Estimation of the degree of inner and outer hair cell dysfunction from distortion product otoacoustic emission input/output functions

ENRIQUE A. LOPEZ-POVEDA, PETER T. JOHANNESEN & MIGUEL A. MERCHÁN
Instituto de Neurociencias de Castilla y León, Universidad de Salamanca, Salamanca, Spain

Abstract
Cochlear hearing loss is one of the most common forms of disability. It frequently relates to selective or combined dysfunction of inner (IHCs) and outer hair cells (OHCs). Current clinical methods do not allow an accurate estimation of the degree of dysfunction of each cell type, yet such estimation could be highly informative for optimizing hearing aid fitting. Here, it is proposed that the degree of IHC and OHC dysfunction may be estimated from DPOAE input/output curves. It is argued that the controversial aspects of the interpretation of these curves may be elucidated by comparing DPOAE input/output curves with corresponding cochlear input/output curves inferred psychophysically in the same subject. The evidence in support of these ideas is reviewed. We conclude that DPOAE input/output curves obtained with current standard clinical parameters may be used to infer the degree of IHC and OHC dysfunction at 4 kHz but not at lower frequencies. Ideas for further research are presented and discussed.

Key words: cochlear hearing loss, hearing aid, cochlear compression, cochlear non-linearity

Introduction
Auditory disorders are an increasing phenomenon in Western societies. The percentage of elderly people with hearing loss continues to increase, due in part to the aging of the population. One of the most common hearing disorders is cochlear hearing loss. Clinically, it is associated with abnormally elevated hearing thresholds at certain frequencies, air- and bone-conduction losses of comparable magnitude, and auditory brain evoked responses with normal latencies. Therefore, it is related to cochlear or inner-ear dysfunction. Most of these cases are treated with hearing aids.

The physiopathological causes of cochlear hearing loss are diverse. It is frequently associated with total or partial dysfunction of the outer (OHCs) and/or the inner hair cells (IHCs). Standard clinical evaluation allows distinguishing between the two to only a limited extent. However, the functional consequences for the patient are different in each case. Furthermore, hearing aids should in principle be programmed differently according to the type of dysfunction. Unfortunately the programming is, at present, identical in the majority of the cases. This paper summarizes our ideas to design a fast, reliable clinical method to estimate the extent to which both cell types are affected in each cochlear region. The method is based on distortion product otoacoustic emission (DPOAE) input/output functions.

Consequences of IHC and OHC dysfunction
The physiological consequences of selective (or combined) IHC and OHC dysfunction have been studied by comparing auditory nerve (1–4) or basilar membrane (5,6) responses of normal-hearing animals with those having controlled cochlear damage. These studies reveal that selective OHC damage alters basilar membrane responses. Specifically, it reduces cochlear amplification and hence basilar membrane sensitivity to sound. Furthermore, the degree of basilar membrane compression and tuning is decreased. The same applies almost certainly to humans. This has important implications for the patients: their auditory thresholds are elevated, their degree of frequency selectivity is decreased and their hearing dynamic range (i.e. the range of sound levels that they perceive comfortably) is narrowed. This impairs the perception of low-level sounds, reduces speech intelligibility (particularly in noisy environments) and produces the phenomenon known as recruitment (7). By contrast, selective IHC damage does not alter basilar membrane responses. In many
cases (but not all), the increase in auditory threshold is caused by a reduction in the efficiency of the mechano-electrical transduction that takes place in the stereocilia of the IHCs or by an abnormal release of neurotransmitter from the IHCs to the auditory nerve. Therefore, the dynamic range of hearing and the degree of frequency selectivity are approximately normal. (n.b. the reason that these characteristics are not completely normal is that frequency selectivity is reduced when the sound level is increased even in a healthy cochlea, and patients with inner hair cell loss do require abnormally high intensities).

At present, hearing aids are programmed from audiological data based on subjective tests. For example, the degree of compression at different frequencies is set based on loudness tests. These criteria, however, may be inadequate as revealed by the fact that in many cases the optimum strategy selected by the patient corresponds to a linear amplification. This result should not be surprising in light of recent studies that suggest that some patients with cochlear hearing loss have close-to-normal compression and whose hearing loss is thus attributed to IHC dysfunction (8,9). These patients prefer quasi-linear amplification almost certainly because the default hearing aid programme provides compression that adds to their residual cochlear compression. We believe that the efficiency of the hearing-aid fitting process may improve significantly with priori information of the degree of residual compression and the range of sound levels over which it occurs in different cochlear regions (equivalent to the frequency bands in the hearing aid); in other words, with knowledge of the relative degree of OHC and IHC dysfunction.

Methods to estimate the degree of IHC and OHC dysfunction

The following ideas are based on the assumption that the amount of hearing loss (HL) at a given frequency can be partitioned into a component due to OHC dysfunction and a component due to IHC dysfunction (7):

\[ \text{HL}_{\text{TOTAL}} = \text{HL}_{\text{IHC}} + \text{HL}_{\text{OHC}} \]  

(1)

where all quantities are in decibels.

Basilar membrane responses are typically described by means of input/output curves. They represent the amplitude of the response in a certain region of the basilar membrane as a function of stimulus sound intensity (10). In healthy cochleae (Figure 1A), as well as in cochleae with selective IHC dysfunction (Figure 1C), input/output functions appear non-linear, i.e. they show segments with slopes of less than 1dB/dB. These curves may be generally described in simplified form as having three segments. They show a linear segment with slope of 1dB/db at low intensities. This is followed by a compressive segment at moderate levels, i.e. a segment with a slope of less than 1dB/db. Over this segment, every decibel increase in sound intensity produces an increase of basilar membrane response magnitude of less than one decibel. The compressive segment is typically followed by a linear (or close-to-linear) segment at very high levels, although it is still controversial whether the presence of this linear segment is a universal feature (10). By contrast, input/output curves appear perfectly linear in cochleae with total (and selective) OHC loss or dysfunction (6). This is illustrated in simplified form by the thick, dotted line in Figure 1B. The effect of moderate OHC dysfunction on basilar membrane responses is still a matter of debate. Physiological studies suggest that it reduces the degree of compression (i.e. it linearizes the response) and/or the range of sound levels over which compression occur (10). More recent human studies, however, indicate that it typically reduces basilar membrane sensitivity and hence the range of intensities over which the compression occurs, but the degree of residual compression is typically close to normal (8,9). The latter case is illustrated by the thick, dashed line in Figure 1B.

In contrast to OHC dysfunction, IHC damage leaves basilar membrane responses intact. The increase in absolute threshold (indicated by the horizontal black arrow in Figure 1C) is the result of the increase in the basilar membrane excitation necessary to compensate the dysfunction of IHC mechano-electrical transduction (indicated by vertical grey arrows in Figure 1C). The magnitude of basilar membrane responses at very high levels is largely independent of the degree of OHC dysfunction (Figure 1B). As a result, increases in the maximum comfortable level (MCL) of the patient are likely to reflect an inefficient IHC. Therefore, the degree of IHC loss (HL_{IHC}) at each frequency might be estimated as the increase of the MCL of the patient (Figure 1C).

Assuming that basilar membrane responses are linear at very high levels, one may reasonably conclude that the subject is solely affected by IHC dysfunction at any given frequency when the MCL increase matches approximately the increase in absolute threshold at that frequency. This method of estimating the degree of IHC dysfunction, however, would require the active participation of the listener and thus would not be adequate for non-cooperative patients (e.g. newborns or the elderly). Furthermore, it would require using very high level sounds (110–130dB SPL) that may cause inner-ear
damage, which would cause the patient’s hearing to further deteriorate. Additionally, as explained above, it is uncertain that basilar membrane responses are actually linear at very high levels.

An alternative way of determining the degree of IHC and OHC dysfunction would be to estimate basilar membrane input/output curves for the patient and compare them with those of normal-hearing listeners. The principal hypothesis is, in very simple terms, that if these responses were close to normal in hearing impaired listeners, their hearing loss would be related to IHC dysfunction, whereas abnormal responses would indicate OHC related hearing loss. In general, combined IHC and OHC damage is expected (Equation 1), although one type of damage is likely to dominate the other.

A more elaborated analysis of the measured input/output curve would reveal the amount of IHC and OHC dysfunction. The degree of OHC dysfunction (HL_{OHC} in decibels) at any given frequency may be estimated by comparing the amount of hearing loss (HL_{TOTAL} in decibels) with the decrease in basilar membrane sensitivity at that frequency. The latter may be estimated by the horizontal displacement of the linear portion of the patient’s input/output curve at low levels with respect to the normal-hearing curve. The horizontal arrows in Figure 1B illustrate the magnitude of this displacement for listeners with moderate and total OHC loss. If the magnitude of this displacement matches the amount of hearing loss, then one may reasonably conclude that the patient is affected solely by OHC dysfunction. If, however, the amount of hearing loss exceeds the magnitude of the horizontal displacement, then it may be concluded that the patient is affected by combined IHC and OHC dysfunction. Based on Equation (1), the excess in question determines the extent of IHC damage (in decibels). This method is based on the implicit assumption that cochlear responses are linear near threshold, but there is strong evidence that this is actually the case (reviewed in (11)). This method requires being able to obtain basilar membrane input/output curves for any patient and for different frequency regions, fast and reliably.

![Figure 1. Idealized basilar membrane input/output functions.](image)

**Figure 1.** Idealized basilar membrane input/output functions. A. For normal-hearing listeners. The curve consists of a linear segment at low sound intensities (slope of 1dB/dB), followed by a compressive segment at moderate intensities, followed by a linear segment at very high intensities. Compressive segments typically have slopes of 0.1–0.2dB/dB. \( L_{NH} \) and \( V_{NH} \) denote sound intensity and basilar membrane excitation, respectively, at hearing threshold for normal-hearing listeners. \( L_{MCL} \) and \( V_{MCL} \) denote sound intensity and basilar membrane excitation at the maximum comfortable level (MCL). B. As in (A) but for listeners with moderate (thick dashed line) or total (thick dotted line) OHC dysfunction. \( L_{MOHC} \) and \( L_{SOHC} \) denote the absolute thresholds when there is moderate and severe OHC loss, respectively. These are the lowest sound intensities (in decibels) at which the associated basilar membrane response is sufficient to evoke an auditory sensation. HL_{MOHC} and HL_{SOHC} indicate the amount of hearing loss (in decibels) for listeners with moderate and severe OHC dysfunction, respectively. C. As in (A) but for listeners with exclusive IHC dysfunction. This input/output curve is identical as for normal-hearing listeners. IHC dysfunction, however, requires a stronger basilar membrane response to evoke an auditory sensation. The necessary increase in basilar membrane response is depicted by the vertical grey arrows. This increase produces a corresponding increase in absolute threshold (depicted by a horizontal black arrow), but also an increase in the MCL (depicted by a horizontal dotted arrow). HL_{IHC} denotes the amount of hearing loss (in decibels).
Methods to infer human basilar membrane responses

Basilar membrane input/output functions may be inferred psychophysically or physiologically. One of the physiological methods that have been proposed for this purpose is a variant of the clinical method known as distortion product otoacoustic emission (DPOAE) (see, e.g., (12,13)). It consists of plotting the amplitude of the $2f_1 - f_2$ component of the otoacoustic emission (OAE) as a function of the level ($L_2$) of primary tone $f_2$. The details can be found, for example, in (12,13). As a first approximation, the resulting graph is interpreted as the basilar membrane input/output curve for the cochlear region tuned to the $f_2$ primary tone.

DPOAE input/output curves share many characteristics with basilar membrane input/output functions (12,14,15). Specifically, both of them are generally linear at low levels but become compressive above a certain compression threshold (12,16) and both of them are similarly labile to OHC damage (17). Indeed, DPOAEs are affected by OHC damage but not by IHC damage (18). Therefore, when the DPOAE input/output functions of hearing impaired listeners are comparable with those of normal-hearing persons, the cochlear hearing loss can be attributed to IHC dysfunction. Measuring DPOAEs is non-invasive, relatively fast, and does not require the active participation of the listener. This suggests that DPOAEs could be used as a fast and universal way to infer individual basilar membrane input/output functions, and thus to estimate the degree of IHC and OHC dysfunction in clinical conditions (19). It is noteworthy that, in principle, this discrimination could be realized for each cochlear region.

Unfortunately, the correspondence between DPOAE and basilar membrane input/output functions is still controversial for various reasons. First, the origin of the DPOAEs is still unclear. The current notion is that they originate at the cochlear site tuned to the $f_2$ primary, but evidence exists that contributions come from additional distant sites (see, e.g., the discussion of Dorn et al. (12)). Secondly, the shape of any given DPOAE input/output curve depends considerably on the levels ($L_1$ and $L_2$) of the primary tones. Until recently, there has been relative consensus that the so-called Kummer parameters (16) are optimal for evoking the strongest possible DPOAE. However, others have proposed alternative parameters or even using individually optimized parameters for this purpose (20). Thirdly, the shape of DPOAE input/output functions also depends largely on the frequencies of the primaries. Indeed, Gaskill and Brown (21) showed rapid variations (known as ‘fine structure’) of the magnitude of the $2f_1 - f_2$ DPOAE with changing the frequencies of the primaries only slightly around the $f_2$ of interest. This fine structure has a large influence on DPOAE input/output curves, especially at low levels because the DPOAE magnitude can change by as much as 20dB for a change in $f_2$ of only 1/32 octave (22–24).

Towards understanding DPOAE input/output curves

There also exist psychoacoustical masking techniques to infer human basilar membrane input/output functions (reviewed in (25,26)). In their current form, these techniques are not useful for clinical purposes because they require long measuring sessions and the active participation of the patients. These techniques, however, rest on assumptions that are very different from those used to interpret DPOAE input/output functions. We propose that the interpretation of DPOAE input/output functions may be facilitated by comparing them with basilar membrane input/output curves inferred psychophysically in the same subject and for the same cochlear region.

Earlier efforts

Several studies have compared DPOAE input/output curves with presumably corresponding functions inferred psychophysically. Müller and Janssen (19) investigated the similarity of loudness and DPOAE input/output curves in the same subject sample (Neely et al. (15) had done it previously using different subject samples and slightly different methods). They found a high resemblance between the characteristics of the two sets of average input/output curves in normal-hearing and hearing impaired listeners. Müller and Janssen (19) acknowledged, however, that loudness may be affected by retrocochlear mechanisms (see also (27)) and it is also thought that loudness is affected by off-frequency effects (e.g. different spreads of cochlear excitation at different levels) that make it difficult to establish a one-to-one relationship between loudness and underlying basilar membrane input/output curves (28). This undermines the conclusions of Müller and Janssen (19). Furthermore, their conclusions applied to average input/output curves and frequencies of 2–4 kHz, and thus may not be valid individually or for other frequencies, particularly 0.5 and 1 kHz.

Gorga et al. (29) measured the degree of cochlear compression in a very large sample of normal-hearing listeners as estimated from DPOAE input/
output functions at 0.5 and 4 kHz. As a consequence, the input/output functions they reported probably provide a good description of average normal responses. Their results supported the conclusion of earlier psychophysical studies that the degree of compression is similar for apical and basal cochlear sites (30). However, their study did not include within-subject psychophysical/physiological comparisons.

Williams and Bacon (13) inferred cochlear input/output curves psychophysically and using DPOAEs in four listeners and for frequencies of 1, 2, and 4 kHz. The results revealed that both methods yield similar average compression estimates. Like the above-mentioned studies, this study was not intended to investigate within-subject correlations between the results of both methods. Furthermore, their DPOAE input/output curves could have been influenced by the DP fine structure. The influence of the fine structure is greater for individual than for average (across subjects) input/output curves, but can also affect average curves when the sample size is small, as was the case in the study of Williams and Bacon (13).

Studies conducted by the authors

We have recently investigated the degree of correlation between psychophysically inferred input/output curves and DPOAE input/output curves measured in the same subjects, for cochlear sites with characteristic frequencies from 0.5 to 4 kHz (24). Unlike earlier studies, the focus of our study was on within-subject as opposed to average psychophysical/physiological correlations. Additionally, special care was exercised to reduce the influence of the fine structure on individual DPOAE I/O curves by averaging the magnitude of the $2f_1 - f_2$ DPOAE for five $f_2$ frequencies near the frequency of interest. A significant feature of our study was that psychophysical input/output curves were inferred using what is arguably the most accurate method available to date for this purpose. This method is known as the temporal masking curve (TMC) method. The details of this method can be found in (30,31). In our study, we measured DPOAEs using primary frequency tones with the levels proposed by Kummer et al. (16).

We showed that the correlation between psychophysical and physiological (DPOAE) curves is reasonably high at 4 kHz but low at 0.5 and 1 kHz. Figure 2 illustrates a case example. The most likely reason for the lack of correlation at low frequencies (0.5–1 kHz) is the presence of notches and plateaus in the DPOAE curves. We conjectured that the presence of these features suggests that the primary level rule of Kummer et al. (16) may not be optimal (i.e., does not reveal the true underlying basilar membrane input/output curves) at low frequencies. Nevertheless, the low correlation at low frequencies

![Figure 2](image-url)
casts doubts on the postulates and interpretation of input/output curves inferred with either (or both) of the two methods. In other words, the low correlation may be due to problems with the psychophysical method (see, e.g., (11,32)).

Given that the two methods rest on fundamentally different assumptions, the high correlation found at 4 kHz supports the proposition that DPOAEs may be used to infer cochlear input/output curves at that frequency in normal-hearing listeners. Doubts exist, however, that the same applies to lower frequencies of 0.5 and 1 kHz. We also concluded that further research is necessary to show whether the lack of correlation below 4 kHz is due to the use of sub-optimal DPOAE parameters.

Unfortunately, our study did not evaluate the merit of DPOAE input/output curves as a (clinical) tool for assessing the degree of IHC and OHC dysfunction in hearing impaired listeners. This is the focus of our current research. Our results to date, however, suggest that DPOAE input/output curves measured with current stimulus parameters (i.e., the Kummer rule) might be useful to assess residual compression at least in listeners with presbyacusis, who are mostly affected by high-frequency loss.

**Some remaining questions**

The efforts described above are only the beginning and much remains to be done in order for DPOAE input/output functions to be used reliably to infer the degree of OHC and IHC dysfunction in hearing impaired listeners. Two important issues still need to be addressed. First, it is necessary to establish DPOAE parameters (specifically, primary levels L1 and L2) that provide the best estimates of basilar membrane input/output functions at different frequencies, particularly below 4 kHz. When this is achieved, it would need to be investigated if, with these new parameters, the psychophysical/physiological correlations found in normal-hearing listeners at 4 kHz extend to other frequencies. The second important issue is that it is necessary to demonstrate that the psychophysical/physiological correlations found in normal-hearing listeners extend to listeners with various degrees and types of cochlear hearing loss. This would be the best way to promote DPOAE input/output curves to infer the relative degree of IHC and OHC dysfunction in the clinic.

There is one important final point to be made: even if DPOAE input/output functions were proven to correspond to cochlear input/output curves in hearing impaired listeners, it would need to be shown that this information is useful to improve hearing aid fitting. Also the procedure to make use of this information would need to be devised. These are the challenges that keep us going!

**Acknowledgements**

This work was supported by The Oticon Foundation and the Spanish MEC (ref. BFU2006-07536). Parts of this review were drawn or adapted from recent publications (Johannesen and Lopez-Poveda, 2008).

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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