sound with an adaptable BC sound. This way, the displacement differences between AC and BC sound, assuming the same psychoacoustic loudness level, were mapped on intracochlear structures. Different force levels were needed to equalize the AC and BC sound in the loudness balancing test, and different velocity amplitudes and phases compared to the input signal were found on the basilar membrane and osseous spiral lamina using OCT vibrometry. Additionally, the stapes, RWM and promontory moved substantially different both in the human temporal bones and human cadaveric head. To the best of the authors' knowledge, this is the first study, investigating the differences between AC and BC in the human cochlea by means of OCT vibrometry. The obtained results were validated against the existing literature on AC and BC hearing, demonstrating that OCT vibrometry is a reliable method for studying the mechanics of the human cochlea.

INTRODUCTION

Bone conducted (BC) sound is the perception of sound travelling through the skull bones and soft tissue towards the inner ear, exciting the basilar membrane (BM) and hair cells causing a hearing sensation [1]. Contrary to air conduction (AC), which only involves one pathway, BC vibrates the BM through multiple frequency-dependent pathways (Fig. 1) [2]. Nobel prize winner von Békésy was the first to question the mechanisms of BC, revealing a similar stimulation of the BM through AC and BC sound [3]. Ever since, research to unravel the BC mechanisms extensively increased, using e.g., laser doppler vibrometry (LDV), intracochlear pressure measurements (ICP) or lumped element models (LEM). Consequently, evidence regarding similarities and differences of BM motion through AC and BC is rising. Additionally, the motion of the bony osseous spiral lamina and non-bony cochlear partition bridge are of high interest to date to predict their influence on the

Auditory Evoked Potentials in Comparison to Hearing Thresholds

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Abstract. Auditory Steady State Response (ASSR) is now commonly used to identify the Pure Tone Audiogram (PTA), especially for uncooperative humans. This work examined the correlation between pure tone threshold audiograms and ASSR at four frequencies (500 Hz, 1 kHz, 2 kHz, and 4 kHz) using a modulation frequency 40 Hz. Statistical evaluations were performed by correlation analysis and the Bland-Altman method, where the variance of the differences from measurement pairs was assessed based on the mean of these measurement pairs. The PTA value in decibels (dB) has established as the gold standard. Paired measurements are determined by the gold standard, while ASSR measurements are made by two measuring systems. Results: (1) The difference between ASSR thresholds and PTA thresholds were frequency-dependent, that is, it decreased with increasing frequency. (2) The ASSR is a useful complementary measuring tool to detect hearing thresholds in normal hearing subjects.

INTRODUCTION

Many different auditory evoked responses can be recorded from humans, and each of them can provide useful information about the auditory function. Pure Tone Audiometry (PTA) is the gold standard to evaluate the frequency dependent hearing thresholds. However, we cannot always measure the reliable thresholds with PTA for all patients, such as some children and patients who have neurologic delays. The Auditory Steady State Response (ASSR) is now generally used to identify the PTA, especially in case of uncooperative humans.

The ASSR is divided into two categories according to the modulation frequency: 40 Hz ASSR and 80 Hz ASSR [1]. The higher modulation frequency ASSR is less affected by the alert state [2], so it is suitable for the hearing test of sedated and sleeping children [3]; the low stimulation rate ASSR has the highest response amplitudes when the subject is awake.

ASSR is divided into single-frequency stimulation and multi-frequency stimulation according to the stimulation methods. Single-frequency stimulation means that the stimulation sounds of 500 Hz, 1 kHz, 2 kHz and 4 kHz are applied separately, while the multi-frequency stimulation uses the above four frequencies at the same time. Even eight signals from both ears (four in each ear) can be applied at the same time [4]. The judgment of the response result is automatically completed by the computer according to certain standards, avoiding the judgment of the examiner's subjective bias [5]. In addition, when applying multiple frequencies simultaneously, the test time is greatly shortened and necessary for clinical practice.

Our purpose is to evaluate the correlations between hearing thresholds detected by PTA and the 40 Hz multi-frequency ASSR in normal hearing adults and explore its value for clinical applications. For comparison ASSR was measured by two machines produced by the companies: PATH-Medical, Germany & Interacoustics, Denmark. We test if ASSR is a reliable method to determine hearing thresholds.

Sound-evoked vibrations along the tonotopic axis in the gerbil cochlea

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Abstract. Our exquisite sense of hearing involves micromechanical inner-ear processes that precede sound transduction by hair cells. These mechanics are however not well understood, especially in the apical regions of the cochlea that are essential for hearing the relatively low frequencies important for the intelligibility of speech. Recent observations in the high-frequency region of the cochlea's sensory organ of Corti (ooc) revealed unanticipated and complex motions, but low-frequency responses are not known. Here, we measured sound-evoked motions from the outer hair cell (OHC) region and the lateral compartment over an extended region in the apex of gerbil cochleae, and compared their phases to the basilar membrane (BM) response. By combining data from multiple tonotopic recording locations, low-frequency traveling waves that propagated along the BM with frequency dependent wavelengths between 1–3 mm were observed. In addition, we found a nonzero OHC–BM phase difference which systematically depended on the angle between the OCT optical beam and the BM along its longitudinal axis. This result establishes that the OHC vibrations were predominantly in the longitudinal direction, orthogonal to the up-down motion of the BM. Such motion is unavoidable in the presence of traveling, surface (BM) waves, but has such a significant magnitude that it masks the detection of OHC vibrations within the cross-sectional plane. With this, interpreting relative ooc motions in terms of the cochlear micro-mechanisms underlying our ear's remarkable sensitivity and frequency selectivity is tentative because their directions are not *a priori* known and vibrations along the third cochlear dimension must be considered as an important contributor to the recorded response.

INTRODUCTION

Sounds entering near the base of the cochlea create a pressure gradient across the basilar membrane (BM) and the sensory organ of Corti (ooc) it supports. This results in a longitudinally propagating traveling wave (TW) that—due to systematic and gradual changes in several physical properties (e.g., BM stiffness and width)—propagates with an amplitude and speed that depends on frequency, level and intracochlear location. This results in a place-based spectral decomposition of sound, or tonotopic organization, in which high frequencies maximally vibrate the cochlear base and low frequencies the apex. It is believed that active processes associated with outer hair cells (OHC) augment the passive, mechanical intracochlear responses to endow our ears with their capability to accurately discriminate tonal frequencies and intensities while maintaining exquisite sensitivity over a broad spectral and amplitude range [1]. Measuring the TWs, and the effects of OHC responses is challenging: the involved cochlear structures are small and poorly accessible, and their responses are on a (sub-)nanometer scale and vulnerable to physiological insults [2]. Because of this, most direct measurements of sound-evoked intracochlear vibrations were from superficial structures (e.g., basilar membrane; BM) at select locations within each cochlea. Vibrometry that uses spectral-domain optical coherence tomography (SD-OCT) alleviates many of these challenges [3, 4], and its recent application to cochlear mechanics has revealed several unanticipated and complex motions within the ooc, even at a single tonotopic location within the cochlea (e.g., [5, 6, 7, 8]). Here we present sound-evoked vibrations that were recorded using SD-OCT from multiple, adjacent longitudinal locations in the low-frequency, second turn of the gerbil cochlea that allowed us to evaluate the responses of individual low-frequency components across multiple tonotopic locations. This showed TWs along the BM with frequency-dependent wavelengths between 1 and 3 μm that slowed down when approaching the tone's characteristic frequency site along the tonotopic axis. Moreover, the natural curvature of the cochlea varied the (longitudinal) angle between the BM and the OCT optical beam across tonotopic locations. This revealed a drastic and sudden phase reversal of the OHC responses, which we interpret as evidence for substantial longitudinal motions (i.e. parallel to the BM) that "mask" radial vibrations (orthogonal to the BM) in the measured response. Responses in the lateral compartment (Hensen's cells and tectal cells) do not exhibit this phase-flipping behavior, suggesting that the large longitudinal motion is most prominent in the ooc-region occupied by the OHCs and/or Deiter cells.

Two operating modes for outer hair cells and implications for cochlear tuning.

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Abstract. The role of cochlear outer hair cells (OHCs) in mammal hearing is compromised by the ‘RC time constant problem’. The issue arises because if the cells are to operate at high acoustic frequencies conventional voltage driven ‘electromotility’ is low pass filtered by the cell membrane. By synthesising a description of the OHC as a piezoelectric actuator and its position between resonant basilar and tectorial membranes it is shown that sharp tuning can arise at high frequency if prestin/SLC26A5 is dynamically tensioned. The model predicts an imaginary (dissipative) component to the OHC capacitance as well as two distinct frequency tuning curve (ftc) shapes: a near symmetrical ftc at low CF, and a low frequency ‘tail’ on the more sharply tuned high CF ftc.

Introduction

The outer hair cells (OHCs) of the mammalian cochlea play an essential role amplifying incoming sound and making normal hearing possible. The evidence stems from a variety of different experiments but most significantly from the observation that OHCs elongate and shorten when their membrane potential is changed, from the cells’ position in the organ of Corti and from evidence that the gene for prestin/SLC26A5 determines cochlear sensitivity (reviewed for example in [1]). The role of outer hair cells and the requirement for an actuator molecule prestin/SLC26A5 thus seems sufficient for cochlear performance over the entire acoustic range. Nevertheless direct measurement from OHC movement both *in vitro* [2] and *in vivo* from basilar membrane measurements of gerbil OHCs [3] highlights a long term concern that the OHC membrane acts like a lowpass filter of voltage, a problem which has come to be known as the ‘RC-time constant problem’ [4]. One escape from the paradox is to propose that the OHC RC time constant, τ , continues to decrease towards the basal end of the cochlea and so mitigate the effect, at least for time scales imposed by patch clamp recording [5].

A line of modelling studies of single OHCs, based on the properties of prestin’s non-linear capacitance, suggest that OHCs are capable of injecting power at the higher end of the acoustic range [6] [7] [8]. The ideas owe much to the suggestion that mechanical loading extends the OHC bandwidth [9]. The present work combines prestin-dependent properties of the OHCs with a simple 1D model of cochlear micromechanics to investigate how such a scheme might enhance cochlear tuning. In the present case, the varying geometry of the organ of Corti along the cochlea and the precise configuration of hair cell excitation will, to first approximation, be neglected. The inclusion of such geometric factors has been considered elsewhere [10] in a model on which some the present considerations are based.

Formulation of the problem

The governing set of equations for the 1-D amplitude motion, ξ , of the basilar membrane (BM) is given by a set of coupled oscillators embedded in fluid,

$$\sum_j (G_{ij} + m\delta_{ij}) \ddot{\xi}_i + h_i \dot{\xi}_i + k_i \xi_i = f_i(\xi, t) \quad (1)$$

represented here by the discretised version (where the dots signify time derivative). The BM amplitude ξ is adopted to distinguish it from longitudinal cochlear position, x , indexed as i . The term $f_i(\xi, t)$, is the local forcing term at position i . The parameter $k = k(x)$ is the stiffness of the partition at each point x along the cochlea, $h = h(x)$ is a viscosity parameter, accounting for both the local fluid viscosity in scala media as well as that arising in the subreticular space.

The Functional Contributions of Links in Mammalian Cochlear Hair Bundles

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Abstract. In the mammalian cochlea, hair bundles of the sensory outer and inner hair cells detect mechanical signals. A hair bundle comprises a set of rod-like stereocilia that pivot around their insertion points in the hair-cell's apex. Stereocilia are linked by gating springs and connectors, also known as top or shaft connectors, side, lateral, or ankle links. Gating springs link neighboring stereocilia of differing height, while connectors link all neighboring stereocilia. Sound-induced gating-spring oscillations open and close mechano-electrical transduction channels attached to the gating springs, causing oscillations in the hair cell's receptor current. In contrast to gating springs, connectors are not attached to channels and their functional role is unclear. To determine how the specific properties of gating springs and connectors contribute to outer-hair-cell bundle function, we use a computational model of an outer-hair-cell bundle, which accounts for nonlinear hair-bundle splaying at rest, nonlinear fluid forces on stereocilia, and nonlinear channel gating. The model is validated by reproducing many experimental observations, including stereocilium splaying at rest and hair-bundle stiffness decreases caused by breaking gating springs or connectors. We discuss how varying the gating-spring and connector stiffnesses affects the receptor current in response to stimulation at the characteristic frequency of the hair cell.

INTRODUCTION

In the auditory, vestibular, and lateral-line organs of vertebrates, hair bundles convert forces induced by sound, head motion or position, and fluid into receptor currents [1]. A hair bundle comprises rows and columns of rod-like stereocilia protruding from the hair-cell's apex and increasing in height toward one edge of the bundle. In a column, stereocilia of increasing height are linked by gating springs, which transmit forces that gate (open and close) mechano-electrical transduction (MET) channels. Rows are formed by stereocilia of similar height, which are not linked by gating springs. Deflection of a hair bundle toward its tallest row (row 1) causes its stereocilia to pivot, gating-spring forces to increase, and MET channels to open. Gating springs comprise tip-links, made of the proteins protocadherin 15 (PCDH15) and cadherin 23 (CDH23), and other elastic elements in series with the MET channels [1, 2]. Stereocilia are also linked within rows and columns by connectors, which do not gate channels. It has been proposed that connectors increase the coherence of stereociliary motions and decrease hair-bundle damping, but recent work in outer-hair-cell (OHC) bundles show that connectors can decrease the uniformity of stereociliary motions and increase hair-bundle damping, calling the role of OHC connectors into question [3, 4, 5]. Connectors comprise different elements in different types of bundles and include top and shaft connectors, side, lateral, and ankle links [6, 7, 8, 9, 10].

The structure and function of hair bundles differ between species, between organs, and between different locations within an organ, but we have a limited understanding of the relationship between a hair bundle's structure and its function [1]. Gating-spring and connector stiffnesses differ between different types of bundles and between different locations within an organ, but we do not know how specific gating-spring or connector stiffnesses contribute to bundle function in the mammalian cochlea [3, 11, 12, 13]. In addition, connector stiffness may differ between rows and columns within the same bundle and we have no information about gating-spring or connector damping [12]. Here we focus on the contribution of gating-spring and connector stiffness to OHC-bundle function in the mammalian cochlea.

The function of an OHC bundle is to convert sound-induced forces into receptor currents. OHC structure changes from the cochlear base to apex: bundle stiffness decreases, stereocilium number decreases, stereocilium height increases, pivot and gating-spring stiffness decrease, and gating-spring resting tension decreases [11, 14, 15, 16, 17]. OHC connectors comprise stereocilin, immunolabeling of which decreases in intensity from base to apex, suggesting a decrease in connector stiffness and damping from base to apex [9]. Because OHC mechanics changes with characteristic place along the cochlea, we study OHC bundles corresponding to a specific characteristic-frequency (CF) region (4 kHz). Using a computational model, we determine the OHC bundle receptor current in response to

Not so presto? Can prestin be sluggish?

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Abstract. Prestin (SLC26A5), a protein essential for the sensitivity of the mammalian ear, was so named from *presto*. The assumption was that this membrane protein supports fast movement of outer hair cells (OHCs) that matches the mammalian hearing range, up to 20 kHz in general and beyond, depending on the species. *In vitro* data from isolated OHCs appeared to be consistent with such frequencies. However, some recent reports cast doubts on this assumption, suggesting that the intrinsic transition rates of this protein are much lower, about 3 kHz for guinea pigs, not covering the auditory frequency range of the animal. Recent *in vivo* data also show that the amplitude of OHC motion rolls off well below the best frequency of the location. The present report examines whether or not these recent observations are compatible with the physiological function of OHCs by using simple piezoelectric models.

INTRODUCTION

The significance of prestin for the sensitivity and frequency selectivity of the mammalian ear has been well established [1]. However, the detailed mechanism, with which this piezoelectric membrane protein plays its physiological role, remains not as clear. The frequency range that this protein is capable of responding is a critical issue.

Earlier *in vitro* studies on isolated OHCs confirmed that their fast motile response is based on piezoelectricity [2, 3, 4]. Force generation under quasi-isometric condition was shown to have flat frequency dependence up to 60 kHz [5]. The characteristic frequency of the power spectrum of membrane current due to prestin was about 40 kHz [6]. Those frequencies were considered to be lower bounds imposed by experimental conditions.

However, recent reports on OHCs in *in vitro* [7, 8] appear to contradict these earlier observations. In addition, *in vivo* data obtained with optical coherence tomography (OCT) [9] have been interpreted as evidence against fast motile response of OHCs.

The present report examines the implications of these two kinds of reports by asking two questions. First, can OHCs counteract local viscous drag incurred by the movement of the organ of Corti in the cochlea if gating rates of prestin are as low as these recent reports suggest? At the basal end, where the traveling wave initiates, viscous drag must be counteracted by OHCs. This condition determines the frequency limit of the ear.

Second, should the movement of OHCs large at their best frequencies *in vivo*? The first issue is addressed by evaluating power generation by OHCs driven by prestin with finite transition rates. The second issue is addressed using a simple model system, which consists of two harmonic oscillators, one of which has a driver and the other with a damper.

1. TRANSITION RATES

First, let us derive the equation of motion for a cell, which is driven by a motile molecule with finite intrinsic transition rates. An earlier version has been published as Appendix to Santos-Sacchi et al. [8].

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Digitization and Reanalysis of Fiber-optic Displacement Data: An Elephant in the Chamber?

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Abstract. Over the last half century, the intense activity upon the mechanics of mammalian hearing falls into two broad categories: 1) Studies by sensory physiologists (e.g. Brownell, Flock, Russell) interested in the holistic active mechanical properties of the outer hair cells (OHC) and 2) studies by theoreticians and practitioners who have been attracted into the field seeking to explain the central question of audition, i.e. What accounts for the extreme sensitivity and vulnerability of mammalian hearing? How can the critical mechanism which goes missing *not* be best described as amplification, if, when sensitivity is lost, it can be compensated by use of an external amplifier? The historic starting point has been the Bekesy two-chamber model of the cochlea. The general, the Fourier transform of basilar membrane (BM) vibrations would normally have a zero-frequency (or dc-) component. However, because of the historic basis of the standard model, any such component has been systematically disqualified from consideration. This presenter was the first to publish that a dc-component of BM motion not only does exist, but it covaries with the vibrational component in ways which mimicked the polarity variation of the summing potential ([LePage JASA, 1987](#)). The later published data (full method details, [LePage, Hear. Res., 1989](#)) did not have the full support of all collaborators beyond the development of the fiber-optic sensor. However, using the finished device, it was shown, to the real-time disbelief of B.M. Johnstone, that the BM displacement displayed properties very similar to the contractile components of the OHC both in temporal dependence and amplitudes equalling fractions of the length of the OHC. These fiber-optic data have been extracted from many paper chart records, digitised, then reprocessed with MATLABTM to generate a video to bring to new life what was originally only rapid large excursions of the pen on the single channel chart recorder. These BM dc-shifts are indeed highly tuned. Their tuning varies as expected with the manipulations originally described. Moreover, the velocity of these excursions is of the same order with the estimates of velocity of BM vibrations from dozens later investigations which have uniformly assumed the unseen motion was exclusively a vibration at the stimulus frequency. This presentation therefore raises deep questions about whether the two-chamber model has remained a dominant influence on the progressively-refined design of BM measurements – as well as the widespread rejection of data from many studies whose results made no sense in conventional terms of a fragile and "mysterious" cochlear amplifier (CA). Could it be that the expected super fragile tuning mechanism was the oft-employed explanation, when an equally plausible explanation could be a robust mechanism based on the OHC, modulated by an unknown but critical tiny BM baseline bias?

BACKGROUND

There have been two streams of experimental investigation into basilar membrane motion in mammals – those preferring to use velocity sensors and those using displacement sensors. The velocity sensors delivered much cleaner data particularly coupled with liberal use of standard noise-rejection techniques. By contrast the displacement measures of basilar membrane motion produced such confusing data they have been widely dismissed, particularly because they tended to need invasion of the cochlea to get access to the basilar membrane. Such a disturbance was unacceptable essentially because it tends to destroy the high sensitivity and sharp tuning which is the target objective: 1) vibrations due to incoming sound at threshold levels are submicroscopic demanding very high sensor sensitivity, and 2) the tuning mechanism appears very delicate – it can be disturbed by a host of influences, each of which must be carefully controlled. In a half-century of achievement, the source of OHC motility has been tied to contractile behavior of isolated OHC soma easily observed under a regular microscope (Brownell et al 1985). The unresolved issue has been how that is tied to hearing sensitivity. On the

High Speed Imaging of Active Motility in Hair Cells

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Abstract. Hair cells of the auditory and vestibular systems are capable of detecting sub-nanometer deflections due to air-borne or ground-borne vibrations. Further, hair bundles of some end organs are known to spontaneously oscillate without external stimulation, indicating the presence of internal active processes. Ionic influx upon the deflection of hair bundles elicits changes in the somatic potential, leading to a conversion of mechanical input to electrical signals. While the transduction process has been well-studied in hair cells, the possible presence of mechanical distortions in the hair cell soma has not been explored in non-mammalian species. In this work, we applied optical techniques based on transmitted and scattered light to detect active motility in the hair cell soma under different experimental conditions. We developed image processing tools tailored for semi-intact preparations of the sensory epithelium, observed with wide-field microscopy. Accordingly, we recorded light intensity distributions of hair cells of the American bullfrog (*Rana catesbeiana*) at high speed during spontaneous oscillations and mechanical deflection of the hair bundles. We imaged the hair cells at various optical sections along the z axis, with a specific focus on the innervation area, and observed mechanical fluctuations at localized positions within the hair cell. We aim to further develop optical techniques that would enable the study of hair cells somatic activity with a non-invasive and dye-free approach, so as to minimize mechanical or physiological disturbance of natural conditions.

INTRODUCTION

The auditory system plays a vital role in living organisms, allowing them to navigate in space and communicate and providing important cues for the avoidance of danger. These features require not only sensitivity that is sufficient to detect signals as low as 0 dB [1] but also the ability to extract that information from environments containing multiple competing streams of information. Specialized cells located in internal sensory organs within the ear are responsible of the hearing and balance capabilities of vertebrates [2]. The key functional units performing the first step of detection are known as hair cells (HCs) due to their characteristic stereocilia that emerge from a cuticular plate (Fig. 1(A)). The hair bundle is composed of 30 to 50 stereocilia that protrude from the apical surface of the cell body, which is embedded in the surrounding tissue. HCs of the auditory and vestibular systems are finely tuned sensory detectors, capable of perceiving sub nanometer mechanical perturbations of the hair bundle. These displacements can be induced by air- or ground-borne vibrations that are transduced into electrical signals [3]. Therefore, mechanical inputs trigger a mechanism that elicits spike trains in the neurons that innervate the cell body.

The process by which HCs detect mechanical input from the surrounding environment and transmit that information to the brain involves a cascade of cellular events. Upon deflection of the hair bundle, which pivots the stereocilia at the base, tension increases in the tip links that connect adjacent pairs of stereocilia (Fig. 1(B)). The increased tension opens mechano-sensitive transduction channels that are coupled to the tip links, enabling the influx of ionic currents, leading to depolarization of the HC. As a consequence, vesicular release of neurotransmitters is triggered at the afferent synapse, which triggers spike trains in the neurons and ultimately conveys a signal to the brain [4]. The opposite pathway, transmission of signals from higher order processing centers of the brain back to the sensory epithelium, is managed by the efferent neurons, which provide a protective feedback mechanism [5, 6]. Both conduits interact with the HC at the lower area of the cell body through the synaptic boutons of innervating fibers, as shown in Fig. 1(A).

The auditory system further contains an active amplifier, which expends energy to enhance the response to extremely small signals. At the level of the hair bundle, internal adaptation process involving myosin motor activity have been shown to lead to spontaneous oscillations. One of the manifestations of the active process, these oscillations can be modulated by mechanical, electrical, and chemical manipulations and provide a useful probe of internal mechanics of the bundle.

In this study, we explore the use of widefield microscopy combined with analysis of light intensity fluctuations, to study mechanical perturbations of the hair bundle as well structures with the hair cell soma. We aim to develop

On Natural Selection of Outer Hair Cell Electro-Mechanical Properties

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Abstract. The biophysical and mechanical properties of outer hair cells (OHCs) vary systematically with location along the cochlear tonotopic map following monotopic relationships that apply universally across all mammalian species studied to date. To reasonable approximation, OHCs located at a specific characteristic frequency (CF; ω_{cf} , rad-s⁻¹) all have the same length, linear capacitance, nonlinear capacitance, basolateral conductance, axial stiffness and mechano-electrical transduction (MET) current kinetics. Such correlations do not arise in nature by chance, but in the Darwinian view arise through natural selection. We hypothesized that OHC biophysical and mechanical properties evolved simply to maximize frequency tuning and OHC electro-mechanical power efficiency. To test this hypothesis, we analyzed a linear toy model consisting of an OHC working against a simulated cochlear load. Analytical methods were used to optimize tuning and efficiency at the same time by adjusting: prestin expression (non-linear capacitance), cell length (linear capacitance), compliance (stiffness), voltage-gated ion-channel expression (basolateral conductance), and MET channel kinetics (gain and adaptation). Results demonstrate these factors are interrelated, and when optimized together predict key relationships between OHC properties and CF observed experimentally. To overcome viscous dissipation and optimize tuning, the MET current must be gated by both displacement and velocity, and have a magnitude quantitatively related to prestin expression, basolateral conductance and OHC stiffness. To maximize efficiency at CF, the resistive-capacitive corner frequency (ω_{rc} , rad-s⁻¹) must be below CF ($\omega_{rc}/\omega_{cf} \sim 0.35$), prestin expression must yield a nonlinear capacitance roughly equal to the linear capacitance (C ; $C_n/C \sim 0.9$) and the OHC axial stiffness (k_o , N-m⁻¹) must exceed the stiffness of the cochlear load (stiffness per OHC without OHCs; $k/k_o \sim 0.2$). If any of these optimized parameters are changed, tuning and power efficiency drop precipitously in the toy model. Based on this finding, we further hypothesize that an important role for tonic firing of olivo-cochlear efferent (MOC) neurons is to optimize the tuning, and that changing MOC activity would have a much stronger effect on power output than predicted by a reduction in the voltage modulation alone.

INTRODUCTION

Outer hair cell (OHC) length, ionic conductance, mechano-electrical transduction current, passive capacitance, axial stiffness and prestin expression all vary monotonically along the logarithmic cochlear tonotopic map. Cells located at the 0.2 kHz characteristic frequency (CF, ω_{cf}) place have a length of ~ 80 μm while cells located at the 10 kHz CF place have a length of ~ 40 μm [1-3]. The reduction in length causes an increase in OHC whole-cell stiffness (k_o) with CF [4], which has log-linear scaling similar to the stiffness of the cochlear partition (k) [5]. The correlation between OHC length and CF is universal across mammalian species, but precisely why the correlation exists is not completely known. The change in length is much too small to support a purely mechanical hypothesis, suggesting electro-mechanical properties of OHC might drive the correlation. Passive capacitance (C) and peak nonlinear capacitance (C_n) scale roughly in proportion to the membrane surface area [6], while ion channel expression and

Low-Level Distortion Product Otoacoustic Emissions in Lizards are Influenced by Spontaneous Activity of the Inner Ear

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Abstract. Distortion product otoacoustic emissions (DPOAEs) from lizards can display a rapid variation in intensity level upon changes in the distortion frequency. The level functions of both cubic distortion products elicited by low- to moderate-level stimuli exhibit pronounced notches across range of the distortion frequencies. The emission level varies more smoothly with the distortion frequency at higher stimulus intensity. To understand the variation in DPOAE level, we measured DPOAEs from tokay geckos and demonstrated that the level of the distortion signals, evoked by primary tones with intensity levels below approximately 60 dB SPL was strongly correlated with the amplitude spectrum of spontaneous otoacoustic emissions (SOAEs). The DPOAE intensity level was significantly enhanced when the distortion frequency coincided with the center frequency of an SOAE peak. Manipulations of the body temperature revealed that peaks in the SOAE amplitude spectrum and the DPOAE level function displayed systematic shifts to lower frequencies of comparable magnitudes upon cooling. Our results suggest a common underlying mechanism of low-level DPOAEs and spontaneous activity in the inner ears of tokay geckos.

INTRODUCTION

In response to two-tone stimuli at frequencies f_1 and f_2 , the inner ears can produce acoustic energy at frequencies corresponding to linear combinations of f_1 and f_2 . These intermodulation distortions can be detected externally as distortion product otoacoustic emissions (DPOAEs). When evoked by low- to moderate-level stimuli, the intensity level of the cubic distortion products observed at $2f_1-f_2$ and $2f_2-f_1$ can vary drastically upon changes in the stimulus frequency. In lizards, the DPOAE level functions can exhibit multiple peaks and notches across range of the distortion frequencies [1-3]. At higher stimulus intensity, however, the emission level varies more smoothly with the distortion frequency [1-2].

The distinct characteristics of the DPOAE level functions elicited by low- and high-level stimuli suggest multiple mechanisms that involve in the generation of DPOAEs. While high-level distortions are likely contributed by the passive nonlinearity of the inner ear, low-level DPOAEs potentially involve the active processes performed by hair cells. This has been partly evidenced by the alterations of low-level DPOAE intensity upon physiological insults to the inner ear, such as hypoxia [1]. Moreover, previous investigations suggest that low-level DPOAEs can be amplified when the primary tone's or distortion frequency coincide with the center frequency of a peak in the spontaneous otoacoustic emission (SOAE) amplitude spectrum, measured in the absence of stimulus [1].

To illustrate whether low-level distortions can be influenced by the SOAE activity from the inner ears of lizards, we recorded the pressure signals from the ears of tokay geckos in the presence of two-tone stimuli. The intensity level of DPOAEs measured across range of the distortion frequencies was compared to the SOAE amplitude spectrum. We found that the level of DPOAEs evoked by primary tones with large frequency differences varied consistently with the SOAE amplitude spectrum. Finally, we decreased the body temperature of tokay geckos to reveal the correlation between the SOAE activity and the level of DPOAEs evoked by two-tone stimuli at small frequency differences.

Synchronization and Sensitive Signal Detection by Coupled Systems of Chaotic Hair Cells

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Abstract. Auditory and vestibular systems display mechanical coupling of active, oscillating components. The strength and extent of this coupling varies across species and organs, depending on the specific task of each system. It is believed that this mechanical coupling is essential to achieve sufficient sensitivity, frequency selectivity, and temporal resolution for reliable signal detection. These characteristics depend heavily on the ability of the active oscillators to synchronize with each other. It has previously been shown that spontaneous otoacoustic emissions may arise through a dynamical systems phenomenon known as frequency clustering, where active oscillators synchronize with those of similar characteristic frequency, forming several distinct clusters. In this work, we demonstrate that nonisochronicity enhances the stability of these clusters, yielding larger, sharper spectral peaks. Further, we show that nonisochronicity enhances the ability of the system to detect weak signals. We propose that auditory and vestibular systems utilize nonisochronicity as a mechanism of facilitating synchronization among oscillating components to enhance signal detection.

INTRODUCTION

The auditory and vestibular systems are astounding signal detectors. They respond to sounds, vibrations, and accelerations that produce motion on the order of angstroms, comparable to or below the levels of intrinsic noise in the system [1]. Humans are able to resolve two tones that differ by only 0.1% in frequency [2]. We are also able to resolve two acoustic impulses that are separated by only 10 microseconds, where the stimulus waveform is presented simultaneously into both ears [3]. These characteristics of sensitivity, frequency selectivity, and temporal resolution are essential for complex tasks such as localizing sound sources and comprehending speech. How these systems reliably achieve such signal detection properties remains an open question, and the physics of hearing continues to be an active area of research [4].

Mechanical detection of sound, vibration, and acceleration is performed by sensory hair cells. These specialized cells get their name from the hair-like stereovilli that protrude from their apical surfaces. This cluster of interconnected stereovilli is collectively called the hair bundle, and performs the essential task of converting external mechanical signals into electrically conveyed information [5, 6, 7]. The external signal pivots the hair bundle, modulating the tension in the connective tip links between adjacent stereovilli. This tension modulates the opening probability of the mechanically sensitive ion channels embedded in tips of the stereovilli and connected to the tip link. The hair bundles are further mechanically coupled to each other through overlying structures, with the strength and extent of coupling varying with the species and the role of the sensory organ.

Auditory detection has been shown to require an active, energy-consuming process in order to overcome the dissipation in the surrounding fluid and to achieve such remarkable signal detection [8]. This active process manifests itself in several ways, one of which is the occurrence of autonomous oscillations of hair bundles in several species [9, 10, 11]. These spontaneous oscillations were shown to violate the fluctuation dissipation theorem, proving them to be active [12]. While the role of these spontaneous oscillation *in vivo* is unknown, prior studies have suggested that they could be utilized to amplify external signals and thereby improve signal detection [13].

Another manifestation of the active process is the emission of faint tones from the external ears of living animals [14]. These spontaneous otoacoustic emissions (SOAEs) exhibit several sharp peaks in their power spectra and are metabolically sensitive, indicating that they utilize an energy consuming process. SOAEs are ubiquitous across the vertebrates and serve as one of the probes for studying the active process of hearing. Although they have been used as a diagnostic for hearing-related disorders, the mechanism by which SOAEs arise remains controversial [15, 16, 17]. One theory suggests that they are locally generated by the spontaneous activity of hair cells, through a phenomenon known as frequency clustering [18, 19]. Dynamical-systems theory shows that frequency clustering can occur when active oscillators with frequency dispersion are coupled together. The oscillators synchronize with one of several distinct clusters, forming sharp peaks in the power spectrum of the collective motion.

Nonlinear Effects Basal to the Best Place Manifest in the Reticular Lamina's Response due to its Low Impedance Relative to the Basilar Membrane

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Abstract. Based on a plethora of basilar membrane vibration measurements, it had been presumed that cochlear nonlinearity due to outer hair cell (OHC) forces is limited to the peak region of a given stimulus. However, recent experiments showing two-tone suppression of the reticular lamina (RL) indicate that OHCs provide electromotile feedback over a much broader basal region. In this work, a computational model of the cochlea containing organ of Corti (OoC) structures, a fluid domain coupled to the basilar membrane (BM), and an electrical model to represent OHC activity is calibrated to experimental data for the mechanical and electrical responses to a pure tone and then used to make two-tone suppression predictions. These predictions are in line with recent experimental measurements, capturing extended nonlinearity in the RL response compared to that of the BM. By comparing the OHC force of pure tone and two-tone model predictions, we examine the root cause of broader nonlinearity seen in the response of OoC structures at the top end of the OHCs.

INTRODUCTION

Two-tone suppression (TTS) is a phenomenon that arises due to cochlear nonlinearity, and specifically refers to the reduction in the cochlear response due to a pure tone stimulus presented alone compared to when that same stimulus is presented in the presence of a second tone. In this case, the original stimulus is referred to as a probe tone and the second as a suppressor tone. The underlying mechanism of this phenomenon is saturation of the mechano-electrical transduction (MET) channels of the outer hair cells (OHCs), whereby the mechanical response to the suppressor tone saturates the OHCs, reducing the potency of their feedback to the probe tone.

Experimentally, suppression of the basilar membrane (BM) is well-studied and established. Ruggero et al. [1] demonstrates the effect of a variety of probe and suppressor frequency and level combinations in chinchillas. Computational work has enriched understanding of the phenomenon [2, 3, 4]. With recent developments in experimental techniques allowing for extensive micromechanical measurements, characterization of suppression in the response of the reticular lamina (RL) has been made possible. Dewey et al. [5] recently showed that, in the mouse cochlea, high-frequency suppressors (peaking basal to probe best place (BP)) can suppress the RL response but not the BM response at sub-BP locations. This challenges the notion that OHCs only provide active feedback in the immediate region near a particular response's BP, and instead indicates that OHC feedback extends to a broader basal region. Nevertheless, this extended feedback does not manifest in BM suppression, indicating that the mechanics of the cochlea are such that OHC feedback at basal locations affects structures at the top end of the OHCs only.

In this study, a computational model of the gerbil cochlea with a high level of physiological detail is used to make predictions of two-tone suppression for a range of suppressor frequencies and levels, and to assess whether these predictions are in line with recent experimental findings. From there, the flexibility afforded by the computational environment allows further exploration of the underlying force that underpins the suppression phenomenon.

MODEL

Physiologically Based Model

The gerbil model used in this study is heavily motivated by the detailed physiology of the cochlea [6]. As seen in Figure 1A, it contains structural degrees of freedom at both ends of the organ of Corti (OoC) complex, with the BM

Forms of longitudinal coupling in the organ of Corti

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Abstract. The effect of different forms of longitudinal coupling on the active response of the cochlea are analysed using an elemental approach, based on a previous finite element model of the guinea pig cochlea. The forms of coupling in the organ of Corti include mechanical longitudinal coupling along the basilar membrane (BM) and the tectorial membrane (TM). An intuitive and efficient method is used for representing the longitudinal coupling in the fluid, by decomposing the 3D fluid coupling into a local near-field mass loading of the organ of Corti and 1D fluid coupling to represent long range fluid-structure coupling. As has been shown in previous studies, mechanical longitudinal coupling in the TM, together with 3D fluid coupling, have the greatest effect on the predicted response and are most important in obtaining a frequency response that is both tall and broad, as observed in experimental data. The 3D fluid coupling is also necessary to obtain a phase variation that is consistent with experimental measurements. The effect of BM longitudinal coupling is not as significant as that due to the TM in determining the response. The overall BM admittance can be readily calculated using the elemental method, and since this is the only aspect of the organ of Corti dynamics that couples into the fluid, it is a useful indicator of its overall behaviour. Whereas in the locally reacting case, the BM velocity at a given position depends only on the pressure difference at the same point, when longitudinal coupling is introduced, the BM velocity also depends on the pressure difference some distance away. For excitation at a single point and at a given frequency, the BM admittance thus has a distribution along the cochlea, with a form that depends on excitation frequency and on the assumed types of longitudinal coupling. It is also shown that the broadening of the cochlear response due to longitudinal coupling is accompanied by an extension of the frequency range over which power is supplied by the BM into the fluid.

INTRODUCTION

Different approaches can be taken to modelling the mechanics of the cochlea. One approach considers the detailed physical processes involved, using a realistic geometry, in order to understand how the various elements combine together to give the observed behaviour. In another approach, the details of these processes are disregarded, and a simplified, but potentially more insightful, description of the behaviour is sought, typically involving wave propagation. This paper is the first of two which try to make a connection between these two approaches by reformulating a previous detailed model of the physical processes within the organ of Corti, OC, to provide such a simplified interpretation. In this first paper, the model is briefly described, initially emphasising the individual forms of longitudinal coupling in the OC. The fluid coupling is then divided into a 1D component and a component due to the near field fluid pressure, with the latter being associated with a modified OC model. This can then be combined with the 1D fluid coupling to derive both the overall response and the properties of the waves that could propagate in such a model. There are many mechanisms for longitudinal coupling in the OC. Table I lists the approximate lengthscale of several of these mechanisms when analysed in isolation. It should be emphasised, however, that the importance of each of these mechanisms depends on the way in which they react together within the OC. The bending response of a sandwich depends in a rather complicated way on the properties of the individual layers (Richardson et al., 2008). The coupling along the tectorial membrane, TM, has been singled out as being particularly important in determining the overall response (Meaud and Grosh, 2010; Lukashkin et al., 2010).

TABLE I. The lengthscale of the individual mechanisms of longitudinal coupling in the OC at CF, in isolation.

Element	Mechanism	Lengthscale	Quantity	Reference
BM	Orthotropic plate	20 μm	wavelength	Meaud and Grosh (2010)
TM	Viscoelastic	60 μm	wavelength	Meaud and Grosh (2010)
OHC	Electrical	40 μm	Decay rate	Teal and Ni (2016)
Fluid	Near field acoustic	120 μm	Decay rate	Ni and Elliott (2015)

Wave motion in the longitudinally coupled cochlea

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Abstract. A detailed model of the physical processes occurring within the organ of Corti can be compared with experimental data and can give an indication of the mechanisms of its active behaviour. On the other hand, a model that involves wave propagation in the cochlea can give more insight into its coupled response. In principle many kinds of wave can propagate in the cochlea, but it is a single travelling wave that mainly determines its coupled response, which can be characterized by the frequency variation of its complex wavenumber. In the case of a cochlear model using a locally reacting basilar membrane (BM) and 1D fluid coupling, this wavenumber can be calculated explicitly. When longitudinal coupling, due to the mechano-electrical structure of the Organ of Corti or other forms of fluid coupling, are introduced however, additional wave types are possible, and it is not so straightforward to calculate the wavenumber of the main travelling wave. This paper is the second of a series, in which a method is presented of deriving the wavenumber distribution associated to different wave types, based on an elemental model of the cochlea. This allows an investigation of the effect of different forms of longitudinal coupling on the wave motion. In general, the main travelling wave dominates the BM response, and when the model is active, the imaginary party of its wavenumber is positive in a frequency region just before the characteristic frequency. The extent of this active region depends on the form of longitudinal coupling assumed in the organ of Corti.

INTRODUCTION

It is usually assumed that the properties of the cochlea can be explained in terms of the propagation of a single travelling wave, which is generated by the interaction between the inertia of the fluid in the chambers and the dynamics of the basilar membrane (De Boer, 1996). The properties of this wave are characterized by a complex wavenumber, whose real part, called the propagation function, determines the wave speed and wavelength while the imaginary part, called the gain function, determines whether the wave is amplified or attenuated by the active processes in the Organ of Corti (Shera, 2007). In the case of a model of the passive cochlea which includes a locally reacting basilar membrane (BM) with 1D fluid coupling, only one wave type is present (De Boer, 1996). This is characterized by a propagation function that starts with a small value at low frequencies, increases up to the characteristic frequency (CF), and then decreases at higher frequency. The rising value of the propagation function indicates that the phase and group velocities are decreasing, so that the wave is slowed down as it propagates along the cochlea and so its amplitude is concentrated near the CF. The gain function, on the other hand, remains small at low frequencies and increases only just before the CF, reaching a negative and high value at higher frequencies, where the wave is greatly attenuated. When 2D or 3D fluid coupling is included, the models predict an infinite number of wavenumber distributions corresponding to multiple wave types (Steele and Taber, 1979; Taber and Steele, 1981). In this case, only one wavenumber distribution corresponds to a travelling wave, while the others describe non propagation modes, characterized by a large value of the imaginary part at the lowest frequencies, which do not have a significant effect on the coupled response. Using an inverse method to derive the wavenumber distribution from experimental measurements, in (Shera, 2007) it is shown that in the active cochlea, the propagation and gain functions are similar in shape to those of the travelling wave in the passive case, apart from two main differences. The propagation function has a higher peak, indicating a smaller wavelength and the gain function is positive just before the peak of the real part. Shera also noted that a positive value of the imaginary part corresponds to a power transfer to the travelling wave and thus to an amplification of the response. This is in agreement with (Dewey et al., 2019; Dong and Olson, 2013) in which it is shown, from experimental measurements, that the amplification of the cochlear wave occurs in a frequency region just below the CF. In this paper, a method is presented of deriving the wavenumber distribution associated to different types of waves that propagate in the cochlea.

Fluid viscosity versus solid damping in a cochlear FEM

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Abstract. For reasons of computational efficiency, most cochlear models simulate power dissipation solely by damping inside the solid cochlear partition, disregarding viscous dissipation in the fluid. In recent years, however, simulation incorporating fluid viscosity became reasonably affordable. In this study, we compared the effect of both types of power dissipation using a passive 3D box model implemented in the commercial finite-element modelling (FEM) package COMSOL. Indeed, memory requirements and computation time was approximately 10 time larger when simulating fluid viscosity compared to solid damping only. But the qualitative difference was striking: As expected, when lowering the solid damping in a model without fluid viscosity, the peak of the travelling wave (TW) got higher, moved apically and the apical slope of the TW got much shallower. (I.e., the distance over which the wave amplitude decayed increased substantially.) When lowering the fluid viscosity in a model without solid damping, the peak of the TW also got higher and moved apically, but the slope of decay remained constant. The slope of approximately 30 dB/mm was much steeper than could be achieved with solid damping and compares to the more than 100-dB/octave slopes at the high-frequency side of experimentally measured frequency tuning curves. We conclude that that solid damping cannot replace the computation of viscous dissipation when intending to simulate the sharp TW decay. They have qualitatively different effects.

INTRODUCTION

Fluid-mechanically, the cochlear ducts are small relative to the thickness of the Stokes boundary layer and power dissipation herein are likely to dominate the damping of the travelling wave (TW). But because the simulation of viscous dissipation requires large computational resources, cochlear finite-element models (FEMs) have commonly generated losses in their solid cochlear partition. Although commercial software with thermo-viscous solvers became affordable within the last decade, the mesh density required to resolve the Stokes boundary layers requires a large number of small elements, and therefore, large scale computers. In our experience with COMSOL Multiphysics, just the switching to using its Thermoacoustics Interface increased the requirement for both working memory and computation time by a factor of ten, even with identical mesh density. Thus, we wondered whether expensive simulations with viscous solvers are strictly necessary to simulate a realistic TW.

METHODS

The cochlea was implemented as an uncoiled box with two fluid compartments separated by a 35-mm long solid that represented the cochlear partition (Fig. 3a). The cochlear partition had the density of water, a width of 150 μm at base, 450 μm at the apex and a constant thickness of 10 μm . It was an orthotropic solid with a Young's modulus in the longitudinal direction (E_x) a thousand times smaller than across (E_y). Along the longitudinal location (x), E_y was adjusted to give the model roughly the tonotopy of the human cochlea, resulting for characteristic frequencies above 500 Hz in an octave spacing of roughly 5 mm^1 . It was achieved by adjusting empirically the parameter values in the following formula that gives E_y in Pascals. (The distance from the base (x) is given in meter.):

$$E_y = 5 \cdot 10^7 \left(1 - \frac{x}{0.045}\right)^{4.5} \quad (1)$$

Energetic Depletion and IsK Mutations Destabilize Potassium Resupply to the Endolymph

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Abstract.

In the process of mechanotransduction, auditory and vestibular hair cells drain potassium ions (K^+) from the endolymph. The resupply of K^+ to the endolymph requires significant energy expenditure and is accomplished by a layer of specialized epithelial cells in the cochlea (marginal cells) and vestibular system (dark cells). We constructed a biophysical model of ion transport across these epithelial layers by implementing mathematical expressions that describe the activity of known ion channels and transporters expressed in the marginal/dark cells. This network constitutes a dynamical system and the net transepithelial potassium current (i_{K^e}) can be studied as a function of parameters such as external potassium concentration and ATP levels which influence ion transporter activity and affect K^+ homeostasis in the endolymph. The dependency of i_{K^e} on external potassium concentrations is nonlinear and can be used to study the stability of the K^+ cycle and gain insight into how potassium resupply is altered as a result of energetic depletion and genetic mutations. A particularly interesting result is that increasing the *Isk* conductance expressed on the apical surface of marginal cells and dark cells causes the development of hypersensitive regions in the transport phase diagram that provide insight into the mechanism of-induced hearing loss.

INTRODUCTION

In the inner ear, the apical surfaces of hair cells are bathed by endolymph, a specialized fluid within the cochlea and the vestibular system. The endolymph has a large potassium ion concentration (150 mM) that serves as the driving force for transduction by hair cells; in the cochlea the endolymph is also at an elevated electrical potential and the driving force is greater. Deflection of hair cell stereocilia by sound (cochlea) or head motion (vestibular system) opens mechanosensitive channels (MET). Potassium ions (K^+) flow through the MET channels into the hair cells and cause hair cell depolarization. The two types of hair cells in the cochlea respond differently to membrane depolarization - inner hair cells release neurotransmitters which signal the auditory nerve, while outer hair cells undergo mechanical deformation which amplifies vibrations of the organ of Corti. In the vestibular system, type I and type II hair cells release neurotransmitters to signal the vestibular nerve; type I cells additionally support non quantal transmission.

Hair cell mechanotransduction process drains K^+ from the endolymph. Sustaining a potassium current into the endolymph to replenish the lost K^+ is an energy intensive process that takes place in the stria vascularis (cochlea) and the dark cell layer (vestibular system). The stria vascularis is a highly vascular multilaminar epithelium composed of two functional cellular layers. The layer facing the scala media is composed of marginal cells that have extensive basolateral infoldings rich in mitochondria and a high density of the $Na^+-K^+-ATPase$ and $NKCC1$. The apical ends of the cells contain an I_{sk} current composed of subunits of $KCNQ1/KCNE1$ that returns potassium to the endolymph. A similar arrangement occurs in the dark cells and is shown in Figure 1a. Due to the complexity of the cochlea and vestibule, the biophysics of marginal cell and dark cell ion transport processes are not fully understood but are essential for understanding function and dysfunction in these systems.

Energetic Depletion and IsK Mutations Destabilize Potassium Resupply to the Endolymph

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In the process of mechanotransduction, auditory and vestibular hair cells drain potassium ions (K^+) from the endolymph. The resupply of K^+ to the endolymph requires significant energy expenditure and is accomplished by a layer of specialized epithelial cells in the cochlea (marginal cells) and vestibular system (dark cells). We constructed a biophysical model of ion transport across these epithelial layers by implementing mathematical expressions that describe the activity of known ion channels and transporters expressed in the marginal/dark cells. This network constitutes a dynamical system and the net transepithelial potassium current (i_{K^e}) can be studied as a function of parameters such as external potassium concentration and ATP levels which influence ion transporter activity and affect K^+ homeostasis in the endolymph. The dependency of i_{K^e} on external potassium concentrations is nonlinear and can be used to study the stability of the K^+ cycle and gain insight into how potassium resupply is altered as a result of energetic depletion and genetic mutations. A particularly interesting result is that increasing the *Isk* conductance expressed on the apical surface of marginal cells and dark cells causes the development of hypersensitive regions in the transport phase diagram that provide insight into the mechanism of-induced hearing loss.

INTRODUCTION

In the inner ear, the apical surfaces of hair cells are bathed by endolymph, a specialized fluid within the cochlea and the vestibular system. The endolymph has a large potassium ion concentration (150 mM) that serves as the driving force for transduction by hair cells; in the cochlea the endolymph is also at an elevated electrical potential and the driving force is greater. Deflection of hair cell stereocilia by sound (cochlea) or head motion (vestibular system) opens mechanosensitive channels (MET). Potassium ions (K^+) flow through the MET channels into the hair cells and cause hair cell depolarization. The two types of hair cells in the cochlea respond differently to membrane depolarization - inner hair cells release neurotransmitters which signal the auditory nerve, while outer hair cells undergo mechanical deformation which amplifies vibrations of the organ of Corti. In the vestibular system, type I and type II hair cells release neurotransmitters to signal the vestibular nerve; type I cells additionally support non quantal transmission.

Hair cell mechanotransduction process drains K^+ from the endolymph. Sustaining a potassium current into the endolymph to replenish the lost K^+ is an energy intensive process that takes place in the stria vascularis (cochlea) and the dark cell layer (vestibular system). The stria vascularis is a highly vascular multilaminar epithelium composed of two functional cellular layers. The layer facing the scala media is composed of marginal cells that have extensive basolateral infoldings rich in mitochondria and a high density of the $Na^+-K^+-ATPase$ and $NKCC1$. The apical ends of the cells contain an I_{sk} current composed of subunits of $KCNQ1/KCNE1$ that returns potassium to the endolymph. A similar arrangement occurs in the dark cells and is shown in Figure 1a. Due to the complexity of the cochlea and vestibule, the biophysics of marginal cell and dark cell ion transport processes are not fully understood but are essential for understanding function and dysfunction in these systems.

The Inner Spiral Sulcus and Outer Tunnel Alter Inner-Hair-Cell Bundle Motion in a Finite-Element Model of the Mouse Cochlea

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Abstract. The inner hair cells (IHCs) situated within the organ of Corti (OoC) inside the cochlea translate mechanical sound vibrations into electrical potentials via mechano-electrical transduction (MET) channels within the IHC stereocilia bundles. Exactly how the IHC bundles are stimulated by their environment within the OoC remains unclear. The current work utilizes a 3D finite-element (FE) model of a slice from the middle-turn 20-kHz region of a mouse cochlea to study the passive modes of vibration within the OoC at different frequencies and how they influence IHC-bundle stimulation. The results indicate that the OoC exhibits different modes of motion at different frequencies, and that the IHC-bundle stimulation magnitude peaks at the best frequency (BF). The results also indicate that the inner spiral sulcus and outer tunnel of Corti can both have a significant effect on the IHC-bundle stimulation at BF.

INTRODUCTION

The intricate cellular structure within the organ of Corti (OoC) provides the structural basis for how the stereocilia bundles of the inner hair cells (IHCs) are stimulated, which triggers the mechano-electrical transduction (MET) channels of individual IHC stereocilia. The stimulation mechanisms of the IHC bundles play a crucial role in how the mechanical motions of the traveling wave and the OoC get translated into electrical signals in the hair cells via MET channels. However, the mechanisms by which the IHC bundles are stimulated by their surroundings and the fluid spaces within the OoC remain to be determined¹. Recent experimental data measured on the individual stereocilia within *in situ* IHC bundles reveal that the intra-bundle stereocilia do not move together as a cohesive whole². This finding provides a motivation for employing modeling studies to better understand the stimulation mechanisms for the IHC stereocilia in terms of the surrounding anatomy and fluid environment.

The present work studies the cytoarchitectural motion of the OoC and the resulting stimulation of the IHC bundles via a 3D finite-element (FE) model of the mouse OoC in the middle turn. Based on recent data, the two key hypotheses tested by the model are: 1) whether the OoC exhibits different modes of concerted motion at different frequencies that lead to different stimulation modes for the IHC bundles, and 2) whether the inner spiral sulcus (ISS) and outer tunnel (OT) of the OoC fluid spaces³ (Fig. 1A) have a significant influence on IHC-bundle stimulation.

An FE model of a cross section of a passive mouse cochlea from the middle-turn 20-kHz best-frequency (BF) region has been constructed with details relevant to the mechanical and fluid responses pertaining to OoC motion. The modes of OoC motion at different frequencies are studied, and the IHC-bundle motions are compared against experimental data. Furthermore, model versions with geometric variations to the ISS and OT have also been created for testing the structural significance of the two fluid spaces to OoC motion.

The Drive to Inner and Outer Hair-Cell Bundles in a Slice Model of the Gerbil Cochlea

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Abstract. Despite the importance of inner hair cells (IHCs) and outer hair cells (OHCs) to cochlear physiology, we have an incomplete understanding of the motions that stimulate these hair cells. Among the unanswered questions are: What is the phase relationship between stereocilia deflections of the three rows of OHCs and the IHCs? How does basilar-membrane (BM) transverse motion translate into radial drive to OHC and IHC stereocilia? Gross motions of the organ of Corti (OoC) in the gerbil apex have been experimentally shown to have low-pass characteristics, yet neural-fiber responses are bandpass. Does the mechanical drive to the IHC stereocilia differ from low-pass and can it explain the difference between mechanical and neural responses? To begin to address these questions, we developed a finite-element model of a 20- μm slice of the passive gerbil cochlea at the middle turn. The model used realistic anatomy of the organ of Corti with stereocilia bundles represented by the series of stereocilia in the tallest row. OHC stereocilia spanned the subtectorial gap, but IHC stereocilia attached only at the reticular lamina. The model included viscous fluid-structure interaction. Material properties of the model elements that were not described in literature were estimated, aided by parameter tuning to emulate key characteristics of experimental data. The cochlear traveling wave was simulated with a Floquet boundary condition that constrained the phase differences between the slice edges to be consistent with the local frequency-dependent wavelength of the traveling wave. Input pressure was applied to the BM on the scala tympani side. The model showed that OHC stereocilia deflection was low-pass, similar to experimentally measured gross OoC motion, but IHC stereocilia deflection was band-pass. At low frequencies, the RL stretched and caused the bases of OHC stereocilia to move predominantly in the radial direction, with more stretching and more stereocilia deflection around the pillar cells and OHC row 1. At frequencies approaching the 2.5 kHz best frequency and higher, the motion was more complex with substantial longitudinal components of motion. OHC stereocilia deflections were generally in phase with each other, and at high frequencies were in phase with IHC stereocilia deflections, but at low frequencies OHC and IHC deflections were out of phase.

INTRODUCTION

The cochlea is a complex structure with many parts whose roles are poorly understood. To make models that are mathematically tractable it has been necessary to simplify, and sometimes use lumped-parameter representations of parts of the organ of Corti (OoC) that are, at best, crude approximations of the mechanical properties of the anatomy. To get a realistic assessment of the important OoC mechanical properties, a model must be realistic. Only with realistic models can we hope to answer such questions as how the mechanical drive to the outer-hair-cell (OHC) stereocilia achieves the required phase to produce cochlear amplification at frequencies within $\sim 1/2$ octave below the best frequency (Dong and Olson, 2013).

It is essential to choose a modeling method that is not built upon pre-conceived views of how the OoC functions. With this consideration in mind, we chose a finite-element (FE) modeling approach that used reasonably accurate mechanical anatomy, although we have been limited by a lack of detailed knowledge about many of the structurally important cochlear elements. FE models are computationally expensive, so in this model we included only a 20- μm longitudinal extent of the cochlea, i.e., a cochlear slice. To model the effects of the slice being driven by a traveling

The Transepithelial Potential Can Control Gating Compliance of the Hair-Cell Bundle

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Abstract. Taking advantage of a two-chamber excised preparation of the frog saccule, we study the effects of imposing a static transepithelial current, and in turn a transepithelial potential, on the force-displacement relation of single hair-cell bundles. Our observations suggest that the transepithelial potential may serve as a control parameter of gating forces of the transduction channels and in turn of hair-bundle mechanosensitivity.

SUMMARY

Hearing is initiated by vibrations of the hair bundle, which operates as a mechanosensitive antenna for the sensory hair cells of the inner ear [1]. Mechanosensitivity is thought to result from the direct mechanical activation of ion channels by tension change in tip links interconnecting the stereocilia of the hair bundle, resulting in an electrical transduction current [2,3]. Within this framework, mechano-electrical transduction is reciprocal: gating of the transduction channels affects tip-link tension, which effectively reduces the stiffness of the hair bundle — a phenomenon known as ‘gating compliance’ [4].

This defining mechanical signature of hair-cell mechanosensitivity has been reported with variable magnitudes across animal species and ex-vivo preparations of sensory epithelia [4-10]. Despite its importance, the regulation of gating compliance, and more generally of hair-cell mechanosensitivity, by physiological parameters remains poorly understood. Here, using a two-chamber excised preparation of the frog saccule [9], we studied the effects on hair-bundle mechanics of an electric potential difference applied across the sensory epithelium, mimicking the endocochlear potential observed in the mammalian cochlea.

By imposing a static transepithelial current of $\pm 7 \mu\text{A}$, the potential into the artificial endolymph that bathes the hair bundles, with respect to the perilymph to which the hair-cell somas are exposed, was varied within a range of $\pm 80 \text{ mV}$. In addition to the expected adaptive shift of the force-displacement relations, we found that the magnitude of the whole-bundle change in tip-link tension upon channel gating—the global gating force—displayed a negative correlation with the transepithelial potential. Correspondingly, upon application of a negative potential in endolymph, the gating force could increase from an average value of $18 \pm 8 \text{ pN}$ ($n = 12$) by as much as by 30 pN or about 100%. These effects were graded and reversible. Although a negative correlation was also observed between the hair-bundle stiffness and the transepithelial potential, stiffness

A nonlinear mechano-electro-acoustic model of the human cochlea

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Abstract. While direct measurements of the basilar membrane (BM) and auditory nerve fiber tuning are possible in lab animals [1] but no psychoacoustic measurements (with rare exceptions [2]), only otoacoustic emission and psychophysical tuning curve measurements [2,3,4] are possible in humans. In an attempt to partly address this missing link, the three-dimensional physiology-based nonlinear mechanical-electrical-acoustic (MEA) model of the human cochlea is developed in this study to enable prediction of both otoacoustic emissions as well as BM and organ of Corti vibration tuning. The nonlinear MEA model of the human cochlea adapts our prior linear MEA model of the guinea pig cochlea [5,6] to humans and includes the nonlinearity due to mechanoelectrical transduction in hair bundles. The transmission line human middle ear model, inspired by O'Connor and Puria [7], is integrated with the nonlinear MEA model. The passive BM displacement predicted by the model is compared with the *in vivo* physiological measurements for the BM displacement in human cadavers [8], and the predicted active BM tuning curves are compared with human psychophysical tuning curves (PTC) from Moore (1978) [9]. The distortion product otoacoustic emissions (DPOAE), predicted by the model at equal stimulus levels and at different stimulus frequencies, have a maximum at around $f_2/f_1 = 1.2$, agreeing with measured data in the literature [10,11].

INTRODUCTION

Nonlinear compressive growth is a characteristic of healthy mammalian cochleae [12], which enables the stimulation of distortion products (DPs). The mammalian cochlea also demonstrates high sensitivity, sharp tuning, and tonotopic frequency separation of the incoming sounds along the basilar membrane (BM) [12]. Consequently, each sensory hair cell responds to sound within the limited frequency range due to this frequency separation or filtering. Owing to its role as a frequency analyser, the cochlea has been represented as filter banks [13], also referred to as cochlear filters [12]. The frequency tuning of these filters signifies our ability to distinguish sounds. The loss of cochlear tuning and deficits in the ability to extract the correct sound from background noise [3] are associated with hearing loss and broadening the cochlear filters. A physiological study based on otoacoustic emissions indicates that human cochlear filters may be sharper than other species [3]. However, this view has been challenged by Ruggero et al. (2005) [4] where it is argued that the sharpness of the human tuning curve is not exceptional, and that it is similar to other mammals. In Ruggero et al. (2005) [4], an equal tuning in humans is proved using a compound action potential tuning curve against auditory nerve fibers tuning curve. The sharpness of cochlear tuning in humans, as well as several other aspects of human cochlear responses are unclear yet. The primary challenge is that, so far, only otoacoustic emissions [12,14] and psychophysical tuning curve measurements [2,9] are possible in humans.

DPOAE is a robust phenomenon routinely used for clinical purposes. The intermodulation of two tones in the cochlea generates the acoustic distortion product (ADP), $2f_1-f_2$, measured in the ear canal of animals and humans. DPOAEs of humans have been measured for a wide range of stimulus frequencies and levels [10]. DPOAE level had

Interpeak characterizations for spontaneous otoacoustic emissions

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Abstract. One manifestation of the “active ear” is the presence of spontaneous otoacoustic emission (SOAE), which also exhibit salient connections to perception such as threshold microstructure. Historically, SOAE modeling efforts initially focused upon a single limit-cycle oscillator. However, SOAE spectra from a given ear typically exhibit multiple peaks, and more current models consider a spatially-distributed tonotopic system with various types of coupling. SOAEs have nonstationary properties (e.g., amplitude and frequency modulations), which may be crucially tied to the coupling of active elements in the ear. Thus to better biophysically constrain models, this study seeks to improve characterization of general non-stationary features of SOAE peaks as well as interrelations of such between them. Given the ubiquitous nature of SOAE across the animal kingdom, we analyze SOAE waveforms from a variety of species exhibiting disparate inner ear morphologies (e.g., human, barn owls, Anolis lizards). This manuscript provides a preliminary account of our analyses and focuses on the *Anolis* lizard. Upon filtering in the spectral domain, we characterize temporal properties of individual peaks, including possible amplitude-modulation (AM) and frequency-modulation (FM). Further, we perform correlation analyses of such between peaks to determine types of interactions and how such might vary across time. Initial results are consistent with previous reports (e.g., [1, 2]) in that an SOAE interpeak correlations for a given ear are idiosyncratic: Sometimes peaks (adjacent or not) exhibit correlated (positive or negative) AM and/or FM fluctuations with delays up to the order of milliseconds (typically longer for humans, shorter for lizards), while sometimes no correlation is observed. We attempt to frame these results within the broader context of specific SOAE modeling approaches.

BACKGROUND

A common feature of the healthy ear across the animal kingdom is the generation of spontaneous otoacoustic emission (SOAE). This phenomenon is often described as a by-product of an underlying active mechanism that metabolically boosts the sensitivity and selectivity of the ear. While many theories have been proposed (e.g., [3, 4, 5, 6]), SOAE generation remains relatively poorly understood, especially when considering gross inner ear morphological differences across the animal kingdom [7].

Several key characteristics of SOAE are commonly observed. First, not all ears emit. A healthy individual can have normal hearing but exhibit no SOAE. Further, the presence of SOAE is common but not universal across the animal kingdom: While relatively robust in primates and numerous lizard species, SOAE activity is conspicuously absent in many animals commonly used in auditory neurophysiology. For example, SOAE in mice are exceedingly rare unless mutations to their tectorial membrane are present [8]. Second, SOAE activity is mostly confined to the most sensitive portion of the audiogram. Third is the general characteristic that SOAE commonly manifest as peaks of variable width in the spectrum of the measured microphone signal (hence “SOAEs” from an ear). This narrowband feature has provided a focal point for many facets of SOAE analysis and theory, despite the fact SOAE activity can also be present in a broadband fashion (e.g., the “baseline” activity in geckos [9] and skinks). Fourth, these peaks can (but not always) exhibit statistical properties consistent with self-sustained sinusoids [10, 11, 12]. Lastly, SOAE activity appears to readily interact with external acoustic stimuli, allowing for measurements such as “suppression tuning curves” that can exhibit selectivity similar to that of single auditory nerve fibers (e.g., [13]).

To help constrain theoretical models, the present study focuses on characterizing the distinctive set of SOAE peaks that an individual ear can exhibit. Assuming that hair cells are a key element for SOAE generation (i.e., they act as a primary unit of force generation), and that the inner ear is a collection of coupled hair cells, we seek to elucidate how

Elliptical Sound-Induced Motion in the Bushcricket Hearing Organ

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Abstract. The bushcricket *Mecopoda elongata* can hear a wide range of frequencies, utilizing less than 50 sensory units. It is known that transduction takes place in the sensory dendrite but the underlying mechanisms are still unexplained. In a recent study we used optical coherence tomography (OCT) to characterize the relative motion in the dorsal-ventral direction between anatomical structures near the transduction site. In the current study, we combined OCT vibrometry with the use of a mirror to measure vibrations of the same structures from two different angles. By developing a method to identify measurement locations across the two viewing angles, we were able to decompose the motion into an anterior-posterior and a dorsal-ventral component. In the structures surrounding the transduction site we observed elliptical sound-induced motion that varied systematically with frequency. The motion in the cap cells (CC) was more tilted towards the anterior-posterior axis than that of the dorsal wall (DW). Finally, the two-dimensional relative motion between the DW and the CC, a candidate for the drive of transduction, was sharply tuned, and for ultrasound it was similar to the neural tuning described in the literature for this species.

INTRODUCTION

Katydid are acoustically communicating insects. They have minuscule hearing organs, smaller than 1 mm, in their front tibia, the crista acoustica (CA). These organs allow them to hear a wide range of frequencies, from few hundreds of Hertz up to ultrasounds [1]. This is achieved by few sensory units (less than 50 in *Mecopoda elongata* [2, 3]) that are tonotopically organized along the proximal-distal axis [4, 5]. The sound input reaches the CA through the acoustic trachea and the two tympana that surround the sensory tissue [6, 7, 8, 9, 10]. Each sensory unit consists of a sensory dendrite, that is located dorsally to the dorsal wall (DW) and a cap cell (CC) that is found on the dorsal tip of the sensory dendrite (Fig. 1 C,D). The sensory dendrite is surrounded by a scolopale cell.

The frequency-selective transduction of mechanical energy to electrical responses is thought to take place through stretching of the sensory dendrite [11, 12]. The neural tuning of the sensors is sharper and shifted towards lower frequencies compared to the mechanical tuning [12]. The actual mechanism of sensory transduction remains unknown. A step towards unraveling the mechanism was taken by Vavakou et al. [13], who used OCT-vibrometry to measure sound-induced vibrations of both the DW and the CC. A crucial aspect of that study was the use, for the first time in insect hearing, of OCT vibrometry, a technique that allows for depth resolution of the recorded tissue. They reported that the CC and the DW mechanical responses to sound stimuli differ in response phase, best frequency, and bandwidth. Further micromechanical exploration of the recorded structures revealed that the relative motion among the DW and the CC is tuned more sharply and to higher frequencies than the individual structures [13].

However, with the customary vibrometry approach, it is only possible to measure the projection of the overall motion of the recorded structure on the recording beam [14, 15]. Vavakou et. al [13] aligned their measurement beam with the dorsal ventral axis of the recorded structures. As a result, any other possible directions of motion are underrepresented in their measurements. As discussed by the authors, transduction could be driven by more complex, two-dimensional motion of the CC relative to the DW, and they concluded that an accurate description of the overall motion requires the measurement of the same structure from different recording angles [13]. Facing a similar challenge, Lee et. al in 2016 [14] disentangled two motion directions in structures within the mouse cochlea, by rotating the preparation relative to the recording beam.

In the current report, we measured sound-induced vibrations of the CA from two different angles, using a mirror (Fig. 1 A). The direct view (DV) was aligned with the dorsal-ventral axis, and the CA was imaged through the dorsal cuticle. Using the mirror, the CA were imaged through the anterior tympanum (Fig. 1 B-D). An important step in the processing of the data is an accurate method of “registration”, i.e., finding the corresponding recorded positions across

Nonlinearity in Hearing: The Role of Inner-Hair-Cell Saturation in Neural Coding

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Abstract. Psychophysical models often begin with a filterbank and assume that energy in the filter outputs is the basis for coding complex sounds. Filter bandwidths are estimated based on masked detection thresholds and are referred to as critical bands. While this conceptual model structure can explain many psychophysical phenomena, it also fails for many tasks. We propose a different conceptual model: a bank of peripheral filters, each followed by a saturating nonlinearity that represents transduction by inner hair cells (IHCs). The metric of interest is the amplitude of low-frequency fluctuations in hair-cell responses. Low-frequency fluctuations in the IHC voltage drive fluctuations in auditory-nerve (AN) responses, referred to here as “neural fluctuations” (NF). NFs are a temporal response feature distinct from phase-locking to temporal fine structure.

The saturating nonlinearity that follows each peripheral filter results in neural fluctuations that differ markedly from both the envelope of the stimulus and the envelope of a bandpass-filtered stimulus representing the basilar membrane response. A key difference between neural fluctuations and stimulus-related envelopes occurs when IHCs tuned near a spectral peak are “captured” (or dominated) by the spectral peak (Deng and Geisler, 1987; Zilany and Bruce, 2007). A peripheral channel that is captured has relatively small fluctuations in its response, whereas channels that are not captured can have strongly fluctuating responses, due to beating between multiple stimulus components. The profile of neural fluctuation amplitudes along the characteristic-frequency (CF) axis encodes key features of the stimulus spectrum. For example, in the case of masking paradigms, a local decrease in the neural-fluctuation amplitude profile encodes the presence and frequency of the target tone.

The role of the saturating IHC transduction nonlinearity in the proposed model was explored using a computational model for the periphery that includes the interaction between the saturating nonlinearity and compressive cochlear gain. We demonstrate that NF profiles in response to psychophysical masking paradigms can predict performance in several tasks for which the classical critical-band model fails (as well as those for which it succeeds.) Our goal is to determine whether a single model can predict results for several masked-detection tasks, including band-widening paradigms, with or without roving-levels, and co-modulation masking release.

The profile of NFs along the tonotopic axis is of interest because most midbrain neurons are excited or suppressed over a range of amplitude-modulation frequencies (Kim *et al.*, 2020). Fluctuation profiles that are set up in the periphery are thus transformed into rate profiles in the auditory midbrain. Rate profiles across populations of model midbrain neurons were the basis for the psychophysical predictions described below. Finally, the degree of contrast in the NF profiles is reduced by sensorineural hearing loss, suggesting that fluctuation profiles may provide insight into deficits associated with hearing loss.

Convergent Otoacoustic Tuning Estimates in the Anole Lizard?

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Abstract.

Spontaneous otoacoustic emissions (SOAEs) are one hallmark of an active ear and provide insight into the underlying biomechanics. SOAEs interact readily with external tones and correlate with stimulus-frequency emissions (SFOAEs) evoked by low-level stimuli (≤ 40 dB SPL). Such findings are consistent with a canonical model of emission generation based upon the principle of coherent reflection, which predicts relationships between OAE-derived tuning estimates. These predictions, in part, have been empirically validated even for non-mammalian vertebrate ears that lack the classic (mammalian) basilar membrane travelling wave. However, inconsistencies persist and require additional research, such as the incompatible tuning estimates between SOAE “suppression-tuning curves” (STCs) and stimulus frequency emission (SFOAE) phase-gradient delays (N_{sf}). Further complications stem from the nonlinear, stimulus level-dependent nature of SFOAE delays. To reconcile these uncertainties and elucidate the relationship between otoacoustic tuning estimates, we examined correlations between SOAE and SFOAE tuning estimates in the green anole lizard (*Anolis carolinensis*). Specifically, we characterize the level-dependence of N_{sf} across frequency for swept-tone stimuli while extracting SOAE “interaction tuning curves” (ITCs) measured simultaneously. These allow us to quantify both N_{sf} and Q_{10dB} values of the ITCs from the same ear using the same stimuli. Preliminary results suggest that it is possible to obtain convergent otoacoustic tuning estimates from the same data.

BACKGROUND

Spontaneous otoacoustic emissions (SOAEs) occur across tetrapod classes (e.g., [1]) and provide an objective, non-invasive method for investigating the biomechanics underlying active hearing. Further, SOAEs are closely tied to peripheral auditory function, correlating with psychoacoustic measures such as threshold microstructure [2, 3, 4]. SOAEs interact readily with external tones, and this characteristic can be exploited to create “suppression tuning curves” (STCs; [5]) that are comparable to auditory nerve fibre tuning in a variety of species (e.g., barn owls [6]; Bobtail skinks [7]; macaque monkeys [8]). Clinical applications of SOAEs are scant because of their inherent idiosyncrasy; while unique to an individual ear when present, SOAEs are absent from many ears [9]. Fortuitously, healthy ears typically still produce evoked otoacoustic emissions (eOAEs), such as stimulus-frequency otoacoustic emissions (SFOAEs).

SFOAE magnitudes and phase-gradient delays (expressed in number of stimulus cycles, N_{sf}) show clear correlations with SOAE peaks when evoked with stimuli below 40 dB SPL [10, 11]. Both N_{sf} and STC-derived quality factor (Q) values correlate with tuning measured directly from auditory nerve fibres (N_{sf} and neural Q [12, 13]; STC Q and neural Q [14, 15]). Additionally, there are correlations between N_{sf} values and N_{SOAE} values (an SOAE tuning estimate based on interpeak spacing; [14]). Conversely, SFOAE phase-gradients do not produce consistent tuning estimates with STCs when measured in humans [16]. Rather, Manley and van Dijk [16] reported greater similarities between STC-derived Q values and psychophysical simultaneous masking paradigms [17]. The lack of a relationship between STC-derived Q values and N_{sf} is difficult to interpret given documented correlations between N_{sf} and other tuning measures, including neural tuning and forward masking [18, 19].

To reconcile some of the discrepancies in otoacoustic tuning estimates, we simultaneously measured SOAEs and SFOAEs in green anole lizards (*Anolis carolinensis*). Anole emissions are robust and qualitatively similar to those of mammals, despite disparate inner ear morphologies, providing an opportunity to assess tuning correlations in a relatively simpler model. Building upon previous work (e.g., [12]), we compared SFOAE delays (N_{sf}) to Q_{10dB} values from SOAE tuning curves, expecting compatible tuning estimates since both measures come from one response to swept-tone stimuli. We refer to these SOAE tuning curves as “interaction” tuning curves (ITCs) since a stimulus may not necessarily suppress SOAE activity per se but instead entrain it. Here, we present preliminary SOAE and SFOAE tuning estimates from a single individual to examine the extent to which these values converge.

A Comparison of Implantable Microphones Constructed Around a Piezoelectric Polymer

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Abstract. Cochlear implants are neural prosthetic devices that restore hearing in individuals with severe-to-profound sensorineural hearing loss. As of 2019, an estimated 736,900 cochlear implants had been deployed throughout the world. In conventional cochlear implants, the microphone and speech processing electronics are located externally. This external placement has functional and cosmetic drawbacks. Generally, cochlear implant users must remove the external components for showering, swimming, or participating in certain sports. Users typically do not wear the device during sleep, preventing them from detecting auditory danger signals and influencing auditory development in children. Additionally, the acoustics of the outer ear and ear canal provide information that enhances sound localization and signal discrimination in noisy environments. These shortcomings could be addressed by a fully implantable device. With technological advances in batteries, electronics and wireless charging, all components could potentially be implantable. However, internalizing the microphone remains a challenge. We have been developing implantable microphones based on a piezoelectric material, polyvinylidene fluoride (PVDF) and its co-polymer PVDF-trifluoroethylene (PVDF-TrFE), available as a thin film. The internal placement of the microphones takes advantage of natural enhancement and filtering of the outer and middle ear. We have developed three prototype devices: (1) the *coch-mic*, which is inserted into the cochlea much as a cochlear implant, senses cochlear pressure as a hydrophone using a strip of silicone-coated PVDF-TrFE film, (2) the *drum-mic*, which senses the motion of the umbo (the tip of the malleus), has a circular PVDF membrane mounted onto a cylindrical base inserted between the umbo and the cochlear promontory, and (3) the *cantilever-mic*, which is a substrate-mounted PVDF beam where one end senses umbo motion, and the other end is anchored to the bone of the skull.

INTRODUCTION

Current cochlear implants use state-of-the-art *external* electret condenser microphones. To achieve totally implantable cochlear implants, the challenge of a fully implantable microphone must be overcome. Assistive hearing systems combining a fully-implantable microphone and electronics with a cochlear implant would enhance directional and focused hearing by taking advantage of outer and middle ear mechanics. They would be usable in all environmental conditions throughout the day and night. Various approaches to the fully implantable microphone have been explored, including MEMS-based, piezoelectric, and optical strategies [1]. However, current implantable microphones suffer from unstable mechanics, poor signal-to-noise ratio (SNR), low bandwidth, and/or internal body noise.

Piezoelectric films, such as polyvinylidene fluoride (PVDF), are a promising candidate for the sensitive transducer material needed in the miniaturization and implantation of microphones. The direct piezoelectric effect allows us to create sensors that convert mechanical motion into charge [2]. The mechanical deformation can be produced through a pressure boundary condition or a displacement boundary condition [3]. PVDF is a semi-crystalline polymer which is piezoelectric in the beta phase [4]. Although piezofilms exhibit weaker piezoelectric coupling than ceramic piezoelectric materials, PVDF's advantages for implantable microphones are that it is safe, easily obtainable commercially, and is flexible due to its form as a thin film [5, 6]. Furthermore, PVDF can provide better electromechanical coupling to the structures of the middle and inner ear due to its mechanical impedance. Through analytical derivations we have previously shown that the co-polymer, PVDF-Trifluoroethylene (PVDF-TrFE), can show higher sensitivity when used as a pressure sensor in fluid [7]. Charge amplifiers are preferred for use with piezoelectric sensors as their sensitivity is more stable than voltage amplifiers [8]. We have developed a custom differential charge amplifier with miniature coaxial connectors that is designed specifically to maximize SNR and attenuate electromagnetic interference (EMI) when used with a shielded design such as the *cantilever-mic*. Amplifier design considerations are the subject of another paper. Here we describe the development of a PVDF-based microphone with our three microphone types.

Design and Testing of Ultraminiature MEMS Middle Ear Accelerometers

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Abstract. The goal of this work is to develop a completely implantable ossicular vibration sensor utilizing microelectromechanical systems (MEMS) technology in combination with integrated-circuit approaches as part of a larger effort to enhance auditory prostheses by eliminating their external components. To develop a completely implantable device, sensors are required to replace the external microphones used in traditional systems (e.g., cochlear implants and hearing aids). Present-day implantable sensors do not meet the stringent requirements for acoustic performance or size to fit in the middle ear; however, in our lab, a dual-resonance design has been developed that holds the potential to achieve these results. In this paper, we show the analytical model used to predict and understand the behavior of these sensors. We discuss preliminary cadaveric temporal bone results, show how a fabricated MEMS proof-of-concept prototype mounted on a printed circuit board (PCB) along with the amplifying electronics and covered with a high-resolution 3D printed lid results in a packaged size small enough to fit in the middle ear, and outline future testing protocols.

INTRODUCTION

Hearing loss is a debilitating condition that affects over 5% of the world's population and can negatively impact an individual's quality of life by hindering their ability to communicate, socialize, receive education, and work [1]. In the United States, approximately 37.5 million people report some hearing disability, making it one of the most prevalent conditions in the country [2]. Depending on the severity of the hearing loss and the location of the damage within the ear, devices such as hearing aids (HAs) and cochlear implants (CIs) are beneficial by amplifying speech and environmental sounds to audible levels or stimulating hearing electrically [2]. Although HAs can significantly improve the lives of those suffering from hearing loss, their adoption rate is less than 14.2%. Surveys and analyses have indicated several key issues associated with the low HA adoption rates. These include cost (Medicare does not cover any HAs), lack of perceived effectiveness, and a multitude of issues associated with the external processing components. HA and CI users express the inconvenience of the externally worn, detachable parts that make them self-conscious of their disability and can easily be lost, damaged or stolen [2, 3, 4]. Additionally, these external elements cannot be worn underwater, during intense physical activities, or sleep. Thus, the long-term goal of this work is to utilize MEMS technology to build ultraminiature accelerometers that can be packaged to fit within the middle ear and effectively replace and eliminate those external components.

In typical externally worn auditory prostheses, sounds are detected by microphones and analyzed by signal processors. To create a completely implantable auditory prosthesis (CIAP), implantable sensors must be developed that meet certain operating requirements (e.g., size, bandwidth) -specifically match or even exceed the performance of current microphone capabilities between the frequency range of 100 Hz and 8 kHz. No present-day implantable sensors meet these specifications [4, 5]. Our approach includes the use of piezoelectric accelerometers as acoustic sensors whose performance holds the potential to address this issue by utilizing the dual resonance design, inspired by our first generation of MEMS prototypes [6]. Our objective is to fabricate and test these dual resonance devices. As preparations for manufacture are underway, we are creating new testing protocols using newly miniaturized printed circuit boards (PCBs) with amplification circuitry, 3D printed cover lids, and the first generation single resonance

Bio-inspired, Adaptive Acoustic Sensor: Sensing Properties in Dependence of Feedback Parameters

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Abstract. Pre-processing of the sound signal during sensing is an integral functionality of the cochlea, the part of human hearing responsible for sound sensing. This pre-processing, which is integrated into the sensing stage directly, enables the remarkable properties of human hearing. Similarly, integrating some of these pre-processing functionalities in technological speech processing systems strongly improves their recognition performance.

We developed a bio-inspired, adaptive acoustic sensor with pre-processing capabilities like nonlinear amplification and frequency filtering functionality. The sensor is composed of a single clamped silicon beam with integrated deflection sensing and thermo-mechanical actuation, subjected to a real-time feedback. While the resonance frequency and bandwidth are determined by the geometry of the sensor beam, its transfer characteristics can be switched dynamically from linear to nonlinear regime by changing the feedback parameters. In the linear regime, the feedback controls the sensitivity and bandwidth of the sensors. Here, we elaborate on the influence of the sign of feedback strength and offset on the sensor behaviour. Changing the sign of the feedback parameters switches between amplification and damping behaviour, enabling the change of sensitivity by 44 dB. Thereby, complex oscillation modes are observed for feedback parameters with similar polarity.

INTRODUCTION

The process of human hearing is full of intriguing properties like a dynamic range of 120 dB sound pressure level (SPL), resolving tones only 0.2% apart in frequency and understanding speech in noisy environments [1, 2]. These properties originate partly from the sound capturing and pre-processing capabilities of the cochlea [3]. The cochlea is the organ for sound sensing, and it incorporates a number of signal conditioning and feature extraction steps in the sensing process as well. Thereby, the most important steps are a frequency decomposition and amplification of the input signal, compressive (nonlinear) transfer characteristics and adaptation of amplification and transfer characteristics properties based on local and efferent feedback. These steps take place before and during the transduction process. The nonlinear amplification characteristics are discussed to stem from the sensor system acting as a Hopf oscillator [4, 5]. This hypothesis is further underlined by the fact, that the ear itself can produce tones without sound input, the so-called oto-acoustic emissions [6].

Introducing some of these steps into a technological speech processing system strongly improves the performance of the system, as was recently shown by Araujo et al. [7]. Thereby in particular, the nonlinear transfer characteristics improve the clustering of data, as was tested for spoken digits, which simplifies the classification task for the subsequent neural network. Most speech processing systems nowadays include, after the actual sensing step, a signal conditioning and feature extraction step, typically calculating the envelope and the frequency of the signal and transforming it into a frequency-time representation, often referred to as spectrogram [8]. Thereby, software-based realisations are quite common, but hardware-based implementations, often referred to silicon or FPGA cochlea, exist as well (cf. Refs. [9, 10, 11, 12]). Despite the remarkable increase in performance of speech processing systems, these still struggle in particular with noisy conditions, i.e., low signal-to-noise ratios, or multi-source situations. To address this issue, a bio-inspired approach targets the integration of the signal conditioning and feature extraction step into the sensing process, similar to the operation of the cochlea, rather than after the sensing process, as it is done in current technological realisations.

Several bio-inspired acoustic sensors have been developed, which differ mainly in the integrated functionalities and the number of sensors necessary to cover the frequency range [13]. The most common approach is the integration of frequency decomposition into the sensor system. However, these are the level used of bio-inspired sensors, which has been tested and applied already in speech processing systems [14]. Other approaches of bio-inspired sensors include nonlinear transformation and/or adaptation.

What Do Recent Discoveries in Cochlear Mechanics Tell Us About Otoacoustic Emissions?

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Abstract. Recent optical measurements of vibrations of the organ of Corti contrast with those of the basilar membrane in their larger amplitude and much wider bandwidth of active gain and nonlinearity [6-9, 14, 15, 18, 19]. A report by Ren and He (15) demonstrates a considerably richer spectrum of intermodulation distortion in the motion of the reticular lamina than in the basilar membrane of the Mongolian gerbil cochlea. Data from this species from my lab also show a broad distortion spectrum much more similar to the reticular lamina than the basilar membrane in the Ren and He data. This result, along with other evidence of broad-band nonlinearity in ear canal acoustics strongly suggests the need to reevaluate otoacoustic emission (OAE) phenomena. In particular, these experimental data do not support reverse slow basilar membrane traveling waves [22] as the dominant mode of conducting OAE signals to the ear canal, but they are instead conducted primarily by fluid pressure in scala vestibuli, at least for this species in the basal region of the cochlea. Several important unresolved issues in OAEs may be resolved by simultaneous measurements of vibrations in the organ of Corti and basilar membrane, together with comparable measurements in ear canal acoustics.

INTRODUCTION

Recent discoveries using advanced optical techniques [6-9, 14, 15, 18, 19] have allowed great progress in understanding how the hair cells in the organ of Corti cause amplification of vibrations of the basilar membrane, particularly in the peak region of the basilar membrane response. It was surprising that the organ of Corti vibrations in living animals were consistently larger than those of the basilar membrane, but also show a broader range of frequencies where apparently active gain and nonlinearity was observed. It is particularly striking that gain well below the local characteristic frequency (CF) does not couple into enhancing basilar membrane traveling waves [7, 9]. There is currently no explanation for where energy generated well below-CF flows and what purpose it has, yet conservation of energy demands that it must be dissipated somewhere, if not by the basilar membrane. It is a common assumption that efficiency must have guided the evolution of the cochlear amplifier, but there appears to be a limit. One possibility is that this excess power is funneled into the ear canal and contributes to otoacoustic emissions.

The new intracochlear mechanical discoveries lead me to propose several questions about the origins of otoacoustic emissions and the route(s) by which the emission signals leave the cochlea and enter the middle ear. The most commonly proposed route of transmission of OAE signals has been via slow-wave retrograde transmission along the basilar membrane, where transmission to the middle was envisioned to result from the pressure in scala vestibuli at the basal end of the cochlea [22]. However, Ren and colleagues [10, 11] measured only forward-propagating distortion waves (or responses to localized current injection [12]) and reasoned that the coupling from

Stimulus Frequency Otoacoustic Emissions Extracted by Pharmacologic Blocking of Outer Hair Cells Without Sound Suppression or Subtractive Scaling

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Abstract. Stimulus-frequency otoacoustic emissions (SFOAEs) are important non-invasive probes of cochlear function. The SFOAE is usually separated from the probe sound by measuring a response that contains both the probe sound and the SFOAE, and then subtracting a separate measurement of the probe sound alone. The probe-alone measurement is obtained using (1) a high-level, near-frequency “suppressor” sound assumed to suppress the SFOAE, or (2) the probe sound at a high level where the SFOAE is small compared to the probe (i.e., is compressed) and is presumed to be negligible after the high-level measurement is scaled down to the probe level. To the extent that the high-level sound has a negligible SFOAE, the complete SFOAE should theoretically be extracted by the subtraction. However, a potential complication is that the high-level sounds may produce unintended SFOAE components, particularly from basal cochlear regions. Here we use a novel technique to address the extent to which the high-level suppressor sound and subtraction extracts the full SFOAE without producing unintended additional energy at the probe frequency. Measurements were made with a standard high-level suppressor-tone extraction paradigm, and the resulting SFOAEs were compared to SFOAEs obtained using a pharmacologic SFOAE reduction that does not require a high-level sound. We made SFOAE measurements in guinea pigs while sequentially abolishing outer-hair-cell (OHC) function and SFOAE amplification by slowly perfusing salicylate or KCl solutions into the cochlear apex. The solution fronts were driven uniformly along the cochlear length toward the cochlear aqueduct in the cochlear base. This approach removes cochlear amplification at a given cochlear place without simultaneously affecting amplification or responses that originate basal to this place. At the end of the perfusion when OHC function and SFOAE production were pharmacologically blocked throughout the entire cochlear length, the probe sound alone (i.e. with no accompanying SFOAE) could be measured directly without the need for a high-level suppressor. SFOAEs were calculated by subtracting probe-only ear canal measurements made after the perfusion from measurements made before and during the perfusion. SFOAEs extracted using the apical perfusion technique, i.e. pharmacologic blocking, differed little from the SFOAEs extracted using a near-frequency high-level suppressor sound but were, on average, a few dB higher in amplitude. This suggests that the near-frequency high-level tone suppressed most, but not all, of the SFOAE.

INTRODUCTION

Measurements of auditory and vestibular function are used in laboratories, clinics, and operating rooms worldwide each day. The overarching goal of our work is to improve the interpretation of functional measurements from ear-brain system by improving our understanding of their cellular and spatial origin. At present, we are addressing the origin of measurements in the auditory periphery, in particular: otoacoustic emissions (OAEs). One of our novel approaches includes the use of a cochlear perfusion technique in which solutions are delivered through a pipette sealed into the cochlear apex and travel along the length of scala tympani towards the cochlear aqueduct in the base. Solutions containing ototoxic drugs are used to sequentially abolish closely spaced regions along the cochlear length while changes in cochlear function are measured. The apical perfusion technique provides a method to remove cochlear amplification and responses from one place along the cochlea without simultaneously affecting amplification or responses that originate basal to this location. For example, apical perfusions overcome the limitations of acoustic

Suppression of Organ-of-Corti Vibrations and Otoacoustic Emissions in Mice

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Abstract. The inner ear response to a tone can be diminished in the presence of another tone through the process of suppression. Typically, the strongest suppression is expected when both tones, the probe and the suppressor, are of similar frequency and fall within the region of active amplification on the basilar membrane (BM). However, suppression can occur in otoacoustic emission (OAE) responses even when the suppressor tone is more than an octave above the evoking probe stimulus—a result that does not mimic BM behavior. The recent development of new imaging techniques (Optical Coherence Tomography, OCT) has brought an unexpected twist to these results: Whereas two-tone suppression is limited to the tonotopic peak region when measured at the BM, the same does not hold true when vibrations are measured in the organ of Corti (OoC). For instance, vibrations at the top of OoC are actively amplified and suppressed over a broad region corresponding to the tail of the traveling wave. The purpose of this study is to compare suppression patterns as measured in ear-canal pressure and organ of Corti vibrations. We measured cochlear vibrations and ear-canal pressure in mice in response to tones swept in frequency at narrow (1.1) and wide (2.1) suppressor-to-probe ratios. The OAE response (residual) is extracted by vector subtraction of ear-canal responses to probe-alone *vs.* probe swept together with the suppressor. Preliminary data reveal that OAE residuals can be detected for both narrow (1.1) and wide (2.1) ratios in mice. The OAE residuals obtained with wide ratios grow linearly with the stimulus. In contrast, the narrow-ratio OAE residuals tend to have more compressive growth. When residual responses are extracted from the vibrations of the organ of Corti, a similar pattern emerges: the wide-ratio residuals tend to have more linear growth compared to the narrow-ratio residuals. These patterns suggest that wide-ratio OAE residuals may correlate more closely with vibrations within the organ-of-Corti vibrations than with the BM.

INTRODUCTION

Otoacoustic emissions (OAEs) are sounds generated by the cochlea of the inner ear either spontaneously or in a response to a probe stimulus. Despite decades of research on OAEs, the mechanisms behind their generation and propagation out of the cochlea are still not fully understood. Intuitively, emissions evoked with a relatively simple stimulus—such as a pure tone—should be the easiest to interpret. The potential advantage of a single-tone (stimulus-frequency, SF) OAEs over emissions evoked with more complex stimuli, is also the source of their major drawback: Because SFOAE overlaps in time and frequency with the evoking tone, the two signals cannot be easily separated at the recording microphone. To overcome this difficulty, SFOAEs are typically measured indirectly, where the stimulus pressure is estimated *in situ* and subtracted from the mixture of the probe and OAE signals [1]. Here we use a secondary high-level tone to suppress the OAE signal and provide an *in situ* estimate of the stimulus pressure. The vector difference of the ear-canal pressure measured in response to probe-alone and probe presented concomitantly with the suppressor represents the SFOAE residual. Only when the suppression is complete, the SFOAE residual would be representative of the total SFOAE evoked by the probe tone [2].

Typically, SFOAE is extracted with a suppressor tone (f_s) at a frequency close to the probe frequency (i.e., narrow f_s/f_p ratio). In such a case, the SFOAE magnitude grows compressively with increasing probe level, and SFOAE phase-gradient group delays are longer than the cochlear travel time to the probe's best frequency (BF) place in the cochlea. These characteristics agree well with the predictions of coherent reflection theory of OAE generation and propagation in the cochlea, where the active basilar membrane (BM) vibrations in the peak-region of traveling wave are the primary source of the emission signal [3, 4]. However, SFOAEs can be also measured in a

Imaging the ratio dependence of distortion products at apical regions of the gerbil cochlea

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Abstract. Distortion product otoacoustic emissions (DPOAEs) exhibit features at low frequencies that are distinct from high-frequency ones in that they are less ratio-dependent: their characteristics (amplitude and phase) vary little with the frequency separation of the primary tones. The underlying mechanism may arise from the unique apical cochlear mechanics that are poorly understood. Intracochlear observations provide straightforward evidence for the generation mechanism of DPOAEs. In the current study, two-tone induced distortion products (DPs) were recorded from the apically located organ of Corti complex [OCC includes the organ of Corti, the basilar membrane, and the tectorial membrane] of alive gerbil cochleae using optical coherence tomography (OCT) together with simultaneously measured ear canal DPOAEs. Within the OCC, DPs were robust and recorded from all key structures. The ratio-dependency of DPs appeared to link to the characteristics of the primary tones that were broadly tuned and exhibited nonlinearity in a broad region. The upper sideband, $2f_2 - f_1$ DP was found ratio independent due to the invariant overlapping region of the primary tones. The lower sideband, $2f_1 - f_2$ DP differed, and varied with f_2/f_1 ratio. It included both locally and non-locally (i.e. traveling) DP components. Thus, their correlation to related DPOAEs was not straightforward. Our observation provides insights into the generation of low-frequency DPOAEs and related cochlear mechanics, which helps a more precise DPOAE applications in detecting sensory auditory damage in the clinic.

INTRODUCTION

Normal cochlear operation relies on active nonlinear outer hair cell (OHC) processes that compress mechanical responses into a manageable dynamic range, but which also introduces distortions in the cochlea's response [?]. As a consequence, the response to a two-tone stimulus with frequencies f_1 and f_2 (ratio $f_2/f_1 > 1$) contains—in addition to these primary frequencies—a family of intermodulation tones at frequencies $f_1 - n(f_2 - f_1)$ and $f_2 + n(f_2 - f_1)$, with $n \in \mathbb{N}$. The intracochlear locations that generate these distortion products (DPs) depend on: (1) the overlap in the responses to the two stimulus tones [?], and (2) the extent of the nonlinearity within the cochlea. After generation, DPs go through similar signal processing as externally presented tones (i.e. they may propagate, get amplified and/or filtered). As a consequence, DPs measured at a certain intracochlear location are a mixture of local and non-local (i.e., traveling) components [? ?].

Based on the tuned responses observed at the basilar membrane (BM) [?], varying f_2/f_1 ratio is believed to modify the spatially distributed, region of DP generation such that larger f_2/f_1 ratios result in less overlap of the primaries' responses and smaller DPs. Observations of BM responses support this notion in that larger DPs are generated with (narrow) f_2/f_1 ratios close to unity [? ?]. However, recent intracochlear observations in the outer hair cell/reticular lamina (OHC/RL) region, both at high-frequency basal [?] and low-frequency apical regions [?], have demonstrated broader tuning and a more basally extended nonlinear region compared to the BM response. With this, DPs originate from a broader region within the cochlea, as confirmed by robust DPs measured at the RL region [?], and argues against a strong f_2/f_1 ratio dependence of DP generation by the OHC.

Once generated, DPs may propagate back to the ear canal, where they can be recorded as distortion product otoacoustic emissions (DPOAEs). These sounds are the sum of DP wavelets that arise from a spatially distributed generation region, which includes the regions of nonlinear distortion generation and linear, coherent reflection [?].

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Similar tuning of distortion-product otoacoustic emission ratio functions and cochlear vibrations in mice

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Abstract. When elicited by two stimulus tones (at frequencies f_1 and f_2 , $f_2 > f_1$), the amplitudes of specific distortion-product otoacoustic emission (DPOAE) components exhibit a characteristic bandpass shape as the ratio between f_2 and f_1 is varied. This bandpass shape has been attributed to various mechanisms including intracochlear resonance, suppression, and wave interference, and has been proposed to be related to cochlear frequency tuning. While human studies suggest modest correlations between psychophysical tuning and the tuning of DPOAE amplitude vs. f_2/f_1 ratio functions, a relationship between the latter and the tuning of cochlear mechanical responses has yet to be established. This was addressed here through direct comparisons of DPOAEs and cochlear vibrations in wild-type CBA/CAJ mice. DPOAEs were elicited using a fixed- f_2 , swept- f_1 paradigm, and optical coherence tomography was used to measure displacements from cochlear locations with characteristic frequencies near f_2 . The tuning sharpness of $2f_1-f_2$ DPOAE ratio functions was found to be remarkably similar to that of basilar membrane and/or tectorial membrane responses to single tones, with the tuning sharpness of all responses increasing similarly with decreasing stimulus level. This relationship was observed for f_2 frequencies ranging from ~8 to 22 kHz. Intracochlear distortion products did not exhibit a bandpass shape as the f_2/f_1 ratio was varied, indicating that interference between distortion products traveling to the stapes may be responsible for the tuning of the DPOAE ratio function. While these findings suggest that DPOAE ratio functions could be used to noninvasively infer cochlear tuning, it remains to be determined whether this relationship holds in other species and for lower frequency regions.

INTRODUCTION

Due to nonlinear amplification of cochlear vibrations by the outer hair cells (OHCs), stimulation of the ear with two tones (at frequencies f_1 and f_2 , $f_2 > f_1$) results in the generation of mechanical distortion products (DPs)¹. Some of this DP energy is transmitted to the ear canal as DP otoacoustic emissions (DPOAEs), with the $2f_1-f_2$ DPOAE being the most readily measurable component². While DPOAEs undoubtedly provide a window onto OHC function and cochlear mechanics, their interpretation is complicated by the fact that they represent the sum of DP waves generated over a potentially broad cochlear region. DP waves arriving at the stapes from different locations can therefore interfere constructively and destructively, obscuring the relationship between the measured DPOAE and the DP generated at any particular cochlear location. Thus, beyond identifying whether OHCs are present and functional, it remains uncertain whether DPOAEs can accurately convey more specific information about the macro- and micromechanical processes that generate them.

A particularly intriguing example of the complexity in DPOAEs is the bandpass shape observed in the amplitudes of certain components, including $2f_1-f_2$, as the ratio between f_2 and f_1 is varied³⁻⁶. In fact, DPs at frequencies with the form $(n+1)f_1 - nf_2$ ($n = 1, 2, 3, \dots$) all peak at the same frequency, typically falling ~0.5–0.7 octaves below f_2 ^{4,6}. While a decrease in DPOAE amplitude at large f_2/f_1 ratios can be explained by the reduced interaction between the vibrations elicited by the two stimulus tones, the decrease in amplitude at smaller ratios is

A Component of Stimulus-Frequency Otoacoustic Emissions Evoked due to Perturbation of Nonlinear Force in a Cochlear Model

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Abstract. Stimulus-frequency otoacoustic emissions (SFOAEs) are evoked by a single tone presented into the ear. The emissions are generated by reflection of a forward traveling wave (TW) on localized irregularities in the impedance along the basilar membrane. The strongest wavelets are reflected from the place where the TW reaches its largest amplitude. Since the irregularities are localized in fixed places along the basilar membrane, latency of the SFOAE phase can be used to estimate delay of cochlear filters. We used an iterative approach of Shera et al. [JASA (2005) 118:287-313] to obtain an analytical solution for SFOAEs in a nonlinear two-dimensional cochlear model. The solution allowed for decomposition of a reflection component and a component due to perturbation of the nonlinear force. The nonlinear force which in the smooth cochlea may reflect the forward TW backwards [Talmadge et al., JASA (2000) 108, 2911-2931], is perturbed due to irregularities. The perturbed nonlinear force in the model generates an SFOAE component with latency comparable with the latency of the component due to reflection. This means that although the component is evoked due to nonlinear force, it has a comparable (long) latency to the SFOAE component due to reflection. Amplitude of this component due to perturbation of the nonlinear force grows as the amount and amplitude of irregularities increases. In addition, the component amplitude also grows with the tone intensity. The growth is determined by the amplitude of the nonlinear force. It is almost cubic at the lowest intensities and quickly saturates at levels above about 40 dB SPL (the intensity is determined by the position of the compressive nonlinearity in the input/output function of the basilar membrane displacement). An interesting result is that the nonlinear component partly cancels the reflection component because its phase is roughly by 0.5 cycles shifted invariantly to the stimulus intensity and frequency. As the level increases, the component due to perturbation reaches comparable amplitude to the component due to coherent reflection, especially in the portions of SFOAEs with the longest latencies. The destructive interference between the components due to perturbation of the nonlinear force and coherent reflection emphasizes shorter latency wavelets in the overall SFOAEs as stimulus intensity increases and contributes to the saturation of SFOAE amplitude reported, for example, in human experimental data of Abdala and Kalluri [JASA (2017) 142, 812-824].

INTRODUCTION

If a single tone is presented, amplitude of the pressure recorded in the external auditory canal usually quasiperiodically fluctuates as a function of the tone frequency; see Fig. 1 in Shera and Guinan [1]. The fluctuations are most apparent for low intensity (<40 dB SPL) tones and their cause is the interference between the evoking stimulus (presented tone) and emission from within the cochlea. The emission is generated due to coherent reflection of traveling wave [2, 3] from spatial randomly distributed mechanical irregularities along the organ of Corti [4]. For tones used as evoking stimuli, the emission is denoted stimulus-frequency otoacoustic emission (SFOAE) and it can be extracted by various techniques [5].

In this paper, we present the solution for SFOAEs in a two-dimensional, nonlinear cochlear model by using the cochlear "Born expansion" technique presented by Shera et al. [6]. The presented solution is composed of two SFOAE components: (1) a component due to coherent reflection and (2) a component which we denoted *a component due to perturbation of the nonlinear force*. This latter component would not be present in the solution if the model was linear. The paper presents SFOAEs derived from the cochlear model and the both SFOAE components. Similarly as in the solution for DPOAEs presented in [7], the component due to perturbation of the nonlinear force has approximately opposite phase than the component due to coherent reflection. Interaction of both components contributes to the saturation of SFOAE amplitude with increasing intensity of the evoking probe tone.

Relationship between DPOAE and pure tone hearing levels: Numerical analysis with human cochlear finite element model

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Abstract. Dysfunction of the outer hair cells (OHCs) is thought to lead to hearing loss. However, direct diagnosis of the OHC dysfunction is difficult, and the activity of the OHC is indirectly estimated by measuring distortion product otoacoustic emissions (DPOAEs). In this study, a finite-element model of the normal cochlea considering the activity of the OHC and hearing impairment models in which the activity of the OHC was partially absent were constructed. A pure tone or a complex tone was applied to the models, and the relationship between DPOAE level and non-active portion on the BM was investigated. As a result, it was speculated that the dysfunction of the OHC at the basal side of the position of the characteristic frequency for the input frequency affects pure tone hearing and DPOAE levels.

INTRODUCTION

DPOAEs are considered to be derived from the active nonlinear behavior of the OHCs. However, the generation mechanisms of the DPOAEs have not been fully clarified, and the relationship between cochlear function and DPOAEs is still unclear. The level of the distortion component of $2f_1-f_2$ (DP level) is generally considered to be correlated with hearing level at f_2 .¹ However, the relationship between the generated DP components and excitation force of the OHC at each part of the basilar membrane (BM) has not been clarified. In this study, to clarify the mechanism of the DPOAEs, we created four types of the cochlear models, i.e., a passive model, an active model, a model of high-tone sensorineural hearing loss and a model in which the activity of the OHCs is partially absent. Then, by comparing the vibration amplitude of the basilar membrane caused by a pure tone and the distortion component level caused by a complex tone while changing the part where the activity of the OHC is absent, the relationships among partial dysfunction of the OHC, hearing level, and levels of DPOAEs were examined.

METHODS

Geometries and Mechanical Properties of Cochlear Model

Figure 1 shows a FE model of the human cochlea used in this study. This model has been improved based on the previous model^{2,3}. The structures and dimensions are the same as that of the passive model previously reported³, the outline is hence explained briefly here. Although the cochlear takes a spiral form, the shape of the FE model was straightened out. The cochlear model consists of structural parts and liquid parts. The structural parts are the stapes, the stapedial annular ligament, the oval window (OW), the round window (RW), the BM, and the osseous spiral lamina (OSL). The liquid parts are the vestibule, the scala vestibuli (SV), the scala tympani (ST), and the cochlear aqueduct, which are all filled with lymph fluid. To avoid complication of the analysis, the structures in the cochlea were simplified as follows. Although the inner hair cells (IHCs), the OHCs, and the supporting cells exist on the BM, these cells were ignored, and the BM was assumed to be a thin flat membrane. The Reissner's membrane was also ignored

The Effect of Broadband Elicitor Duration on Transient-Evoked Otoacoustic Emissions and a Psychoacoustic Measure of Gain Reduction

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Abstract. Physiological and psychoacoustic studies of the medial olivocochlear reflex (MOCR) in humans have often relied on long elicitors (> 100-ms). This is largely due to previous research using otoacoustic emissions (OAEs) that found multiple MOCR time constants, including time constants in the 100s of milliseconds, when elicited by broadband noise. However, the effect of the duration of broadband noise elicitors on similar psychoacoustic tasks is currently unknown. Additionally, the relationship between gain reduction measured psychoacoustically and using OAEs as a function of elicitor duration are unknown. The current study measured the effects of ipsilateral broadband noise elicitor duration on transient-evoked OAEs (TEOAEs) and psychoacoustic gain reduction estimated from a forward-masking paradigm. Changes in the TEOAE were measured in terms of magnitude and phase. When phase was accounted for in the TEOAEs, the time constants were approximately equal to the psychoacoustic time constants, and were relatively short (~80 ms). When only changes in TEOAE magnitude were measured, and phase was omitted, the average time constant were longer (~172-ms). Overall, the psychoacoustic and physiological data in the study were consistent with the time course of gain reduction by the MOCR. Near-maximal MOCR effects can be measured with ipsilateral broadband elicitor durations of 200 ms or less in a forward-masking paradigm.

INTRODUCTION

The medial olivocochlear reflex (MOCR) is a bilateral reflex loop at the level of the brainstem that can adjust the gain of the cochlear amplifier in response to sound. The temporal dynamics of the MOCR have been well documented through the use of otoacoustic emissions (OAEs), which have found a combination of fast, medium, and slow time courses when elicited by broadband noise [1, 2]. Both physiological and psychoacoustic studies have typically used continuous or long-duration elicitors (> 100 ms) to maximally stimulate the MOCR. In many studies, the elicitor has been presented contralaterally to the probe or signal ear to avoid excitatory masking of the probe by the elicitor. Additionally, broadband elicitors are known to be strong MOCR elicitors when measuring OAEs. However, Roverud and Strickland (2014) [3], using a psychoacoustic measure of gain reduction, found differential effects of duration for on- and off-frequency tonal elicitors. For the on-frequency elicitor, thresholds increased with increasing duration up to about 50 ms, and then oscillated or plateaued. In contrast, thresholds with off-frequency elicitors continued to increase with elicitor duration. These results are consistent with cochlear gain reduction, possibly by the MOCR, in which the on-frequency elicitor is affected by gain reduction at the signal frequency place, but the off-frequency elicitor is not. DeRoy Milvae and Strickland (2021) [12] found that for a fixed 50-ms elicitor, the amount of gain reduction was only slightly higher for a pink broadband noise elicitor than for an on-frequency tone, when elicitor levels were calculated as the energy that would pass through a filter centered at the signal frequency. However, the effect of the duration of broadband noise elicitors on similar psychoacoustic tasks is currently unknown. Additionally, the relationship between gain reduction measured psychoacoustically and using

Lumped Element Models of Sound Conduction in the Human Ear: a Systematic Review

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Abstract. Lumped element models (LEMs) have been used to simulate and investigate the fundamental mechanisms of sound conduction in the human ear for decades. This systematic review aims to guide researchers to the most optimal LEM for the parameters under investigation and provide considerations for creating a new model. For this purpose, the literature was reviewed up to March 11, 2022, according to the PRISMA guidelines. We included 6 models via database searching and another 18 models via cross-referencing. The models differ based on six aspects. 1) The number of elements. 2) The type of elements: electrical or mechanical. 3) The parts of the ear: outer, middle or inner ear. 4) The type of conduction: air or bone conduction. 5) The method to determine the elements: reused from previous models, based on anatomical properties, or fit to experimental data. 6) Whether the model predictions are compared to empirical data. The quality of the LEMs is assessed by comparing the predicted middle ear transfer function, the tympanic membrane impedance, the energy reflectance, and the intracochlear pressures (scala vestibuli, scala tympani, and differential) with experimental data. Regarding air conduction, LEMs characterize the pathways from the outer to the inner ear and accurately predict all six aforementioned parameters. This contrasts with the few existing models for bone conduction, where only a part of the ear is modeled. In addition, bone conduction models often excel at predicting one observable parameter in particular, namely the intracochlear pressure. There is a need for complete bone conduction LEMs, incorporating accessible parameters, such as the ear canal pressure, for non-invasive pre-clinical testing and clinical fitting. Moreover, the existing models only simulate one bone conduction pathway, except Stenfelt's model, which simulates five pathways. Furthermore, a model that allows variation of external parameters, such as the implant's position and the stimulation amplitude, enables optimizing implant parameters and may improve the quality of life for people with hearing loss. To conclude, this review provides recommendations to determine the appropriate model for a specific application, including clinical applications.

INTRODUCTION

Sound conduction in the human ear occurs via multiple modes, including air conduction (AC), where air vibrations in the ear canal induce hearing sensation, and bone conduction (BC), where vibrations of the skull induce hearing sensation. AC vibrations are transferred to the basilar membrane via one main pathway. In contrast, BC vibrations are transferred to the basilar membrane via five main pathways: 1) compression of the ear canal, 2) relative motion of the middle ear ossicles due to inertia, 3) compression of the cochlear space, 4) inertia of the cochlear fluid and 5) secondary fluid paths between the inner ear and cranial cavity [1]. Hearing implants

Can You Hear Me Now? Binaural Brainstem and Spatial Hearing Deficits in a Guinea Pig Model of Noise-Induced Cochlear Synaptopathy

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Abstract. Noise-induced cochlear synaptopathy has been studied for over 20 years with no known diagnosis for this disorder within the human population. This type of “hidden hearing loss” induces a loss of synapses in the inner ear but no change in audiometric thresholds. Animal studies to this point have focused primarily on peripheral hearing measures to diagnose ribbon synapse loss. Here, we measure binaural hearing deficits in a model of noise-induced cochlear synaptopathy for the first time. Our results show that while common audiological assessments show no change in threshold post moderate noise exposure, measurable binaural hearing deficits persist long-term.

INTRODUCTION

Sensorineural hearing loss is typically diagnosed via permanently raised auditory thresholds due to cochlea dysfunction [19,26]. This can be easily assessed and diagnosed using traditional audiological tools such as subjective hearing tests (the audiogram) as well as objective tests of peripheral auditory function including otoacoustic emissions (OAEs) and auditory brainstem responses (ABRs) to assess hair cell and auditory nerve function, respectively. Perplexingly, up to 10% of people report difficulty hearing in noisy environments, such as classrooms and workplaces, despite normal audiometric thresholds [25,14,36,27]. The reasons for this are not yet known because the hearing difficulty is ‘hidden’ from routine hearing tests. Recent animal studies have shown that a moderate intensity noise exposure can cause temporary hearing threshold shifts, but permanent loss of synapses between inner hair cells (IHC) and the auditory nerve (ANF) in the cochlea [8,16]. This has been termed cochlear synaptopathy.

The cochlea contains IHCs that relay acoustical information about our environment to ANFs as well as outer hair cells (OHCs), which amplify the signal from IHCs to the cochlear nerve [15]. OHC function can be evaluated by measuring distortion product otoacoustic emissions (DPOAEs) [1]. DPOAE loss and its recovery post noise exposure has been shown in noise-induced synaptopathy studies [5,16] suggesting normal OHC functioning in synaptopathy. Ascending auditory pathway function can be assessed by ABRs. Each ABR peak roughly corresponds to synchronized neural activity at a specific point along the auditory pathway. The ABR waveforms thus provide insight into the functioning of the auditory brainstem; for example, wave I tells us about the synchronous firing of ANFs in the cochlea. While studies in mice have reported reliable and robust wave I amplitude depletion post noise exposure that persists despite recovery of audiometric and DPOAE thresholds, wave I has not proven to be a reliable biomarker for noise-induced cochlear synaptopathy in humans; wave I can be difficult to measure reliably even in humans that have perfectly normal hearing [13,18,11,15,3].

Individuals with histories of moderate noise exposure, but normal thresholds, can develop decreased ability to discriminate sounds in complex environments [30]. Numerous studies demonstrate the importance of binaural cues for localization and accurate perception of sounds like speech in the presence of noise [4]. Animal studies of synaptopathy to date have not measured binaural hearing abilities or binaural brainstem function. Brainstem binaural function can be assessed non-invasively via binaurally evoked ABRs by measuring the binaural interaction component (BIC) amplitude. The BIC is a residual waveform resulting from subtracting the sum of the monaurally evoked ABRs from the binaurally evoked ABRs. The BIC has been studied as a biomarker for binaural hearing abilities [2,6,7,17,33,35] and correlates with binaural behavioral abilities in normal and hearing-impaired subjects [17]. The BIC is known to vary with the two cues to horizontal sound localization: interaural time difference (ITD) and interaural level difference (ILD). These acoustical cues are generated by the filtering of sound by the head and body [9,10,23]. The BIC amplitude is maximum at 0 μ s ITD, corresponding to a sound source directly in front of a subject, and systematically decreases in amplitude with increasing ITD and ILD [24,32]. Because the BIC and its source is the same in animals and humans [2,31], this physiological marker, while difficult to measure in humans, is a reliable

Whole Stimulus DPOAE Analysis

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Abstract. Distortion Product Otoacoustic Emissions (DPOAE) offer great potential for hearing diagnosis, but are complicated by the interaction of components generated by different mechanisms. Separation of these components from DPOAE measurements may allow conclusions to be drawn about the functionality of these separate mechanisms of a cochlear. However, the signal processing methods for performing this separation are imperfect. Existing methods are based on time windowing of DPOAE generated from frequency sweep stimuli.

This paper presents a method in which the entire spectra of both distortion (D) and reflection (R) components are simultaneously estimated. This approach has several advantages. Firstly, the method removes the need for a compromise between frequency precision and signal to noise ratio. Secondly, the method can be made to include models of the stimulus signals, so that the stimulus does not strongly interfere with the estimation process. Thirdly, the method can be arranged to make efficient use of data that has been corrupted by measurement artefacts. Fourthly, the method can be easily adapted to track DPOAEs that are changing in response to chemical or acoustic treatments.

The basic modelling assumptions made are that the sum of R and D measurements can be represented as the sum of convolutions with the stimulus signal, the frequency representation of the D component is more smooth than the R component, and that a reasonable estimate of the noise level in the signal is available. These assumptions are combined into a linear convex problem.

In this paper we compare the proposed approach with three other methods. While it is not superior to the earlier methods at every frequency, it does offer some improvement, particularly with regards reducing the contamination of D by R.

INTRODUCTION

Distortion product otoacoustic emissions (DPOAE) are widely used for research and clinical practice, the latter particularly in infant hearing screening programs. DPOAE typically exhibits rapid variation with frequency, which has been termed “fine structure” and is thought to arise from the interaction of two propagating waves [1, 2, 3, 4]. The first of these is the distortion (D) component, which is generated near the characteristic place of the higher of the two stimulus frequencies, and which propagates both backwards towards the stapes, and forwards towards the apex. The second, reflection (R), component arises from the reflection of the first component near the characteristic place of the distortion product frequency. Separation of these two components considerably enhances the information contained in the DPOAE for both research and diagnostic purposes [5]. Typically this separation has been performed by time windowing of DPOAE generated from frequency sweep stimuli [6, 7], usually accompanied by a least-square fit [8]. In effect each window generates an estimate of each of the D and R components in a narrow frequency band.

This paper presents a method in which the entire spectra of both D and R components are simultaneously estimated. This approach has several advantages. Firstly, the method removes the need for a compromise between high frequency precision (obtained by using a narrow window) and high signal to noise ratio (obtained by using a wide window). Secondly, the method can be made to include models of the stimulus signals, so that these do not interfere with the estimation process (although in the method presented here, these models are not included). Thirdly, the method can be arranged to make efficient use of data that has been corrupted by measurement artefacts. Fourthly, the method can be easily adapted to track DPOAEs that are changing in response to chemical or acoustic treatments [9, 10].

In this paper we compare the proposed approach with three other methods: least squares fitting (LSF) [8], inverse Fourier Transform (IFFT) [11, 12, 13], and wavelet transform (CWT) [14, 15] on simulated data using the approach of [7]. The proposed approach is not superior to the earlier methods at every frequency, but the whole-stimulus approach offers improvement in many parts of the extracted spectra, particularly with regards reducing the contamination of D by R.

Temporal adjustment of interaural stimulation timing leads to improved sound localization but not to improved spatial release from masking in bimodal listeners

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Abstract. In bimodal cochlear implant (CI) / hearing aid (HA) users a constant interaural time delay in the order of several milliseconds occurs due to differences in signal processing of the devices. For MED-EL CI systems in combination with different HA types, we have quantified the respective device delay mismatch.

In the current study, we investigate the effect of the device delay mismatch in actual bimodal listeners on sound localization accuracy. To deal with the device delay mismatch we delayed the CI stimulation according to the measured HA processing delay and two other values. To determine potential effects of procedural learning, we applied an A-B-B-A testing paradigm.

With all delay values highly significant improvements of the RMS error were observed compared to the test without the delay (14.7° improvement in average) in 9 bimodal listeners. Also the Signed Bias of sound localization improved significantly from 25.2° to 10.5° averaged across listeners.

At all times we also tested spatial release of masking (SRM) of speech (S) in noise (N). S and N were either collocated at 0° or S was situated at 0° and N at 90° at the HA side. In none of the bimodal listeners an improvement of SRM by the temporal adjustment of modalities was observed.

The results reveal that sound localization in bimodal listeners improves from a reduction of the device delay mismatch between CI and HA. With this form of temporal adjustment of modalities, spatial re-centering seems possible. However, transmission of temporal information via the CI and thus binaural processing seems to be not sufficient for improved SRM.

INTRODUCTION

Bimodal provision is very common in CI centers nowadays. In such cases one ear is provided with a cochlear implant (CI) and the contralateral ear with a conventional digital hearing aid (HA). Many studies were published showing a benefit for most bimodal listeners, when using both devices instead of just one in binaural performance (Ching et al., 2004, 2006; Hoppe et al., 2018; Sheffield et al., 2017) as well as in quality of life (Farinetti et al., 2015). Despite the reported benefits, Dorman and colleagues could show that in tRMS of sound source localization bimodal CI/HA users perform poorer than e.g. bilateral CI users or single sided deaf CI users (Dorman et al., 2016). One of many reasons for this poor performance is that both modalities are not synchronized in tRMS of processing delay. Zirn et al. (2015) showed that there can be a temporal asymmetry in the range of 3 to 10 milliseconds between the ear provided with a MED-EL CI and the ear provided with a HA.

Two-Tone Suppression and Power Balance in a 2D Nonlinear Cochlear Model

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Abstract. Two-tone suppression (TTS) is the nonlinear phenomenon in which cochlear responses in the region most sensitive to a probe tone are reduced if a second tone (suppressor) of different frequency is simultaneously presented. TTS occurs due to saturation of mechano-electrical transducers (MET) in the outer hair cells. The nonlinear dependence of MET channel conductance is the main cause of nonlinearity in cochlear amplification. Although the cochlear amplifier primarily acts locally, it influences distant fluid coupled parts of the basilar membrane (BM). The question therefore arises, how the fluid coupling contributes to the TTS. To answer this question, TTS was analysed using 2D nonlinear cochlear model in two cases: for a suppressor of higher frequency and for a suppressor of lower frequency than the probe tone. It was shown that the BM-BM hydrodynamical coupling redistributed the excess of the power generated by the OHC electromechanical feedback force. It was also shown that the short-range part of the BM-BM coupling plays important role in power balance along the BM. Moreover, it turned out from the model simulations that the suppression by a low-frequency suppressor causes a basal shift of the amplitude maximum and affects the phase of the BM stationary response. In contrast, the suppression by a high-frequency suppressor does not significantly affect the BM response phase. It flattens the amplitude of the BM stationary response, which leads to an apical shift of the amplitude maximum.

INTRODUCTION

Two-tone suppression (TTS) is the nonlinear phenomenon in which cochlear responses in the region most sensitive to a probe tone are reduced if a second tone (suppressor) of different frequency is simultaneously presented. TTS occurs due to saturation of mechano-electrical transducers (MET) in the outer hair cells [1]. The nonlinear dependence of MET channel conductance is the main cause of nonlinearity in cochlear amplification. Although the cochlear amplifier primarily acts locally it influences distant fluid coupled parts of the basilar membrane (BM) [2]. The question therefore arises, how the fluid coupling contributes to the TTS. To answer this question, we used a nonlinear 2D cochlear model to simulate and analyse TTS. TTS is in the model simulated due to the change in the nonlinear force elicited by a suppressor.

We briefly introduce the used nonlinear cochlear model, i.e. a nonlinear integrodifferential BM motion equation together with a differential motion equation of the outer hair cell (OHC) stereocilia displacement, which is coupled to the BM motion equation via the OHC electromechanical feedback force. These motion equations are formulated in the time domain and in the frequency domain. The nonlinear force is calculated in the frequency domain as a deviation of the nonlinear feedback undamping force from the undamping force in the linear regime. In the end of the theoretical part of the current paper, a power balance equation for the BM motion is presented. The results then present TTS simulations and power balance analysis.

THEORETICAL ANALYSIS

The nonlinear 2D cochlea model

This study uses a nonlinear hydrodynamic cochlea model introduced by Nobili and Mammano [3]. The model's dynamics are described by combining two equations: one integro-differential for the transverse BM displacement, $\xi(x, t)$, and the other differential for the OHCs stereocilia displacement $\eta(x, t)$, both of which are functions of time t and the BM longitudinal coordinate x .

The BM is modeled as a continuous array of harmonic oscillators of mass, $m(x)$, damping, $h(x)$, and stiffness, $k(x)$, per unit BM length, longitudinally coupled by the shearing viscosity term, $\partial_x s(x) \partial_x$, and the hydrodynamic force

Investigating the Effect of Change in Cochlear Micromechanics and Activity Levels on Stimulus Frequency Otoacoustic Emissions Phase-gradient Delay

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Abstract. Stimulus frequency otoacoustic emissions (SFOAEs), which are sounds emitted by the cochlea at the frequency of the stimulus, have been used as a noninvasive measure of cochlear function. The gradient of the SFOAE phases characterizes the latency of emission and is associated with the frequency selectivity and sharpness of tuning of the mammalian cochlea. However, whether the phase-gradient delay of SFOAE can be used as an indicator of cochlear tuning and sensitivity reliably when the properties of the cochlea change remains unclear. The objective of this study is to address this question by varying cochlear model activity, tectorial membrane (TM) properties and organ of Corti (OoC) micromechanical properties to change cochlear tuning. In this work, a three-dimensional gerbil cochlear model that couples mechanical, electrical and acoustic domains with cochlear roughness has been used. The roughness is implemented on outer hair cells (OHCs) force acting on the basilar membrane (BM). Parameters that control the activity levels, TM longitudinal coupling and OoC impedance are varied. The results show that changes in sharpness of tuning due to reduction in cochlear activity and TM longitudinal coupling can be detected by using SFOAE phase-gradient delay. However, changes in cochlear tuning due to changes in OoC impedance are not necessarily reflected by corresponding changes in SFOAE phase-gradient delay.

INTRODUCTION

Otoacoustic emissions (OAEs) are sounds generated inside of cochlea, which are caused by the active feedback by outer hair cells (OHCs) and can be measured at the ear canal (EC). OAEs have been used as a simple, efficient and noninvasive measure of cochlear function in both research and clinical practice [1]. Based on coherent reflection theory, a linear reflection mechanism due to impedance perturbations gives rise to reflection OAEs [2, 3]. Rapidly rotating phase has been found to be one of the key characteristics of reflection OAEs [3]. This study focuses on one type of reflection OAEs called stimulus frequency OAEs (SFOAEs), which are sounds emitted by the cochlea at the frequency of the external stimulus. The gradient of the SFOAE phase characterizes the latency of emission and is associated with frequency selectivity and sharpness of tuning of the mammalian cochlea. The phase-gradient delay of SFOAEs has been proposed to estimate the quality factor of the basilar membrane (BM) response [4, 5]. A more recent study has found the tuning ratio (ratio of tuning sharpness to SFOAE phase-gradient delay expressed in periods) to be approximately invariant among cat, guinea pig, and chinchilla, opening the possibility of determining cochlear tuning from SFOAE phase-gradient delay [6]. However, whether the phase-gradient delay of SFOAE can be used as an indicator of cochlear tuning and sensitivity reliably when the properties of the cochlea change remains unclear. The objective of this study is to address this question by varying cochlear model activity levels, tectorial membrane (TM) properties and organ of Corti (OoC) impedance that can affect the cochlear tuning and sensitivity. Varying TM properties in the case study is inspired by studies that have shown that changing tectorial membrane (TM) longitudinal coupling affects cochlear tuning [7, 8, 9], spontaneous OAEs (SOAEs) [10] and SFOAEs [11].

METHOD

In this work, a three-dimensional gerbil cochlear model that couples mechanical, electrical and acoustic domains with cochlear roughness is used, which has been described in detail in previous works [12, 13]. The parameters of the baseline model can be found in [12]. The smooth version of this cochlear model has been calibrated based on in vivo recent experiments, with both mechanical and electrical data. In order to simulate reflection OAEs, cochlear roughness on the OHCs electromechanical coupling coefficient (which relates the electromotile force applied on the

Numerical Analysis of Nonlinearity of Outer Hair Cells Based on Comparison with Measurements of DPOAEs

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Abstract. Distortion-product otoacoustic emissions (DPOAEs) are considered to be generated by nonlinear force of the outer hair cells (OHC), and those frequencies and levels depend on the function curve of the force. Each order of distortion component is generally generated by different degree term of a nonlinear function which is approximated by a power series. In this study, the nonlinear force of OHC was formulated based on the distortion components detected in measurements of DPOAEs. The input/output (I/O) functions of DPOAEs were measured in normal-hearing human ears. The I/O functions of each component showed different nonlinear curve and varied by stimuli conditions. Odd-order of distortion components (e.g. $2f_1-f_2$ or $3f_2-2f_1$) were generated in all the ears, on the other hand, even-order of distortion components (e.g. f_2-f_1 or $3f_1-f_2$) were seldom detected. Thus, the force of the OHC, P_{OHC} , was formulated as a function including both of saturability and symmetry around operating point, because even-order of distortion components were barely detected. The I/O functions of DPOAEs obtained from numerical analysis using the finite-element model of the human cochlea which includes the force were compared with the measurements in normal-hearing human ears, and validity of the force was evaluated. As the result, the I/O functions of each component obtained from the displacement of the stapes footplate of the model showed different nonlinear curve. If the sound pressure gains of the middle ear are assumed to be constant at a certain frequency regardless of sound pressure level, the ease of saturation of the I/O function obtained from the model is considered to be comparable to that obtained from the measurements in the human ear. The curve of the I/O functions of each component obtained from the model approximately matched that obtained from the measurements.

INTRODUCTION

The outer hair cells (OHCs) show somatic motility which non-linearly amplifies the vibration of the basilar membrane (BM). Distortion-product otoacoustic emissions (DPOAEs) are considered as intermodulation distortion components ($mf_1 \pm nf_2$, here, m and n are integers) produced by the nonlinear activities of the OHCs when the cochlea was simultaneously stimulated by two pure tones with different frequencies (f_1 and f_2). Intermodulation distortion is generated when a complex signal is applied in a nonlinear system and is a general acoustic phenomenon. Each order of distortion component is generally generated by different degree term of a nonlinear function which is approximated by a power series, i.e. N -order (here, N is an integer number) of distortion components are generated by N -degree term of the function. The coefficient of each distortion component can be calculated by plugging an expression composed of sum of sinusoidal wave of f_1, f_2 into a variable of the power series. For example, distortion component (f_1+f_2) and harmonics ($2f_1, 2f_2$) are generated when expand and convert the square of the expression. The coefficient of each components are represented by polynomial expression of coefficients of the sinusoidal waves. The non-linear activity of the mammalian OHC has been investigated experimentally, e.g., its transfer function between the current and stereocilia bundle deflection is shown as a sigmoid-shaped Boltzmann function¹. The frequencies and levels of DPOAEs depend on the shape of the nonlinearity curve², and the optimum frequency ratio f_2/f_1 of the stimuli varies for each component of DPOAE³, e.g. $2f_1-f_2$ and $2f_2-f_1$. Therefore, a nonlinear function of the OHCs can be formulated based on the levels of each distortion component obtained from measurement of the DPOAEs. In this study, we aimed

Speech-DPOAEs for probing speech processing in the inner ear

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Abstract. Speech is a complex real-world stimulus that consists of time-varying contributions in many frequency bands. The inner ear, or cochlea, not only transduces the acoustic vibrations into electrical signals, but also spatially segregates the acoustic waveform into different frequency components, as well as mechanically amplifies the vibrations in frequency bands where the amplitude is low. This processing of the speech signal can potentially be controlled through efferent nerve fibers that extend from higher processing centers in the brain to the cochlea. However, we are currently lacking methodological tools to non-invasively investigate the putative role of top-down feedback on speech processing in humans. Here we develop such a method that builds on distortion-product otoacoustic emissions (DPOAEs) related to the temporal fine structure of the voiced parts of speech (speech-DPOAEs).

INTRODUCTION

Understanding speech is crucial for human interaction and communication [1]. Humans are indeed experts at understanding speech even in adverse listening conditions such as loud background noise in a noisy restaurant, coffee shop or in traffic.

Our ability to understand speech in noise is, however, vulnerable. Hearing impairments affect more than 16% of the adult population in the E.U., and more than 5% in children [1, 2, 3, 4, 5]. Moreover, hearing impairments progress with age and are hence a particular problem in the E.U.'s aging society: 40% of people above age 50 and 70% of those above age 70 have some form of hearing disorder. Such hearing impairment impacts first and foremost the ability to understand speech in noisy backgrounds, and current hearing aids are unfortunately of little help [6]. The resulting difficulties in communicating in many social settings have major effects on an afflicted person's personal, social and economic development [4, 7].

A better diagnosis of hearing impairment as well as the development of corresponding treatments require a better understanding of the neural pathways of hearing, and in particular of the neural mechanisms that allow a healthy person to understand speech in noise. This issue has traditionally been tackled by investigating the underlying processes in the ear and brain through simple acoustic signals such as pure tones or clicks. As an example, pure-tone audiometry uses pure tones of different frequencies to assess the hearing threshold of a subject at those frequencies. As another example, click-evoked auditory brainstem responses record the electrical activity of the brainstem at different latencies when a subject hears a series of short clicks. These methods are highly useful for assessing the basic functioning of different parts of the auditory system, such as the inner ear and the auditory brainstem. However, they do not fully reveal the neural mechanisms that allow us to process more complex signals such as speech in background noise.

Recent research has therefore sought to measure neural responses to natural speech, and therefrom learn more about the neural mechanisms of speech processing. An important example concerns the neural response to the temporal fine structure of speech. Many parts of speech are voiced, originating from vibrations of the vocal fold. The vibration occurs at the so-called fundamental frequency, typically between 100 - 300 Hz. This frequency as well as its many

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Does Endolymphatic Hydrops Shift the Cochlear Tonotopic Map?

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Abstract. The cochlear tonotopic map determines where along the basilar membrane traveling waves of different frequencies peak. Endolymphatic hydrops has been hypothesized to shift the tonotopic map by altering the stiffness of the cochlear partition, especially in the apex. In this exploratory study performed in a handful of normal and hydropic ears, we report preliminary measurements of interaural differences assayed using behavioral pitch-matching supplemented by measurements of reflection otoacoustic-emission phase-gradient delays.

INTRODUCTION

The stiffness gradient along the basilar membrane determines where the traveling wave peaks. In ears with endolymphatic hydrops, the increased fluid volume is thought to stiffen the cochlear partition, particularly near the apex where the hydrops is more pronounced [1]. This increased stiffness alters the motion of the traveling wave along the cochlear partition by increasing the local characteristic frequency, thus altering the tonotopic map.

Binaural diplacusis is the perceptual anomaly where the perceived pitch of a tone is different between ears. Diplacusis has been observed sporadically and anecdotally in ears with endolymphatic hydrops and attributed to a change in the cochlear frequency-place map of the affected ear [1-4]. If the traveling wave peaks in a different physical place along the cochlear length in each ear, the frequency coded (and hence the pitch perceived) might be expected to differ, at least if the perceived pitch is dominated by the cochlear place code. In normal ears with a frequency range of ~10 octaves, interaural pitch differences are small, typically less than one semitone [5-7], indicating that the interaural pitch agreement is better than 1% of the audible frequency range. The theories of Tonndorf [1] predict that the stiffened basilar membrane shifts the site of the traveling-wave peak, producing diplacusis in ears with unilateral endolymphatic hydrops. Recent work in guinea pigs with induced endolymphatic hydrops suggests that a perceptual shift in pitch between ears could be produced by mechanical changes in the frequency-place map [8]. Guinan et al. [8] estimated apical shifts of 0.5 to 2 octaves in the affected ear of guinea pigs with induced endolymphatic hydrops.

To determine if there is a corresponding shift in the tonotopic organization of humans with endolymphatic hydrops, we conducted an interaural pitch-matching task for diplacusis in a small group of subjects diagnosed with endolymphatic hydrops. Figure 1 provides a schematic of inter-aural pitch matching in (A) one normal-hearing subject and (B) one subject with unilateral endolymphatic hydrops who shows a pitch mismatch between ears. Reflection-source otoacoustic emissions (i.e., stimulus-frequency otoacoustic emissions, or SFOAEs) were also measured in each subject, with the eventual goal of comparing perceptual and otoacoustic results in larger groups with and without endolymphatic hydrops. No such comparison was conducted in this preliminary study.

Transverse-Longitudinal Structure Registration and Vibration Measurement via Optical Coherence Tomography

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Abstract. Intra-organ of Corti displacement measurements made via optical coherence tomography have provided significant information about cochlear micromechanics in recent years. However, several ambiguities inherent to this modality have complicated interpretation of these measurements. For one, optical coherence tomography measures the one-dimensional projection onto the optical axis of a three-dimensional motion. Also, the optical axis may make a substantial angle with the basilar membrane normal, meaning that structures along the optic axis, measured in a single measurement, may lie in different tonotopic cross-sections. We have developed a method that accounts for both of these ambiguities, to reconstruct the two-dimensional longitudinal-transverse components of displacements of structures within the organ of Corti. This is performed by taking data at multiple longitudinal positions at two viewing angles, without any *a priori* knowledge of the measurement locations or viewing angles. We present a sample data set in which we have applied this program to reconstruct the transverse-longitudinal motion of the base of the outer hair cells in the base of the sensitive gerbil cochlea. The results reinforce the importance of accounting for viewing angle when analyzing and reporting vibration results.

INTRODUCTION

Historically, the *in vivo* study of basal cochlear mechanics was limited to measurements of the basilar membrane (BM). The advent of optical coherence tomography (OCT) in the last decade has allowed for vibrometry at a depth, facilitating the study of intra-organ of Corti complex (OCC) motions. Of particular interest is the motion of the electromotile outer hair cells (OHCs), which play an important role in amplifying vibration responses and improving the range of sound-pressure levels (SPLs) over which hearing operates.

Several issues complicate the interpretation of OCT measurements. Firstly, the motion of the OHC region is not uniform. The OHCs are 40 μm long and 10 μm wide, and come in rows of three per longitudinal cross-section. The apical surface of the OHCs, called the reticular lamina (RL), moves differently from the basal surface attached to the Deiters' cells as the OHC compresses and expands due to electromotility [1]. Moreover, the OHCs within a row move differently from each other [2].

A second complication is that measurements are generally taken at an angle with respect to the transverse anatomical orientation of the cochlea, and this angle is not known *a priori*. This introduces two ambiguities: (1) displacements measured via OCT are projections of the three-dimensional motion onto an unknown axis, and (2) measured points at the OHC and BM within a single optical axis measurement (A-scan) will in general lie in different longitudinal cross-sections. The first of these ambiguities was discussed by Cooper et al [3]. Their measurements showed that the phase difference between OHC and BM motion relied heavily on the viewing angle. The second of these ambiguities was discussed by Frost et al [4], wherein we developed a program that measured the relative anatomical distances between structures imaged with OCT. We used this program to measure displacement of the OHC and BM at the same cross-section, and showed that this correction revealed up to 1/4 cycle difference in OHC-BM displacement phase when displacement-accounted (single cross-section) results were compared to single-measurement (two different cross-section) results.

With these complications in mind, it is difficult to fully interpret OCT measurements of OHC displacement that are reported without the viewing angle specified. The group of Ren has achieved BM and OHC-region displacement measurements taken at a purely transverse angle, thus measuring purely transverse motion in a single tonotopic cross section, both in gerbil and mouse [5, 6]. The instrument they use is similar to

Otoacoustic Emissions in a Deep-Neural-Network Model of Cochlear Mechanics

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Abstract. Otoacoustic emission (OAE) generation depends on global cochlear mechanics as well as on the properties of local cochlear nonlinearities associated with outer-hair-cells. A popular method to simulate OAE generation is via nonlinear transmission-line models of cochlear processing that incorporate the coherent reflection theory and cochlear distortion-products. In this study, we investigate whether another type of cochlear models can also be used to simulate realistic OAE properties. In particular, we consider a deep-neural-network approximation of a cochlear transmission-line model that accounts for nonlinear, dispersion and tuning properties of human basilar-membrane displacement (CoNNear). Because convolutional-neural-network (CNN) models have a fundamentally different architecture than that of a longitudinal coupled filterbank, it is not trivial how reverse traveling waves would emerge from such models. We investigated the properties of simulated click-evoked and distortion-product OAEs in this study, and conclude that trained CNN architectures of cochlear models are able to simulate properties associated with local OAE generation, but fail to account for the global phenomenon of reverse traveling waves. While not all aspects of OAE generation are captured in CoNNear, the method holds promise because CNN architectures can be used in connection with measured DPOAEs in closed-loop back-propagation systems to design new stimuli for hearing diagnostics or auditory research experiments.

INTRODUCTION

Otoacoustic emission can be simulated using 1-D transmission-line (TL) models of cochlear processing that represent basilar-membrane (BM) vibration as a cascade of fluid-coupled bandpass filters (e.g. [1, 2]). When introducing small impedance mismatches along the simulated cochlear transmission-line, energy in the forward traveling wave can back-propagate to the cochlear base and generate reflection-source emissions [3]. At the same time, the characteristics of the cochlear nonlinearity will determine the compressive growth features of basilar-membrane processing, and correspondingly the frequencies and strength of simulated distortion-product OAEs. Over the years, both cochlear model descriptions (e.g. [4]) and OAE generation theories [3] have been refined, but from an application perspective, we cannot wait until the theory of hearing is complete. In fact, (imperfect) models of OAE generation have a long history in explaining the mechanisms underlying experimental observations, generating hypotheses for new experiments, or in the design of auditory stimuli that result in OAEs that are quantify frequency-specific hearing deficits. For example, recorded OAEs and auditory evoked potentials can be used to individualize the hearing-impairment parameters in cochlear models [5, 6], that subsequently can be used to design of hearing-aid algorithms (e.g. [7]).

However, the full potential of *in-silico* approaches for hearing diagnostics and treatment can presently not be fully exploited. In particular, the numerical optimization of a stimulus or hearing-aid algorithm using a closed-loop system requires *reverse engineering* of, or *back-propagation* through, the state-of-the-art nonlinear analytical cochlear model inside the loop (Fig.1b). This operation is non-trivial for state-of-the-art auditory models with coupled nonlinear differential equations. To enable back-propagation and speed up the computations, we recently developed a neural-network framework that uses convolutions and differentiable operations to represent cochlear, inner-hair-cell and auditory-nerve processing, i.e. CoNNear (Fig.1a). With an appropriate set of hyperparameters, we showed that a CNN architecture can simulate (end-to-end) time-domain BM displacement responses and properties (Fig.1c-f). Simulations were fairly accurate and the model architecture was shown to generalize well to stimuli and auditory response features it did not see during training [8, 9]. For example, even though the model was never trained to simulate distortion-product otoacoustic emissions (DPOAEs), they simply emerged from the solution. This emerging model property holds promise, because if CNN versions of cochlear models can capture the dominant generators of OAEs, we could embed them into closed-loop systems.

In this paper, we further investigate to which extent CNN models of cochlear processing *learnt* key features of OAE generation as part of their parameter constraining procedure. On the one hand, we study whether local OAE phenomena are captured when CoNNear training was based on 1-D TL model simulations of time-domain BM responses to a

Diagnosis of mechanical ear pathologies using a classification model

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Abstract. Wideband tympanometry (WBT) has potential as a non-invasive diagnostic tool for pathologies that cause changes to mechanics of the middle and inner ear. However, because WBT data are complex and thus difficult to interpret, WBT has not been widely implemented in the clinic. Adult patients with conductive hearing loss and normal otoscopic exam have diagnostic uncertainty which can be helped by early diagnosis. In addition to middle-ear pathology, inner-ear pathology such as superior canal dehiscence (SCD) can be better managed with early detection. In this study we measured WBT in adult ears with SCD, stapes fixation (SF) and normal ears. A total of 204 ears were included. WBT was measured using the Titan WBT hardware and the Research Platform software (Interacoustics, Middelfart, Denmark) to obtain the raw WBT recordings which were then filtered by our mitigation software to reduce low-frequency noise. Air-bone gap (ABG) was calculated from audiometric measurements. We developed an automated classification model that used multivariate logistic regression, and based on the highest probability, classified ears as SCD, SF or normal. The model features included principal components of WBT absorbance and frequency-averaged ABG. A cross-validation approach with 1000 iterations was used to train and validate the model to improve generalizability of results. In the validation set, correct classification of SCD, SF and normal ears were achieved for 94.8% of ears. Sensitivity for SCD was 80.9% and for SF 97.1%, whereas specificity for SCD was 97.5% and for SF 99.2%. Performance of an absorbance-only and an ABG-only model was also tested. The technique we developed performed surprisingly well for the ABG-only model for the dataset recorded. Adding WBT absorbance to the ABG-only model further improved performance, especially for SF sensitivity. We find that automation of SCD and SF differential diagnosis based on our regression models on absorbance and ABG is feasible and will provide clinicians with a powerful user-friendly diagnostic tool.

INTRODUCTION

Several studies have shown that wideband tympanometry (**WBT**) and the derived metric *absorbance* have great potential to diagnose mechanical pathologies of the ear (Feeney, Grant and Marrayott, 2003; Hunter, Bagger-Sjöbäck and Lundberg, 2008; Shahnaz, Longridge and Bell, 2009; Nakajima et al., 2012, 2013; Merchant et al., 2015, 2021; Feeney et al., 2020). However, WBT has not been widely adopted by clinicians. A major reason clinicians cannot use WBT data to diagnose pathology is because WBT data are complex, and no diagnostic algorithm exists to interpret the complex data for various diagnoses. Additionally, much of the research in this area has been on group level (e.g. averaged) effects and patterns associated with certain conditions. Translation of group-level effects to what a clinician will observe in an individual patient is not straightforward. For example, many of the fine structure details in individual WBT and absorbance measurements are smoothed by group-level summation metrics such as averaging. As such, there is a need for automated methods that can perform accurate diagnosis from an individual ear's measurements.

Modelling the Recovery of Residual Acoustic Hearing after Cochlear Implantation by Using Feasible Intracochlear Acoustic Devices

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Abstract. Cochlear implants are now used to enhance the high frequency hearing of patients that still have significant residual acoustic hearing at low frequencies. The hybrid combination of electrical and acoustic hearing can give significant improvements in speech perception, compared with just one or the other. The process of cochlear implantation, however, typically degrades the low frequency residual acoustic hearing. To study the mechanical effects of cochlear implantation on residual acoustic hearing, a two-chamber model of the cochlea has been developed that enables the upper and lower chambers to be modelled with different physical characteristics, so that the effects of an implant in the lower chamber can be predicted. In particular, the model has been used to predict the reduction in residual acoustic hearing caused by the stiffening of the round window, due to its penetration by the electrode array of an implant. In the frequency range 100 – 1000 Hz, the predicted hearing loss is of the order of 20 dB, which is consistent with the average post-operative hearing losses measured previously [1]. The new model has been used to show that the loss can be reduced substantially by incorporating a gas bubble of a few cubic millimetres near the round window; the bubble then fulfils the pressure release function of the normal round window. The effect on the residual acoustic hearing of changing the size and position of the bubble will be discussed. The model has also been used to simulate the intracochlear stimulation that could be achieved by incorporating an acoustic actuator within a cochlear implant, as an alternative to the high-powered external hearing aids that are currently used. To study the feasibility of designing an actuator with sufficient output to overcome the patient's low frequency hearing loss, yet that is small enough to fit within an electrode array, both its acoustic output and its internal acoustic impedance need to be considered. At least two types of actuator appear to be feasible in this application. Combined intracochlear electrical acoustic excitation opens up the possibilities of both ipsilateral and bilateral hybrid hearing.

INTRODUCTION AND MOTIVATION

Introduction

A cochlear implant, CI, is now an established procedure that is approved by health regulators in most countries, including NICE in the UK, for patients with profound or severe hearing loss.

Generally, cochlear implantation enables hearing of speech and its recognition for those who had not been able to do so. However, it can also impair low frequency hearing. One cause of such impairment is the stiffening of the round window (RW), thereby reducing its ability to allow the movement of cochlear fluid at frequencies below 1 kHz. This can cause a hearing loss up to 30 dB, which diminishes the ability to hear traffic noise, music and non-verbal sounds that are helpful to speech recognition and understanding.

The aim of the work has been to improve the experience of implanted patients that have suffered low frequency hearing loss as a result of RW stiffening.

Approach and Method

To fulfill the aim of the work, it was necessary first to confirm the magnitude of the hearing loss due to the stiffening, and then to assess the extent of mitigation of the loss by various remedies, with a view to finding an achievable remedy that would significantly reduce the loss or eliminated it. (Hearing loss occurring after implantation can result from a variety of causes [2].)

The approach taken has been that of deriving a model of the cochlea from well-established first principles. This gives assurance that the model can be used to cover different circumstances, without need to produce a new derivation to suit the circumstances of each use.

A graph signal processing model of the cochlea

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Abstract.

We take a novel graph approach to study the complex cochlear mechanics during music encoding for patients with normal hearing and hearing loss. Audiograms from AudGenDB, a pediatric clinical database, are used in tandem with the UR Ear 2020b simulation of inner hair cell voltage responses to different sound stimuli. The music stimuli that we test consisted of single pitches, single timbres, pitch combinations (chords), timbre combinations, and song excerpts. Graph signal processing is used to model the inner hair cell responses of each patient as a new data structure that we term a “cochlea graph.” By calculating various graph-theoretic properties, we show that these cochlea graphs carry distinguishing information based on a patient’s hearing loss diagnosis. Our results are poised for application to a data science approach for improving cochlear implant signal processing of music, in which these music-encoding cochlea graphs can be used to develop individualized signal processing solutions based on a user’s underlying hearing health.

INTRODUCTION

The cochlea is a spiral-shaped organ responsible for converting acoustic information into neural signals in the peripheral auditory system [1, 2]. Briefly, acoustic vibrations coming into the cochlea cause a traveling wave to move through the Organ of Corti, which contains approximately 12,000 outer hair cells and 4,000 inner hair cells (IHC). Often compared to a piano, the cochlea exhibits linear tonotopy: there is a one-dimensional spatial arrangement of positions where different frequencies of the incoming sound are processed along the cochlear spiral [3]. In other words, high-frequency components cause peak excitation in sensory cells near the base of the cochlea, low-frequencies cause peak excitation in cells near the apex, and mid-range frequencies cause peak excitation along a logarithmic spacing of cells in between. The excited IHCs release neurotransmitters to about 30,000 auditory nerve fibers, which then relay their signals to the central auditory system via the vestibulocochlear nerve.

For those who are deaf or severely hard-of-hearing due to hair cell damage, the linear tonotopy along the cochlear spiral has been the mathematical basis for multi-channel cochlear implant design and surgical placement [4]. The device filters incoming sound into frequency channels that excite 12–22 electrodes in a configuration that loosely mimics the tonotopy of the undamaged cochlea. The electrodes then each stimulate a group of underlying auditory nerve fibers. There is inevitably a large reduction in the frequency resolution due to device hardware limitations, which is one of the major hinderances for processing complex auditory signals such as music [5]. Additionally, individual differences in hearing performance for cochlear implant users are not well understood but are thought to be related to differences in underlying neural health. There is a need for improved music processing in cochlear implants. A data-based approach that incorporates individual users’ hearing health with a representation of cochlear mechanics that is more nuanced than linear tonotopy has high potential.

In working towards that goal, here we report on a graph signal processing model for encapsulating a patient’s hearing health information and the auditory biophysics of music processing into a new data structure that we term a patient’s “cochlea graph.” A graph in biology is a network comprised of units (nodes) that are linked to one another by means of anatomical connections or based on relationships in the functional activity of different units. The set of links between nodes define the graph’s topology. Signals on a graph are a set of values associated with the nodes, and thus graph signal processing is the application of concepts and techniques from classical signal processing to these graphs [6]. Furthermore, graph-learning methods can be used to determine the topology of a graph based on the observation of signals on the nodes [7]. In our cochlea graphs, we designate IHCs as nodes, the sets of IHC voltage responses to various musical stimuli are signals, and the links between nodes are learned based on the voltage signals.

Though we obtain the IHC voltages using an existing model of the human auditory periphery that incorporates linear tonotopy [8], our model encodes a more complex representation of cochlear mechanics (Figure 1). Indeed, the one-dimensional, piano-likeness of the cochlea appears in the IHC responses, the second layer in our model. The first layer contains information about how healthy or damaged each IHC node in the model is, thereby influencing how the

Simulation of Conductive Hearing Loss and Its Impact on Distortion-product Otoacoustic Emissions Using a Hydrodynamic Cochlea Model

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Abstract.

Distortion-product otoacoustic emissions (DPOAEs) are sound signals in the ear canal arising from nonlinear amplification of hydrodynamic oscillations in the cochlea. The analysis of the growth behavior of DPOAE pressure as function of stimulus level offers a quantitative assessment of the mechanical state of the cochlea. However, middle-ear dysfunction directly influences DPOAEs and their diagnostic accuracy. The present work simulates the impact of middle-ear dysfunction on DPOAEs using a hydrodynamic model of the human cochlea coupled to a middle-ear model for five frequencies $f_2 = 1$ to 4 kHz. DPOAEs in the ear canal are simulated by simultaneously solving the equations of motion representing the dynamics of the middle-ear and cochlea model in the time domain. Increasing the damping and stiffness of the annular ligament in the middle-ear model introduces conductive hearing loss (CHL) of various degrees. The changes in estimated distortion-product thresholds (EDPTs) and slopes of input-output (I/O) functions derived from the simulated DPOAE growth behavior are compared to changes in the middle-ear transfer functions (METFs). Pooled over all frequencies and degrees of CHL, the relative change of the METF at f_2 exhibits a linear dependency on the relative change of EDPT level while the relative change of the METF at the distortion-product frequency f_{DP} is linearly related to the relative change of the slope. The statistically significant linear relationships of the change in EDPT level and slope of the I/O functions with changes in the METF indicate that conductive hearing loss can be objectively quantified from the DPOAE growth behavior.

INTRODUCTION

Distortion-product otoacoustic emissions (DPOAEs) are sound signals in the ear canal that emerge from nonlinear amplification of hydrodynamic oscillations in the cochlea in response to two tones of frequencies f_1 and f_2 ($f_2/f_1 = 1.2$). DPOAEs at the cubic distortion-product frequency $f_{DP} = 2f_1 - f_2$ offer a quantitative assessment of the mechanical state of the cochlea [1], and, according to a widely accepted model [2], mainly consist of two components, a nonlinear-distortion and a coherent-reflection component. Semi-logarithmic DPOAE input-output (I/O) functions that plot the DPOAE amplitude as function of stimulus level L_2 enable the computation of estimated distortion-product thresholds (EDPTs), which have been shown to predict behavioral thresholds with high accuracy [3] when accounting for wave interference between the nonlinear-distortion and coherent-reflection components [4].

However, middle-ear dysfunction directly influences DPOAEs and their diagnostic accuracy since conductive hearing loss (CHL) reduces both the forward propagation of the acoustic stimuli and the backward transmission of the DPOAEs. For example in neonates, middle-ear dysfunction due to amniotic fluid hampers the identification of cochlear disorders using otoacoustic emissions [5]. CHL has been shown to yield an increase of EDPT accompanied with a reduced slope in the I/O function [5]. Additionally, changes in middle-ear transfer function (METF) result in an altered optimal relationship between the stimulus levels L_1 and L_2 that facilitate DPOAE generation in the cochlea [6], further decreasing the amplitude of the DPOAE response.

Recently, the computation of I/O functions was refined using a least-squares fit approach to reproduce the DPOAE growth behavior from so-called DPOAE level maps, which sample the DPOAE growth behavior at multiple stimulus-level combinations in the L_1, L_2 space [7]. The derivation of ridge-based I/O functions from these model level maps provide EDPTs with high precision but without the need of predefined optimal stimulus-level pairs, therefore, presenting a promising method to acquire DPOAEs in the presence of CHL. The present work simulates the growth behavior of the nonlinear-distortion component, i.e. without an interfering reflection component, in the time domain using a hydrodynamic model of the human cochlea coupled to a middle-ear model [8] for various degrees of CHL.

Bone Conduction Stimulation of the Temporal Bone with the Inner Ear: a Finite Element Study

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Abstract. A numerical model of the human temporal bone with a precisely reconstructed cochlea was used to investigate bone conduction stimulation applied on the otic capsule. A passive cochlear model was used. Validation of the cochlea was based on the experimental data. The round window membrane and cortical bone were assumed as viscoelastic, with the storage and loss moduli defined as functions of frequency. Other solid tissues were modelled as linear isotropic, and the perilymph fluid was assumed as viscous and compressible. The model was subjected to harmonic analysis in the frequency range from 0.2 to 10 kHz. The bone conduction stimulation was applied as a harmonic force to the mass attached to the otic capsule surface. The boundary of the temporal bone was fixed on the sutures between the adjacent skull bones. The aim of the study was to examine: 1) the type of boundary condition applied on the surface of the petrous part of the temporal bone adjacent to the petro-occipital synchondrosis, 2) the value of the surface density used in the model to include the mass of soft tissues in the vicinity of the temporal bone, assumed as uniformly distributed on its outer surface (inside and outside the skull). Two conditions related to the mobility of the stapes were considered. To assess effects of the above-mentioned factors, amplitude and phase of vibrations obtained from numerical simulation were used, including the volume displacement on the round window membrane, displacements on the basilar membrane and at the spiral lamina along the cochlea, and vibration of the promontory bone at the edge of the round window. The values of forces needed for bone conduction stimulation corresponded to those used in previous experimental studies on cadavers. The results from numerical analysis were compared with the experimental data.

INTRODUCTION

Bone conduction implants placed in the skull surface have been known for many years and used in clinical practice, but new sites of stimulation, such as the otic capsule, are also being investigated [1]. The closer to the cochlea, the less energy is needed for stimulation [2]. Research on bone conduction (BC) can be conducted using experimental tests [3, 4] and the models using electro-mechanical analogy [5] or finite element (FE) method [6, 7].

In the case of BC stimulation of the FE model of the temporal bone, some parameters seem to be important, such as the associated mass of soft tissues and cerebrospinal fluid vibrating with the bone, the effect of inertia of the middle ear ossicles [5] and the type of support applied at the bone boundary. These parameters can affect vibration amplitudes on the flexible parts of the cochlea, such as the basilar membrane (BM) and the round window membrane (RW) but can also affect vibrations of the cochlear promontory bone in the proximity of the RW. In this study, the type of support at petro-occipital synchondrosis (POS), mobility of the stapes, and soft tissues mass were investigated to help validate the FE model based on the experimental data.

METHODS

The subject of the analysis was a three-dimensional model of the temporal bone, previously published in [7]. The FE model (Fig. 1) had well-reconstructed structures of cortical and trabecular parts and included the cochlea, semicircular canals, annular ligament, RW membrane, BM, spiral lamina (SL), spiral ligament, perilymph fluid, helicotrema, and a titanium cylinder representing the bone conduction implant, which was attached to the otic

Difference in bone conduction analysis between a head model and an isolated cochlea model

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Abstract. The bone deformation and the inertia from cochlear fluid or middle ear (ME) ossicles are generally considered as two significant components causing bone conducted (BC) hearing among several components. In order to clarify the BC hearing mechanism and the important components, finite element (FE) models have been widely used. The FE model can be divided into two types, (1) isolated cochlea model composed of ME and cochlea including basilar membrane (BM) and (2) head model including the isolated cochlea structure. Using the two types of the FE model, specific pathological condition such as otosclerosis was simulated and the results were compared with clinical data. If we assume the BC hearing ability is proportional to the BM velocity in the FE simulation, the bone deformation and the inertia components were still more important factors to cause the BC hearing than cartilage near an ear canal or pressure from cerebrospinal fluid. However, when the simulated results were reasonably consistent with the clinical data, the inertia effects on BC hearing were magnified in the isolated cochlear model whereas the bone compression effect was intensified in the head model although the bone compression was not the most significant factor for BC hearing. The results suggest that care is needed not only in the analysis of BC experiments using a temporal bone but also in applying the results to patients directly.

1. INTRODUCTION

Temporal bone or cadaver head has been generally used in experimental bone-conducted (BC) hearing analysis, and the experiments have contributed to understanding of BC hearing mechanism. For example, Stieger *et al.* (2018) used the temporal bones to measure promontory velocities and intracochlear pressure which are important cochlear responses to elucidate the BC hearing mechanism¹. Specifically, they varied the method to hold the temporal bones and investigated the effect of the holding method on BC responses represented by promontory velocities. Stenfelt *et al.* (2002) have measured the motion of the umbo and stapes footplate during BC stimulation induced by shaker using the temporal bones². In the result, they showed that the stapes footplate is closely coupled to the temporal bone more than the malleus. On the other hand, there have been several experiments to measure BC responses using cadaver heads. Eeg-Olofsson *et al.* (2018) measured mechanical point impedance and promontory velocities from cadaver heads to clarify the BC stimulation position causing the largest cochlea response³. Furthermore, the study was expanded by measuring cochlea promontory velocity in living human, and concluded that the average promontory

Finite-element modeling of the effect of superior canal dehiscence on intracochlear pressures in bone conduction

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Abstract. Superior canal dehiscence (SCD) is a pathological opening of the bone encapsulating the superior semicircular canal, causing various vestibular and auditory symptoms. One of the most debilitating symptoms associated with SCD is bone conduction (BC) hyperacusis, manifested as awareness of self-generated sounds (one's own heartbeats, voices, joint movements, eye movements) and increased sensitivity to certain external sounds and vibrations (machinery, noise experienced inside an automobile) that can be heard via BC. While BC hyperacusis is increasingly recognized by clinicians and researchers, how SCD enhances BC sensitivity is not well understood.

To better understand the underlying mechanism, we simulated the effect of SCD on intracochlear sound pressures in BC using a finite element (FE) model of a human ear. SCD was modeled by creating an opening in the bony wall in the middle of the superior canal arch. The model was first validated with air conduction (AC) excitation. BC excitation was subsequently simulated by applying rigid-body vibrations to the model along the stapes piston-motion direction and the other two orthogonal directions. The BC-evoked intracochlear sound pressures in scala vestibuli (P_{SV}) and scala tympani (P_{ST}) at the basal cochlea and the pressure difference ($P_{DIFF}=P_{SV}-P_{ST}$) were simulated under normal and SCD conditions.

The comparison between the simulated and measured intracochlear pressures in AC suggests that the damping of the cochlear channels (scala vestibuli and scala tympani) in the current model is lower than that of a real ear. In BC, the model predicts that SCD increases P_{DIFF} – the cochlear input drive – for all three excitation directions, indicating an increase in BC sensitivity. However, the simulated changes in P_{SV} and P_{ST} due to SCD in BC are inconsistent with our previous measurements and are highly dependent on the excitation direction. The discrepancy between the simulated results and the experimental data may stem from this direction-dependent nature of the SCD effect and insufficient damping of the cochlear fluid channels.