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Effect of Metabolic Presbycusis on Cochlear Responses: A Simulation Approach Using a
Physiologically-based Model

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Abstract

In the presented model electrical, acoustical, and mechanical elements of the cochlea are explicitly integrated into a signal transmission line where these elements convey physiological interpretations of the human cochlear structures. As a result, this physiologically-motivated model enables simulation of specific cochlear lesions such as presbycusis. The hypothesis is that high-frequency hearing loss in older adults may be due to metabolic presbycusis whereby age-related cellular/chemical degenerations in the lateral wall of the cochlea cause a reduction in the endocochlear potential. The simulations quantitatively confirm this hypothesis and emphasize that even if the outer and inner hair cells are totally active and intact, metabolic presbycusis alone can significantly deteriorate the cochlear functionality. Specifically, in the model, as the endocochlear potential decreases, the transduction mechanism produces less receptor current such that there is a reduction in the battery of the somatic motor. This leads to a drastic decrease in cochlear amplification and frequency sensitivity, as well as changes in position-frequency map (tuning pattern) of the cochlea. In addition, the simulations show that the age-related reduction of the endocochlear potential significantly inhibits the firing rate of auditory nerve which might contribute to the decline of temporal resolution in the aging auditory system.

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I. INTRODUCTION

Age-related hearing loss (ARHL) is currently one of the top three most widespread chronic health issues among individuals over 65 years old (Gordon-Salant, 2010). As the life expectancy is rapidly increasing globally, ARHL will impose even more social and economic costs on both individuals and the welfare system. In spite of this, its underlying mechanisms are not entirely known; moreover, today's regular clinical tests do not clearly differentiate the physiological origins of the inner-ear pathologies (Stenfelt and Ronnberg, 2009).

It is strongly believed that many major features of human auditory system such as compression, dynamic range, active amplification, frequency discrimination, and temporal coding are firmly attributed to functionality of the cochlea (Moore, 2003), a spiral-shaped cavity in the inner ear. Several human and animal studies have suggested that ARHL may substantively take root from age-related metabolic/cellular degenerations in the lateral wall of the cochlea and especially the stria vascularis (Schmiedt *et al.*, 2002; Mills *et al.*, 2006; Lang *et al.*, 2010). This leads to decline of the electrical potentials inside the mammalian cochleae, a medical condition known as metabolic presbycusis.

The stria vascularis is a vascularized tissue at the lateral wall of the cochlea which injects the potassium ions (k^+) into the scala media (SM). This is directly linked to the existing 89mV endocochlear potential (EP) along the human cochlear duct (Slepecky, 1996). Most of the lateral wall cells are fibrocytes. Because of the age-related changes in these cells, the k^+ recycling is impaired and is not capable of maintaining the original EP anymore. One candidate for being an underlying metabolic cause of such age-related degenerations is the trans-membrane protein Cadherin (calcium-dependent adhesion). Trowe *et al.* (2011) showed that age-related loss of E-cadherin in wild mice interferes with the architectural maintenance of the basal and marginal fibrocystic cells which leads to loss of stria vascularis integrity and eventually a notable decrease of the EP inside the cochlea.

Models have been exploited as powerful analytical tools to sharpen our understanding of various mechanisms and systems. Over the last five decades, several auditory filter models have been developed to analyse hearing-related mechanisms and apply to various psychoacoustical measures of the auditory system. These computational models classically exploit different types and combinations of filters such as gammatone filters including all-pole versions and the gammachirps [e.g. (Irino and Patterson, 2001)] to mimic the processing stages of the auditory system. As a matter of fact, the more recent auditory filter models are capable of reproducing several key features of the auditory system such as tuning, critical bands, compression and frequency- and level-dependent amplitude responses [see (Meddis and Lopez-Poveda, 2010) for a review]. Moreover, these computational models are very useful for being incorporated within advanced machine hearing-systems. However, for such models the strategy is to mimic the over-all psychoacoustic outcomes by means of filter banks without directly linking these outcomes with fundamental biophysical details and undergoing cellular subprocesses.

In the last decade or so, the evolution of measurement techniques have led to experimental data on cell-level structural details and their corresponding mechanisms inside the inner ear (Cooper, 1998; de Boer and Nuttall, 2000; Rubles and Ruggero, 2001; Nowotny and Gummer, 2005; Ghaffari *et al.*, 2007; Chen *et al.*, 2011). Based on these explicit findings, new models have been developed to either explain functionality of specific parts of the mammalian cochlear system (Lopez-Poveda and Eustaquio-Martin, 2006; Liu and Neely, 2009) or to simulate the entire cochlear responses (Ramamoorthy *et al.*, 2007). The difference between these newer models and the classic filter models is that these newer models comprise more fundamental biophysical parameters such as electromechanical properties of the cochlear structures rather than solely computational filters.

The physiologically-based model presented here belongs to this latter generation of auditory models. The model incorporates passive vibrations; nonlinear transduction of the hair cells, the outer hair cell's (OHC's) somatic motor, as well as the tectorial membrane (TM), shearing and vibration to neural conversion at the inner hair cells (IHCs). The input to the model is the sound-induced acoustical vibration of the stapes and the output of the model is the neural activity on the afferent auditory nerve (AN). The current model is developed with the aim of simulating how an age-related degeneration of the EP (metabolic presbycusis) modifies the frequency characteristics and the temporal features of the cochlear responses.

According to the simulation results, the model overcomes the issue of the OHC's body time-constant meaning that the somatic motor is capable of supplying power at frequencies way above the cut-off of the OHC basolateral membrane. Besides, the model incorporates longitudinal coupling whereas most of the 'classical' models assume that cochlear structures are longitudinally de-coupled except for the energy propagation through the fluid, to obtain simplicity (Ghaffari *et al.*, 2007). Here however, the structural coupling is included and its significant influence on the amplification and tuning pattern of the cochlea is discussed.

The human cochlea is totally buried in petrous bones which makes it rather inaccessible for *in vivo* measurements. However, experimental data on the guinea-pig and gerbil cochleae are partly available (de Boer and Nuttall, 2000; Cooper, 1998; Schmiedt, 2002). Therefore, wherever it is necessary, the electromechanical parameters of the model are modified to those of the guinea-pig to enable the quantitative comparison between these experimental data and the predictions of the model.

II. MODELING METHOD

Inside the SM lies the organ of Corti which is sandwiched between two cellular matrices, the basilar membrane (BM) and the tectorial membrane (TM) (Nam and Fettiplace, 2011). An airborne sound pressure field is transmitted via the outer and middle ear to the

inner ear. It causes the stapes to vibrate resulting in a travelling wave along the organ of Corti propagating from the base towards the apex (Bekesy, 1960). The organ of Corti rests on the BM; The displacement on the BM deflects the OHC's stereocilia, opens the mechanoelectrical transduction (MET) channels and eventually triggers an active electro-mechanical element –the OHC- which stretches against the reticular lamina (RL) on one side and the BM on the other side (Lu *et al.*, 2009). This molecular force generator is known as the somatic motility.

The somatic motor boosts the vibrations along the cochlear duct by pumping active force and energy into the transmission line. These boosted vibrations are transmitted to the IHCs via RL-TM shearing and are converted to changes in receptor potentials that instantly modulate neurotransmitter release at synapses on the auditory nerve afferents towards the central auditory cortices (Slepecky, 1996).

----- Please Insert Figure 1 here-----

As depicted in Fig. 1, the entire organ of Corti is modeled to consist of 'N' discrete partitions along the cochlear duct extending from the base (on the left) to the apex (on the right) according to the lumped element modeling approach. Each vertical branch of the transmission line in Fig. 1 represents a single cochlear partition. Each partition comprises three passive mechanical loads: BM, RL and TM. The OHCs are suspended between the RL and the BM; and the OHC motile forces (depicted by f_{OHC} in Fig. 1) are represented by a pair of forces inside the organ of Corti which on a cycle-to-cycle basis alternately pull the RL and the BM (via Dieters cells) together and push them apart. For simplicity, the Dieters supporting cells have been considered as incompressible masses here.

As illustrated Fig. 1, the EP controls the functionality of both OHCs and IHCs by providing them with the necessary supply voltage. Thus, a reduction of the EP modifies the functionality of both OHCs and IHCs and consequently reshapes the frequency characteristic

and temporal features of the cochlear response. Figure 2 illustrates a single cochlear partition along the organ of Corti. This i^{th} partition consists of two passive loads (BM and RL) and an active electro-mechanical component (OHC) acting between them.

----- Please Insert Figure 2 here-----

A. The Passive Loads

In order to explain the vibrations, each single passive mechanical load is modeled by a viscous ‘mass-spring-damper’ combination. Thus for a typical i^{th} partition, the BM is represented by its mass (Mb_i), its stiffness (Kb_i) and its damping coefficient (Rb_i). Similarly, RL and TM are modeled by (Mr_i , Kr_i , Rr_i) and (Mt_i , Kt_i , Rt_i), respectively. Here, only the shearing impedance of the TM is included and the bending impedance has been neglected.

The OHC’s body is similarly modeled by a passive ‘mass-spring-damper’ (M_{OHC_i} , K_{OHC_i} , R_{OHC_i}). For simplicity, the OHC’s molecular motor is assumed to be centered in the middle of the OHC. Therefore, the OHC’s mass (M_{OHC_i}) can be equally distributed between the two loads, RL and BM. The values of these mechanical parameters are presented in Table I of Appendix A.

B. Active Processes

To explicitly investigate the active force generation inside the cochlea a 3-stage system is introduced in Fig. 3. The corresponding sub-processes are: 1) The stria vascularis: the biological battery. 2) The MET: the driver of OHC’s molecular motor. 3) The somatic motility: the OHC’s molecular motor.

----- Please Insert Figure 3 here-----

1. *Stria Vascularis: The Biological Battery of the Somatic Motor*

The stria vascularis continuously pumps potassium ions (k^+) into the cochlear endolymph of SM (Slepecky, 1996). The flow of these electrically-charged ions (k^+) directly

contributes to the existing potential difference of 89mV between SM and scala tympani (ST) observed in a healthy human cochlea.

The stria vascularis as a vascularized cellular body can be represented by a resistance, R_{st} . The electromechanical gradients driving the flow of the K^+ ions into the SM is represented by an ideal voltage source (battery), EP , and the fluid resistance inside the SM is denoted by R_{sm} , as shown in Fig 3. This biological battery supports the cochlear system by providing the MET channels of both the OHCs and the IHCs with the current (I_{sat}). Thus, EP is illustrated as a controller of the OHC and the IHC blocks in Fig. 1.

2. MET: The Driver of the Somatic Motor

There are approximately 10 000 outer hair cells per human cochlea and there may be up to 200 MET channels per cell (Fettiplace and Hackney, 2006). The key element of existing models of transduction is that the MET channels are opened by the applied elastic forces, the ‘gating springs’, which are stretched when the hair bundle (HB) is swerved. The MET channel is a cation channel most selective for Ca^{2+} (Fettiplace and Hackney, 2006). The opening of the MET channels results in release of charged Ca^{2+} ions which induce a receptor current (i_r). This receptor current, in turn, triggers the somatic motor. Thus the OHC MET mechanism can be regarded as the ‘driver’ for the somatic motor and the whole cochlear amplifier.

----- Please Insert Figure 4 here-----

The MET channels open in approximately 100 microseconds (fast adaption) generating a peak current(Fettiplace and Hackney, 2006); the channels then re-close slowly (slow adaption) and the receptor current decays to a non-zero residual level (I_{res}) with a specific time constant. The relation between RL displacement (Δx_r) and the peak current induced by opening of the MET channels is estimated by a first-order Boltzmann function (Slepecky, 1996). Equation (1) gives the curve shown in Fig. 4(a).

$$i_r = \frac{I_{sat}}{1 + \left(\frac{I_{sat}}{I_{res}} - 1\right) \cdot e^{-Z \cdot \Delta x_r}} \quad (1)$$

According to Eq. (1), the shape of the MET curve is determined by three physiological parameters I_{sat} , I_{res} and Z . The saturation current (I_{sat}) is the maximal receptor current inside the SM which is provided by the ‘physiological battery’ of the stria vascularis, as previously described. The non-zero residual current (I_{res}) is an off-set parameter for the MET curve and is measured in some mammals to be between 3% to 7% of the saturation current [(Holt et al., 1997), Fig. 3]. The parameter Z denotes the instantaneous potential difference between the opened and closed states of the MET channels (Patuzzi and Moleirinho, 1998).

These three parameters may differ from basal to apical regions leading to various MET curves; however, such variations are not considered in the current model. In other words, the MET curve seen in Fig. 4 is assumed here to apply to all positions along the cochlear duct. It has been shown that using a second-order Boltzmann function (a three-state MET channel) results in more sensitivity around the resting position and thus can be a more realistic model of the MET mechanism (Slepecky, 1996). However, here a first-order Boltzmann is used to keep the parameters to only three biological parameters. The values for these MET parameters are presented in Table III of Appendix A.

Figure 4(a) illustrates the Boltzmann function [Eq. (1)] for two conditions: 1. a healthy cochlea where the stria vascularis is capable of recycling and pumping sufficient amount of potassium ions in order to maintain the maximum EP of 89 mV (solid lines), 2. an impaired cochlea where the EP has degenerated to half of its maximum (EP=44.5 mV) as a result of age-related metabolic failures in stria vascularis. When the EP is decreased to its half, the saturation current (I_{sat}) in Fig. 3 is decreased to its half as well. According to Eq. (1) this reshapes the MET curve [Fig. 4, dashed lines].

Equation (1) includes only information about the peaks of the receptor current known as the ‘fast adaption’ and not the whole process. To also include the ‘slow adaption’ concept

above (re-closure of the MET channels) as well, Eq. (1) should be combined with Eq. (6), described shortly.

3. OHC Motility: the Somatic Motor

The experiments have demonstrated that individual OHCs, dissociated from the cochlea and then electrically stimulated, shorten in response to depolarization and lengthen for hyperpolarization (Fettiplace and Hackney, 2006). Because of the high speed of their mechanical response, these cells can theoretically alter their length in synchrony with the incoming acoustical stimulus for the frequencies spanning the entire auditory range, pulling/pushing the RL and the BM and thereby pumping energy into the transmission line of Fig. 1. This molecular motor is modeled here as proposed by Liu and Neely (2009). The OHC's membranous body has a conductance G and capacitance C ; thus the receptor current (i_r) induces a receptor voltage (V_r). The somatic motor is believed to be driven by this receptor voltage (Liu and Neely, 2009).

The piezoelectric component [the dashed box in Fig. 3] represents the electromechanical interaction whereby the gating current i_d is converted to a mechanical contraction force (f_{OHC}) with the piezoelectric transform ratio of T . This leads to a mechanical velocity ($\dot{x}_o$) acting over the output mechanical load impedance (Z_{load}), which consists of the RL from one side and the BM from the other side. If the contraction of the OHC (x_o) is the output of the somatic motor, the nonlinear circuit shown in Fig. 3 can be solved in the time domain according to Eq. (2) below. The values for the parameters of this piezoelectric model are presented in Table II of Appendix A.

$$x_o(t) = i_r(t) \cdot \frac{T \cdot \left(Z_{load} \cdot \int \frac{1}{c_g} dt \right)^{-1}}{\frac{d \left[\left(G + \frac{dC}{dt} \right) + \left(\int \frac{1}{c_g} dt + Z_{load} \right) \right]}{dt}} \quad (2)$$

As shown in Fig. 2, the OHC contraction force (f_{OHC}) pulls/pushes two parallel mechanical loads in relation to each other: 1. a BM load (via path 1) with an impedance of $Z_{BM} = \left(Mb + \frac{M_{OHC}}{2}\right) \cdot j\omega + R_b + \frac{K_b}{j\omega}$ and 2. a RL load (via path 2) with an impedance of $Z_{RL} = \left(Mr + \frac{M_{OHC}}{2}\right) \cdot j\omega + Rr + \frac{Kr}{j\omega}$ where j denotes the imaginary unity ($\sqrt{-1}$) and ω is the angular velocity. The load impedance, Z_{load} , can then be written according to Eq. (3).

$$Z_{load} = Z_{BM} || Z_{RL} = \frac{Z_{BM} \cdot Z_{RL}}{Z_{BM} + Z_{RL}} \quad (3)$$

C. Inner Hair Cells (IHCs)

The IHCs convert sound-induced motion of the RL (via TM) into changes in receptor potentials that instantly regulate neurotransmitter release at synapses on the auditory nerve afferents (Fettiplace and Hackney, 2006). One of the most poorly understood details of cochlear mechanics is how RL motion leads to deflection of IHC HB and finally excitation of the auditory nerve fibers. The common conception is that IHC excitation is due to shearing between RL and TM (Slepecky, 1996); however, recent works indicate that deflection of the OHC HB changes the RL-TM space (the gap between RL and TM) and produces a fluid flow in the gap that bends the IHC HB (Li *et al.*, 2011).

Nowotny and Gummer (2005) also confirm this by showing the phase difference between the TM and the RL which results in a stimulus-dependent modulation of the width of the subtectorial gap leading to pulsating of the subtectorial fluids. They conclude that instead of the RL-TM shearing, this subtectorial flow may directly couple somatic electromotility of the OHCs to the HB of the IHCs. For simplicity, such a subtectorial flow is neglected in this work and the classic ‘RL-TM shearing’ view is adopted for the current model.

Ninety-five percent of the auditory nerve fibers innervate the IHCs (Slepecky, 1966); they carry the temporal information necessary for auditory processing by the central nervous system (Slepecky, 1996). The IHCs lack prestin and, therefore, any associated active somatic

contractility; they are believed to function as sensory elements (Fettiplace and Hackney, 2006). The peak receptor current (i_r) induced by opening of the IHC MET channels as a function of HB displacement is also estimated by a Boltzmann function similar to that of the OHC MET. However, two of the three physiological parameters (I_{res} and Z) differ from that of the OHC MET. These two parameters were estimated from measurements on the IHC receptor currents in the gerbil cochlea [(Jia *et al.*, 2007), Fig. 1]. Those measurements have been carried out in both apical and basal turns of the cochlea leading to two different MET curves; here such variations have been neglected for simplicity and the averaged parameters are generalized for the entire cochlear length [Fig. 4(c)].

D. The Transmission Line, Coupling and the Loading Effect

Cochlear models typically assume that BM is longitudinally uncoupled. Mathematically, the decoupled BM is very attractive to modelers; it allows the equations that describe the motion of a single partition to be independent of the equations that describe the motion of other adjacent partitions along the cochlear duct. As a result, most cochlear models today are based on locally reacting representation of the discrete cochlear partitions, whereby the cochlear partitions are assumed to be longitudinally uncoupled except for energy propagation through the fluid (Ghaffari *et al.*, 2007).

Naidu and Mountain (2001) have quantified longitudinal coupling along the BM of gerbils. Besides, Meaud and Grosh (2010) have also introduced a 3-dimensional model of the cochlea and simulated the effect of TM longitudinal coupling on the cochlear response; they demonstrated that structural longitudinal coupling is non-negligible.

In the current model, the longitudinal coupling along the organ of Corti is modeled by springs and dampers between the cochlear partitions along the transmission line (Kh_i, Rh_i in Fig. 1). This approach is very similar to the one-dimensional model of [Naidu and Mountain (2001), Fig. 7], except that, here the longitudinal damping (Rh_i) is also included. By adding

the longitudinal coupling (Kh_i, Rh_i) in the transmission line of Fig. 1, the i^{th} cochlear partition has an equivalent impedance of $(Z_{passive})_i$ according to Eq. (4) below.

$$(Z_{passive})_i = Mb_{eff_i} \cdot j\omega + Rb_{eff_i} + \frac{Kb_{eff_i}}{j\omega} + [(Z_{passive})_{i+1} \parallel (Rh_i + \frac{Kh_i}{j\omega})] \quad (4.a)$$

$$Mb_{eff_i} = Mb_i + M_{OHC_i} + Mr_i + Mt_i \quad (4.b)$$

$$Kb_{eff_i} = Kb_i + K_{OHC_i} + Kr_i + Kt_i \quad (4.c)$$

$$Rb_{eff_i} = Rb_i + R_{OHC_i} + Rr_i + Rt_i \quad (4.d)$$

Where $Mb_{eff_i}, Kb_{eff_i}, Rb_{eff_i}$ are respectively the effective acoustical mass, stiffness and damping of i^{th} partition resting on the BM. The term $(Z_{passive})_{i+1}$ denotes the passive impedance loaded to the partition by the proceeding $(i + 1)^{th}$ partition via the longitudinal coupling. This phenomenon, addition of the impedances of proceeding partitions on the previous ones, is referred to as loading effect.

The passive system is solved by converting it to its equivalent electrical analogy, as described by Saremi and Stenfelt, (2011). The longitudinal components (Rh_i and Kh_i) are assumed to be fractions of the partition's effective stiffness and damper resting on the BM. The fraction is determined so that Eq. 4 above gives characteristic frequencies (CFs) similar to the position-frequency map of a passive cadaver cochlea [(Bekesy, 1960), Fig. 11-43].

E. Linearization and Small-Signal Analysis

The nonlinearity in this cochlear model originates from two different sources: 1) the MET mechanism [as seen in the curves of Fig. 4], and 2) the OHC's gating capacitance (c_g) in the piezoelectric circuit of the somatic motility [Fig. 3].

The gating capacitance (c_g) depends on the density of the motor molecules (prestin) in the OHC lateral membrane and is decreased as the cell is hyperpolarized (Santos-Sacchi, 1991). It was argued by Pattuzi (1996) that linearization of c_g is mathematically legitimate as long as the membrane potential (V) does not fluctuate more than tens of millivolts. Liu and

Neely (2010) showed in their simulations that changes in membrane potential (V) as a result of stimuli was no larger than 4 mV for single tones at a high intensity of 110 dB SPL at the frequency range of 0.125 to 8 kHz. Also, they showed that with typical stiffness-dominated loads, the nonlinear gating capacitance can be assumed linear.

1. Small-signal Analysis of the MET

A non-linear system such as the cochlea can be analyzed in time domain only, withholding the analysis of the cochlear frequency response. Fortunately, the MET curve created by Eq. (1) [seen in Fig. 4(a)] can be linearized using a small-signal approach whereby the linearization is formed around a specific point (operating point) on the MET curve. The linearization is regionally valid for small excursions around this operating point [the small line in Fig. 4(a)]. This enables further investigation and simulation of the cochlear response in the frequency domain at different sound intensities as long as the fluctuation in the sound intensity is small enough. As the small-signal model takes different operating points on the MET curve, the linear relation between the displacement and the receptor current around that operating point is given according to Eq. (5) below:

$$i_r = \alpha_d \cdot x_{rl} \quad (5)$$

Here x_{rl} is the RL displacement and α_d denotes the first derivative (slope) of the MET curve at the operating point [see Fig. 4(b)]; it also represents a displacement-to-current gain. Experiments have demonstrated that the receptor current has a fast adaption to a step deflection of the HB (Fettiplace and Hackney, 2006); the peaks of the receptor current corresponding to the fast adaption were estimated by Eq. 1 and were shown in Fig. 4. However, there is a slow adaption as the MET channels re-close. Thus, the receptor current has a low-pass filtered response to a velocity impulse which has not been included in Eq. (5); this requires addition of an extra term leading to Eq. (6) below (Liu and Neely, 2010).

$$i_r = \alpha_d \cdot x_{rl} + \alpha_v \cdot \left(\frac{dx_{rl}}{dt} \right) \rightarrow I_r(j\omega) = X_{rl}(\alpha_d + \alpha_v \cdot j\omega) \quad (6)$$

Where the term $\frac{dx_{rl}}{dt}$ is the RL velocity and α_v denotes a velocity-to-current gain corresponding to MET's sensitivity to RL velocity (Liu and Neely, 2010). An interpretation of Eq. (6) is that the receptor current is sensitive to the velocity of the HB as well as to its displacement. As emphasized by Lu *et al.* (2009), a velocity-sensing HB accounts for more features of cochlear amplification than a displacement-sensing HB only. According to Eq. (6), i_r can be written in frequency domain as $I_r(j\omega)$.

Another interpretation of Eq. (6) is that it introduces a linear time-invariant (LTI) system with a time constant of $\frac{\alpha_v}{\alpha_d}$ modeling the 'gating spring'. The MET current is induced in response to a displacement step of the HB (fast adaption) [the peak currents are estimated by Eq. (1)] then the MET channels are slowly reclosed and the induced current is adapted with a sub-millisecond time constant (slow adaption). The experiments in-vivo showed a time constant of 230 μ s [Fettiplace *et al.* (2005), Fig. 2(B)] for mice. However for humans, as Liu and Neely (2009) proposed, we used a tenfold larger time constant to calculate α_v here.

2. Frequency Response of a Single Cochlear Partition

The passive mechanical components of the transmission line (masses, springs and dampers) are all linear components. Therefore, the frequency response of a single passive cochlear partition [H_{trig} in Fig. 2(b)] , defined as its displacement with regards to the displacement of the previous partition, can be calculated using Eq. (4.a).

An important benefit of linearization is that the OHC somatic motor can be regionally characterized by a transform function $H_o(j\omega) = \frac{X_o(j\omega)}{X_{rl}(j\omega)}$ as well; which relates OHC contraction (X_o) with the RL displacement (X_{rl}). This transfer function can be regarded as an open-loop displacement gain produced by the OHC.

Converting Eq. (2) from time domain into the frequency domain and inserting $I_r(j\omega)$ from Eq. (6) in it, gives the following equation (Liu and Neely, 2010).

$$H_o(j\omega) = \frac{X_o(j\omega)}{X_{rl}(j\omega)} \rightarrow H_o(j\omega) = \frac{T(\alpha_d + \alpha_v j\omega)/c_g}{j\omega \cdot c_g + (G + j\omega C)[1 + T^2 \cdot c_g(K + j\omega \cdot Z_{load})]} \quad (7)$$

Since the OHC somatic motor pulls BM and RL towards each other, RL and BM are two parallel loads [Eq. (3)]; the OHC contraction is distributed between them according to following Eq. (8.a) and Eq. (8.b).

$$H_{o_{BM}}(j\omega) = H_o(j\omega) \cdot \frac{Z_{RL}}{Z_{BM} + Z_{RL}} \quad (8.a)$$

$$H_{o_{RL}}(j\omega) = H_o(j\omega) \cdot \frac{Z_{BM}}{Z_{BM} + Z_{RL}} \quad (8.b)$$

Here $H_{o_{RL}}(j\omega)$ denotes the amount of OHC contraction which is added to the RL displacement (path 2 in Fig. 2) and $H_{o_{BM}}(j\omega)$ denotes the amount of OHC contraction which contributes to boosting the vibration on the BM (path 1 in Fig. 2). Since the BM's impedance is larger than the RL's impedance ($Z_{BM} > Z_{RL}$), the OHC contraction boosts the RL displacement more than it does the BM displacement [$H_{o_{RL}}(j\omega) > H_{o_{BM}}(j\omega)$] according to Eq. (8.a) and Eq. (8.b). This is consistent with laser-Doppler-vibrometer measurements by Nowotny and Gummer (2005) which indicate that the RL vibration pattern under the influence of the OHC somatic electromotility is much greater than the vibration on the BM.

Liu and Neely (2009) simplify Eq. (3) to $Z_{load} = Z_{RL}$; as a result, the longitudinal feed-forward on the BM (path 1 in Fig. 2) is ignored. It will be shown [Fig. 9(a) and Fig. 9(b)] that although the boosted displacement on BM [$H_{o_{BM}}(j\omega)$] is relatively small to that of RL [$H_{o_{RL}}(j\omega)$], such a simplification ignores some significant features of the cochlear amplifier.

According to Fig. 2, the frequency response (H) of a single cochlear partition is calculated by Eq. (9) below. Equation (9) formulates the feed-forward nature of the OHC's contraction force on the RL vibration pattern. Equations (7-9) are valid as long as the variations in stimuli around the operating point are small enough.

$$H = H_{trig} \cdot [1 + H_{o_{RL}}(j\omega)] \quad (9)$$

3. Frequency Response of a Cochlear Partition as a Part of the Transmission Line

So far, the linear approximation for a single cochlear partition has been made and its transform function (H) has been calculated leading to Eq. (9). However, since the vibration is assumed to propagate from the base towards the apex (Bekesy, 1960) along a transmission line, the cochlear frequency response at any specific location along the cochlea with respect to the base (RL/base velocity ratio) must be obtained by computing all the prior partitions in series. Thus, the frequency response of the i^{th} partition is calculated by multiplying all the frequency responses of the prior partitions leading to Eq. (10.a) and Eq. (10.b) below. The notations are similar to those illustrated in the block diagram of Fig. 2(b).

$$(H_{trig})_i = (H_{trig})_{i-1} \cdot [1 + (H_{o_{BM}})_{i-1}] \cdot (H_{passive})_{i-1} \quad (10.a)$$

$$H_i = (H_{trig})_i \cdot (H_{o_{RL}})_i \quad ; \quad i = 1, \dots, N \quad (10.b)$$

III. SIMULATION RESULTS

The simulations of the linear model are implemented in MATLAB where the number of cochlear partitions is arbitrary and is here chosen to 100 ($n=100$) as a trade-off between computation time and resolution.

All the presented results are linearly calculated at the sharpest point on the MET curve [Fig. 4(a), the small lines] corresponding to a 300 nm displacement of the RL (where $\alpha_d = 1.37 \times 10^{-3}$).

A. Simulations of Cochlear Amplification

Figure 5(a) illustrates the RL/base velocity ratios according to the transfer function H at three locations along the cochlea (30%, 50% and 70% of the cochlear length from the base) and it illustrates the hundredfold amplification of vibrations as a result of the cochlear amplification. The CF of the curves decreases from base to apex and the cochlear amplification becomes less, near the apex.

----- Please Insert Figure 5 here-----

Figure 5(b) shows the CFs of the cochlear partitions in this simulation and compares them with CFs predicted by Greenwood (1990). The average difference in the CFs between the current model and those predicted by Greenwood (1990) is approximately 13.5% for the frequencies between 0.25 and 10.0 kHz; the greatest differences are observed at the highest frequencies.

Figure 6 illustrates the RL velocity ratios along the cochlea from base to apex for pure tones of 1, 2, and 4 kHz. Figure 6 illustrates the magnitude and the phase of the wave at different cochlear positions ('panoramic view') in response to specific stimulation frequencies as well as the phase decays corresponding to each stimuli.

----- Please Insert Figure 6 here-----

1. Quantitative Comparison of Model Predictions with the Experimental Data.

Human cochlea is too deeply buried inside the thick petrous bone which makes it inaccessible for *in vivo* measurements. However, *in vivo* data on guinea pig cochlea are to some extent available. In order to compare these experimental data with the model predictions, the corresponding parameters of the human model (listed in tables I to III in appendix A) were modified to those of the guinea pig cochlea presented in [Ramamoorthy *et al.* (2007), table I, II]. The modified model was used for simulating the guinea pig BM velocity ratios at the sharpest point of the MET curve where the somatic motor functions maximally. This point must approximately correspond to the experimental data at a relatively low level of 20 dB SPL which also depicts the highest amplification and sensitivity.

Cooper (1998) measured the BM mechanical responses to pure tone stimuli at the basal turn of the guinea pig cochlea at 3mm from the base (CF=17 kHz) using a displacement-sensitive laser interferometer. de Boer and Nuttall (2000) also recorded data on velocity of the BM at the same location of the cochlea using a laser velocimeter [(de Boer and Nuttall, 2000), Fig. 1]. With this technique they obtained frequency response of the BM velocity ratio with

respect to stapes (BM velocity divided by stapes velocity) for stimulation level of 60,70,80,90 dB SPL.

The data obtained by Cooper, (1998) had been normalized with respect to the lowest measured frequency of the BM vibration whereas the measurements by de Boer and Nuttall, (2000) had been normalized to the peak of the BM response for the stimuli at 20 dB SPL. There is a considerable amount of variation between these two data sets in many aspects. However, both studies report a similar amount of peak-to-peak amplification at the CF. [(Cooper, 1998), Fig. 1(A)] illustrates a 53 dB amplification while [(de Boer and Nuttall, 2000), Fig. 1 upper panel] depicts a 50 dB peak-to-peak amplification. The data from these two experiments are read at several points and are averaged to minimize the variations. Here, we use the amplification at the lowest measured frequency of the BM response as the uniform reference of the normalization.

----- Please Insert Figure 7 here-----

Figure 7(a) compares the averaged data from the experiments at 20 dB SPL with the prediction of the modified model at the sharpest point of the MET curve. The model predicts a peak of 53.5 dB which is only slightly higher than the averaged experimental data. The CF predicted by the model (CF=17.31 kHz) is also slightly higher than that of the experimental data (CF=17 kHz). However, the amplitude prediction of the model exhibits a higher Q_{10dB} factor and is notably sharper than that of the experimental data.

[(de Boer and Nuttall, 2000), Fig. 2(A)] shows experimental data on the phase of the BM vibration at the basal region of the guinea pig cochlea between 2 mm to 5mm from the base which corresponds to 8% to 20% of the animal's cochlear length. These data are fitted with a decaying exponential function and are compared with the model prediction at these locations for the same CF. Figure 7(b) illustrates a reasonable match between the experimental data and the model prediction.

B. Simulation of Metabolic Presbycusis

The presented physiologically-based model is used in this section to simulate the effect of age-related degenerations in the stria vascularis on the functionality of the OHCs and the IHCs and eventually the whole cochlear response.

1. Effect of Metabolic Presbycusis on the Magnitude of the Cochlear Amplifier.

Figure 8(left and middle) shows the RL/base velocity ratios at locations 30% and 70% from the base respectively for three conditions: 1) a healthy fully-active cochlea where the EP is at its maximum value of 89 mV, 2) an impaired cochlea where the EP has degenerated to half of its maximum amount [EP= 44.5 mV] and 3) a passive (dead) cochlea with no active processes (EP=0).

As seen in Fig. 8 (left), when the EP is decreased to its half value both the amplification and the sharpness of the curves are reduced. However, this reduction is not linear (meaning that the amplification's peak does not drop to its half value). When the EP is halved, the peak of the 'healthy' curve drops from 63.1 dB down to 44.3 dB (corresponding to a 19.2-dB loss). The partition's CF is also shifted from 4700 Hz to 4212 Hz. Once the active processes are totally dead (passive cochlea) the curve is flattened, the amplification is significantly decreased and the CF is further down-shifted to 3026 Hz.

----- Please Insert Figure 8 here-----

A similar effect is seen in Fig. 8 (middle) at 70% of the cochlear length where the degeneration of the EP causes the amplification to decrease from 13.6 dB to 11.6 dB (corresponding to a 2-dB loss) and the CF is down-shifted from 340 Hz to 271 Hz. In case of a dead (passive) cochlea, the amplification is further decreased and the CF is shifted to 217 Hz. Figure 8 (right) summarises the changes in the tuning pattern along the cochlea as a result of the EP degeneration.

Equation (7) explains the underlying reason for the declines of the cochlear amplifier in an aging cochlea. Equation (7) states that the amplitude of the somatic motor is linearly proportional to the slope of the MET curve (α_d) and the velocity sensing coefficient (α_v). When the EP degenerates, the MET curve re-shapes [Fig. 4(a), dashed line] which leads to change of its slope, α_d . [Fig. 4(b), dashed line].

If the MET mechanism (defined in Eq. 6) is regarded as a first order LTI system, its time constant is proportional to $\frac{\alpha_v}{\alpha_d}$ indicating that α_v and α_d should vary proportionally to maintain the time constant of the system. Therefore, as the MET mechanism is reshaped, both α_d and α_v decrease according to the new MET curve which consequently causes the OHC contraction force (the output of Eq.7) to decrease as well.

From another perspective, a hearing threshold occurs around 1 nm displacement of BM (and thus approximately 2 nm displacement of the RL) in a healthy and active cochlea (Fettiplace and Hackney, 2006) which corresponds to a slope of 0.00022 [nm/s] on the MET curve. When the EP is halved [EP=44.5 mV, dashed line in Fig. 4(b)] the necessary displacement to result in a same slope of 0.00022 nm/s, and thus the same amount of somatic amplification, is increased to 80 nm. In other words, more displacement (sound pressure) is required to maintain the the same excitation level [small arrow in Fig. 4(b)] which implies that the hearing threshold has been shifted from 2 nm to 80 nm (approximately 32 dB).

2. Effect of Metabolic Presbycusis on the Temporal Features of the Cochlear Responses.

The EP provides the necessary voltage supply not only for the OHC's MET channels to function optimally but also for the IHCs as well. As a result, degeneration of the EP can directly alter the functionality of the IHCs and therefore modify two important features of the cochlear response, 1. temporal resolution of the cochlear system and 2. intensity coding of the sound on the auditory nerve.

The opening of the IHC mechanoelectrical transduction channels results in a flux of calcium ion which induces a receptor current (i_r), a similar mechanism to the OHC MET as shown by the Boltzmann curve in Fig. 4(c). The ion influx into the cell leads to Ca^{2+} build-up at the presynaptic area of the IHC-AN complex. Sumner *et al.* (2002) modeled this time-variant calcium concentration, denoted as $[Ca^{2+}](t)$, as a classic first-order low-pass filtered function of the receptor current $[i_r(t)]$ according to the equation below.

$$i_r(t) = \frac{d[Ca^{2+}](t)}{dt} + \frac{[Ca^{2+}](t)}{\tau} \quad (11)$$

In other words, Eq. 11 characterizes a first-order LTI system where the time constant (τ) determines the speed of the presynaptic calcium concentration. The probability of a neural firing by the IHC on the auditory nerve is proportional to the cube of this presynaptic calcium concentration (Sumner *et al.*, 2002). Equation (12) presents the transmitter release (firing) rate at time t on the auditory nerve, $k(t)$, as a function of the calcium concentration.

$$k(t) = \max(([Ca^{2+}]^3(t) - [Ca^{2+}]_{th}^3)Z, 0) \quad (12)$$

In Eq. (12), Z is a scalar for converting calcium concentration levels into release rate, and $[Ca^{2+}]_{th}$ denotes a threshold constant which depends on the fiber type; e.g it is 44.8 pA for high spontaneous rate (HSR) fibers whose spontaneous rate is higher than 18 spikes per second [(Sumner *et al.*, 2002), Table II]. When the EP is decreased, the IHC's MET produces less receptor current [Fig. 4(c), the dashed line] which means that Ca^{2+} flux is less; this leads to inhibition of the firing rate, $k(t)$, according to Eq. (12).

As shown by the small arrow in Fig 4. (c) at an exemplary point on the IHC MET curve corresponding to a 50 nm displacement of the IHC HB, when the EP is halved the receptor current (proportional to the Ca^{2+} flux) is decreased from 0.1 nA to 0.05 nA. As a result, the transmitter release rate, $k(t)$, on the HSR fibers is drastically decreased according to Eqs. (11) and (12).

The exact timing of the auditory nerve activations is determined by the neurotransmitter firing rate. Therefore, the transmitter release rate has a great impact on the temporal coding features of the auditory signal such as phase locking (Sumner *et al.*, 2002). A decrease in the neurotransmitter firing rate means a longer time interval between the firings which, at least partly, may explain the decline of temporal resolution, the ability to follow rapid acoustic changes over time, in an aging auditory system.

Kurt *et al.* (2012) also studied the role of the IHC ion channels on the temporal structure of auditory information in the mice cochlea. They observed that deficiency of the IHC MET channels decreased the IHC receptor current which consequently impaired the spike timing of the auditory fibers, as predicted here. They concluded that this may have a disadvantageous effect on the detection of signals in noisy environments.

3. Effect of Metabolic Presbycusis on the Rate-Intensity Function of the Auditory nerve.

The sound pressure results in mechanical vibrations within the cochlear structures which are eventually coded into neural information. It is believed that the intensity of the sound-induced cochlear vibrations is coded in terms of neural firing rate (Moore, 2003) on the auditory nerve (AN) according to specific rate-intensity transfer functions at the IHC-AN stage. These transfer functions are shown in [(Sumner *et al.*, 2002), Fig. 3] for various fibers in the guinea pig cochlea. Even if the OHC dysfunction is a very important source of the cochlear loss as already shown in Fig. 8, the IHC dysfunction can also contribute to the audiometric loss. This is because when the rate-intensity transfer function of the IHC-AN is impaired as a result of the EP reduction, there would be a decline in neural coding of the sound intensity leading to an extra loss in addition to the amplification loss attributed to dysfunction of the OHC's somatic motor. How can this additional loss be quantified and analysed?

Lopez-Poveda and Eustaquio-Martin (2006) introduced an electrical-circuit equivalent of an IHC to model the nonlinear (compressive) transfer function of the IHCs. Their model can be used to simulate the effect of age-related EP reduction on the membrane potential [the EP is represented by E_t in the schematic description of (Lopez-Poveda and Eustaquio-Martin, 2006), Fig. 1]. The membrane potential can then be linked to the rate-intensity characteristic of the firings on the auditory nerve synapse according to Eq. (4) to Eq. (12) of (Sumner *et al.*, 2002).

----- Please Insert Figure 9 here-----

There are three major categories of auditory nerve fibers in mammalian inner ear in terms of spontaneous rates. Here we conduct our quantitative analysis solely on the medium spontaneous rate (MSR) fibers which have a dynamic range approximately from 10 dB SPL to 50 dB SPL. The mammalian MSR fibers can typically fire up to approximately 300 times per second before they saturate at this level (Sumner *et al.*, 2002). Figure 9.(left) depicts how this maximum firing rate of the MSR is affected by reduction of the EP. As the EP is halved (EP=44.5 mV) the maximum firing rate decreases from 300 to 261.4 spikes/second.

A second-order Boltzmann function is used to fit the experimental data on the rate-intensity transfer function of the guinea pig M1 fibers (Winter *et al.*, 1990) at CF of 16 kHz as seen in Fig. 9.(middle). The maximum firing rate is in the numerator of the Boltzmann function. Therefore, when the maximum firing rate is reduced to 261.4 spikes/second as explained above, this rate-intensity transfer function is reshaped accordingly; it is illustrated by the dashed lines in Fig. 9(middle). At an exemplary level of 30 dB SPL [Fig. 9(middle), solid line] the auditory nerve was activated with a firing rate of 250 spike/second in the healthy cochlea. However, in the case where the EP is halved [Fig. 9(middle), dashed line] then an intensity of approximately 35 dB SPL is needed to produce the same firing rate (250 spike/second) which indicates a 5-dB loss. The corresponding losses at the CF of 16 kHz

(basal region) in the dynamic range of the MSR fiber (approximately from 10 dB SPL to 45 dB SPL) have been summarised in Fig. 9(right). These IHC-related losses are at the order of 2-4 dB at low and medium intensities (10-35 dB) and becomes greater around the saturation point of the fiber. Figure 9 suggests that, at least in the basal region, the corresponding loss for the low and medium intensity stimuli as a result of the IHC-AN dysfunction caused by the EP reduction to half of its maximum value is relatively small in comparison with the 20-dB OHC-related amplification loss depicted in Fig. 8.

However, the method used here for investigating the IHC-related loss associated with presbycusis is solely via simulating the effect of the EP reduction on the discharge rate of the auditory nerve for different sound intensities. However, near the fiber's threshold, other bio-neural factors (rather than the discharge rate solely) such as temporal integration may contribute to determine whether a specific stimulation will be detected or not. Considering the existence of these factors near the threshold, the presented approach may underestimate the associated IHC-related audiometric loss, defined as the amount of elevation in behavioural thresholds.

Besides, it has been suggested that near threshold, a single spike, rather than a series of neural spikes, may be sufficient to make a sound detectable. Furthermore, Meddis (2006) investigated the timing of the 'first-spike' and the role of the calcium dynamics on the the AN first-spike latency by including a calcium influx model identical to Eq. (11) and Eq. (12) here. He then simulated the absolute thresholds of the auditory nerve fibers based on this 'first-spike latency' concept. In summary, although the analysis presented in this section is capable of quantifying the decline in the rate-intensity function of the IHC-AN complex caused by the age-related EP reduction (Fig. 9), it may not be sufficient to fully account for the IHC-related threshold elevations associated with metabolic presbycusis.

IX. ANALYSIS

A. Time Constant of the Outer Hair Cell's Body.

One, so far, unresolved issue with the somatic motor is the membrane time constant. The OHC's membranous body has a capacitance and a resistance, modeled by C and $1/G$ as shown in Fig. 3. This implies that the receptor voltage (V_r) is low-pass filtered according to the membrane time constant (product of membrane resistance and capacitance). Since the somatic motor is controlled by this receptor voltage (Liu and Neely, 2009), the amplification of the somatic motor must be attenuated at higher frequencies due to the low-pass effect. The highest cut-off frequency corresponding to the physiological parameters (C and G) here is around 1000 Hz. On the contrary, Fig. 5(a) indicates that the somatic motor functions well above this cut-off frequency, even more powerfully than at the low frequencies. This is in line with available experimental data (Pattuzi, 1996). Hence, the model developed here demonstrates how elements of an active electromechanical system can interact to overcome the low-pass filtering due to the membrane RC time constant.

B. High Frequency Profile of the Metabolic Presbycusis.

Comparing left panel of Fig. 8 with the middle panel indicates that at a position corresponding to 30% of the cochlear length from the base (basal region) with a CF of 4700 Hz, the amplification peak drops 19.2 dB as a result of the EP degeneration whereas at 70% of the cochlear length (apical region with CF of 341 Hz) this attenuation is merely 2 dB.

Figure 10(a) shows these shifts as a function of the CFs for frequencies between 50 and 4000 Hz. Similar to Fig 8 (a), (b), they were calculated by comparing the peaks of the RL/base velocity ratios of the healthy cochlea (EP=89mV) with those of the presbycusis cochlea (EP=44.5mV). Since the amplification peaks of the healthy cochlea were regarded as reference, the illustrated shifts have negative values. The result demonstrates a flat loss at low frequencies coupled with a shallow high-frequency sloping loss above 1 kHz as shown in Fig. 10(a). This is consistent with Schmiedt (2010) where he argues that the reason why

presbycusis is associated with higher frequencies is that the cochlear amplification is greater at higher frequencies (basal region) than at lower frequencies (apical region) therefore the lack of amplification is more significantly felt in higher frequencies.

----- Please Insert Figure 10 here-----

1. Quantitative Comparison of the Model Prediction of Presbycusis with the Animal Data.

Schmiedt *et al.* (2002) measured the compound action potential (CAP) thresholds in groups of aged gerbils versus a control group of young gerbils. They recorded the CAP thresholds in the aged gerbil cochleae with reduced levels of the EP (67 mV, 55 mV, 48 mV, 43 mV and 17 mV) versus a control group (young and healthy, EP=95 mV) at 12 different frequencies ranging from 500 Hz to 20 kHz.

In order to quantitatively analyze these data and compare them with the predictions of this model, the data for the EP=48 mV case are read from [(Schmiedt *et al.*, 2002), Fig. 4, bottom panel]. For example at 500 Hz, the CAP threshold has been reported 22 dB SPL for the control group (filled square) whereas it is 36 dB SPL for the aged group with EP=48 mV (filled triangle) which indicates a -14 dB SPL attenuation. The corresponding attenuations are calculated this way for other points and are shown by the crosses in Fig. 10(c). This resulting curve represents the CAP threshold elevations recorded from a very old gerbil cochlea which may also suffer from other types of hearing impairment (sensory and/or neural).

Schmiedt *et al.* (2002) also recorded CAP thresholds from furosemide treated gerbil cochleae. Furosemide is a loop diuretic which disrupts the stria vascularis functionality without significantly affecting the OHCs and therefore is often used for creating a fast experimental model of metabolic presbycusis. The corresponding attenuations are obtained as explained above from the recorded CAP thresholds of the Furosemide treated gerbil cochleae for EP= 46 mV [reported by (Schmiedt *et al.*, 2002), Fig. 4, top panel, empty triangles]. Besides, Schmiedt *et al.* (2002) reported mean CAP threshold shifts of 10

Furosemide treated gerbils as well. The corresponding curve for EP=57.5 mV is also obtained from [(Schmiedt *et al.*, 2002), Fig. 7, top panel, filled circles].

The above three sets of experimental data are shown respectively by crosses, squares and stars in Fig. 10(c) versus the model prediction (solid line). Figure 10(c) indicates that among these three sets of experimental data, the curve representing the CAP thresholds of Furosemide treated gerbil with EP=46 mV (squares) shows the closest match with the model prediction. This curve (squares) is then fitted with a function (dashed line) comprising a constant level at low frequencies followed by a sloping line at higher frequencies with a break point at 4.2 kHz. Figure 10(c) depicts a reasonable correlation between the fitted function (dashed line) and the prediction of the model (solid line), both in terms of the overall shape, a flat loss in lower frequencies followed by sloping loss at higher frequencies, and in terms of quantitatively reproducing the maximum of 40-45 dB loss at 16 kHz.

A comparison between Fig. 10(a) and Fig. 10(c) indicates that both human and animal models depict a similar shape. However, the human model [Fig. 10(a)] illustrates only a 20 dB loss at 4 kHz whereas the clinical data suggests that the corresponding loss may be much more than this [Schmiedt *et al.*, (2002), Fig. 7, bottom panel]. Firstly, unlike the gerbils, there are no *in vivo* measurements available on the EP values inside aged human cochleae; thus it is not very clear how much of the observed audiometric loss in aged human is purely attributed to metabolic presbycusis. Secondly, if the values of two specific parameters (T and/or α_p in table III of Appendix A) are slightly increased, the model is capable of reproducing the suggested 40 dB loss at 4 kHz. However, there is not enough physiological justification to change the values of these two human parameters from their current values.

C. The Phase Difference between Passive Vibration and the Somatic Motor.

Figure 10(b) illustrates a $\frac{\pi}{2}$ phase difference between the BM velocity (H_{trig}) and the OHC motility force (H_o) in the middle of the cochlear duct. It implies that the BM and the RL

move separately, squeezing the fluid in between inside the tunnel of Nuel which produces a flow in longitudinal direction (fluidal coupling). Figure 10(b) also indicates that age-related decrease of the EP does not influence this existing phase difference between the BM velocity and the OHC motile force. The phase conveys information about the timing of the corresponding mechanism. Therefore, it can be inferred that while the age-related decrease of the EP leads to drastic declines in the *magnitude* of the OHC's somatic motor [Fig. 8 and Fig. 10(a), (c)], it does not significantly affect the *phase* and the timing of the process.

D. Effect of Metabolic Presbycusis on the Tuning Pattern of the Cochlea.

Figure 8(right) reveals another effect of metabolic presbycusis on the cochlear response. The position-frequency map of the cochlea is modified as the active processes decline. It indicates that the CFs of the cochlear partitions tend to decrease in a presbycusis cochlea. This is consistent with Robles and Ruggero (2001) where they argue that in a passive cochlea (EP=0) the CFs are significantly shifted to lower frequencies.

In other words, Fig. 8(right) depicts the decrease in the CFs along the cochlear duct as the activity level of the hair cells declines due to age-related reduction of the EP.

Ramamoorthy *et al.* (2007) also illustrate how the CFs are shifted basalwards as the activity level of the outer hair cells decreases; their model quantifies the corresponding shifts for 0%, 50%, 75%, 90% and 100% activity levels [Ramamoorthy *et al.* (2007), Fig. 7]. Furthermore, Lopez-poveda *et al.* (2007) measured the behavioral psychophysical tuning curves at different sound intensities using forward masking method at probe frequencies 125, 250, 500 Hz (apical) versus 6000 Hz (basal). Their results experimentally confirmed that at higher sound intensities (where the activity level of the hair cell is relatively lower) the CFs almost always decreased both in the apical and basal regions of the cochlea.

E. Effect of Common Simplifications on the Output of the Model.

All cochlear models are a simplification of the undergoing mechanisms and complex kinematics of the cochlea. Longitudinal feed forward, structural coupling and the TM passive load are commonly neglected by modelers to obtain computational simplicity (Ghaffari *et al.*, 2007). Figure 11(left) demonstrates that if the longitudinal feed-forward on the BM (path2 in Fig. 2) is neglected, which is the case in typical cochlear models that lack longitudinal structural coupling, the cochlear amplification drastically deteriorates. In this case, as Fig. 11(middle) shows, the model produces a different frequency-position map, approaching that of a dead (passive) cochlea.

These are consistent with the results from [Meaud and Grosh (2010), Fig .2 and Fig. 10], which emphasize that the structural coupling along the BM and the TM is significant. Figure11 (right) indicates that excluding the TM passive load (represented by Mt_i , Kt_i and Rt_i in Fig. 1) from the model, causes both the cochlear amplification and the frequency sensitivity to significantly decrease. This is consistent with measurements by Gummer *et al.* (1996) which emphasize the crucial role of the TM in boosting both magnitude and sensitivity of the cochlear amplifier. Therefore, the TM passive load must also be included in a realistic cochlear model.

----- Please Insert Figure11 here-----

F. Effect of Metabolic Presbycusis on Distortion Product Otoacoustic Emissions.

Discovery of the otoacoustic emissions (OAE) provided the first evidence for existence of a nonlinear active process inside the mammalian cochlea. Since then, OAEs have been considered as a direct measure of the compression and the active amplifications. Therefore, one would most likely expect to see a decline in these emissions as a result of aging. On the contrary, animal models of metabolic presbycusis do not show a significant reduction in distortion product otoacoustic emissions (DPOAEs) levels as a result of the EP degeneration (Schmiedt *et al.*, 2002).

The DPOAEs are generated by nonlinearity of the cochlear functions and are related to the resting position of the organ of Corti and the MET channels (Brown *et al.*, 2009). As the dashed circle in Fig. 4(a) shows, around the resting point (zero displacement of the HB) the difference between the solid line (of healthy cochlea EP=89 mV) and the dashed line (of presbycusis cochlea EP=44.5 mV) is small. Thus, the value of the receptor current is almost equal for both conditions regardless of the EP value. The receptor current induces a voltage current which drives the somatic motor (Fig. 3) according to Eq. (7). As the HB starts to deflect, the difference between these two curves rapidly grows. It has been simulated earlier what great impacts this difference would have on the magnitude of the cochlear amplifier [Fig. 8 and Fig. 10(a)].

Since the DPOAEs are related to the resting position and the effect of the EP reduction on the MET mechanism is very small around this resting point, thus according to the model, one would expect that the DPOAE levels are relatively insensitive to changes in the EP. Despite this reasoning is based on the nature of the MET mechanism and the governing equations of the presented modeling work, an elaborate DPOAE simulation may be required to fully confirm this logic.

Schmiedt (2010), [Fig. 2.9, top and middle panels], showed that when the OHCs themselves are manipulated (i.e. by destructive noise exposure), unlike the case of the EP reduction, the DPOAEs are drastically reduced. This suggests that the DPOAEs may reflect the status of the OHCs rather than the pathologies in the stria vascularis. This hypothesis is in line with outcome of the clinical study by He and Schmiedt (1996) where they compare the otoacoustic emission levels recorded from an aged group with those from a group of hearing impaired young individuals. Their results demonstrate that aged subjects can have much greater hearing losses before the decline of the otoacoustic emissions becomes notable as compared to young subjects. They hypothesize that this may be mainly because the hearing

loss of the young group is likely to take root from noise exposure which acts directly on the OHC function, whereas the substantive cause of the hearing loss in the aged group is more likely to be of strial origin (leading to the EP reduction). From another perspective, this differential phenomenon may provide possibilities for developing clinical tests in the future to diagnose how much of a specific hearing loss originates from the hair cell deficit (sensory) and how much of it can be linked to the EP degeneration (metabolic).

X. DISCUSSION

Although the model incorporates some often neglected aspects of the cochlear mechanics such as longitudinal coupling, feed forward of the OHC contraction force and independent motion of the BM and the RL, the model is still a simplification of the complex cochlear kinetics. Therefore, introducing more degrees of freedom to the current model in future versions may reveal more detailed features of the complex human cochlear kinetics.

Moore (2003) indicates that additional frequency tuning may occur in more central parts of the auditory system. This implies that the frequency-map obtained from the current simulations may alter when this model is connected to models of central parts of the auditory system. There is also strong evidence which shows that the central auditory system can manipulate the cochlear functionality via olivocochlear efferents which are linked to the synaptic area of the hair cells by forming a synaptic ‘cistern’ (Slepecky, 1996). This efferent network can activate nicotinic cholinergic receptors (nAChR) that change the membrane conductance of the hair cells [G in the equivalent circuit of Fig. 3] and thereby alter the somatic motor and the active force generation in the cochlea. Although the cholinergic inhibition of mammalian cochlear hair cells is well documented (Katz *et al.*, 2010), the effects of these top-down manipulations are not included in the cochlear models to date.

Even so, the model introduced here integrates electrical, mechanical and acoustical elements of the cochlea in a physiologically-based transmission line. The model is capable of

simulating the effect of age-related degeneration in the lateral wall of the cochlea on the cochlear responses and quantitatively explaining the experimental data. Besides, the model predicts the changes in the position-frequency map (tuning pattern) of the cochlea as the active processes decline in an aging cochlea.

Our simulations confirm and quantify the prevailing hypothesis of metabolic presbycusis and its high-frequency profile. As the electromechanical parameters of the model were modified to those of the guinea pig [Ramamoorthy *et al.* (2007), table I, II], the model could closely predict the experimentally-measured CAP threshold elevations in Furosemide treated gerbils reported by [(Schmiedt *et al.*, 2002), Fig. 7]. Gerbil and guinea pig cochleae are structurally and electromechanically similar (Robles and Ruggero, 2001) and the guinea pig parameters used here seem to be more realistic than the human parameters in terms of quantitative reproduction of the amplification loss associated with presbycusis.

Auditory models classically consider the BM motion as a perfect representative of the vibration pattern and simplify the cochlear mechanics to study of the BM vibration. This is mainly based on the erroneous assumption that the motion of the RL and the BM are similar. However, a key idea behind the current modeling approach is the independence of the RL from the BM which enables them to move separately. This is consistent with the measurements by Nowotny and Gummer (2005). A newer and more explicit report by Chen *et al.*, (2011) also indicates that the motion of the RL is greater in amplitude and has a different timing and phase from the motion of the BM. Furthermore, the presented cochlear model includes the IHC-AN synapse and quantitatively studies the inhibition of the AN firing rate caused by the EP reduction. The consequent impact of the AN firing rate inhibition on the rate-intensity function of the auditory fibers is studied and possible limitations of this approach in fully understanding the IHC-related audiometric loss associated with metabolic presbycusis are discussed.

The non-linear piezoelectric model of the OHC motility here is taken from (Liu and Neely, 2009). However, in their work the TM mechanical load was ignored. Also to simplify Eq. (3), the mass of the RL was neglected and, as a consequence, the feed-forward on the BM was removed from the model. As depicted in Fig. 11, these may not be realistic assumptions. Lu (2009) introduced a multi-compartmental model which included the longitudinal fluid flow. Even though the parameters of the model conveyed physiological interpretations, the simulations did not demonstrate greater cochlear amplification at higher frequencies [Lu (2009), Fig. 1-3 and Fig. 2-4] as expected in accordance with the experimental data.

XI. CONCLUSION AND FUTURE WORKS

A physiologically-motivated electromechanical model of the human cochlea in form of a signal transmission line with finite number of partitions has been presented. A linear analysis of the model was conducted to simulate the cochlear response to acoustical stimuli in the frequency domain. The main idea was that an age-related decrease in the EP alters the MET mechanism leading to a decline of the active force/displacement generated by the somatic motor and, eventually, high-frequency hearing threshold elevation observed in an aging auditory system. In this regard, the model prediction showed a reasonable match with the measured CAP threshold elevations in aged and Furosemide treated gerbils.

The simulations showed that age-related reduction of the EP not only reduces the cochlear amplification by affecting the OHC somatic motor, but also it inhibits the firing rate of the auditory nerve by reshaping the IHC mechano-electrical transduction. A decrease in the firing rate means a longer time interval between the firings which might, at least partly, explain the decline of temporal resolution, the ability to follow acoustic variations over time, in the aging auditory system. In order to optimally process a speech signal in every-day situations listeners must be capable of resolving a number of simultaneous acoustic cues that vary as a function of time both in the speech (target) and in the disturbing background sounds

(noise). If temporal resolution is impaired then the listeners may experience difficulties perceiving speech (Moore, 2003). Furthermore, Lopez-poveda and Barrios (2013) reasoned that since neurotransmitter firing is of a stochastic nature, a reduced firing rate could degrade speech intelligibility in fluctuating background noise more than in quiet.

There have been great efforts and advancements in hair cell regeneration since 25 years ago [see (Stone and Cotanche, 2007) for a review]. These efforts are mainly focused on regenerating hair cells solely, based on a to-some-extent erroneous assumption that age-related hearing loss in humans is largely sensory in nature rather than metabolic. Whereas our simulations quantitatively demonstrated that even if the OHCs are totally intact and fully active, the age-related metabolic degenerations in the lateral wall of the cochlea can result in significant declines of the cochlear responses both in magnitude and temporal features. This means that exclusively focusing on hair cell regeneration may not be fruitful if the main problem lies somewhere else, in the supporting cells of the lateral wall of the cochlea.

The stria vascularis is the only known epithelial tissue where blood vessels pass through its two cellular layers. Therefore, the functionality of these vascularized cellular layers may be dependent on the health of these supporting vessels as well as the blood in them. Thus, the capability of the stria vascularis in keeping the K^+ cycle and thereby the optimum EP inside the cochlear duct may be very sensitive to the underlying metabolic status of the individual.

Apart from the age-related cellular degenerations, the effects of metabolic disorders caused by specific health conditions such as syndrome X (metabolic syndrome), diabetes and cardiovascular diseases on functionality of this vascular tissue have not yet been thoroughly investigated. However, recently Fukushima *et al.* (2006) studied cadaver temporal bones of 18 diabetic humans to measure the effects of diabetes on the cochlear structures. Their results indicated that type 2 diabetes mellitus leads to thickening of stria vascularis reminiscent of aged stria vascularis. Riquelme *et al.* (2010) investigated this underlying similarity by

studying the role of an insulin-related peptide, insulin-like growth factor 1 (IGF-1), on the stria vascularis. Their results showed that the wild mice which lacked IGF-1 developed a prematurely aged stria vascularis resembling the diabetic stria phenotype. Since this model can be regarded as a biophysical foundation for coupling the cochlear mechanics with functionality of the stria vascularis, it can be useful in the future for simulating how these metabolic disorders can manipulate the cochlear responses and thereby the whole auditory system.

Moreover, this modeling approach can potentially be expanded to further simulate the effect of other cell-level cochlear lesions rather than solely in stria vascularis, such as the cellular lesions induced by over stimulation, on the cochlear responses. This is important because from a clinical point of view, aging is often accompanied with some degrees of noise induced lesions since most aged humans have, to some extent, been exposed to destructive levels of noise through their lives [see audiograms in (Schmiedt, 2010), Fig. 2.13]. This modeling approach, together with explicit clinical tests, can be helpful in paving the way towards differential diagnosis and better understanding of these two very common cochlear origins of sensorineural hearing impairments.

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APENDIX A: ASSIGNING PARAMETERS FOR HUMAN COCHLEA

In a normal adult mammalian cochlea, the stiffness of the BM decreases progressively from base towards apex while the mass increases (Bekesy, 1960). The structures of interest are housed in a rather inaccessible part of the skull, totally embedded in bone (Slepecky, 1996) which makes real-time measurements of *in vivo* human cochlea rather difficult.

However, measurements on passive cochleae in cadavers are to some extent available. The available data at some specific locations of the cochlea (such as in basal or apical regions) were fitted by either linear or exponential functions to obtain values for the in-between positions. For example, [Liu and Neely, (2010), table I] gave the mass of the BM per unit area at the base ($8 \times 10^{-5} gcm^{-2}$), in the middle of the cochlea ($2.8 \times 10^{-4} gcm^{-2}$), and at the apex ($2.1 \times 10^{-3} gcm^{-2}$). These data were interpolated by an exponential function to obtain the values for the partitions in between these three points, as seen in table I.

When no data were available for the human, we tried to extrapolate values from other mammalian cochleae. As long as human *in vivo* data are not available, the validity of such extrapolations can be discussed. However, the idea is to use realistic physiological parameters in so far as possible to simulate the effect of specific physiological lesions (specifically metabolic presbycusis) on the output cochlear response. The model consists of a necessarily large number of parameters. The mechanical parameters are presented in table I, the electro-mechanical parameters attributed to the somatic motor are given in table II, and the parameters related to the MET mechanism and stria vascularis are presented in table III. The tables also summarize the sources and the methods used to obtain the parameter values.

TABLE I. Mechanical parameters of organ of Corti

Name	Definition	Value	Unit	Source
N	Number of partitions	100	-	-
L	Length of an average human cochlea	0.035	m	(Bekesy, 1960)
i	Partition's index	1 to N	-	-
W	BM width	$0.031 + [0.02 \times 10^{-4} \times (i - 1)]$	cm	Linearly interpolated from [(Liu and Neely,

				2010), Table I].
A	Cochlear cross-sectional area	$6.3 \times 10^{-3} + [5.99 \times 10^{-4} \times (i - 1)]$	cm^2	Linearly interpolated from [(Liu and Neely, 2010), Table I]
Mb_i	BM mass per unit area	$3.6631 \times 10^{-5} \times e^{0.0405 \times i}$	gcm^{-2}	Exponentially interpolated from [(Liu and Neely, 2010), Table I]
Kb_i	BM stiffness per unit area	$6.777 \times 10^5 \times e^{16.74 \times i}$	$gs^{-2}cm^{-2}$	Exponentially interpolated from [(Liu and Neely, 2010), Table I]
Rb_i	Damping of BM per unit area	$\frac{\sqrt{Mb_{eff_i} \cdot Kb_i}}{Q}, Q=6$ Mb_{eff_i} is defined by Eq. (4.b)	$gs^{-1}cm^{-2}$	[(Lu, 2009), Table 1.1]
M_{OHC_i}	OHC mass per partition	$2.18 \times 10^{-8} \times e^{0.0698 \times i} \times (\frac{100}{N})$	g	Calculated from [(Liu and Neely, 2010), Table I] for a single partition
K_{OHC_i}	OHC stiffness per partition	$201.689 \times e^{-0.0563 \times i} \times (\frac{100}{N})$	gs^{-2}	Calculated from [(Liu and Neely, 2010), Table I] for a single partition

R_{OHC_i}	OHC damping per partition	$7.745 \times 10^{-4} \times e^{0.0107 \times i} \times \left(\frac{100}{N}\right)$	gs^{-1}	Calculated from [(Liu and Neely, 2010), Table I] for a single partition
Mr_i	RL mass per unit area	$0.66 \times Mb_i$	gcm^{-2}	[(Lu, 2009), Table 1.1]
Kr_i	RL stiffness per unit area	$0.2 \times Kb_i$	$gs^{-2}cm^{-2}$	[(Lu, 2009), Table 1.1]
Rr_i	RL damping per unit area	$\frac{\sqrt{Mr_i \cdot Kr_i}}{Q}, Q=4$	$gs^{-1}cm^{-2}$	[(Lu, 2009), Table 1.1]
Mt_i	Effective TM shear mass per partition	$\frac{L}{N} \rho_{TM} \cdot h \cdot l \cdot e^{50 \cdot L \cdot \frac{i}{N}}$ $h = \text{TM thickness}$ $b = \text{TM width}$ $\rho_{TM} = \text{density of the TM layer}$	g	Extrapolated from [(Ramamoorthy <i>et al.</i> , 2007), Table II]
Kt_i	TM shear stiffness per unit area	$6 \times 10^3 \times e^{-220 \cdot L \cdot \frac{i}{N}}$	Nm^{-2}	[(Ramamoorthy <i>et al.</i> , 2007), Table II]
Rt_i	TM damping per unit area	$\frac{\sqrt{Mt_i \cdot Kt_i}}{Q}, Q=4$	$gs^{-1}cm^{-2}$	TM and RL are assumed to have a similar quality factor (Q=4)
G	The geometry gain of organ of Corti per partition	$0.92 - 0.0062 \times i$	-	Linearly interpolated from (Nam and Fettiplace, 2011)

<i>OHC</i>	Total number of OHCs in an average human cochlea	11000	-	(Fettiplace and Hackney, 2006)
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TABLE II: Electromechanical parameters of the OHC.

Name	Definition	Value	Unit	Source
C	membrane capacitance	$13.62 \times e^{0.0175 \times i}$	pF	Exponentially interpolated from [(Liu and Neely, 2010), Table I]
G	Membrane conductance	$89.58 \times e^{-0.0102 \times i}$	nS	Exponentially interpolated from [(Liu and Neely, 2010), Table I]
C_g	Small-signal Linear gating capacitance	$17.364 \times e^{0.0137 \times i}$	pF	Exponentially interpolated from [(Liu and Neely, 2010), Table I]
T	Piezoelectric transmformation ratio	8×10^5	mC^{-1}	[(Liu and Neely, 2009), Table I]
K	Static axial stiffness	0.02	Nm^{-1}	[(Liu and Neely, 2009), Table I]

TABLE III: Electromechanical parameters of the OHC MET and stria vascularis battery.

Name	Definition	Value	Unit	Source
EP	Stria vascularis battery	89	mV	(Slepecky, 1996)
I_{sat}	Saturation current of MET	500	pA	Assumed to be constant along the cochlear duct
$R_{st} + R_{sm}$	Combination of the SM resistance and the Electrical resistance of tstria vascularis	$R_{st} + R_{sm} = \frac{EP}{I_{sat}} =$ 178×10^6	ohm	calculated in order to produce $I_{sat} = 500pA$ by a voltage difference of EP=89 mV
Z	Sharpness of the MET curve	-1.098	-	(Holt <i>et al.</i> , 1997)
I_{res}	Non-zero residual current of MET when there is no stimuli	3.5% of I_{sat}	A	Extrapolated from [(Holt <i>et al.</i> , 1997), Fig. 3(a)]
α_d	Slope of the MET fast adaption curve [Fig. 4(a)]	$\frac{d[Eq. (1)]}{dx}$	Am^{-1}	Calculated according to Eq. (1)
α_v	Velocity-to-current gain defined by Eq. (6)	$(\alpha_v = T \cdot \alpha_d)^a$ where T denotes the time constant under which the MET channels reclose	Asm^{-1}	Fettiplace <i>et al.</i> (2005)

^a The time constant is considered to be tenfold larger than the time constant illustrated in

[Fettiplace *et al.* (2005), Fig. 2(B)]

References

- Bekesy, G. V. (1960). "Part 4: Cochlear Mechanics" in *Experiments in the Hearing* (McGraw-Hill, New York, USA), pp 403-703.
- Brown, D. J., Hartsock, J. J., Gill, R. M., Fitzgerald, H. E., and Salt, A. N. (2009). "Estimating the operating point of the cochlear transducer using low-frequency biased distortion products," *J. Acous. Soc. Am.* **125**, 2129-2145.
- Chen, F., Zha, D., Fridberger, A., Zheng, J., Choudhury, N., Jacques, S. L., Wang, R. K., Shi, X., and Nuttall, A. L. (2011). "A differentially amplified motion in the ear for near-threshold sound detection," *Nature neuroscience* **14**, 770-774.
- Cooper, N. P. (1998). "Harmonic distortion on the basilar membrane in the basal turn of the guinea-pig cochlea," *J. Physiology.* **509 (Pt 1)**, 277-288.
- De Boer, E., and Nuttall, A. L. (2000). "The mechanical waveform of the basilar membrane. III. Intensity effects," *J. Acous. Soc. Am.* **107**, 1497-1507.
- Fettiplace, R., Crawford, A. C., and Kennedy, H. J. (2005). "Signal transformation by mechanotransducer channels of mammalian outer hair cells.," *Auditory Mechanisms: Proceedings of the 9th International Symposium, Portland USA.* **1**, 245-252.
- Fettiplace, R., and Hackney, C. M. (2006). "The sensory and motor roles of auditory hair cells," *Nature reviews. Neuroscience* **7**, 19-29.
- Fukushima, H., Cureoglu, S., Schachern, P. A., Paparella, M. M., Harada, T., and Oktay, M. F. (2006). "Effects of type 2 diabetes mellitus on cochlear structure in humans," *JAMA Otolaryngol Head Neck Surg.* **132**, 934-938.
- Ghaffari, R., Aranyosi, A. J., and Freeman, D. M. (2007). "Longitudinally propagating traveling waves of the mammalian tectorial membrane," *PNAS* **104**, 16510-16515.

- Gordon-Salant S., Frisina, R. D. (2010). "Introduction and overview," in *The Aging Auditory system*, edited by Gordon-Salant S. F., Frisina, R. D., Popper, A. N., Fay, R. R. (Springer Science+Business Media, USA), pp. 1-8.
- Greenwood, D. D. (1990). "A cochlear frequency-position function for several species - 29 Years Later," J. Acous. Soc. Am. **87**, 2592-2605.
- Gummar, A.W., Hemmert, W., Zenner, H. (1996) "Resonant tectorial membrane motion in the inner ear: Its crucial role in frequency tuning" Proc. Natl. Acad. Sci. USA. **93**, 8727-8732.
- He, N. J., and Schmiedt, R. A. (1996). "Effects of aging on the fine structure of the 2f1-f2 acoustic distortion product," J. Acous. Soc. Am. **99**, 1002-1015.
- Holt, J. R., Corey, D. P., and Eatock, R. A. (1997). "Mechanoelectrical transduction and adaptation in hair cells of the mouse utricle, a low-frequency vestibular organ," The Journal of neuroscience : J. Neurosci. **17**, 8739-8748.
- Irino, T., and Patterson, R. D. (2001). "A compressive gammachirp auditory filter for both physiological and psychophysical data," J. Acous. Soc. Am. **109**, 2008-2022.
- Jia, S., Dallos, P., and He, D. Z. (2007). "Mechanoelectric transduction of adult inner hair cells," J. Neurosci. **27**, 1006-1014.
- Katz, E., Elgoyhen, A. B., Fuchs, P. A. (2010). "Cholinergic inhibition of hair cells," in *Auditory and Vestibular Efferents*, edited by Ryugo, D. K., Popper, A. N., Fay, R., R. (Springer Handbook of Auditory Research, USA), pp. 103-133.
- Kurt, S., Sausbier, M., Rüttiger, L., Brandt, N., Moeller, C. K., Kindler, J., Sausbier, U., Zimmermann, U., van Straaten, H., Neuhuber, W., Engel, J., Knipper, M., Ruth, P., and Schulze, H. (2012). "Critical role for cochlear hair cell BK channels for coding the temporal structure and dynamic range of auditory information for central auditory processing," FASEB J. **26**, 3834-3843.

- Lang, H., Jyothi, V., Smythe, N. M., Dubno, J. R., Schulte, B. A., and Schmiedt, R. A. (2010). "Chronic reduction of endocochlear potential reduces auditory nerve activity: further confirmation of an animal model of metabolic presbycusis," *J. Assoc. Res. Otolaryngol.* **11**, 419-434.
- Li, Y., Mead, J., Grosh, K., (2011). "coupling the subtectorial fluid with the tectorial membrane and hair bundles of the cochlea," *AIP: What Fire is in Mine Ears: Proceedings of the 11th International Mechanics of Hearing Workshop* **1403**, 104-109.
- Liu, Y. W., and Neely, S. T. (2009). "Outer hair cell electromechanical properties in a nonlinear piezoelectric model," *J. Acous. Soc. Am.* **126**, 751-761.
- Liu, Y. W., and Neely, S. T. (2010). "Distortion product emissions from a cochlear model with nonlinear mechano-electrical transduction in outer hair cells," *J. Acous. Soc. Am.* **127**, 2420-2432.
- Lopez-Poveda, E. A., and Barrios, P. (2013). "Perception of stochastically undersampled sound waveforms: a model of auditory deafferentation," *Front. Neurosci.* **7**:124.
- Lopez-Poveda, E. A., Barrios, L. F., Alves-Pinto, A. (2007). "Psychophysical estimates of level-dependent best-frequency shifts in the apical region of the human basilar membrane," *J. Acoust. Soc. Am.* **121**(6), 3646-3654.
- Lopez-Poveda, E. A., and Eustaquio-Martin, A. (2006). "A biophysical model of the inner hair cell: the contribution of potassium currents to peripheral auditory compression," *JARO* **7**, 218-235.
- Lu, s. (2009). "A physiologically based nonlinear multicompartment cochlear model with a piezoelectric OHC feedback system." in *Dissertation: a nonlinear multicompartmental cochlear model*, (Boston University, College of Engineering, USA), pp 45-73.

- Lu, S., Mountain, D., and Hubbard, A. (2009). "Is stereocilia velocity or displacement feedback used in the cochlear amplifier?," Concepts and Challenges in the Biophysics of Hearing: Proceedings of the 10th International Workshop on Mechanics of Hearing, 297-302.
- Meaud, J., and Grosh, K. (2010). "The effect of tectorial membrane and basilar membrane longitudinal coupling in cochlear mechanics," J. Acous. Soc. Am. **127**, 1411-1421.
- Meddis, R. (2006). "Auditory-nerve first-spike latency and auditory absolute threshold: A computer model, " J. Acous. Soc. Am. **119** , 406-4017.
- Meddis, R., Lopez-Poveda EA. (2010). "Peripheral auditory system: from pinna to auditory nerve," in: Meddis, Lopez-Poveda, Popper, Fay (eds.) Computer Models of the Auditory System. Springer Handbook of Auditory Research, vol. 35, Springer, New York, pp 7-38.
- Mills, J. H., Schmiedt, R. A., and Dubno, J. R. (2006). "Age-related hearing loss: a loss of voltage, not hair cells," Semin Hear. **27**, 228-236.
- Moore, B. C. J. (2003). "Coding of sounds in the auditory system and its relevance to signal processing and coding in cochlear implants," Otology & Neurotology 24, 243-254.
- Naidu, R. C., and Mountain, D. C. (2001). "Longitudinal coupling in the basilar membrane," J. Assoc. Res. Otolaryngol. **2**, 257-267.
- Nam, J. H., and Fettiplace., R. (2011). "A cochlear partition model incorporating realistic electrical and mechanical parameters for outer hair cells," AIP: What Fire is in Mine Ears: Proceedings of the 11th International Mechanics of Hearing Workshop **1403**, 170-175.
- Nowotny, M., and Gummer, A. W. (2005). "What do the OHCs move with their electromotility? " Auditory Mechanisms: Proceedings of the 9th International Symposium, Portland USA., 101-102.

- Pattuzzi, R. (1996). "Cochlear micromechanics and macromechanics," in *The Cochlea*, edited by Dallos, P., Popper, A. N., Fay, R. R. (Springer-Verlag, USA), pp. 186-257.
- Patuzzi, R., and Moleirinho, A. (1998). "Automatic monitoring of mechano-electrical transduction in the guinea pig cochlea," *Hear. Res.* **125**, 1-16.
- Ramamoorthy, S., Deo, N. V., and Grosh, K. (2007). "A mechano-electro-acoustical model for the cochlea: Response to acoustic stimuli," *J. Acous. Soc. Am.* **121**, 2758-2773.
- Riquelme, R., Cedié, R., Contreras, J., la Rosa Lourdes, R. D., Murillo-Cuesta, S., Hernandez-Sanchez, C., Zubeldia, J. M., Cerdan, S., and Varela-Nieto, I. (2010). "A comparative study of age-related hearing loss in wild type and insulin-like growth factor I deficient mice," *Front Neuroanat.* **4**, 27.
- Robles, L., and Ruggero, M. A. (2001). "Mechanics of the mammalian cochlea," *Physiological reviews* **81**, 1305-1352.
- Santos-Sacchi, J. (1991). "Isolated supporting cells from the organ of Corti: some whole cell electrical characteristics and estimates of gap junctional conductance," *Hear. Res.* **52**, 89-98.
- Saremi, A., and Stenfelt, S. (2011). "A physiological signal transmission model to be used for specific diagnosis of cochlear impairments," *AIP: What Fire is in Mine Ears: Proceedings of the 11th International Mechanics of Hearing Workshop* **1403**, pp. 369-373.
- Schmiedt, R. A. (2010). "physiology of cochlear presbycusis," in *The Aging Auditory system*, edited by Gordon-Salant S. F., Fristina, R. D., Popper, A. N., Fay, R. R. (Springer Science+Business Media, USA), pp. 9-38.
- Schmiedt, R. A., Lang, H., Okamura, H. O., and Schulte, B. A. (2002). "Effects of furosemide applied chronically to the round window: a model of metabolic presbycusis," *J. Neurosci.* **22**, 9643-9650.

- Slepecky, N. B. (1996). "Structure of the mamalian cochlea," in *The Cochlea*, edited by edited by Dallos, P., Popper, A., N., Fay, R., R. (Springer-Verlag, USA), pp. 44-129.
- Stenfelt, S., and Ronnberg, J. (2009). "The Signal-Cognition interface: Interactions between degraded auditory signals and cognitive processes," *Scand J Psychol.* **50**, 385-393.
- Stone, J. S., and Cotanche, D. A. (2007). "Hair cell regeneration in the avian auditory epithelium," *Int. J. Dev. Biol.* **51**, 633-647.
- Sumner, C. J., Lopez-Poveda, E. A., O'Mard, L. P., and Meddis, R. (2002). "A revised model of the inner-hair cell and auditory-nerve complex," *J. Acous. Soc. Am.* **111**, 2178-2188.
- Trowe, M. O., Maier, H., Petry, M., Schweizer, M., Schuster-Gossler, K., and Kispert, A. (2011). "Impaired stria vascularis integrity upon loss of E-cadherin in basal cells," *Dev Biol* **359**, 95-107.
- Winter, I. M., Robertson, D., and Yates, G. K. (1990). "Diversity of characteristic frequency rate-intensity functions in guinea pig auditory nerve fibres," *Hear. Res.* **45**, 191-202.

FIGURES

FIG. 1. An overview of the model (mechanical analogy): each vertical branch represents a cochlear partition, from base (left) to apex (right). Each partition incorporates passive loads as well as active elements. Each passive load (BM, RL, and TM) is represented by a classic mass-spring-damper combination. Here, the OHC's somatic motor acts between the BM and the RL while the HB motor acts between the RL and the TM. If x-coordinate corresponds to the longitudinal direction, RL and BM vibrate in x-y plane whereas TM shear motion is in y-z plane. The EP is regarded here as a controller of the OHC and the IHC blocks providing them with necessary supply voltage. The output of the model is the IHC's afferent neural firing towards the brainstem.

FIG. 2. (a) A single cochlear partition along the organ of Corti (the i^{th} partition) depicting a model of the BM and RL and the OHC. The OHC's somatic motor generates a pair-force (f_{OHC}) pushing BM (path 1) and RL (path 2) towards each other. (b) A schematic of how the somatic motor boosts the passive vibrations by means of two feed-forwards; one on the RL and the other one on the BM.

FIG. 3. The *Stria vascularis* is modeled by its body resistance (R_{st}) together with an ideal voltage source (EP). The fluid inside SM is assumed to have a resistance of R_{sm} . This physiological battery provides the MET channels of the OHC HB with necessary charge/current to function properly. The *MET mechanism* drives the somatic motor and is defined by Eq. (1) and (6) and the corresponding physiological parameters. The *somatic motor* is taken from the piezoelectric model of [Liu and Neely (2009), Fig. 1]. The dashed box represents a nonlinear piezoelectric component which converts the gating electrical current (i_d) into a mechanical force (f_{OHC}) which results in the OHC's contraction (X_o).

FIG. 4. (a) The peak receptor current (i_r) induced by opening of the MET channels as a function of the HB displacement (Δx_r) estimated by the Boltzmann function in Eq. (1). The MET is illustrated for two conditions: 1. Healthy and fully active cochlea (EP=89 mV, solid line) 2. A presbycusis cochlea where the EP is degenerated to its half value (EP=44.5 mV,

dashed line). (b) The corresponding slopes are illustrated for the two conditions above. (c) The peak receptor current (i_r) induced by the opening of the MET channels as a function of the HB displacement for the IHCs is also estimated by Eq. (1). The IHC MET is illustrated for the same two conditions above.

FIG. 5. (a) The magnitudes of the RL/base velocity ratios at three representative locations, at 30%, 50% and 70% of the total cochlear length from the base. These ratios are calculated at an intensity corresponding to a 300 nm displacement of the RL. (b) The position-frequency map from the simulations and the position-frequency predicted by Greenwood (1990).

FIG. 6. The vibration pattern along the cochlea (the ‘panoramic view’) in response to pure tones of 1,2 and 4 kHz when simulated at a low intensity. (*left*) The magnitudes in dB. (*right*) The corresponding phase in cycles.

FIG. 7. Comparison between experimental data and the model predictions. (a) Averaged data from [de Boer and Nuttall, (2000), Fig. 1] and [Cooper, (1998), Fig. 1(A)] on the amplitude of the BM motion in the guinea pig cochlea in response to a low level (20 dB) stimuli at a location 3mm from the base (crosses) versus the model prediction at the same location on the cochlea (solid line). (b) The phase of the BM vibration have been reported by [(de Boer and Nuttall, 2000), Fig. 2(B)] at locations between 2mm and 5mm from the base, corresponding to 8% to 20% of the guinea pig cochlear length. These data (crosses) have been fitted with a decaying exponential function (dashed line) and shown versus the model prediction of the phase at the same cochlear region (solid line).

FIG. 8. The effect of the EP degeneration on the gain of the cochlear amplifier and the position-frequency map (tuning pattern) of the cochlea for three conditions: 1) healthy and fully-active cochlea [EP=89mV], 2) when the EP is degenerated to half of its maximum value as a result of metabolic presbycusis [EP=44.5 mV] and, 3) dead cochlea [EP=0]. (*left*) Magnitude of the RL/base velocity ratios at a location corresponding to 30% of the total cochlear length from the base. (*middle*) Magnitude of the RL/base velocity ratios at a position corresponding to 70% of the total length from the base. (*right*) The CFs are shifted backwards as a result of the EP degeneration.

FIG. 9(*left*) The decline in firing rate of the MSR auditory fiber as a function of the EP reduction. (*middle*) Data from Winter *et al.* (1990) on the firing rate of the MSR auditory nerve fibers as a function of the sound intensity at a basal region of the guinea pig cochlea tuned to 16 kHz (crosses). These data are fitted by a three-state, second-order Boltzmann curve leading to a rate-intensity transfer function (solid line). The reduction in the maximum firing rate in turn leads to a decline of the rate-intensity characteristic of the MSR fiber (dashed line). The arrow depicts that as the EP drops to half, in order to obtain a rate of 250 [spikes/second] a higher sound intensity is required. (*right*) The intensity loss caused by the rate-intensity transfer function being manipulated by the EP reduction, illustrated in the dynamic range of the MSR fibers.

FIG. 10 (a) the decline of the human cochlear amplification caused by age-related reduction of the EP shown as a function of the CF for the frequencies from 50 to 4000 Hz. It demonstrates a flat loss in the lower frequencies followed by a sloping loss. (b) The phase difference between the BM velocity (H_{trig}) and the OHC motility force (H_o) in the middle of the cochlear duct for the healthy (EP= 89mV) and the presbycusis (EP=44.5mV) cochlea. (c) The predictions of the modified model for guinea pig versus the CAP threshold deteriorations reported by [Schmiedt, *et al.* (2002), Fig. 4 and Fig. 7] from Furosemide treated and aged gerbil cochleae.

FIG.11. The effect of some common simplifications on the output of the cochlear

model. (*left*) Gain of the cochlear amplifier changes after removal of the BM feed-forward [path (1) in Fig. 2] as a result of neglecting the longitudinal structural coupling. (*middle*) After removal of the BM feed-forward, the position-frequency map (tuning pattern) of the cochlea approaches that of a dead (passive) cochlea. (*right*) Changes in amplification and sensitivity as a result of neglecting the TM's passive mechanical load from the model.