Auditory distortion: toward a non-invasive dissection of cochlear micromechanics

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Introduction

The normal auditory system exhibits such exquisite sensitivity and tuning that when considering the rather blunt resonant patterns evidenced by Békésy at the mechanical level in the cochlea, and the absence of any contrast enhancement by peripheral neural circuits, it occurred to Thomas Gold in 1948 that there had to be some resonance-sharpening system at the mechanical level in the cochlea. The discovery that outer hair cells (OHC) in the organ of Corti exert bi-directional transduction, i.e., produce vibrations when their membrane potential oscillates in response to sound, fully confirmed Gold's inspired foresight.

OHC bi-directional transduction allows regenerative mechanical feedback to take place on top of the basilar membrane, thereby making up for energy loss due to viscous drag in the cochlear liquids. As a result, low-level stimuli receive up to 60-dB amplification, in a finely tuned manner on account of OHC activity having to occur at a proper rhythm to be efficient. A consequence of OHC feeding acoustic energy back to the cochlea is the existence of otoacoustic emissions (OAE) that propagate backward from OHC to the external auditory meatus [1].

OAEs reveal several key features of cochlear micromechanics. First, they vanish or get weaker when the OHC-based feedback loop stops functioning. They also tell that in sharp contrast to most acoustic reproduction systems, the cochlea is essentially nonlinear, likely because so are the OHCs. Thus, intermodulation distortion (e.g., at 2f1-f2) is produced when stimulating the cochlea by pairs of pure, primary tones with neighboring frequencies f1 and f2, and it comes out as an OAE (so-called DPOAE). DPOAEs can be - and have successfully been- used for probing OHCs and cochlear function around the place tuned to the primary stimuli. Our goal is to give a brief overview of recent issues regarding the relationships among DPOAEs, local cochlear function and stages in the OHC-based feedback loop.

DPOAEs: generation place

This place has to be located precisely for DPOAE detection to provide a useful objective tool for mapping OHC lesions. Theoretically, DPOAEs must be generated where maximum interaction occurs between stimuli, and this should happen around the places tuned to f1 and f2, as indirectly suggested by masking experiments where a third tone is made to interfere with the primary tones and the distorting process [2]. This can be checked more directly by performing measurements of sound pressure in the cochlea of a small rodent [3]. For this purpose, a specially designed pressure probe made of sensitive piezoresistive transducers [4] was inserted into the scala vestibuli of turns 1 and 2 of the guinea pig cochlea (Fig.1).

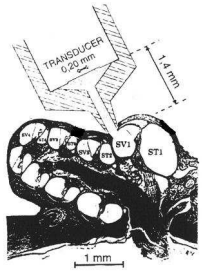

Figure 1: Probe assembly for intracochlear measurements in a guinea pig cochlea as designed in [4]. Here, it is inserted in scala vestibuli of the 1st turn, at a place approximately tuned to 9 kHz.

Its sensitivity and signal-to-noise ratio were such that DPOAEs could be easily analyzed even though their level in the ear canal did not exceed 30 dB SPL. In the example shown on Fig.2, the primary tone levels were 70 dB SPL at f1 and 60 dB SPL at f2, and the resulting DPOAE level was 32 dB SPL in the ear canal.

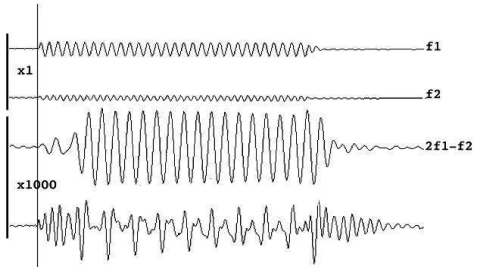

Figure 2: (Top traces) primary stimuli at frequencies f1 and f2 (in this example, short, repeated tone bursts around 8 kHz). (Bottom trace) acoustic response of the intracochlear probe in the first turn of a guinea pig cochlea. A special stimulation protocol with appropriate phase rotation of primaries f1 and f2 allows primary contributions to get cancelled out, thus the acoustic response contains only distortion. (Second trace from bottom) The DPOAE at 2f1-f2 is then extracted by bandpass filtering. Its appearing after a delay relative to stimulus onset is evident. When measured at various places along the cochlea, the DPOAE phase increasingly lags when the measurement place gets farther from the DPOAE source.

Frequencies f1 and f2 varied such that the places tuned to them could be made to fall basalward to the probe position in turn 1, apicalward to the probe position in turn 2 and at all places in between. The phase difference between the DPOAE as measured in turn 1 and 2 was computed (Fig.3): it reached a minimum when the DPOAE source was just midway between the two measurement points, and this happened, as expected, when f2 was tuned to the place just midway between the measurement points [3].

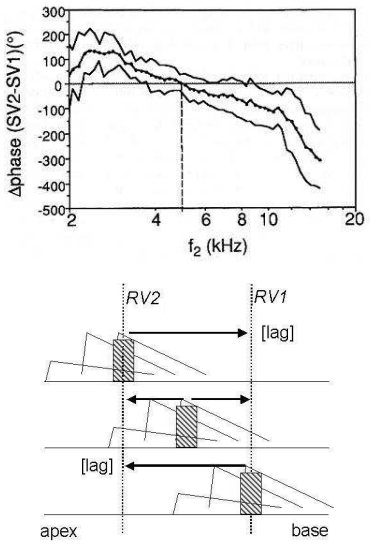

Figure 3: (top) phase shift between DPOAEs as measured in the scalae vestibuli of turn 1 and 2, against frequency f2. (bottom) model of expected phase shift. The envelopes of the primary tones on the basilar membrane, and that of the 2f1-f2 DPOAE, are represented in thin lines. When the DPOAE source is just beneath one of the measurement points (marked with dashed lines), the DPOAE measured there should lead the one recorded at the other measurement point, whereas when the DPOAE source is midway between the measurement points, the two detected DPOAEs should have identical phase lags relative to the signal at its source (shaded areas, assuming that the DPOAE is generated at f2)

Besides, it has been shown that some of the DPOAE emitted from the place tuned to f2 propagates forward to the place tuned to its own frequency (2f1-f2), where it can be reflected backward. Thus, a secondary DPOAE source can interfere with the main one and create a complex microstructure. Nonetheless, damage to the primary source at f2 is expected to knock out both contributions, while damage to the secondary source is hardly visible as long as the DPOAE microstructure is not the object of scrutiny. Furthermore, there are reasons to believe that special conditions have to be met for the secondary DPOAE source to become dominant relative to the primary one coming directly from f2. The intracochlear measurements mentioned previously show no trace of a source around 2f1-f2, and were performed with frequency ratios f2/f1 around 1.20, whereas f2/f1 should have to be < 1.10 for the 2f1-f2 source to be large enough to show up.

DPOAEs, cochlear status and feedback loop

In the normal cochlea, the tuning is so sharp that the excitation pattern of a pure tone along the basilar membrane barely spreads beyond a few hundred micrometers at low levels. The place where DPOAEs are generated (f2) is thus equally narrow and it should be possible to correlate presence or absence of DPOAEs at 2f1-f2 with intact or damaged nonlinear elements around a well-defined place.

Mapping damaged areas

There is clinical evidence that indeed, DPOAE-based mapping of the cochlea provides a sort of objective frequency-specific audiometry as long as damage to OHC is the main cause for cochlear impairment [5]. Mapping is conveniently revealed with the help of so-called DPgrams plotting DPOAE levels against frequency f2. Studies of the fine structure of audiograms as assessed by high-resolution automatic audiometry (Audioscan or Békésy plots) have confirmed that DPgrams match audiometric notches within less than 1 kHz, as shown by the example of Fig.4. Let y- and y+ be the lower and upper boundaries of DPgrams notches whereas x+ and x- are the corresponding limits of the audiometric notches, then we found on a sample of 40 patients that a Pearson linear-regression analysis led to y- = 0.21 + 1.02 x- (r^2 = 0.70) and y+ = 0.4 + 0.91 x+ (r^2 = 0.74; $p<0.0001$ in both cases).

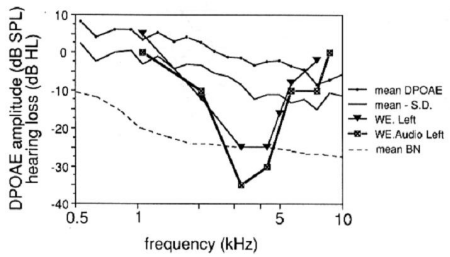

Figure 4: high-resolution audiogram (squares) vs. DPgram (triangles) in an ear with noise-induced hearing loss. The DPgram is conventionally plotted for the 2f1-f2 DPOAE referred to frequency f2 along the horizontal axis. The thin, almost parallel lines delineate the area where normal DPOAEs should fall. The dashed line marks the limit of background noise.

It suggests that DPgrams could reliably serve objective audiometric purposes as far as the damaged frequency intervals were concerned. This can be of interest for forensic purposes, in case of noise-induced damage and related claims for reparation. Yet, it has to be kept in mind that the degree of hearing loss turned out to be less predictable: the amount of residual DPOAEs at 2f1-f2 only showed a weak correlation with audiometric thresholds at f2. This is probably, in part, because DPOAEs generally vanish when the corresponding hearing loss exceeds 30-40 dB HL, and also because noise-induced hearing loss may also damage cochlear inner hair cells, which of course will add up their contribution to the OHC-related hearing loss.

Conditions for persisting DPOAEs despite cochlear impairment

It is widely acknowledged that DPOAEs tend to survive complete interruption of cochlear oxygen supply for a few minutes –up to one hour- provided high-level stimuli are used (> 60 dB SPL) [6]. This has been initially brought forward as a warning that DPOAEs produced by high-level tones were less vulnerable than those produced by low-level tones –which is obviously true- and thus, that they had to come from another source than OHCs [6] as OHCs need oxygen for bi-directional transduction to go on. If it were true that DPOAEs could come from some structure in no

relation whatsoever to the cochlear feedback loop, it would prevent their being useful as probes of OHC function and would pose serious concerns as regards their reliability in auditory screening. Hopefully, more and more data challenge this double-origin view and instead, point to a common OHC-borne structure for all DPOAEs, regardless of stimulus level cochlear status. The arguments are as follows.

Firstly, there are several categories of cochlear damage. The most commonly observed ones involve structural damage to OHC stereocilia (e.g., noise-induced) or OHC cell bodies (e.g. genetic defects, ototoxicity), while others are limited to functional impairment. For example, when stria vascularis is impaired and can no longer maintain a positive endocochlear potential, OHCs cannot work efficiently, however undamaged they can be [This is because OHC electromotility occurs only in response to membrane potential changes, which in turn happen only if potassium ions flow inside OHCs, driven by the endocochlear potential]. In the former cases, DPOAEs never survive cochlear impairment regardless of stimulus levels. Only in the specific cases –the latter ones- where OHCs remain intact but can no longer work properly for lack of suitable endocochlear potential do DPOAEs persist.

A straightforward model explains why and how. For DPOAEs to exist, there must be a nonlinear structure: the most likely candidate is the OHC-borne stereocilia. Their stiffness is known to increase with stereocilia deflection [7]. Next, the nonlinear element must receive an input large enough to be driven in the nonlinear part of its characteristic. When normal, the cochlear feedback loop ensures amplification of the stimulus, while cochlear pathology disrupts the loop-induced gain, thereby inducing deafness. Yet, as far as distortion is concerned, all that is needed is to increase the input level by as many dB as the cochlear gain has dropped, in order to fully make up for the hearing loss. Presence or absence of DPOAEs produced by high-level stimuli thus allows intact OHC to be singled out as they keep intermodulating at high levels, while damaged OHC stereocilia cannot generate DPOAEs regardless of stimulus level.

Confirmations of this model have been recently brought forward [8, 9], showing in addition that neither a coupled tectorial membrane nor an electromechanically active cell body is necessary for DPOAEs to be present, thus pointing to stereocilia as *the* source of DPOAEs.

DPOAE tuning, cochlear tuning and feedback

Several important issues remain open. Even when the cochlea loses its normal tuning due to strial failure, extant OHCs keep generating DPOAEs (Fig.5) and these keep exhibiting tuning of their own. This can be indirectly studied by investigating how a third tone added to the primary tones influences the DPOAE levels, in the presence of a stria vascularis functioning normally at first, then deprived of oxygen supply. Fig.5 shows that normally, the third tone can interact only with the primary tones whose frequencies fall within about 1 kHz of its frequency, owing to the high tuning of the cochlea, so that a narrow V-shaped "iso-suppressor" pattern is obtained, whose width hardly depends on stimulus levels. Several min after ischemia onset (usually for 45 min on), the V-shaped suppression pattern hardly changes (Fig.5). Yet, the basilar membrane in the cochlea is known to have lost its mechanical tuning within minutes, as expected since the OHC-based cochlear feedback loop has become ineffective.

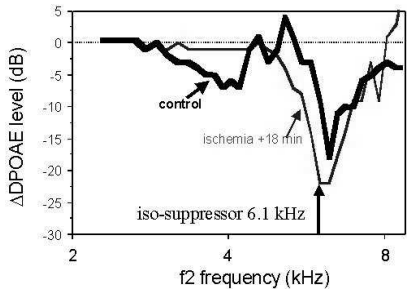

Figure 5: iso-suppressor plots of DPOAE level shifts observed by adding a third tone at fixed frequency and level (vertical arrow, 70 dB SPL) to a couple of pure primary tones (70 dB SPL as well) swept in frequency from 2 to 8 kHz, in a gerbil ear, before (bold line, marked 'control') and 18 min after ischemia onset.

This suggests the existence in the distortion-generating elements of resonance, irrespective of how tuned the whole cochlea is. The nature of these elements and the significance of their resonance –likely, a mechanical one- remains to be investigated. Recall that in [7], OHC stereocilia were said to be resonant, at about the same frequency as the whole cochlea at the place where OHC had been harvested.

Acknowledgments

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