Optimal Primary Tone Levels in Distortion Product Otoacoustic Emissions and the Role of Middle Ear Transmission

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Regensburg, April 2017

The truth is not distorted here,
but rather a distortion is used to
get at truth.

—Flannery O'Connor

Contents

List of Abbreviations

ABG	air-bone gap
ABR	auditory brainstem response
ANOVA	analysis of variance
BM	basilar membrane
cc	cubic centimeter
CHL	conductive hearing loss
CHL_{DP}	DPOAE-based estimate of CHL
CHL_{PT}	pure tone audiometry-based estimate of CHL
daPa	dekapascal
dB	decibel
DPOAE	distortion product otoacoustic emission
EA	energy absorbance
Expt	experiment

F	female
f_1	frequency of the lower-frequency primary tone
f_2	frequency of the higher-frequency primary tone
f_{2param}	value of the multivariable model parameter associated with f_2
f_{DP}	frequency of the DPOAE
FFT	fast-Fourier transform
GM	geometric mean
HL	hearing level
I/O	input/output
kHz	kilohertz
ΔL_{1OPT}	change in L_1 needed to recover an optimal L_1-L_2 relationship
L	left
L_1	level of the lower-frequency primary tone
L_{1ERROR}	error in the prediction of L_{1OPT}
L_{1OPT}	optimal L_1
L_2	level of the higher-frequency primary tone
L_{DP}	level of the distortion product
L_{DPMAX}	maximal L_{DP} observed within a given series
M	male

ml	milliliter
mm	millimeter
n	number
NA	not applicable
NH	normal hearing
OAE	otoacoustic emission
OHC	outer hair cell
PC	personal computer
peSPL	peak equivalent sound pressure level
R	right
RM ANOVA	repeated measures analysis of variance
SD	standard deviation
sec	second
SEM	standard error of measurement
SNR	signal-to-noise ratio
SPL	sound pressure level
TPP	tympanometric peak pressure
TW	tympanometric width
UHF	ulta-high frequency

V_{ea}	equivalent ear canal volume
Y_{tm}	peak-compensated static acoustic admittance

Abstract

Distortion product otoacoustic emissions (DPOAEs) are low-level, audio frequency signals emitted from the cochlea in response to sound, which are measurable within the external ear canal. DPOAEs represent an objective means of assessing the integrity of active cochlear mechanics and are evoked in response to stimulation with two sinusoids, or primary tones, of levels L_1 and L_2. Despite great progress towards predicting the primary tone level relationships which maximize DPOAE amplitude, and thereby clinical utility, in the average ear, significant inaccuracies are routinely observed when attempting to predict optimal characteristics within any given ear. Individual differences in middle ear energy transmission, capable of affecting both the absolute, as well as relative, primary tone level relationships effective within the cochlea, represent an as yet unaccounted for contributor to the predictive difficulties. The purpose of this dissertation was to evaluate the relationship between ear-specific middle ear energy transmission characteristics and optimal DPOAE stimulation parameters with an eye towards increasing personalization, and thereby accuracy, of predicted optimal stimulus levels, expanding the clinical utility of DPOAEs in ears both with normal hearing and minor conductive hearing loss, and increasing insight into the basic mechanisms of DPOAE function in humans. To that end, both univariate and multivariable primary tone level optimization formulas were developed from a sample of 30 participants (57 ears)

with normal hearing. In the univariate model [$L_1 = 0.49L_2 + 41$ (dB SPL)], the average optimal L_1 is predicted for each L_2 in the traditional manner, irrespective of the potential characteristics of a given middle ear. In the multivariable model [$L_1 = 0.47L_2 + 2.40\text{EA} + f_{2param} + 38$ (dB SPL)], the L_1 recommendation is influenced not only by L_2, but also by an ear- and frequency-specific measure of energy absorbance into the middle ear and the primary tone frequency. Results suggest that use of the multivariable formula leads to statistically significant reductions in L_1 recommendation error, as compared to the univariate formula. In contrast to the mean improvement (mean = 0.18 dB, SD = 1.54 dB), which was too small to be considered clinically meaningful, sizable improvements in L_1 recommendation accuracy were identified within individual ears. Though generally weak in the absence of measurable conductive hearing loss (CHL), a stronger relationship between middle ear function and optimal primary tone levels was identified in the presence of mild CHL (3-10 dB). For a single ear of 30 adults with normal hearing, the effect on auditory threshold of increased air pressure within the ear canal was estimated via comparisons between optimal DPOAE primary tone level relationships determined both in the presence and absence of the excess air pressure. A highly significant linear dependence was identified between DPOAE- and pure tone audiometry-based estimates of CHL, $\text{r}(19) = 0.71$, $p < 0.001$. However, the correlation was only significant when ear-specific optimization formula parameters were known. Viewed together, the preceding studies suggest that, for ears presenting normal middle ear function, differences in middle ear energy transmission, as quantified using clinical measures, do not meaningfully influence optimal DPOAE primary tone level relationships on average. However, significant effects can occur in individual ears. Mild conductive hearing loss, on the other hand, has a significant impact on optimal separations. Further, this effect can be exploited

under certain conditions, constituting an additional objective source of information regarding middle ear health.

1 Introduction

Otoacoustic emissions (OAEs) are low-level, audio frequency signals emitted from the cochlea in response to sound, which are measureable within the external ear canal. First recorded in 1978 (Kemp, 1978), OAEs have since revolutionized the understanding of cochlear function, though their origins, as well as clinical potential, are still not fully appreciated. OAEs convey a wealth of information regarding the integrity of active inner ear and middle ear mechanics and have, consequently, found their largest impact in the area of clinical hearing assessment. Distortion product otoacoustic emissions (DPOAEs), a tonal subtype of OAE resulting from intermodulation distortion produced by nonlinear aspects of cochlear processing, are evoked through the simultaneous presentation of two pure tones and have proven useful for myriad clinical purposes. Specifically, DPOAEs have shown utility as an objective means of identifying normal and hearing impaired ears, such as for use in newborn hearing screening programs or in the evaluation of other difficult-to-test populations (Gorga et al., 1997; Musiek and Baran, 1997; Johnson et al., 2007, 2010; Kirby et al., 2011), estimating hearing threshold (Boege and Janssen, 2002; Gorga et al., 2003; Oswald and Janssen, 2003; Janssen et al., 2005), differentiating sensorineural and conductive hearing loss (CHL) (Gehr et al., 2004; Janssen et al., 2005; Janssen, 2013), differentiating cochlear and neural pathology for the diagnosis of auditory neuropathy/synaptopathy (Hood, 2015),

and monitoring for deleterious side-effects of ototoxic medications (Reavis et al., 2011; Konrad-Martin et al., 2012), among other uses. Recently, DPOAEs were also shown to potentially be of use for the objective quantification of conductive hearing loss (Kummer et al., 2006; Olzowy et al., 2010; Deppe et al., 2013). It is this latter role, predicated upon the existence of a systematic relationship between CHL magnitude and DPOAE amplitude, which is of primary interest for this dissertation. In particular, the relationship between ear-specific middle ear energy transmission characteristics and optimal DPOAE stimulation parameters was assessed with an eye towards increasing personalization, and thereby accuracy, of predicted optimal stimulus levels, expanding the clinical utility of DPOAEs in ears both with normal hearing and minor conductive hearing loss, and increasing insight into the basic mechanisms of DPOAE function in humans.

Figure 1.1 presents a schematic representation of a typical computer-based DPOAE measurement system, which includes a probe for stimulus presentation and response collection, digital signal processing (DSP) unit for stimulus generation and response processing, and personal computer (PC) for measurement control. The probe, which contains two miniature receivers and a low-noise microphone, is sealed within the ear canal using a soft rubber ear tip. The DSP unit synthesizes two pure tone signals of frequencies f_1 and f_2, which are subsequently routed to separate receivers within the probe following digital to analog conversion. Independent receivers are used in an effort to prevent the creation of artificial intermodulation distortion products, which can potentially be observed when driving a single receiver by both the f_1 and f_2 signals simultaneously. In this way, the signals are first mixed acoustically within the ear canal, as opposed to electrically at some earlier stage in the stimulation process. The cochlear response, as well as any biological, system, or external noise present within the ear canal, is

collected by the microphone and fed to the DSP unit following analog to digital conversion. Within the DSP unit, a number of signal processing techniques can be applied in an attempt to optimize detection of the DPOAE, with signal averaging being prevalent. Additionally, fast-Fourier transformation is utilized to allow for comparison of the level of the signal+noise in the frequency bin corresponding to the desired distortion product with those surrounding bins containing only noise. A valid DPOAE result is obtained when the level of the signal+noise exceeds the average level of the surrounding noise by a criterion amount or when some other set of measurement quality control standards are met.

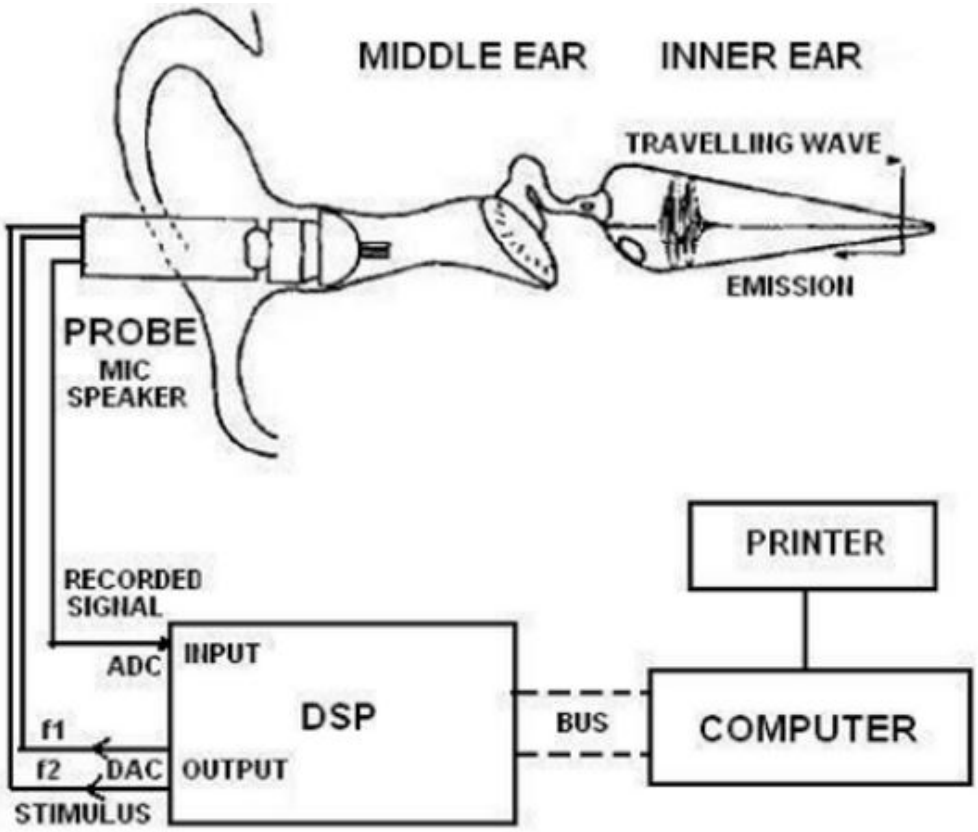

Figure 1.1: Schematic representation of a typical computer-based DPOAE measurement system. Sinusoids of frequencies f_1 and f_2 are synthesized and presented via miniature receivers sealed within an ear level probe. A low-noise microphone collects the response and feeds it to a digital signal processing unit for noise reduction and further processing. Reprinted from "Diagnosis of hearing disorders and screening using artificial neural networks based on distortion product otoacoustic emissions."In Lim, C. T. & Hong, J. C. H (eds.), 13th International Conference on Biomedical Engineering, Jyothiraj, V. P. & Kumar, A. S., 2009, pp. 626-630. Copyright 2009, Springer Verlag - Berlin Heidelberg.

Graphical output of the DPOAE system to the user following measurement within a normal hearing ear is presented in Figure 1.2. The filled circles represent sound pressure levels within $2f_1$-f_2 frequency bins in response to stimuli with frequencies f_1 and f_2 ($f_2/f_1 = 1.22$) and levels $L_1 = 65$ and $L_2 = 55$ (dB SPL). The location of each circle along the abscissa is determined by the f_2 of the associated stimulus pair. Though dependent upon numerous technical, as well as physiological, factors, average DPOAE levels in response to moderate level stimuli range between approximately 5–25 dB SPL and are generally 40–50 dB below the levels of the stimulus tones. The open circles represent the average level of the 5 frequency bins on either side of the bin containing $2f_1$-f_2, or the noise present at the time of measurement. Due to the spectral characteristics of ambient and physiological sounds, noise levels are frequently observed to rise as DPOAE frequency decreases. If the obtained DPOAE amplitudes were purely quantifications of the DPOAE signal, any observed DPOAE level could be taken as evidence of a cochlear response. However, these values reflect the combined contributions of both the DPOAE, as well as any noise present within the given $2f_1$-f_2 bin. Clinical convention dictates that an arithmetic difference between DPOAE and noise levels of approximately 6 dB is sufficient to acceptably limit the contribution of any noise to the overall DPOAE response level, though the arbitrary nature of this rule should be noted. Depending on the aims of the particular study, differences of 12 dB or more are often preferred for research purposes.

1.1 DPOAE generation

A simplified, one-dimensional transmission-line model, which aids in understanding the bi-directional acoustical / mechanical signal flow between the ear canal

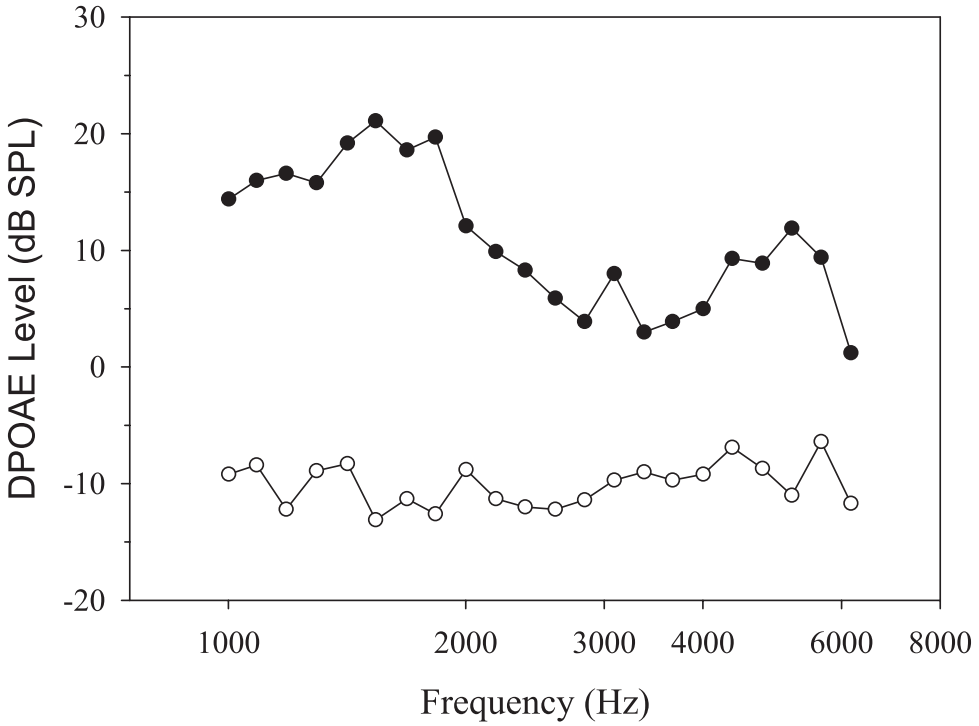

Figure 1.2: Diagnostic DPOAE results obtained within a normal hearing ear. Filled circles represent the levels within the various $2f_1$-f_2 frequency bins. Open circles represent the average level of the 5 frequency bins on either side of the bin containing $2f_1$-f_2, or the noise.

and cochlea during the DPOAE generation and measurement process, is presented in Figure 1.3. Sound pressure (P_e), as observed at any location within the ear canal, is obtained through summation of all pressure waves propagating forward towards the tympanic membrane with those propagating away from the tympanic membrane ($P_e = P_e^+ + P_e^-$), with superscript + and - denoting forward and reverse transmission, respectively. Of note, these waves consist not only of the direct-path signals from the receivers and DPOAE generation region, but also any pressure waves arriving at the measurement location following reflection. The si-

nusoids used to evoke DPOAEs, known as primary tones, are calibrated for level within the ear canal and are of frequencies f_1 and f_2 ($f_1<f_2$) and levels L_1 and L_2 ($L_1 \geq L_2$). The acoustic pressures of the presented tones act on the tympanic membrane ($P_o = P_o^+ + P_o^-$), resulting in mechanical vibrations propagating through the middle ear, which serves as an impedance matching system. Specifically, the effective areal difference between the tympanic membrane and the stapes footplate and the lever constituted by the length of the manubrium of the malleus relative to that of the long process of the incus result, when combined with the middle ear's frequency-dependent spring-mass properties, in a frequency-specific pressure gain, which approximates that loss attributable to the higher impedance of the cochlear fluids as compared to the air within the ear canal (Aibara et al., 2001). This approximately 29-fold pressure increase applied at the base of the cochlea ($P_b = P_b^+ + P_b^-$) allows for the efficient creation of hydromechanical waves within the fluid of the inner ear. These waves subsequently establish a pressure differential across the basilar membrane ($P_c = P_c^+ + P_c^-$), setting up traveling waves along its surface which peak at the characteristic place of each primary tone frequency.

It is currently hypothesized that DPOAEs, as measured within the ear canal, are the vector sum of the products of two distinct generation mechanisms, which are depicted schematically in Figure 1.4. The primary mechanism is an intermodulation distortion mediated by nonlinear aspects of outer hair cell (OHC) transduction, which occurs at the location of maximal overlap between the two traveling waves, or the f_2 region. Consensus regarding the specific nature of the distortive mechanism has not yet been achieved, though a joint effect of OHC (Brownell, 1990) and stereocillia (Liberman et al., 2004) electromotility is suspected. The secondary generator is known as the coherent-reflection mechanism and can be understood as impedance perturbances on the basilar membrane in the area of the

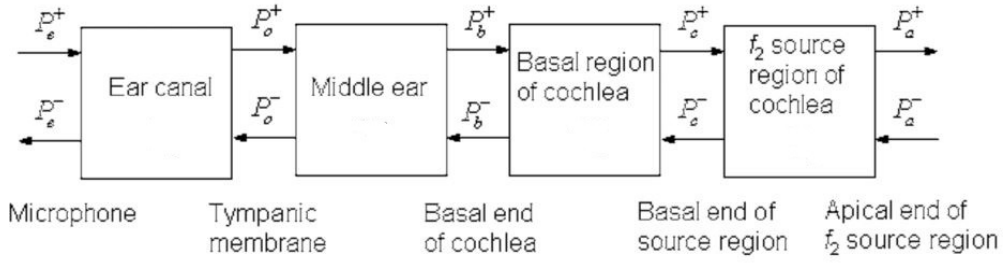

Figure 1.3: Schematic representation of signal flow through the ear canal, middle ear, and cochlea. Superscript + and - represent forward and reverse signal transmission, respectively. Adapted from "Theory of forward and reverse middle-ear transmission applied to otoacoustic emissions in infant and adult ears,"D. Keefe & C. Abdala, 2007, *J Acoust Soc Am*, 121(2), p. 979. Copyright 2007, Acoustical Society of America.

tonotopic place of each distortion product (Shaffer et al., 2003; Shera, 2004).

As a given distortion product is created, its associated pressure wave spreads basally along the basilar membrane from the f_2 region towards the ear canal (P_c^-), as well as apically towards the DPOAE's tonotopic place (P_a^+), where it is partially reflected and re-directed towards the ear canal (P_a^-). Therefore, the DPOAE observed at the probe microphone constitutes a mixture of direct and reflected signals, which have driven the middle ear system in reverse and become measurable at the distortion product frequency. The phase of the product of the distortion mechanism has been shown relatively invariant with frequency, while the component resulting from the coherent-reflection mechanism exhibits a steep phase gradient (Talmadge et al., 1998, 1999; Mauermann et al., 1999; Shera and Guinan, 1999). Due to this difference between the components in terms of the rate of phase change as a function of frequency, quasi-sinusoidal patterns of constructive

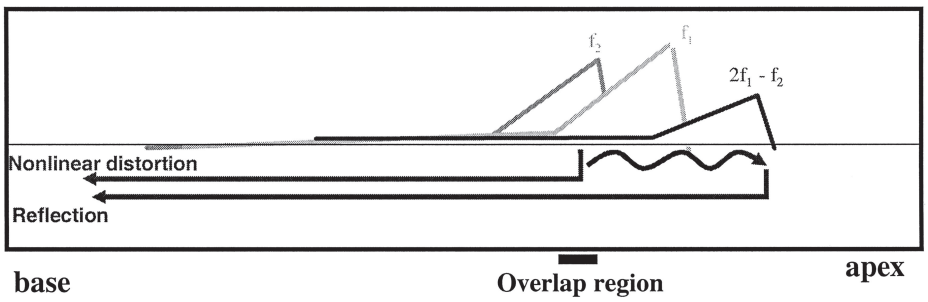

Figure 1.4: Schematic representation of the nonlinear distortion and coherent-reflection mechanisms of DPOAE generation. Compressive nonlinearities in the overlap region of the two stimulus traveling waves, f_1 and f_2, generate distortion products which spread along the basilar membrane in both directions. In this example, energy of the $2f_1$-f_2 distortion product travels basally from the overlap region towards the ear canal, as well as apically towards its tonotopic place, where it is partially reflected by impedance discontinuities. Reprinted from "Sources and Mechanisms of DPOAE Generation: Implications for the Prediction of Auditory Sensitivity,"L. Shaffer et al., 2003, *Ear Hear*, 24, p. 369. Copyright 2003, Lippincott Williams.

and destructive interference can emerge. The level of the observed DPOAE, and thereby the clinical utility of the measure itself, depends greatly upon the phase relationship of the two components at the frequency of interest, with significant peaks or dips, known as fine structure, occurring for frequencies at which interference approaches its extremes. Recent research efforts on the topic of fine structure have largely focused on developing methods to limit the effects of interference on DPOAE amplitude, whether through segregation of the distortion and reflection components in the time domain (Vetesnik et al., 2009; Dalhoff et al., 2013; Zelle et al., 2013) or through use of an additional tone to suppress the reflection component (Heitmann et al., 1998; Talmadge et al., 1999; Dhar and Shaffer, 2004;

Johnson et al., 2007; Kirby et al., 2011). However, multiple studies have also assessed the potential clinical utility of analyzing characteristics of the overall fine structure itself (Brown et al., 1993; Engdahl and Kemp, 1996; Rao and Long, 2011; McMillan et al., 2012; Poling et al., 2014). For example, Engdahl and Kemp (1996) reported significantly reduced fine structure depth in human ears following exposure to moderate-level noise. DPOAE fine structure might therefore prove a sensitive means of detecting noise-induced hearing damage, prior to its impacting subjective auditory thresholds. Despite both areas of research having produced promising results, much is yet to be done, as there currently exists neither a widely-accepted clinical method for reducing fine structure nor a deep understanding of the implications of its presence.

The largest and most commonly utilized DPOAE in humans occurs at the cubic difference frequency $2f_1$-f_2, though multiple mathematically-related distortion products are frequently observable in response to stimulation with a single pair of primary tones ($2f_1$-f_2, $3f_1$-$2f_2$, $4f_1$-$3f_2$, etc., as well as $2f_2$-f_1, $3f_2$-$2f_1$, $4f_2$-$3f_1$, etc.). Figure 1.5 displays the various distortion products measurable within one particular normal hearing ear in response to stimulation with primary tones of frequencies $f_1 = 1.639$ kHz and $f_2 = 2.000$ kHz. In addition to the clinically-utilized distortion product at $2f_1$-f_2 (dashed line), other signals are observable at $3f_1$-$2f_2$ and $2f_2$-f_1 (dotted lines), though the potential clinical utility of these additional distortion products is not well-understood. Attempts to include distortion products at frequencies other than $2f_1$-f_2 in clinical protocols, such as for the objective identification of hearing status, have met with limited success (Gorga et al., 2000; Fitzgerald and Prieve, 2005; Kirby et al., 2011).

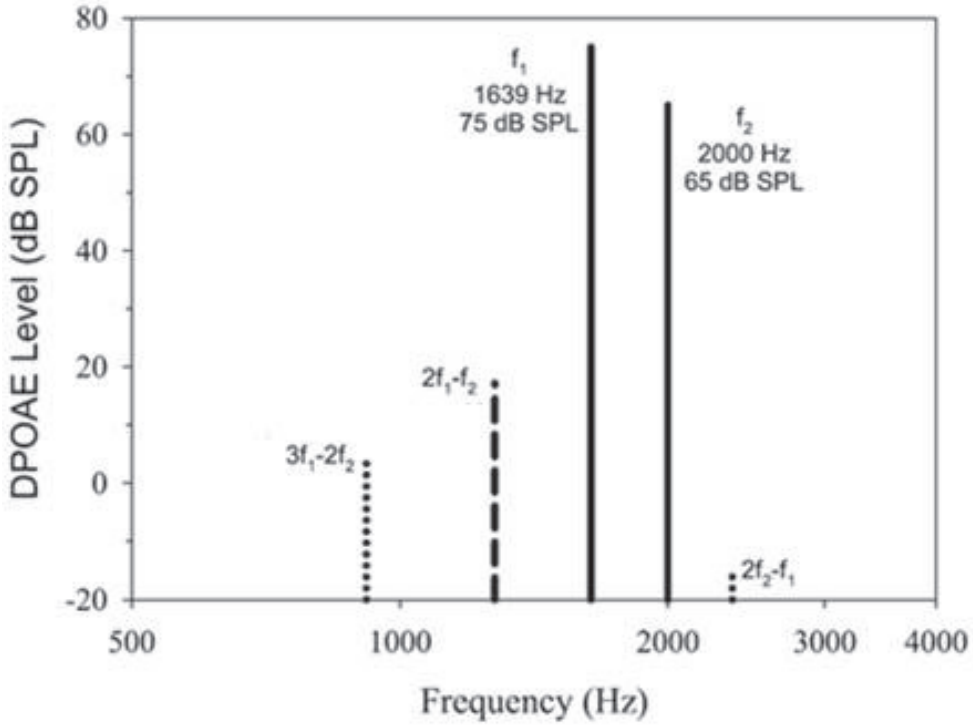

Figure 1.5: Results of a DPOAE measurement with $f_1 = 1.639$ kHz and $f_2 = 2.000$ kHz (gray lines). Numerous distortion products are created simultaneously, including the clinically-meaningful DPOAE at $2f_1$-f_2 (dashed line). Though other distortion products are also apparent (dotted lines), they are currently of limited clinical utility.

1.2 Primary tone optimization

The basilar membrane (BM) can be conceptualized as a frequency analyzer, in that traveling waves resulting from signals of differing frequency achieve their maximum displacements at specific and roughly distinct locations along its surface (Plomp, 1964). This frequency resolving capability results partly from the membrane's passive mechanical properties. Specifically, the basilar membrane becomes progressively wider and less stiff from base to apex, with these gradients resulting in the base of the BM responding with the largest displacements to high-frequency signals, while the apex responds to low-frequency signals best. However, this mechanism in isolation is not capable of producing the high-degree of frequency resolution associated with normal basilar membrane function. Rather, an active mechanism, commonly described as the cochlear amplifier (Davis, 1983), is additionally needed. The term cochlear amplifier refers to the nonlinear, frequency-selective amplification of the traveling wave by means of outer hair cell electromotility and stereociliary active bundle movements.

In the case of DPOAEs, distortion generation is maximal when BM displacement due to stimulation with the two primary tones is equivalent near the characteristic place of f_2. However, the frequency-selective nature of the cochlear amplifier dictates that growth of the basilar membrane response with alteration of stimulus level will differ between the BM locations maximally responding to the two primary tones. Specifically, growth for the f_2 primary tone will be significantly more compressive than for the f_1 primary tone, which generally peaks between 0.25 and .50 octaves below f_2. Figure 1.6 shows how the growth of basilar membrane displacement velocity changes as a function of distance from the measurement location (characteristic place for 8.5 kHz). For test frequencies surrounding the

measurement location, growth is compressive. However, for frequencies below 7 kHz or above approximately 11 kHz, growth becomes more linear. Equalizing displacement resulting from the primary tones, and thereby optimizing primary tone characteristics, therefore necessitates an increasing level difference between the primary tones as the level for f_2 is decreased.

Numerous studies have attempted to identify the DPOAE stimulus parameter relationships which optimize traveling wave overlap, and therefore DPOAE level, for the average ear. Table 1.1 displays the results of a systematic review summarizing available studies having investigated the effect of primary tone frequency and level relationships on the level of the $2f_1$-f_2 distortion product. While results in humans have generally revealed an optimal primary tone frequency ratio of approximately $f_2/f_1 = 1.2$–1.22 (Harris et al., 1989), findings in terms of optimal level separations of the primary tones have been more divergent (Whitehead et al., 1995; Stover et al., 1996; Kummer et al., 1998; Neely et al., 2005; Johnson et al., 2006). However, despite variability in the specific parameter values suggested, more recent primary tone level optimization formulas tend to be consistent in their recommendations of increasing L_1-L_2 separation with decreasing L_2. Kummer et al. (1998), for example, suggested the optimization formula $L_1 = 0.4L_2 + 39$ [dB SPL], thereby recommending a 0.4 dB reduction in L_1, and therefore a 0.6 dB increase in L_1-L_2, for each 1 dB reduction in L_2. However, several trends are also apparent in the available datasets, which serve to threaten their utility and necessitate further research. First, sample sizes have tended to be small, with 14 of 32 studies consisting of 10 or fewer participants. This limitation serves not only to restrict the generalizability of findings, but also the range of statistical methods available for use during data analysis. For the set of identified studies, inferential statistics were provided in only 10 of 32 reports. Second, perhaps due to

the significant time investment involved in more complete experimental protocols, the majority of studies investigated only a narrow range of the available L_1,L_2 space and f_2, leaving open the possibility of different behavior in other parameter regions. Third, in spite of the recognized significance of primary tone level separation for the optimal generation of DPOAEs and the potential for middle ear characteristics to impact this separation through alteration of primary tone levels during forward transmission (see Figure 1.3), no primary tone level optimization formula currently attempts to account for ear- and frequency-specific middle ear effects.

Aural acoustic immittance measures, such as 226-Hz tympanometry and wideband energy absorbance (EA), represent time-efficient methods through which the signal transmission properties of specific ears can be quantified. Indeed, both have been successfully implemented clinically for the differentiation of healthy ears and those exhibiting middle ear pathology, such as otitis media with effusion (Marchant et al., 1986; Johansen et al., 2000; Beers et al., 2010). Of significance for the present work, owing to relatively high test-restest reliability, these measures can even be used for the assessment of differential transmission characteristics within healthy middle ears. Incorporating tests of middle ear energy transmission into the development of primary tone level optimization formulas could therefore allow for a more accurate estimate of the L_1-L_2 effective within a given, as opposed to average, cochlea, and thereby simultaneously contribute not only towards a better understanding of middle ear function, but also allow for an ear-specific customization of recommended DPOAE primary tone levels. Furthermore, improved understanding of the nature of the systematic relationship between middle ear and primary tone characteristics could potentially be leveraged for diagnostic use, such as the objective identification of CHL and estimation of its magnitude.

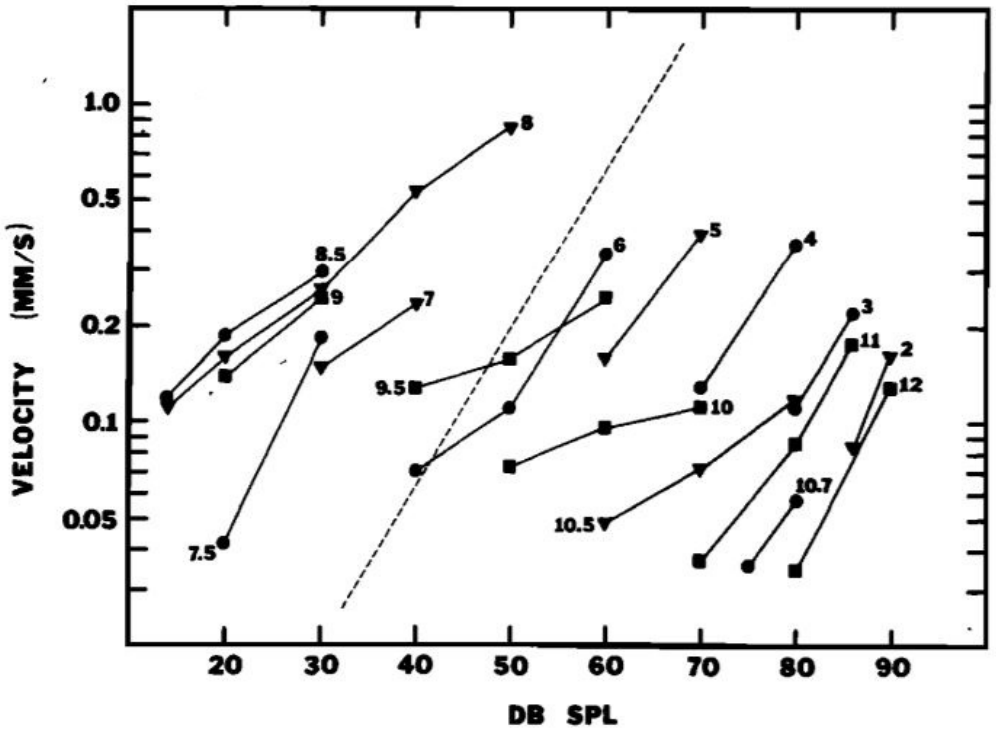

Figure 1.6: Basilar membrane velocity input-output functions obtained for several frequencies at the tonotopic place for 8.5 kHz in chinchilla. The dashed line represents linearity. Functions for frequencies around 8.5 kHz display more compression than those below 7 kHz or above 11 kHz. Primary tone pairs will be increasingly affected by this difference in growth rate as f_2-f_1 increases. Adapted from "Basilar membrane mechanics at the base of the chinchilla cochlea. I. Input-output functions, tuning curves, and response phases,"Robles et al., 1986, *J Acoust Soc Am*, 80(5), p. 1366. Copyright 1986, Acoustical Society of America.

Table 1.1: Studies investigating the influence of primary tone frequency and level relationships on the level of the $2f_1$-f_2 DPOAE. ANOVA – analysis of variance, dB – decibel, Expt – experiment, F – female, GM – geometric mean, HL – hearing level, Kruskal-Wallis H – Kruskal-Wallis one-way analysis of variance, L – left, M – male, n – number, NA – not applicable, NH – normal hearing, R – right, RM ANOVA – repeated measures analysis of variance, SPL – sound pressure level, UHF – ultra-high frequency. Reprinted from "A systematic review of stimulus parameters for eliciting distortion product otoacoustic emissions from adult humans,"L. Peterson et al., 2017, *Int J Audiol*, 1-10. doi:10.1080/14992027.2017.1290282. Copyright 2017, Taylor & Francis.

Study	Subjects	Stimulus parameters	Findings
1. Abdala (2000). USA	10 subjects (6M, 4F), 24 to 35 y	**f_2:** 1.5, 3, 6 kHz **f_2/f_1 ratio:** 1.14; 1.20; 1.35 **L_1/L_2:** L_1 80 to 30 dB SPL in 5 dB steps. L_2 always 10 dB below L_1	**Best f_2/f_1:** 1.20 **Best L_1/L_2:** ≥60/50 dB SPL No inferential statistics used
2. Abdala (1996). USA	10 subjects (6F, 4M), 23 to 34 y	**f_2:** 1.5, 6 kHz **f_2/f_1 ratio:** 13 different ratios from 1.03 to 1.39 **L_1/L_2:** L_1 65, 60, 55, 50 dB SPL. L_2 fixed at 50 dB SPL	**Best f_2/f_1:** Overall best = 1.203 (dependent on L_1/L_2, 1.21 for f_2 = 1.5 kHz, 1.19 for f_2 = 6 kHz) **Best L_1/L_2:** 65/50 & 60/50 dB SPL Based on ANOVA
3. Beattie & Ireland (2000). USA	55 ears (55F), 20 to 26 y	**f_1/f_2 GM:** 0.531, 1, 2, 4 kHz **f_2/f_1 ratio:** 1.21 **L_1/L_2:** 55/55, 45/45, 35/35 dB SPL	**Best f_2/f_1:** NA (fixed at 1.21) **Best L_1/L_2:** 55/55 dB SPL No inferential statistics used
4. Beattie & Jones (1998). USA	30 ears (30F), 21 to 30 y	**f_2:** 0.593 to 6.093 kHz (11 test frequencies) **f_2/f_1 ratio:** 1.21 **L_1/L_2:** L_1 75, 65, 55, 45 dB SPL. L_2 +5, 0, -5, -10, -15 dB SPL relative to L_1	**Best f_2/f_1:** NA (fixed at 1.21) **Best L_1/L_2:** 75/75 dB SPL. If L_1=65, best 65/60 and 65/55 dB SPL. If L_1=55 dB SPL, best 55/50, 55/45 & 55/40 dB SPL Based on ANOVA
5. Beattie et al. (2004). USA	50 ears (50F), 19 to 26 y	**f_2:** 1, 2, 4 kHz **f_2/f_1 ratio:** 1.2 **L_1/L_2:** L_1 75 to 40 dB SPL in 5 dB steps. L_2 always 10 dB below L_1	**Best f_2/f_1:** NA (fixed at 1.2) **Best L_1/L_2:** 75/65, 70/60, 65/55, 60/50 dB SPL No inferential statistics used on DPOAE absolute levels
6. Bian & Chen (2008). USA	8 ears in phase 1, 8 in phase 2, 23 to 40 y	**f_2:** 4 kHz **f_2/f_1 ratio:** 1.2 to 1.8 in 0.1 steps (phase 1); 1.15, 1.185, 1.22, 1.255, 1.29, 1.325, 1.36 (phase 2) **L_1/L_2:** L_1 and L_2 swept independently from 75 to 54 dB SPL in 3 dB steps	**Best f_2/f_1:** 1.22 to 1.25 **Best L_1/L_2:** 75/72 dB SPL No inferential statistics used
7. Bonfils et al. (1991). France	20 ears in expt 1, 18 to 28 y	**f_2:** 0.813 to 1.161 kHz; DPOAE frequency kept constant at 707.5 Hz **f_2/f_1 ratio:** 1.06 to1.38 in 0.2 steps **L_1/L_2:** 30/30 to 80/80 dB SPL in 6 dB steps	**Best f_2/f_1:** 1.22-1.30 **Best L_1/L_2:** 84/84 dB SPL No inferential statistics used

8.	Chida et al. (2001). Japan	177 ears (30M, 64F), 6 to 69 y. NH – 97 ears	**f_2:** 1, 2, 4 kHz **f_2/f_1 ratio:** 1.22 **L_1/L_2:** 70/70, 60/60, 60/50 dB SPL	**Best f_2/f_1:** NA (fixed at 1.22) **Best L_1/L_2:** 70/70 dB SPL Based on ANOVA
9.	Dhar et al. (1998). USA	40 ears (10M, 10F), 18 to 30 y	**f_2:** 1, 1.5, 2, 3, 4, 5, 6 kHz **f_2/f_1 ratio:** 1.22 **L_1/L_2:** 70/70, 60/60, 50/50, 40/40 dB SPL. Then for each, L_1 increased in 5 dB steps until L_1 - L_2=15 dB SPL, except 85/70 dB SPL, which was replaced with 80/65 dB SPL	**Best f_2/f_1:** NA (fixed at 1.22) **Best L_1/L_2:** 75/70 dB SPL Based on ANOVA
10.	Dhar et al. (2005). USA	3 subjects (3 ears)	**f_2:** 1.55 to 1.95, 1.8 to 2.2 & 2.25 to 2.65 kHz in 4 to 8 Hz steps **f_2/f_1 ratio:** 1.053, 1.065, 1.08, 1.11, 1.14, 1.18, 1.22, 1.26, 1.30, 1.32, 1.34, 1.36 **L_1/L_2:** a) 75/75, 65/65, 45/45 dB SPL. b) L_1 65 & L_2 60, 55, 50, 45 dB SPL	**Best f_2/f_1:** 1.22 **Best L_1/L_2:** not reported Based on ANOVA
11.	Dreisbach & Siegel (2001). USA	*Expt 1.* 6 ears (3F, 3M), 22 to 30 y *Expt 2.* 8 ears (3F, 5M), 19 to 30 y	*Expt 1.* **f_2:** 2, 2.5, 3, 4, 5, 6, 8 kHz **f_2/f_1 ratio:** 1.2 **L_1/L_2:** L_1 65 to 30 dB SPL in 3 dB steps. L_2 -15 dB SPL relative to L_1 *Expt 2.* **f_2:** 2, 4, 8 kHz **f_2/f_1 ratio:** 1.11 to 1.33 in steps of 0.02 **L_1/L_2:** not stated	*Expt 1.* **Best f_2/f_1:** NA (fixed at 1.2) **Best L_1/L_2:** 70/60 dB SPL *Expt 2.* **Best f_2/f_1:** 1.23 for 2 kHz, 1.198 for 4 kHz, 1.17 for 8 kHz **Best L_1/L_2:** not stated No inferential statistics used
12.	Dreisbach & Siegel (2005). USA	8 subjects (5F, 3M), 22 to 32 y	**f_2:** 2, 5 kHz **f_2/f_1 ratio:** 1.2 **L_1/L_2:** L_1 70, 60, 50, 40, 30 dB SPL and L_2 varied for each L_1 from 70 to 30 dB SPL in 3 dB steps. L_1 varied for each L_2 from 70 to 30 dB SPL in 3 dB steps & L_2 70, 60, 50, 40, 30 dB SPL	**Best f_2/f_1:** NA (fixed at 1.2) **Best L_1/L_2:** 70/70 dB SPL No inferential statistics used
13.	Gaskill & Brown (1990). UK	3 expts, 34 ears in total (19F, 15M), 15 to 50 y. N varies within expts	3 expts **f_1:** variable from 0.5 to 8 kHz **f_2/f_1 ratio:** variable from 1.075 to 1.375 **L_1/L_2:** L_1 variable from 30 to 70 dB SPL with variable **L_1/L_2** levels	**Best f_2/f_1:** 1.225 **Best L_1/L_2:** Levels <60 dB SPL with L_1> L_2 by 15 dB SPL No inferential statistics used on DPOAE absolute levels. Samples for individual expts as low as n=4. Samples for individual results as low as n=1
14.	Harris et al. (1989). USA	5 subjects (4M, 1F), 10 ears, 21 to 27 y	**DPOAE *f*:** 1, 2.5, 4 kHz **f_2/f_1 ratio:** 0.2 steps from 1.01 to 1.79 (1 kHz), 1.01 to 1.59 (2.5 kHz), 1.01 to 1.41 (4 kHz) **L_1/L_2:** 85/85, 75/75, 65/65 dB SPL	**Best f_2/f_1:** 1.2 **Best L_1/L_2:** 85/85 dB SPL for 1 kHz, 65/65 dB SPL for 2.5 & 4 kHz No inferential statistics used

15.	Hauser & Probst (1991). Switzerland	10 subjects (5M, 5F), 20 ears, 22 to 32 y	**GM**: 1, 2, 4 kHz **f_2/f_1 ratio**: 1.25 (1 kHz), 1.23 (2 kHz), 1.21 (4 kHz) **L_1/L_2**: L_1 75 or 65 dB SPL. L_2 varied in 5 dB steps from 20 to 90 dB SPL	**Best f_2/f_1**: NA (fixed at 1.25 for 1 kHz, 1.23 for 2 kHz, 1.21 for 4 kHz) **Best L_1/L_2**: 75/65 & 65/55 dB SPL at 1 & 2 kHz, 75/75 & 65/60 dB SPL at 4 kHz No inferential statistics used
16.	Johnson et al. (2006). USA	20 subjects, gender & age not stated	**f_2**: 1, 2, 4, 8 kHz **f_2/f_1 ratio**: 1.05 to 1.4 in steps of 0.05 **L_1/L_2**: L_1 from 43 to 76 dB SPL. L_2 ranged from 17 to 69 dB SPL	**Best f_2/f_1**: 1.2 when L_2<40 dB SPL, >1.2 when L_2>40 dB SPL **Best L_1/L_2**: absolute best not stated No inferential statistics used
17.	Kummer et al. (2000). Germany	22 ears (12F, 10M), 19 to 35 y	**f_2**: 0.977, 1.456, 1.953, 2.979, 3.955, 5.597, 7.959 kHz **f_2/f_1 ratio**: 1.2 **L_1/L_2**: L_1 70 to 30 dB SPL in 5 dB steps. L_2 65 to 5 dB SPL in 5 dB steps (giving 61 L_1/L_2 combinations)	**Best f_2/f_1**: NA (fixed at 1.2) **Best L_1/L_2**: $L_1 = 0.4\ L_2 + 41$ dB SPL Based on linear regression
18.	Lasky (1998). USA	*Expt 2:* 6 subjects, 21.8±1.7 y *Expt 3:* 6 subjects, 22.4±1.6 y	*Expt 2.* **f_2**: 2, 4, 8 kHz **f_2/f_1 ratio**: 1.2 **L_1/L_2**: L_1 80 to 25 dB SPL in 5 dB steps. L_2 0, -10 & -15 dB SPL relative to L_1 *Expt 3.* **f_2**: 1, 2, 4, 8 kHz **f_2/f_1 ratio**: 1.1, 1.2, 1.3 **L_1/L_2**: L_1 65 to 40 dB SPL in 5 dB steps. L_2 65 to 40 dB SPL in 5 dB steps	*Expt 2.* **Best f_2/f_1**: NA (fixed at 1.2) **Best L_1/L_2**: For higher L_1 values, L_1 should be equal to L_2 *Expt 3.* **Best f_2/f_1**: 1.2 **Best L_1/L_2**: 65/60 dB SPL No inferential statistics used
19.	Londero et al. (2002). France	11 ears with NH, 20 to 39 y	**f_2**: 2, 3, 4, 5, 6, 7, 8 kHz **f_2/f_1 ratio**: 1.05 to 1.70 in steps of about 0.02 **L_1/L_2**: 70/70, 60/60 dB SPL	**Best f_2/f_1**: 1.16 to 1.24 **Best L_1/L_2**: 70/70 dB SPL No inferential statistics used
20.	Lonsbury-Martin et al. (1990). USA	44 ears (10F, 12M), 21 to 30 y	*Expt 1.* **GM**: 1 to 8 kHz in 100 Hz steps **f_2/f_1 ratio**: 1.21 **L_1/L_2**: 85/85, 75/75, 65/65 dB SPL *Expt 2.* **GM**: 1, 1.2, 1.5, 2, 2.3, 2.8, 3.5, 4.3, 5.3, 6.5, 8 kHz **f_2/f_1 ratio**: 1.21 **L_1/L_2**: 85/85 to 25/25 dB SPL in 5 dB steps	*Expt 1.* **Best f_2/f_1**: NA (fixed at 1.21) **Best L_1/L_2**: 85/85 dB SPL *Expt 2.* **Best f_2/f_1**: NA (fixed at 1.21) **Best L_1/L_2**: 85/85 & 75/75 dB SPL for GM >1.5, 85/85 dB SPL for GM ≤1.5 kHz No inferential statistics used
21.	Marcrum et al. (2016). Germany	57 ears (30 subjects), 21 to 33 y	*Expt 2.* **f_2**: 1, 2, 3, 4, 6 kHz **f_2/f_1 ratio**: 1.22 **L_1/L_2**: $L_1 = 0.4\ L_2 + 39$ dB SPL and up to 15 dB above and below this point in 3 dB steps, L_2 varied from 20 to 75 dB SPL in 5 dB steps	**Best f_2/f_1**: NA (fixed at 1.22) **Best L_1/L_2**: $L_1 = 0.49\ L_2 + 41$ dB SPL Based on linear regression and Kruskal-Wallis H
22.	Meinke et al. (2013). USA	17 ears (17M) with NH, 18 to 50 y	**f_2**: 5160 points between 0.258 to 18.023 kHz **f_2/f_1 ratio**: 1.025 to 1.5 in 0.025 steps **L_1/L_2**: 75/75, 65/55 dB SPL	**Best f_2/f_1**: 1.2 to 1.35 **Best L_1/L_2**: 75/75 dB SPL No inferential statistics used

23.	Mills et al. (2007). USA	40 ears (10F, 10M), 18 to 24 y	f_2: 1, 2, 3, 4, 6, 8 kHz **f_2/f_1 ratio**: 1.21 & 1.28 **L_1/L_2**: L_1 85 to 20 dB SPL in 5 dB steps, L_2 always -10 dB SPL relative to L_1	**Best f_2/f_1**: 1.28 **Best L_1/L_2**: 85/75 dB SPL No inferential statistics used
24.	Moulin (2000a). France	18 ears (10F, 8M), 24 to 46 y	f_2: 0.757, 0.879, 1, 1.257, 1.5, 2.002, 3.003, 4.004, 5.005, 6.006 kHz **f_2/f_1 ratio**: 1.02 to 1.50 in steps of 0.012 to 0.02 **L_1/L_2**: 65/60 dB SPL	**Best f_2/f_1**: $1.244 - 0.105 \log(f_2)$, ranging from near 1.24 at $f2$=1 kHz to near 1.18 at f_2=5 kHz **Best L_1/L_2**: NA (L_1/L_2 fixed at 65/60 dB SPL) Polynomial function used to fit best f_2/f_1 curve
25.	Neely et al. (2009). USA	322 ears (176 subjects), 11 to 80 y	f_2: 0.7 to 8 kHz in half-octave steps **f_2/f_1 ratio**: $1.22+\log_2(9.6/f2)(L_2/415)^2$ **L_1/L_2**: $L_1=80+0.137\log_2(18/f2)(L_2-80)$ dB SPL. L_2 80 to -20 dB SPL in 5 dB steps	**Best f_2/f_1**: not stated **Best L_1/L_2**: L_2=80 dB SPL for f_2=0.7 to 2 kHz. L_2=70-80 dB SPL for f_2=4 or 8 kHz Polynomial function used to fit best f_2/f_1 curve
26.	Nielsen et al. (1993). Denmark	10 ears (2F, 3M), 22 to 42 y	**GM**: 0.5, 1, 1.5, 2, 3, 4, 6, 8 kHz **f_2/f_1 ratio**: 1.15 to 1.4 in 0.05 steps **L_1/L_2**: 75/75 dB SPL	**Best f_2/f_1**: 1.2 to 1.25 **Best L_1/L_2**: NA (fixed at 75/75 dB SPL) No inferential statistics used
27.	Rasmussen (1993). Denmark	14 ears (3F, 4M), 25 to 55 y	**GM**: 0.5, 1, 1.5, 2, 3, 4, 6, 8 kHz **f_2/f_1 ratio**: 1.23 **L_1/L_2**: L_1 75, 70, 65 dB SPL with L_2=75 dB SPL, L_1=75 dB SPL with L_2 75, 70, 65 dB SPL	**Best f_2/f_1**: NA (fixed at 1.23) **Best L_1/L_2**: 75/75 dB SPL No inferential statistics used
28.	Smurzynsky et al. (1990). USA	10 ears (5 subjects), 21 to 41 y	**DPOAE f**: 1.53 kHz **f_2/f_1 ratio**: 1.03 to 1.4 in 0.02 steps **L_1/L_2**: 70/70 dB SPL	**Best f_2/f_1**: 1.18 **Best L_1/L_2**: NA (fixed at 70/70 dB SPL) No inferential statistics used
29.	Stover et al. (1999). USA	14 subjects with NH, young adults	f_2: 1 to 8 kHz in half-octave steps **f_2/f_1 ratio**: 1.01 to 1.5 kHz, where f_1 was moved in 25 Hz steps for each f_2 frequency **L_1/L_2**: L_1 75 to 45 dB SPL in 5 dB steps. L_2 -10 dB SPL relative to L_1	**Best f_2/f_1**: Not stated **Best L_1/L_2**: 75/65 dB SPL No inferential statistics used
30.	Vento et al. (2004). USA	36 ears (18F, 18M), 18 to 25 y	f_2: 2, 4, 6 kHz **f_2/f_1 ratio**: 1.01 to 1.4 **L_1/L_2**: 65/55, 50/40 dB SPL	**Best f_2/f_1**: 1.203 to 1.4 **Best L_1/L_2**: 65/55 dB SPL Based on ANOVA
31.	Vinck et al. (1996). Belgium	101 ears (58F, 43M), 19 to 28 y	f_2: 0.696 to 6.348 kHz in 11 steps **f_2/f_1 ratio**: 1.22 **L_1/L_2**: 80/80, 75/75, 70/70 dB SPL	**Best f_2/f_1**: NA (fixed at 1.22) **Best L_1/L_2**: 75/75 dB SPL No inferential statistics used
32.	Whitehead et al. (1995a). USA	16 ears (11 subjects), 18 to 44 y	**GM**: 1 to 8 kHz in 139 Hz steps **f_2/f_1 ratio**: 1.21 **L_1/L_2**: L_1 85, 75, 65 dB SPL. L_2 0, -5, -10, -15 dB SPL relative to L_1	**Best f_2/f_1**: NA (fixed at 1.21) **Best L_1/L_2**: 85/85, 85/80, 75/75, 75/70 dB SPL No inferential statistics used

1.3 Outline

Optimal DPOAE primary tone levels in normal-hearing adults: In this chapter, theory underlying optimal stimulation of distortion product OAEs is introduced and published primary tone level optimization formulas are reviewed. In Experiment 1, relevant technical and physiological sources of variability, heretofore not acknowledged in DPOAE optimization formula development, are evaluated. Specifically, a clinical DPOAE system is assessed for signal stability, reliability, and stimulation accuracy. Additionally, test-retest reliability of evoked DPOAE levels is assessed in an effort to quantify, among other features, the reliability of the physiological mechanisms of DPOAE generation. In Experiment 2, frequency-specific and nonspecific DPOAE primary tone level optimization formulas are developed, which incorporate the findings of Experiment 1. Finally, formula performance is compared with that of formulas currently utilized clinically (see Chapter 2).

Acoustic immittance measures in the prediction of optimal DPOAE primary tone levels: In this chapter, 226-Hz tympanometry and wideband energy absorbance measures are evaluated in terms of their utility for the improvement of primary tone level recommendation accuracy, resulting in the inclusion of energy absorbance results into a multivariable model. Recommendation accuracy is then compared between the multivariable formula developed here and the univariate formula developed in Chapter 2. Additionally, normative ranges for 226-Hz tympanometry and wideband energy absorbance are presented. (see Chapter 3).

Estimation of minor conductive hearing loss in humans using distortion product otoacoustic emissions: In this chapter, the feasibility of objectively quantifying experimentally-produced, minor CHL in humans is assessed by comparing CHL estimates resulting from DPOAE- and traditional pure tone

audiometry-based methods. Additionally, the accuracy of DPOAE-based CHL estimates obtained when using generic, as opposed to ear-specific, optimal primary tone level formula parameters is investigated. The method's potential for clinical implementation is discussed (see Chapter 4).

Conclusions: The primary findings of this dissertation are reviewed and discussed in context. An effort is made to highlight potential clinical implications and directions for future research (see Chapter 5).

2 Optimal DPOAE Primary Tone Levels in Normal Hearing Adults

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2.1 Introduction

Distortion product otoacoustic emissions (DPOAEs) are low-level signals, which are emitted from the cochlea in response to the simultaneous presentation of two primary tones. Primary tones are sinusoids presented at frequencies f_1 and f_2 ($f_2 > f_1$) and levels L_1 and L_2 ($L_1 \geq L_2$). Current understanding of DPOAE generation suggests that they originate from two sources. The primary source is a compressive nonlinearity in basilar membrane (BM) mechanics near the f_2 characteristic place. The second is the coherent-reflection mechanism, which reflects the apically-spreading energy of the $2f_1$-f_2 distortion product at its tonotopic place (Shaffer et al., 2003). Due to differences between the products of these sources in terms of the rate of phase change as a function of frequency, quasi-sinusoidal patterns of constructive and destructive interference can emerge. The level of the

DPOAE as measured within a given ear can depend greatly upon the phase relationship of the two products at the frequency of interest. Clinically-significant peaks or dips, known as fine structure, can occur for frequencies at which interference approaches its extremes. Across many ears, however, systematic effects of phase will be reduced and DPOAE level will be greatest when overlap of the BM excitation patterns for the primary tones is maximized near the f_2 place (Shaffer et al., 2003; Young et al., 2012).

As excitation patterns along the BM are strongly affected by the functional state of outer hair cells (OHC) and OHC function is reduced in hearing loss, DPOAEs have been found useful as an objective means of identifying hearing impairment (Gorga et al., 1993; Kim et al., 1996; Stover et al., 1996; Gorga et al., 1997; Musiek and Baran, 1997; Dorn et al., 1999; Johnson et al., 2007, 2010; Kirby et al., 2011), estimating subjective auditory threshold (Nelson and Kimberley, 1992; Suckfull et al., 1996; Boege and Janssen, 2002; Gorga et al., 2003; Oswald and Janssen, 2003; Janssen et al., 2005; Johnson et al., 2010), and even quantifying minor conductive hearing losses (Kummer et al., 2006; Olzowy et al., 2010).

Optimizing primary tone characteristics is essential for maximizing the level, and therefore utility, of DPOAEs. Gaskill and Brown (1990) reported that for a given f_2/f_1 ratio and L_2, the level of the DPOAE (L_{DP}) will be maximized in response to a certain optimal L_1 (L_{1OPT}) and will be reduced in response to other values of L_1. Multiple investigations have since reported optimization formulas attempting to predict L_{1OPT} in both normal and hearing impaired ears (Whitehead et al., 1995; Stover et al., 1996; Kummer et al., 1998; Neely et al., 2005; Johnson et al., 2006). Utilizing data from Gaskill and Brown (1990), Kummer et al. (1998) identified the relationship $L_1 = 0.4L_2 + 39$ [dB SPL] as that which maximizes DPOAE level. In an extensive follow-up investigation with the f_2/f_1 ratio fixed

at 1.2 in accordance with the findings of Harris et al. (1989), Kummer et al. (2000) similarly reported $L_1 = 0.4L_2 + 42$ [dB SPL] as optimal for L_2 ranging from 20 to 65 dB SPL and for frequencies from 1 to 8 kHz. Utilizing a more time-efficient method of varying L_1 continuously, Neely et al. (2005) explored a broad range of L_2 values for frequencies ranging from 1 to 8 kHz and suggested the formula $L_1 = 0.45L_2 + 44$ [dB SPL]. In addition to recommending greater differences between L_1 and L_2 than those of Kummer et al. (1998), the authors also identified an effect of frequency on optimization formula parameters, grounding it in theory of frequency-selective basilar membrane mechanics (Ruggero et al., 1997; Reichenbach and Hudspeth, 2014).

Johnson et al. (2006) suggested that if L_{DP} is maximized via optimized overlap of excitation patterns on the BM, then all parameters affecting the excitation patterns should be varied simultaneously. To that end, they varied both the levels and the frequency ratio of the primary tones over a much wider range of values than had previously been done (Gaskill and Brown, 1990; Abdala, 1996), developing an optimization formula with both level- and frequency-specific components. This result is consistent with the premise that overlap near the f_2 characteristic place is affected by raising or lowering the peak of the excitation pattern at the f_1 place via L_1 modifications, shifting the f_1 place itself via f_2/f_1 ratio modifications, or some combination of both. Though Johnson et al. (2006) reported that DPOAE levels in response to such a complex stimulation paradigm either matched or exceeded those obtained using the recommendations of either Kummer et al. (1998) or Neely et al. (2005), the effect was generally small and did not appear to provide consistent benefit (Johnson et al., 2010; Kirby et al., 2011). Attempting to control for the effects of the coherent-reflection mechanism, such as through the use of suppressor tones, has likewise led to mixed results (Kirby et al., 2011).

Despite great progress in the theory and practice of evoking DPOAEs, several important factors have yet to be properly accounted for in L_{1OPT} recommendations. First, optimization formulas do not currently account for the imperfect repeatability of the DPOAE itself. Formulas to predict L_{1OPT} are traditionally derived via linear regression through the L_1 points found to have evoked the largest DPOAEs for the various L_2. To date, all studies appear to have considered a given L_1 superior to its neighboring values if its associated L_{DP} was higher by as little as 0.1 dB. This method neglects variability attributable to the stimulating system, the physiological processes which create the DPOAE, as well as the recording of DPOAEs. Wagner et al. (2008) reported data on the repeatability of DPOAE measurements without probe replacement and with stimuli characteristics held constant, finding a mean standard error of measurement (SEM) across frequencies of 0.67 dB. SEM can be interpreted as the standard deviation of the L_{DP} distribution which could be expected if a given test condition were repeated numerous times. These results call into question the practice of accepting minimal differences in L_{DP} in optimization formula creation, as L_1 leading to statistically equivalent L_{DP} would then have to be discarded. Second, determining the presence and influence of frequency effects on optimization formula parameters appears to have traditionally been performed via visual inspection of data sets. As the presence of frequency effects would strengthen the integration of theories of BM mechanics with those of DPOAE generation, it is worthwhile to evaluate results for effects of frequency using appropriate statistics. Furthermore, should such effects be found, it remains unclear if their inclusion, given the real-world limits of stimulation precision achievable with clinical OAE systems, would result in actionable differences in L_{1opt} when compared with frequency-independent recommendations.

This study was conducted in order to: 1) Assess reliability of DPOAEs when

evoked without probe replacement to determine the smallest significant change in L_{DP}. 2) Develop an L_1 optimization formula incorporating findings from objective 1 and evaluate it for effects of frequency.

2.2 Methods

2.2.1 Participants

Participants were normal hearing adults, with normal hearing defined as air-conduction thresholds at or below 15 dB HL (IEC 60655, 1979), as measured with ER-3A insert earphones (Etymotic Research, Elk Grove, IL), for audiometric test frequencies between 0.125 and 8 kHz. No participants exhibited a significant air-bone gap (ABG), with ABG defined as a difference between air-conduction and bone-conduction thresholds exceeding 10 dB at any octave frequency between 0.5 and 4 kHz. Middle ear function was screened via 226-Hz tympanometry using an Interacoustics A/S Titan (Middelfart, Denmark). A given ear passed the screen if it exhibited tympanometric peak pressure between -100 and +50 daPa and peak-compensated static acoustic admittance between 0.3 and 1.5 mmhos (Roup et al., 1998). Otoscopy was completed to confirm that ear canals were free of cerumen. All participants denied a history of middle ear infection, noise exposure, tinnitus, and any other otologic symptoms.

Participants were non-randomly assigned to either the first or second experiment based solely upon personal time constraints. Eleven participants (21 ears) between the ages of 20 and 44 years (mean = 24.4 years, SD = 2.8 years) were enrolled in and completed the first experiment. Thirty participants (57 ears) between the ages of 21 and 33 years (mean = 25.5 years, SD = 2.6 years) were enrolled in and completed the second experiment. Research methods for both

experiments were approved by the Institutional Review Board of the University Hospital Regensburg.

2.2.2 Equipment & stimuli

The commercially available Echoport ILO292-II otoacoustic emission system with a GD TE+DPOAE probe (Otodynamics, Hatfield, UK) was used for stimulus generation and calibration, DPOAE recording, and response analysis. A 2048-point fast-Fourier Transform (FFT) was used to analyze responses, resulting in a bin size of approximately 12 Hz. Noise level was defined as the average level in dB of the five FFT bins on either side of the bin containing 2f1-f2. Signal level was defined as the level in dB of the bin containing $2f_1$-f_2, after the acoustic pressure of the noise had been subtracted from that of the signal. The system was controlled via the Windows 7-based ILOv6 software package installed on a PC. All measurements were performed in a sound-treated booth.

Calibration of primary tones was conducted in-situ at the plane of the probe using an SPL-based method and a chirp stimulus. Concerns have been expressed regarding the potential impact of standing waves on the calibrated level of primary tones when using this method (Gilman and Dirks, 1986; Siegel and Hirohata, 1994); however, it was selected for the following reasons. First, participants with a wide range of ear canal dimensions were tested in this study, thereby reducing the systematic impact of standing waves. Second, the resilience against standing waves in the frequency range of interest offered by other calibration methods, such as the Sound Intensity Level (Neely and Gorga, 1998) or Forward Pressure Level methods (Neely and Gorga, 2010), is not yet well-established and potentially small (Burke et al., 2010; Rogers et al., 2010; Kirby et al., 2011; Reuven et al., 2013). Third, the SPL method is utilized by a significant majority of clinical OAE measurement

systems and therefore represents the current standard, if imperfect.

2.2.3 Evaluation of probe signal stability

As reliability of evoked DPOAEs decreases with increases in the variability of primary tone stimuli over the course of a measurement or across measurements, initial technical measurements within a 2 cc coupler were conducted. The DPOAE probe was sealed into one end of a hard-walled, plastic tube with a residual distance from the probe tip to the other end of 20 mm, approximating the separation observed when DPOAEs are measured in adult ears (Siegel and Hirohata, 1994). The microphone of a Bruel-Kjaer 2236 sound level meter (Type 1) was sealed into the tube opposite the probe. For frequencies 1, 2, 3, 4, and 6 kHz, stimulus level was varied from 20 to 75 dB SPL in 5 dB steps, with stimulation lasting 60 seconds at each level. Third-octave filtering around the frequencies of interest and a slow time constant (1 second) were activated. Maximum deviation of the sound pressure level registered by the sound level meter from its value after 3 seconds of stimulation was recorded for each level. The first 3 seconds of stimulation were not included to allow for stabilization of the initial level reading. This process was repeated 3 times per level for each of 2 probe channels, resulting in a total of 180 measurements.

2.2.4 Experiment 1: Evaluation of L_{DP} reliability

In an effort to quantify the magnitude of L_{DP} variability in the absence of stimuli changes, DPOAEs were recorded at f_2 = 1, 2, 3, 4, and 6 kHz with f_2/f_1 = 1.22 and $L_1 = L_2$ = 65 dB SPL in 21 normal hearing ears. Stimulus pairs were presented a minimum of 10 seconds each, with response averaging continuing, if necessary, until a 12 dB signal-to-noise (SNR) ratio was achieved. Measurements

at each frequency were conducted twice without replacement or re-calibration of the probe. The standard error of measurement was calculated for each frequency and taken as a measure of L_{DP} reliability.

$$\text{SEM} = \text{s} \cdot \sqrt{1 - r},$$

where s is the standard deviation of the combined baseline and follow-up measurements and r represents the correlation between the baseline and follow-up measurements. Accepting the assumption of a normal distribution and requiring a confidence level of 95%, a level difference between two measurements of at least 1.96 SEM is needed before it can be accepted as greater than the effects of test-retest reliability.

2.2.5 Experiment 2: Development of an optimization formula

The second experiment was conducted in order to identify the average L_1-L_2 differences resulting in maximally evoked DPOAEs for a broad range of frequencies and stimulus levels. The data were collected in 57 normal hearing ears for f_2 = 1, 2, 3, 4, and 6 kHz with $f_2/f_1 = 1.22$, while L_2 was varied from 20 to 75 dB SPL in 5 dB steps. For each discrete L_2, L_1 was stimulated according to the formula $L_1 = 0.4L_2 + 39$ [dB SPL] (Kummer et al., 1998), as well as up to 15 dB above and below this point in 3 dB steps. Stimulation 15 dB above the recommended level was not possible for values above 65 dB SPL due to the probe's upper output limit of 80 dB SPL. Measurements within an artificial ear simulator (Type IEC 60711) revealed no significant impact of system distortion for any test frequency at 80 dB SPL or below. Stimuli were presented for a minimum of 20 seconds, with response

averaging continuing, if necessary, until a 12 dB SNR was achieved or the noise level fell below -20 dB SPL.

The L_1 of a given primary tone pair was defined as L_{1OPT} if it fulfilled the following conditions. First, SNR for the measurement of interest, as well as for the measurements immediately preceding and following in the L_2 series, was $\geq$12 dB. This requirement reduces the potential impact of undetected system distortions on outcomes and is consistent with previous work (Kummer et al., 1998, 2000). A result of this condition, however, is that the maximum L_{DP} for a given L_2 could not be associated with either the highest or lowest L_1 in the L_2 series. While this ensured that only points representing growth function peaks were included in further analyses, it also had the consequence that growth functions exhibiting no saturation within the primary tone level constraints were not included in the analysis. Follow-up testing to assess the impact of excluding these functions revealed no effect on the final optimization formula. Second, the resultant L_{DP} was within 1 dB of the maximum L_{DP} obtained from a measurement fulfilling the first condition in the L_2 series. This requirement reduces the bias of only including the L_1 associated with the highest L_{DP}, when test-retest reliability of DPOAE measurements, rather than primary tone level differences, might be responsible for the difference. The criterion of 1 dB is in agreement with a previous report of DPOAE reliability without probe replacement (Wagner et al., 2008).

2.2.6 Data analysis

Consistent with previous work, the primary tone level optimization formula was derived as a linear function ($L_{1OPT} = aL_2 + b$). For each ear and frequency, L_{1OPT} were plotted against L_2 and a linear regression analysis was performed to obtain the optimization formula slope and y-intercept. Mean coefficients for each

frequency were obtained by averaging across ears. Averaging across frequencies provided the final formulas. The Kruskal-Wallis H Test was used for comparisons between frequency groups, as well as optimization formulas. Pairwise comparison was performed using Dunn's method with a Bonferroni correction for multiple comparisons. Statistical analyses were conducted using Sigmaplot 12.5 (Systat Software Inc., San Jose, CA).

2.3 Results

2.3.1 Evaluation of probe signal stability

A contributing factor to the variability of any evoked response is the stability of the evoking stimuli. For the equipment used in this study, stability was found to be very high. For frequencies 1, 2, 3, 4 and 6 kHz and levels ranging from 20 to 75 dB SPL, level readings via the sound level meter varied over the course of the 60 second measurements by a maximum of 0.1 dB SPL. While a high degree of stability could have been predicted due to the use of professional-grade, digital equipment, its quantification nonetheless allows for a more precise attribution of any variability observed in real ears.

2.3.2 Experiment 1: Evaluation of L_{DP} reliability

The purpose of a primary tone level optimization formula is to predict the L_1 required to maximize L_{DP} for any given L_2. As this formula is determined by directly comparing the L_{DP} associated with various L_1, the reliability of L_{DP} is of great importance. Table 2.1 displays standard errors of measurement for each of five f_2 frequencies, as well as a mean across frequencies. SEM appears relatively

stable for f_2 = 3–6 kHz, while reaching its maximum and minimum at f_2 = 1 and 2 kHz, respectively. It should be noted, however, that SEM for 1 and 2 kHz differed by only 0.3 dB. Combining all frequencies, L_{DP} exhibited a mean SEM of 0.52 dB (SD = 0.11). According to these results, the minimum L_{DP} difference between two measurements which can be accepted as reliable is approximately 1.96 x 0.52 dB, or approximately 1 dB. Wagner et al. (2008) investigated reliability over a wide range of stimulus levels, with results generally indicating increasing variability as stimulus level was lowered below 50 dB SPL. However, their across-frequency and across-stimulus level mean SEM of 0.67 dB agrees well with the present findings. To date, no study on primary tone optimization has explicitly accounted for the random variability of L_{DP} when establishing optimization formula parameters.

Frequency (kHz)	**SEM**
1	0.67
2	0.37
3	0.54
4	0.47
6	0.53
average (1-6 kHz)	0.52

Table 2.1: Standard error of measurement (SEM) calculated separately for five f_2 frequencies and for the 1–6 kHz range of f_2 frequencies. Reprinted from "Average optimal DPOAE primary tone levels in normal-hearing adults,"S.C. Marcrum et al., 2016, *Int J Audiol*, 55, p. 328. Copyright 2016, Taylor & Francis.

2.3.3 Experiment 2: Development of an optimization formula

Table 2.2 displays optimization formula coefficients for each of five f_2 frequencies, as well as across-frequency means. As frequency increased from 1 to 6 kHz, slopes of the optimization formulas decreased from 0.57 to 0.38 dB/dB and y-intercept values rose from 34 to 48 dB. The overall pattern of these results is consistent with the presence of frequency effects on coefficient values.

Frequency (kHz)	**Slope (a)**	**95% CI**	**Y-intercept (b)**	**95% CI**
1	0.57	[0.49. 0.65]	34	[29.46, 38.54]
2	0.52	[0.45. 0.59]	40	[35.63, 44.37]
3	0.48	[0.42. 0.54]	43	[39.53, 46.47]
4	0.48	[0.43. 0.53]	41	[37.88, 44.12]
6	0.38	[0.34. 0.43]	48	[45.14, 50.86]
average (1-6 kHz)	0.49	[0.46. 0.52]	41	[39.28, 42.79]

Table 2.2: Coefficients of optimization formula: $L_{1OPT} = a^*L_2 + b$. Means and confidence intervals (CI) were calculated separately for five f_2 frequencies and for the 1–6 kHz range of f_2 frequencies. Reprinted from "Average optimal DPOAE primary tone levels in normal-hearing adults,"S.C. Marcrum et al., 2016, *Int J Audiol*, 55, p. 328. Copyright 2016, Taylor & Francis.

Statistical comparison of parameters obtained for each ear, when grouped by frequency, confirmed a significant effect of frequency on both slope ($\chi^2(4) = 26.237$, $p < 0.001$) and y-intercept ($\chi 2(4) = 33.098$, $p < 0.001$). Specifically, parameters for $f_2 = 6$ kHz were significantly different from all lower frequencies in terms of both slope ($p < .0001$) and y-intercept ($p < 0.001$). Differences between frequency groups in both slope and y-intercept for $f_2 = 1$ to 4 kHz were not significant ($p > 0.05$). Based on the results of this analysis, the following optimization formulas were proposed:

For the 1–6 kHz range of f_2 frequencies:

$L_1 = 0.49L_2 + 41$ [dB SPL] (Eq. 2.1)

For the 1–4 kHz range of f_2 frequencies:

$L_1 = 0.51L_2 + 39$ [dB SPL] (Eq. 2.2)

For $f_2 = 6$ kHz:

$L_1 = 0.38L_2 + 48$ [dB SPL] (Eq. 2.3)

Before attempting to select between several optimization formulas, it is first necessary to know the degree of precision with which primary tone levels can be delivered by the DPOAE system. If two formulas recommend L_1 that differ by less than the stimulating precision of the system, then the less frequency-specific formula should be preferred. Analyzing the difference between the targeted SPL and the obtained SPL over a wide range of L_2 and within many ear canals is one means of obtaining this information. Figure 2.1 presents differences between the targeted stimulation levels and the levels measured at the plane of the probe microphone for the 33,395 stimulations presented in Experiment 2. Looking across frequency, no clear pattern of error is visible, suggesting that the equipment and

calibration method used were equally capable of meeting low- and high-frequency targets accurately. Median error did not exceed 1 dB for any frequency and mean stimulation error averaged across frequency was found to be 0.14 dB (SD = 1.0 dB). Applying this information to formula selection, it can be argued that optimization formulas recommending L_1 differing by less than approximately 2 dB (0.14 + 1.96 x 1 dB) should be considered functionally equivalent.

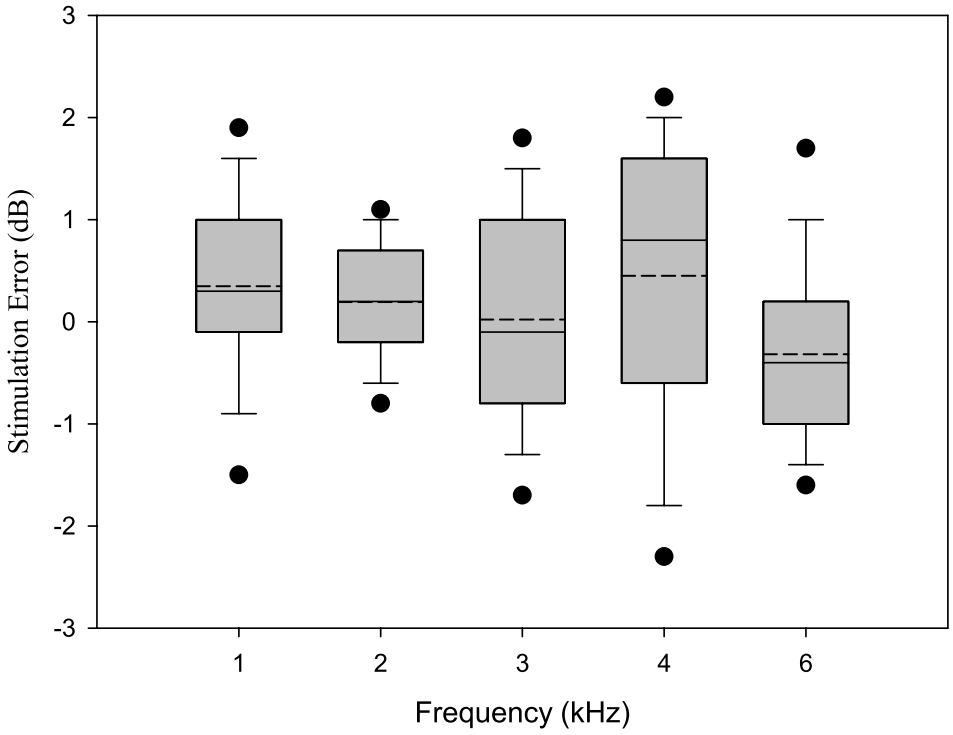


Figure 2.1: Distribution of primary tone level stimulation error (dB) by frequency. The data represent differences between the targeted primary tone levels and the levels obtained in the ear canal as measured by the DPOAE probe for 33,395 DPOAE measurements (Experiment 2). Dashed lines represent arithmetic means. Filled circles represent 5^{th} (lower) and 95^{th} (upper) percentiles. Whiskers represent 10^{th} (lower) and 90^{th} (upper) percentiles. Solid box lines represent 25^{th} (lower), 50^{th} (in-between), and 75^{th} (upper) percentiles. Reprinted from "Average optimal DPOAE primary tone levels in normal-hearing adults,"S.C. Marcrum et al., 2016, *Int J Audiol*, 55, p. 329. Copyright 2016, Taylor & Francis.

Figure 2.2 displays recommended L_1 for each L_2 according to Eq. 2.1–3. For L_2 ranging from 20 to 75 dB SPL, the maximum difference in recommended L_1 between the 1–6 kHz (Eq. 2.1) and the 1–4 kHz (Eq. 2.2) optimization formulas

developed in this study is 1.18 dB. When comparing the 1–6 kHz paradigm (Eq. 2.1) with the frequency-specific formula for 6 kHz (Eq. 2.3), a difference of 2 dB is exceeded only for $L_2 \leq 50$ dB SPL. As this range of L_2 is lower than that generally recommended in the literature for optimal separation of normal hearing and hearing impaired ears (Stover et al., 1996), the 1–6 kHz paradigm (Eq. 2.1) can be recommended for this purpose. However, use of Eq. 2.3 could be preferable when attempting to elicit DPOAEs at $f_2 = 6$ kHz nearer to auditory threshold. Due to the very low L_2 required and the growing difference between Eq. 2.1 and Eq. 2.3 with decreasing L_2, a frequency-specific formula might be expected to outperform.

Figure 2.3 displays the present study's 1–6 kHz optimization formula (solid line), as it compares to other published formulas over a wide range of L_2. Good agreement exists between the present results and those of Neely et al. (2005). For $L_2 = 55$ dB SPL, Whitehead et al. (1995), who notably derived an optimal relationship primarily based on responses from 3 kHz, recommends an L_1 4.5 dB above the present study, while Kummer et al. (1998) recommends stimulation 7 dB below the present study. Unlike the recommendation for this L_2 of Neely et al. (2005), these L_1 differ from the present study's recommendation by more than 2 dB and can therefore be considered functionally distinct. Notably, $L_1 = L_2 + 10$ [dB SPL] (Stover et al., 1996) lies close to the present study when L_2 is moderately-high, but diverges as L_2 is lowered.

2.3.4 Importance of primary tone level optimization

Optimization formulas represent the average optimal L_1-L_2 relationship; however, they are not necessarily optimal in any given ear, especially when unique and highly significant fine structure is exhibited. However, as such average formulas serve well

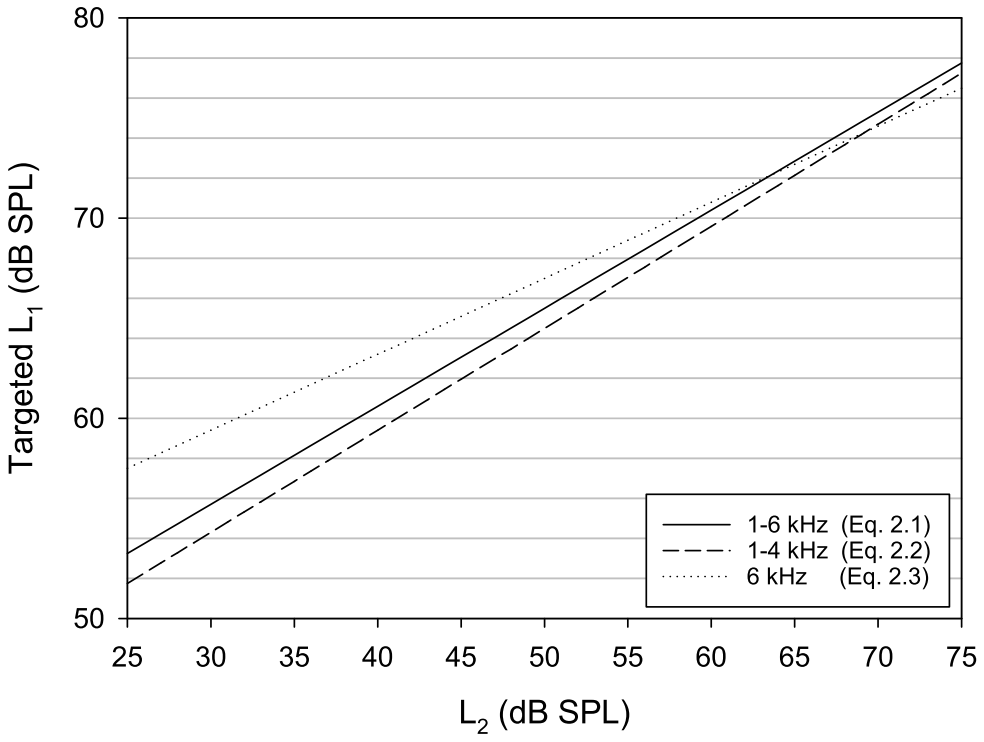


Figure 2.2: Comparison of optimization formulas developed during the present study. Formulas differ in terms of the frequency range from which they were derived. L_2= 55 dB SPL was reported by Stover et al. (1996) as being optimal for the separation of normal and hearing-impaired ears. Reprinted from "Average optimal DPOAE primary tone levels in normal-hearing adults,"S.C. Marcrum et al., 2016, *Int J Audiol*, 55, p. 329. Copyright 2016, Taylor & Francis.

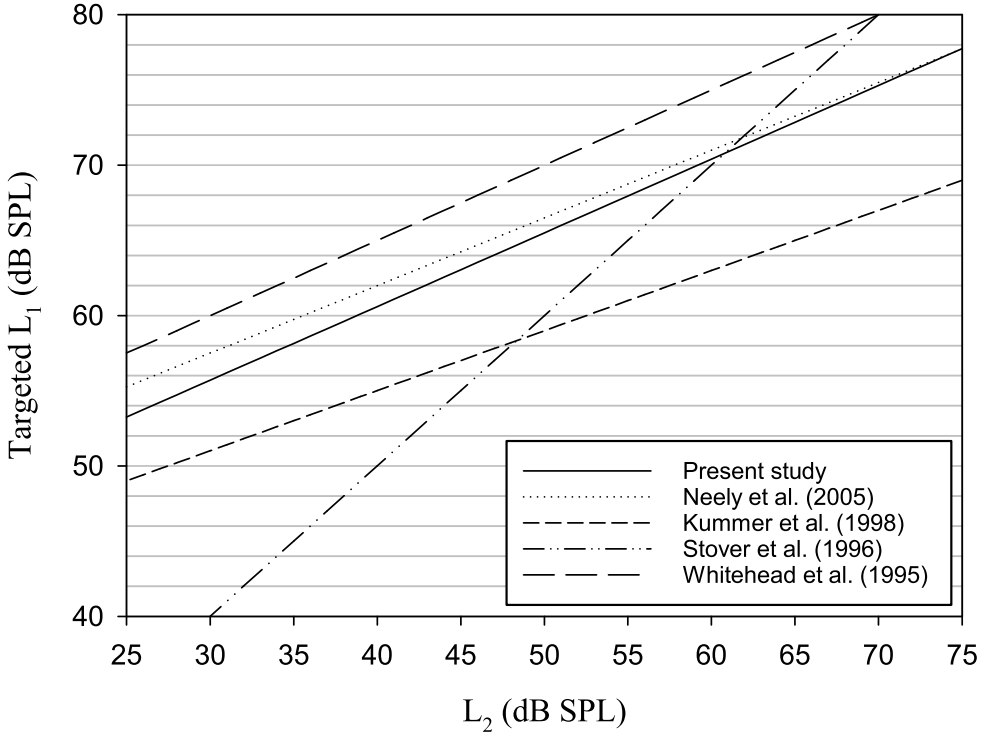


Figure 2.3: Comparison of optimization formulas from various studies. Equation 2.1 was used to process the data of the present study collected for the 1–6 kHz range of f_2 frequencies. L_1 recommendations differing by less than 2 dB SPL could not be differentially stimulated in a reliable fashion. Reprinted from "Average optimal DPOAE primary tone levels in normal-hearing adults,"S.C. Marcrum et al., 2016, *Int J Audiol*, 55, p. 329. Copyright 2016, Taylor & Francis.

as clinically expedient approximations of optimal, their evaluation is worthwhile. To assess the accuracy with which optimization formulas can predict L_{1OPT} in individual ears, the L_1 predicted to be optimal by the formulas of Kummer et al. (1998), Stover et al. (1996), and the present study were compared with the L_1 found to have actually been optimal for each given ear, frequency, and L_2 combination. The first two optimization formulas were chosen due to their widespread usage within the research literature, while the present study's 1–6 kHz formula was selected to represent optimal performance of a generic paradigm. Due to the presence of error in applied stimulation levels, a given measurement was assigned to a particular formula group only if the L_1, as measured in the ear canal, was $\pm$ 1 dB of the L_1 prescribed by the given rule. In this way, only points truly representative of a given formula were utilized.

Figure 2.4 presents box and whisker plots showing the difference between the predicted and observed L_{1OPT} for the three optimization formulas. Statistical testing revealed a significant effect of optimization formula ($\chi^2(2) = 472.299$, $p < .001$), with $L_1 = 0.49L_2 + 41$ [dB SPL] significantly outperforming all other methods ($p < .001$). Additionally, $L_1 = L_2 + 10$ [dB SPL] was found to significantly outperform $L_1 = 0.4L_2 + 39$ [dB SPL] ($p < .001$). The median distance from L_{1OPT} observed when utilizing the present study's formula was 0 dB, with 90% of all deviations within $\pm$ 6 dB. This result can be interpreted as representing the smallest difference between formula-predicted and observed L_{1OPT} which can be expected when utilizing a generic formula in a large number of ears. Results for both $L_1 = 0.4L_2 + 39$ [dB SPL] and $L_1 = L_2 + 10$ [dB SPL] display a bias towards L_1 stimulation being too low. For $L_1 = 0.4L_2 + 39$ [dB SPL], 50% of deviations were 6 dB or greater, while the least accurate half of recommendations for $L_1 = L_2 + 10$ [dB SPL] were at least 3 dB too low.

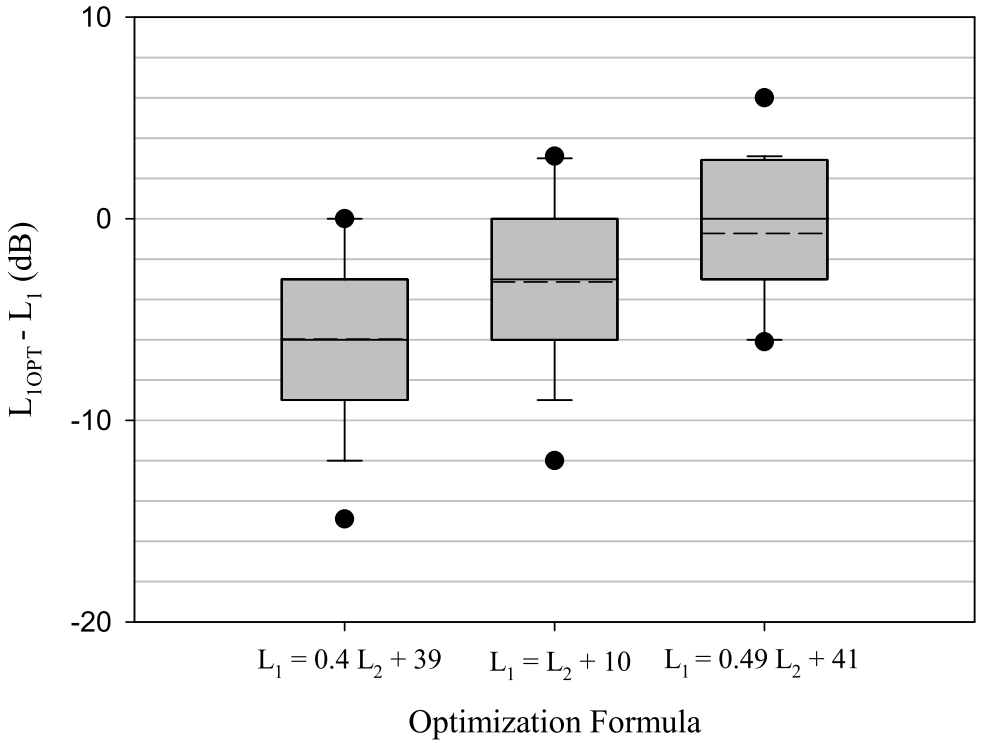


Figure 2.4: Differences between observed L_{1OPT} and its predicted levels using three optimization formulas: $L_1 = 0.4L_2 + 39$ based on the findings of Kummer et al. (1998), $L_1 = L_2 + 10$ proposed by Stover et al. (1996), and $L_1 = 0.49L_2 + 41$ based on the current study. An explanation of box and whisker plot components can be found in the caption for Figure 2.1. Reprinted from "Average optimal DPOAE primary tone levels in normal-hearing adults,"S.C. Marcrum et al., 2016, *Int J Audiol*, 55, p. 330. Copyright 2016, Taylor & Francis.

The use of non-optimal L_1 is significant only inasmuch as it decreases L_{DP}. For all measurements in Figure 2.4, the associated reduction in DPOAE level was grouped by formula in Figure 2.5. Statistical analysis again revealed a significant effect of optimization formula ($\chi^2(2) = 277.004$, $p < .001$), with $L_1 = 0.49L_2 +$

41 [dB SPL] significantly outperforming the other two methods. $L_1 = 0.4L_2 + 39$ [dB SPL] significantly underperformed the other two methods. For the present study's formula, median L_{DP} reduction due to non-optimal L_1 stimulation was found to be 0.98 dB, with the worst 5% of deviations resulting in reductions of more than 6.1 dB. Utilizing the Kummer et al. (1998) rule resulted in a median L_{DP} reduction of 3.4 dB, with the worst 5% of L_1 deviations reducing L_{DP} by more than 11.8 dB. Data for the Stover et al. (1996) formula show a median L_{DP} reduction of 1.5 dB, with 5% of L_1 deviations resulting in reductions of 8.1 dB or more.

A possible bias must be acknowledged, as these data were obtained from measurements fulfilling a very strict set of criteria. The SNR requirement of 12 dB removed approximately one-third of measurement points from the analysis. Additionally, only L_2 series with L_{1OPT} within 15 dB SPL of that predicted to be optimal by Kummer et al. (1998) were included. Due to higher L_2 generally being associated with higher and more readily measureable L_{DP}, these results can be viewed as most representative of moderate to high L_2. As the Stover et al. (1996) recommendations diverge from those of the present study and Kummer et al. (1998) with decreasing L_2 (see Figure 2.3), the detrimental effect of under stimulating L_1 is likely underrepresented here. However, given that the majority of clinical work with DPOAEs is in the moderate L_2 range best embodied by this data, useful information regarding the importance of DPOAE optimization is still provided. The individual clinician is left to decide how much L_{DP} reduction due to non-optimal L_1 stimulation is acceptable.

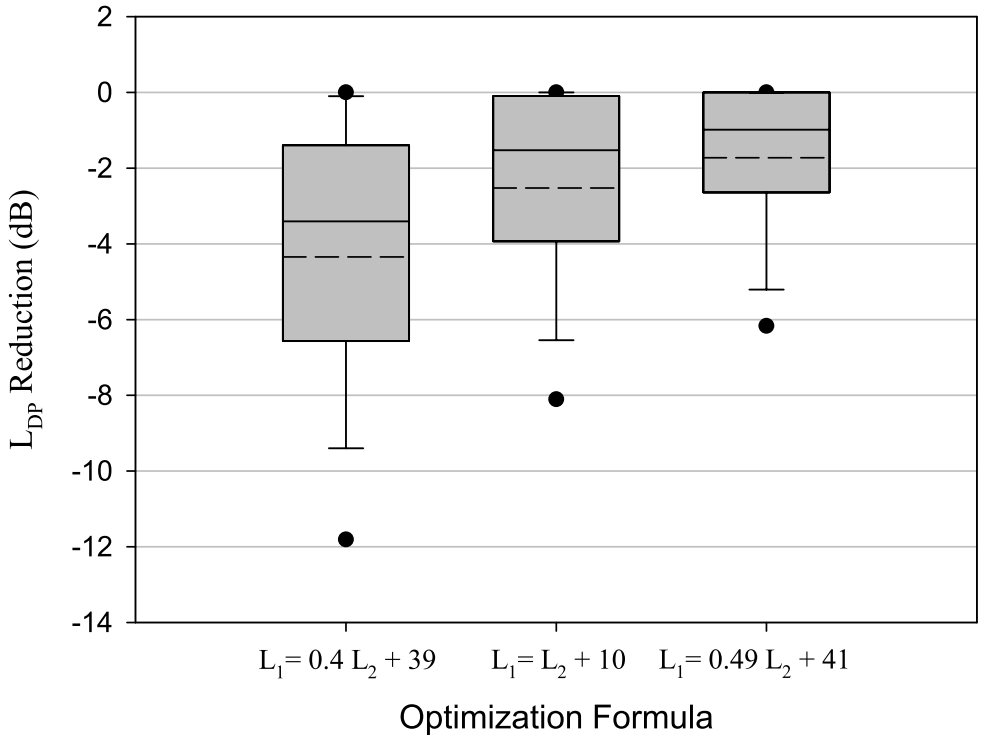


Figure 2.5: Reduction in DPOAE level due to deviation from L_{1OPT} for three optimization formulas: $L_1 = 0.4L_2 + 39$ based on the findings of Kummer et al. (1998), $L_1 = L_2 + 10$ proposed by Stover et al. (1996), and $L_1 = 0.49L_2 + 41$ based on the current study. An explanation of box and whisker plot components can be found in the caption for Figure 2.1. Reprinted from "Average optimal DPOAE primary tone levels in normal-hearing adults,"S.C. Marcrum et al., 2016, *Int J Audiol*, 55, p. 330. Copyright 2016, Taylor & Francis.

2.4 Discussion

Separating a signal of interest from a background of noise is one of the fundamental issues of hearing science. As it pertains to otoacoustic emissions, the DPOAE has traditionally been considered a constant signal, while the background noise fluctu-

ates randomly. In this way, once a satisfactory SNR is achieved, even the smallest differences in DPOAE level can be considered meaningful. However, DPOAEs are measured in complex acoustical environments and are themselves the result of a highly nonlinear physiological process. Frequency-specific interactions between the primary and secondary DPOAE sources can lead to large deviations from expected L_{DP} growth behavior, including the introduction of nonmonotonicities. In agreement with previous work, this study demonstrated that the generation and recording of DPOAEs is associated with approximately 1 dB of L_{DP} variability, even without probe removal and repositioning. Incorporating this finding into the development of an optimization formula has the practical implication that multiple L_1 are included in the calculation of L_{1OPT} for a given L_2, so long as the respective L_{DP} differ by less than the amount of variation found in the absence of stimuli change. This serves to slightly broaden the ridge of a L_2, L_1, L_{DP} growth function viewed in three-dimensional space. Any action other than incorporating all valid L_1 would be to make an active decision regarding the superiority of a given DPOAE, despite the difference being within the test re-test reliability of perhaps the cochlear amplifier itself.

In the present data set, allowing into the L_{1OPT} calculation all L_1-L_2 combinations leading to an L_{DP} within $\pm$1 dB of the maximum for a given L_2 led to an 80% increase in the number of included points. Additionally, it led to a shift in the optimization formula for f_2 = 1–6 kHz from $L_1 = 0.52L_2 + 40$ [dB SPL], which is most similar to that derived by Whitehead et al. (1995), to the current recommendation of $L_1 = 0.49L_2 + 41$ [dB SPL]. It should be noted, however, that the differences in recommended L_1 between these two formulas are beyond the limits of stimulation precision with this DPOAE system for L_2 from 20 to 75 dB SPL.

Current theories of DPOAE generation suggest that DPOAE level will be maximal when overlap of the excitation patterns associated with each primary tone is greatest. Overlap is directly affected by the degree of compression effective at the characteristic place of each primary tone. As low-frequency regions of the BM have been shown to be less frequency-selective than high-frequency regions, it has been suggested that, for a given L_1-L_2 relationship, overlap should be greater for low-frequency as opposed to high-frequency tones. To attain comparable overlap, L_1 in high-frequency regions need to grow at a faster rate than at more apical regions. Several studies have been published showing effects of frequency consistent with studies on BM mechanics (Neely et al., 2005; Johnson et al., 2006). However, Kummer et al. (1998, 2000) identified no such effects.

The present study provides support for both sides of the frequency-specificity debate. Optimization formula slopes decreased monotonically as frequency increased. This finding is consistent with a need to overcome increasingly frequency-selective basilar membrane mechanics with rising frequency. For clinical recommendations, however, real world limitations of OAE system stimulation precision must be accounted for. For the 33,395 primary tone pairs presented for this study, 95% of presentations were within approximately 2 dB SPL of the primary level targets. It can therefore be suggested that the optimization formula for f_2 = 1–6 kHz and the formula for 6 kHz, though statistically distinct, produce L_{1OPT} recommendations that cannot be differentially stimulated until L_2 is lower than 50 dB SPL.

The true measure of an L_1 optimization formula is its ability to accurately guide clinicians in the setting of primary tone levels in individual ears. In this study, an optimization formula was derived, as previously discussed, and compared with the Kummer et al. (1998) recommendation of $L_1 = 0.4L_2 + 39$ [dB SPL] and the

Stover et al. (1996) recommendation of $L_1 = L_2 + 10$ [dB SPL]. Inaccuracy of L_1 predictions, as well as the amount of L_{DP} reduction resulting from those inaccuracies, was assessed for the various formulas. As can be expected for a model derived from the data of the current study, use of Eq. 2.1 resulted in significantly less L_{1OPT} prediction deviation and subsequent L_{DP} reduction than was encountered when using the other two paradigms. Results for the new paradigm can be considered a best case scenario.

No formula utilizing parameter averages will be able to predict optimal stimulation characteristics in every ear. Unfortunately, optimizing stimulation levels in individual ears by searching the entire L_1, L_2 space is not feasible within a clinical setting. It is of considerable interest, then, that for a very wide range of L_2, the truly optimal L_1 varied only 6 dB above and below this study's recommendation for the middle 90% of all identified L_{1OPT}. Should these results be found replicable, clinical use of an efficient L_1 optimization procedure could be considered. Specifically, $L_1 = 0.49L_2 + 41$ [dB SPL] could be used to approximate L_{1OPT}, while a single additional measurement could be made at a pre-determined distance, such as 6 dB, both above and below the predicted L_{1OPT}. In this way, the likelihood of approaching the true L_{1OPT} in a given ear, as opposed to just an average ear, may be dramatically increased, while clinical practicality is maintained. Future studies utilizing $L_1 = 0.49L_2 + 41$ [dB SPL] in new samples of normal hearing and hearing impaired participants are needed to objectively determine the optimal L_1 distance for the additional measurement points, as well as to assess the reliability and clinical viability of such a method. Additionally, as DPOAE reliability is related in part to characteristics of the recording system used, measurement of DPOAE reliability using various systems could augment the generalizability of the present findings.

This study represents the first investigation into the optimization of DPOAE primary tone levels, which explicitly accounts for the reliability of DPOAE level in the absence of stimuli changes and the stimulation precision available with a real-world measurement system. Additionally, it provides support for the presence of frequency effects on optimization formula parameters and a foundation for the development of an efficient primary tone optimization method.

3 Acoustic Immittance Measures in the Prediction of Optimal DPOAE Primary Tone Levels

3.1 Introduction

Distortion product otoacoustic emission level (L_{DP}) is maximal in response to stimulation with primary tones demonstrating optimal frequency and level separations. For all deviations from the optimal relationships, nonlinear distortion generation, and therefore L_{DP}, is reduced (Gaskill and Brown, 1990). Unfortunately, optimal primary tone separations vary across ears and no available model is capable of predicting them consistently. Harris et al. (1989) reported a mean optimal primary tone frequency ratio (f_2/f_1) of 1.22, a finding which has found support in other studies (Gaskill and Brown, 1990; Brown et al., 1994); however, significant ear-specific effects of frequency and level, including nonmonotonicities, were also observed. Numerous other studies have recommended formulas for the prediction of optimal level separation of the primary tones, L_1 and L_2 (Whitehead

et al., 1995; Kummer et al., 1998; Neely et al., 2005). Briefly, these formulas attempt to predict the value of L_1 which maximizes L_{DP} (L_{1OPT}) based solely on the given value of L_2 and recommend increasing level separation with decreasing L_2. In terms of L_{1OPT} prediction accuracy, performance of such optimization techniques differs markedly across ears. For example, results reported in Chapter 2 revealed a mean absolute difference between the formula-recommended (Eq. 2.1) L_1 and L_{1OPT} (L_{1ERROR}) of only 3 dB, though error exceeded 9 dB in 5% of individual measurements. Johnson et al. (2006) developed a model for optimizing both frequency and level separation simultaneously, but nonetheless reported clinically-meaningful L_{1ERROR}, especially for lower L_2. One factor possibly contributing to the less than optimal performance of primary tone optimization formulas is that no reported technique explicitly accounts for the ear-specific impact of middle ear energy transmission on primary tone levels.

The middle ear is a complex mechano-acoustical system which powerfully influences the level and spectral shape of signals as they are conveyed towards the cochlea. As primary tones are presented within the ear canal, their effective levels within the cochlea depend, in part, upon the ear- and frequency-specific stiffness, mass, and resistance effects, which combine to give rise to each unique middle ear transfer function (Goode et al., 1994; Gan et al., 2001). For this reason, any measure which provides a more accurate assessment of middle ear energy transmission in a given ear might allow for a better estimate of effective primary tone levels and, therefore, potentially be of use for the individualization of primary tone recommendations.

The flow of energy from the ear canal to the cochlea has often been modeled as if occurring within a network, with some anatomical elements conducting energy towards the cochlea and others causing dissipation into the middle ear space

(Moeller, 1961; Zwislocki, 1962; Kringlebotn, 1988). Though the impact of each model element cannot be investigated in a clinic environment, it is possible to use time-efficient measures to assess the flow into the system. Aural acoustic immittance is a generic term used to describe a family of tests useful for this purpose and which use acoustic stimuli presented within a sealed ear canal. Tympanometry, the most widely implemented of all immittance measures, has been an integral part of the standard audiological test battery for more than half a century. Wideband energy absorbance (EA), on the other hand, has been the focus of increasing interest in recent years, as it has begun to be more-widely implemented in clinical equipment.

3.1.1 226-Hz tympanometry

Tympanometry is a measure related to acoustic energy flow into the middle ear as a function of air pressure within the ear canal. Features of tympanometric measurements have proven useful for detection of certain middle ear pathologies affecting energy transmission, such as otitis media with effusion (Paradise et al., 1976; Marchant et al., 1986; Johansen et al., 2000), though they are insufficient for definitive diagnoses in isolation. Diagnostic utility is constrained, in part, by variability of tympanometric features across ears lacking clinical pathology. Gender (Wiley et al., 1996; Roup et al., 1998), age (Margolis and Heller, 1987; Wiley et al., 1996), and ethnicity (Meyer et al., 2006; Shahnaz and Davies, 2006) have all been suggested to be significant contributors of variance to normative datasets. Though generally discussed as a drawback, the potential sensitivity of tympanometric features to these factors can alternatively be viewed as suggesting that tympanometry might be of use for differentiating energy transmission characteristics among healthy ears.

Peak-compensated static acoustic admittance (Y_{tm}) is the reciprocal of impedance and the most widely utilized tympanometric feature. The low-frequency tone standardly used in adults (226 Hz) to obtain this measure most directly assesses the stiffness of the middle ear system, which is of primary importance for the transmission of frequencies below the resonant frequency of the middle ear. However, ears with low admittance values have also been shown to demonstrate elevated hearing thresholds at significantly higher frequencies (M. R. C. Multi-centre Otitis Media Study Group, 2009). Admittance values may therefore serve as useful correlates of the attenuation affecting primary tones within pathological middle ears.

Equivalent ear canal volume (V_{ea}) is an estimate of the residual volume of air between the ear probe of the immittance system and the tympanic membrane. Given that for constant sound energy transmitted to the ear canal, intra-canal sound pressure level increases with decreasing volume, V_{ea} systematically impacts both primary tone levels and the level of the evoked DPOAE. Modern DPOAE systems calibrate primary tone levels within a given ear canal, rendering them, excluding effects on the probability of encountering standing waves, effectively independent of ear canal volume. However, potential effects of V_{ea} on L_{DP} remain. Specifically, for equivalent DPOAE energy, a higher L_{DP} can be expected within a smaller ear canal volume, relative to a larger one. As primary tone level optimization formulas are developed from series of L_{DP} measurements, an influence of V_{ea} on L_{1OPT} prediction accuracy cannot currently be excluded.

Tympanometric peak pressure (TPP) indicates the ear-canal pressure for which admittance is maximal and is commonly used as a proxy for middle ear pressure. As excess middle ear pressure increases the stiffness of the middle ear system and has been shown to affect subjective hearing threshold (Lildholdt et al., 1979), ears demonstrating successive degrees of this feature might systematically attenuate

primary tones, especially for lower-frequency f_2.

Finally, tympanometric width (TW) quantifies the width of the tympanogram (in daPa) at 50% of the peak-compensated static acoustic admittance. Normal TW is associated with a more peaked admittance tympanogram and normal middle ear function, while a large TW is associated with a more rounded tympanogram and potentially less-efficient energy transmission, such as in the case of middle ear effusion. TW might be useful as an indirect, quantitative means of assessing overall primary tone level transmission efficiency.

3.1.2 Wideband energy absorbance

In contrast to single-frequency tympanometry, wideband energy absorbance quantifies the sound energy absorbed by the middle ear for a broad range of frequencies (0.226–8 kHz) simultaneously. In addition to its wideband nature, EA measurements also offer a significant advantage over single-frequency tympanometry in terms of relative insensitivity to probe placement (Voss et al., 2013; Abur et al., 2014). EA for any specific frequency is given by

$$\text{EA} = 1 - |\text{R}(f)|^2,$$

, where $\text{R}(f)$ is the complex ratio of reflected sound pressure to that incident upon the tympanic membrane. Varying from 0 (no energy absorbed) to 1 (all energy absorbed), EA measurements provide a frequency-specific analysis, which has been shown to change systematically with type and magnitude of middle ear pathology (Feeney et al., 2009; Shahnaz et al., 2009; Keefe et al., 2012; Nakajima et al., 2013; Terzi et al., 2015)

Normative EA datasets have been reported which suggest potential effects of gender (Feeney et al., 2014b; Mazlan et al., 2015), age (Feeney and Sanford, 2004;

Feeney et al., 2014b; Mazlan et al., 2015), and ethnicity (Shahnaz and Bork, 2006; Shahnaz et al., 2013; Aithal et al., 2014), similar to those for tympanometry. However, existence of such effects has not been conclusively determined. One factor confounding identification of such effects, should they exist, is the large variability in EA values observed for non-pathological ears. However, given that the magnitude of test-retest reliability for EA measures within a given ear has been estimated to be approximately half that observed between ears (Abur et al., 2014), large normative ranges can alternatively be interpreted as an indication that EA is sensitive to normal variations in energy transmission within healthy middle ears. The ability of EA measures to quantify these differences might allow for its use in the individualization of primary tone level recommendations.

Optimal primary tone level separation is known to vary not only by level, but also between ears for a given level. A potential contributor to this variability is differences between ears in terms of middle ear energy transmission. Aural acoustic immittance measures provide mechanisms through which the energy transmission properties of specific ears can potentially be quantified. The primary aim of this study was to determine if the results of 226-Hz tympanometry and wideband energy absorbance measures could be used to improve the accuracy of L_1 recommendations beyond that attained using a traditional primary tone level optimization formula.

3.2 Methods

3.2.1 Participants

Thirty Caucasian participants (17 females, 13 males) between the ages of 21 and 33 years (mean = 25.5 years, SD = 2.6 years) enrolled in and completed this

study. Fifty-seven of 60 available ears demonstrated normal hearing, with normal hearing defined as air-conduction thresholds at or below 15 dB HL (IEC 60655, 1979) for audiometric test frequencies between 0.125 and 8 kHz. No ear exhibited a significant air-bone gap, defined as a difference between air- and bone-conduction thresholds exceeding 10 dB at any octave frequency between 0.5 and 4 kHz. Middle ear function was screened via 226-Hz tympanometry. All ears passed the screen, exhibiting tympanometric peak pressure within the limits of -100 to +50 daPa and peak-compensated static acoustic admittance between 0.3 and 1.5 mmhos (Roup et al., 1998). Otoscopy was completed to confirm that ear canals were free of cerumen. All participants denied a history of middle ear infection, noise exposure, tinnitus, and any other otologic symptoms. Participants were admitted to the study after providing informed consent in accordance with the regulations of the Institutional Review Board of the University Hospital Regensburg.

3.2.2 Equipment & calibration

Aural acoustic immittance

Diagnostic tympanometry and energy absorbance measures were conducted using an Interacoustics A/S Titan (Middelfart, Denmark) with an Impedance OAE WBT Absorbance (IOWA) ear-level probe connected via a clinical extension cable. The probe contains two receivers for stimuli presentation, a microphone for response recording, and a port connected to the main unit's air pump for pressure gradient maintenance. The probe was coupled to the ear canal using a soft rubber ear tip, which provided for both acoustic and hermetic sealing. The system was controlled via the Windows 7-based Titan^{TM} v3.1 software package installed on a PC.

Calibration of the tympanometry and energy absorbance modules was carried

out prior to each research appointment in accordance with manufacturer recommendations. The tympanometry module was calibrated using four standard cavities (0.2, 0.5, 2, and 5 cm^3), while the energy absorbance module utilized four hard-walled, plastic tubes of known diameters and lengths. Each tube was closed on the end opposite the probe, resulting in maximal reflection of incident acoustic energy. The response waveform was isolated by truncating the total response in the time domain before arrival of the first reflection.

Otoacoustic emissions

Distortion product otoacoustic emissions were obtained using an Echoport ILO292-II otoacoustic emission system with a GD TE+DPOAE probe (Otodynamics, Hatfield, UK). Calibration of primary tones was conducted in-situ at the plane of the probe using an SPL-based method and a chirp stimulus. A detailed discussion of the DPOAE equipment and calibration method can be found in Chapter 2.

3.2.3 Procedures

Aural acoustic immittance

Participants were seated in a reclining chair and the probe of the immittance system was secured in the ear canal. Tympanometry was performed using a 226 Hz probe tone and a positive to negative pressure sweep ranging from 200 to −400 daPa. Pressure was altered at a rate of 200 daPa/sec, resulting in a total measurement time of approximately 3 seconds. The static acoustic admittance obtained at 200 daPa was taken as the reference admittance of the volume of air between the probe and tympanic membrane for the compensation procedure. Peak-compensated static acoustic admittance, equivalent ear canal volume, tym-

panometric peak pressure, and tympanometric width were recorded for each ear.

Energy absorbance was assessed at ambient pressure using a wideband click stimulus (0.226–8 kHz) with a level of 100 dB peSPL, as measured in an artificial ear simulator (Type IEC 60711). Clicks were presented at a rate of 21.5 Hz, or approximately one every 46 ms. Response averaging occurred across a maximum of 32 stimulus repetitions, with fewer being included in the final average depending on the actions of an automated artifact rejection algorithm. Total measurement time for energy absorbance was approximately 1.5 seconds per ear. The wideband absorbance response was sampled at 107 points spaced between 0.226–8 kHz and the values for each point were recorded.

Otoacoustic emissions

Following completion of both immittance measures, the probe of the immittance system was removed from the ear canal and replaced with that of the DPOAE system. In order to limit variability introduced by the switching of ear probes, an effort was made to maintain a consistent insertion depth across systems and ears. A detailed description of DPOAE procedures can be found in Chapter 2. Briefly, DPOAEs were evoked for f_2 = 1, 2, 3, 4, and 6 kHz with $f_2/f_1 = 1.22$, while L_2 was varied from 20 to 75 dB SPL in 5 dB steps. For each discrete L_2, L_1 was stimulated according to the formula $L_1 = 0.4L_2 + 39$ [dB SPL] (Kummer et al., 1998), as well as up to 15 dB above and below this point in 3 dB steps. The L_{DP} observed for each stimulation was recorded and the L_1 resulting in maximal L_{DP} for each L_2 series was identified.

Immittance and otoacoustic emission measures were conducted within a sound-attenuating booth during a single appointment.

3.2.4 Multivariable model of optimal primary tone levels

Chapter 2 reported the use of linear regression analysis to develop a univariate formula for the optimization of level separation between DPOAE primary tones across a wide range of L_2 (20–75 dB SPL) and frequencies (1–6 kHz). In this study, a linear mixed model technique was applied to that same DPOAE dataset in an effort to determine if the additional inclusion of ear-specific aural acoustic immittance measures results in L_1 recommendations more accurate than those obtained using $L_1 = 0.49L_2 + 41$ [dB SPL] (Chapter 2). Specifically, the effects of entering the following immittance variables into the model were assessed: peak-compensated static acoustic admittance, equivalent ear canal volume, tympanometric peak pressure, tympanometric width, and mean energy absorbance for the frequency band encompassing f_1 and f_2. The mean EA between f_1 and f_2 was utilized in an effort to increase reliability of the observed EA value, as well as to provide an assessment of absorbance characteristics at both primary tone frequencies without risking overparameterization of the model. As EA measurements do not provide a valid assessment of a given middle ear's reverse transfer function, no attempt was made to assess EA for the DPOAE frequency (f_{DP}). Finally, the demographic factors of gender and ear side were assessed. Covariance parameters for the model were estimated by the maximum likelihood method, with the covariance structure of the repeated measurements per ear being set as banded main diagonal. Primary tone frequency (f_2) was defined as a random effect.

3.2.5 Data analyses

All participants were of similar age and self-reported as Caucasian. Therefore, tympanometric results were only assessed for significant effects of gender using student's t tests. Results were considered significant for $p < 0.05$. A two-way analysis of variance (ANOVA) was used to identify effects of gender and frequency region on normative energy absorbance results. The same technique was also used to identify significant differences in the accuracy with which the univariate optimization formula $L_1 = 0.49L_2 + 41$ [dB SPL] and the multivariable model developed in this study were able to predict L_{1OPT}, as well as any observed error's effect on L_{DP}. A Bonferroni adjustment was used to account for multiple comparisons. Statistical analyses were conducted using Sigmaplot 13 (Systat Software Inc., San Jose, CA) and SAS 9.4 (SAS Institute, Cary, NC).

3.3 Results

3.3.1 Tympanometry

Table 3.1 displays tympanometry results separated by gender, as well as across-gender averages. The existence of tympanometric differences between males and females has been a topic of debate for many years. The present data suggest only a statistically significant difference in terms of equivalent ear canal volume, $t(55)$ = -3.184, $p = 0.002$, with the mean ear canal being larger for males (mean = 1.35 ml, SD = 0.51 ml) than for females (mean = 1.04 ml, SD = 0.22 ml). Y_{tm} ($t(55)$ = -1.003, $p = 0.320$), TPP ($t(55)$ = -0.420, $p = 0.676$), and TW ($t(55)$ = -2.605, $p = 0.695$) did not significantly differ between genders. The normative ranges for male and female ears combined are consistent with previous reports. Taken

together, these results support the use of distinct V_{ea} normative limits for males and females, at least for the age and ethnic group tested.

Feature	**Female**	**Male**	**All**	**90% Range**	**p-value**
V_{ea} (ml)	1.04 (0.22)	1.35 (0.51)	1.16 (0.39)	0.71 - 1.97	0.002
Y_{tm}	0.79 (0.29)	0.87 (0.28)	0.83 (0.29)	0.40 - 1.48	0.320
TPP (daPa)	−6 (16)	−4 (11)	−5 (14)	−26 - 16	0.676
TW (daPa)	83 (27)	86 (21)	84 (24)	45 - 131	0.695

Table 3.1: Normative tympanometric feature values for males and females separately, as well as across-gender averages. Equivalent ear canal volume (V_{ea}) was significantly larger for males than for females. No significant gender difference was identified for peak-compensated static acoustic admittance (Y_{tm}), tympanometric peak pressure (TPP), or tympanometric width (TW). Standard deviations are presented within parentheses.

3.3.2 Energy absorbance

Figure 3.1 displays mean energy absorbance results (solid line) for all ears included in the study. This acoustic energy transfer function can be roughly divided into four distinct sections. Energy absorbance rises from 0.226 to 1 kHz (low), plateaus from 1–4 kHz (middle), falls from 4–6 kHz (high), and rises again for frequencies above 6 kHz (very high). Overall shape, including the steep rise in absorbance beyond 6 kHz, is consistent with previous normative data sets. For the frequency

region between 1–4 kHz, the mean range for the middle 80% of EA data points was 0.37 (SD = 0.08) on a scale of 0 to 1. This finding highlights the large differences observable even in a sample of non-pathological ears.

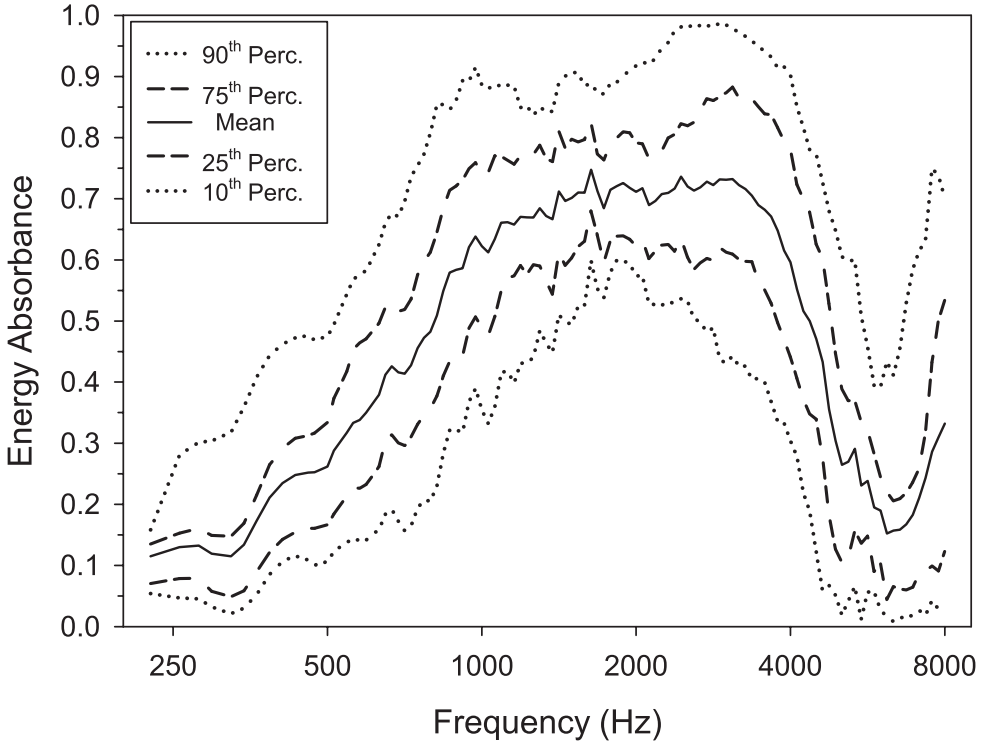


Figure 3.1: Distribution of energy absorbance (EA) results for all ears included in the study. EA is reduced towards the frequency extremes, while a broad plateau exists for the middle frequency region. The effect of gender on EA values was not statistically significant.

Reports of the existence of gender effects on energy absorbance results are inconclusive. Differences in typical middle ear anatomy between males and females, such as in terms of ossicular mass or aeration volume, however, suggest that differences could exist. A two-way ANOVA was conducted on the influence of two independent variables (gender, frequency region) on EA. Gender included 2 levels

(male, female) and frequency region consisted of 4 levels (low, middle, high, very high). The main effect of gender yielded an F ratio of $F(1, 181) = 2.68$, $p = 0.10$, indicating that the effect of gender was not significant, male (mean = 0.39, 95% CI = 0.36–0.43) and female (mean = 0.36, 95% CI = 0.33–0.38). However, the main effect of frequency region yielded an F ratio of $F(3, 132) = 156.65$, $p < .0001$, indicating a highly significant difference between low (mean = 0.37, 95% CI = 0.33–0.40), middle (mean = 0.71, 95% CI = 0.67–0.74), high (mean = 0.30, 95% CI = 0.24–0.35), and very high (mean = 0.13, 95% CI = 0.08–0.18) frequency regions in terms of energy absorbance. Specifically, all frequency regions were significantly different from all other regions ($p < .001$). The interaction effect gender*frequency region was not significant, which suggests that the effect of frequency region on EA does not differ between males and females.

3.3.3 Multivariable model creation and performance

In terms of accuracy in predicting L_{1OPT}, $L_1 = 0.49L_2 + 41$ [dB SPL] has been shown to outperform when compared with certain other univariate models (see Chapter 2). However, while mean performance of the optimization formula was quite good, deviation of recommendations from L_{1OPT} in a given ear was sometimes significant. As a consequence of these deviations, L_{DP} was reduced. Figure 3.2 displays the reduction in L_{DP} from its maximal value for a given L_2 series (L_{DPMAX}) by the magnitude of L_{1ERROR} and f_2 frequency, as observed within a single ear. Averaging across frequency, a 0.71:1 relationship existed between reduction in L_{DP} and the associated underestimation of L_{1OPT}, or negative L_{1ERROR}. Overestimating L_{1OPT}, or positive L_{1ERROR}, also led to decreases in L_{DP}, though at a slightly lower rate (0.67:1). Figure 3.3 displays box and whisker plots for the reduction in L_{DP} due to L_{1ERROR} for all ears in this study. In this figure,

L_{1ERROR} has been grouped in 3 dB steps and collapsed across frequency. These results suggest that even relatively minor errors in L_1 stimulation can result in clinically-significant reductions in L_{DP} for a meaningful proportion of ears.

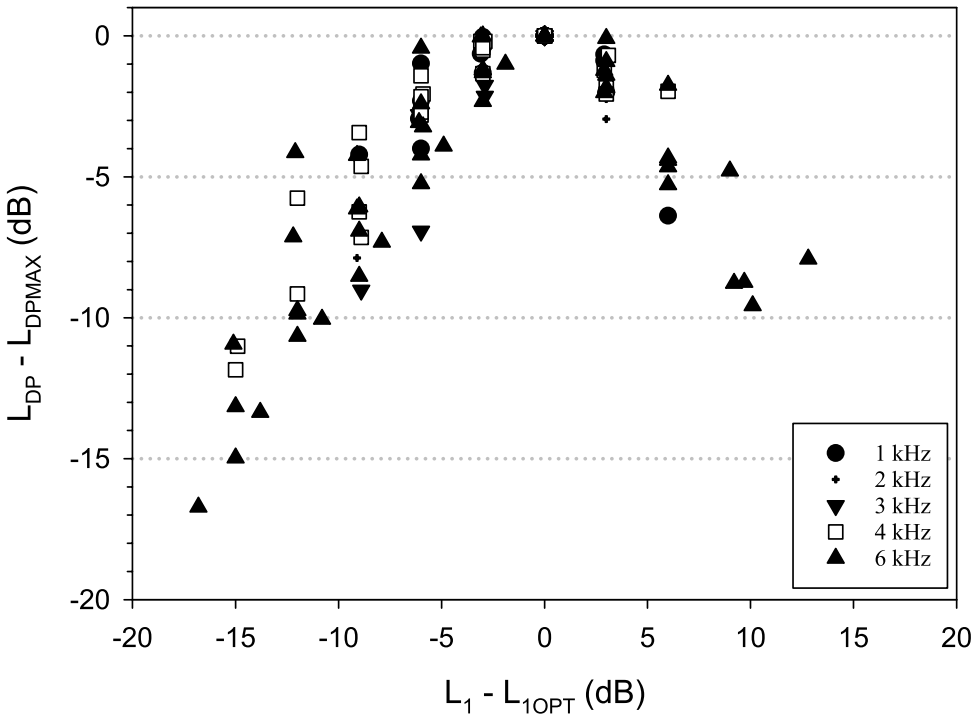


Figure 3.2: Reduction in L_{DP} observed within a single ear by the magnitude of L_{1ERROR} and f_2 frequency.

Visual inspection of figures 3.2 and 3.3 suggests that negative and positive L_{1ERROR} have similarly negative effects on L_{DP}. To test this assertion, ear- and frequency-specific linear regressions were fitted to the data for both error types. Analysis revealed a significantly steeper slope for negative (mean = 0.72, SD = 0.17), as compared to positive (mean = 0.55, SD = 0.14) errors, $t(112) = 6.036$, $p < 0.001$. This result remained even after removal of the more highly varying data points for 15 dB overestimation and suggests that underestimating L_{1OPT} is

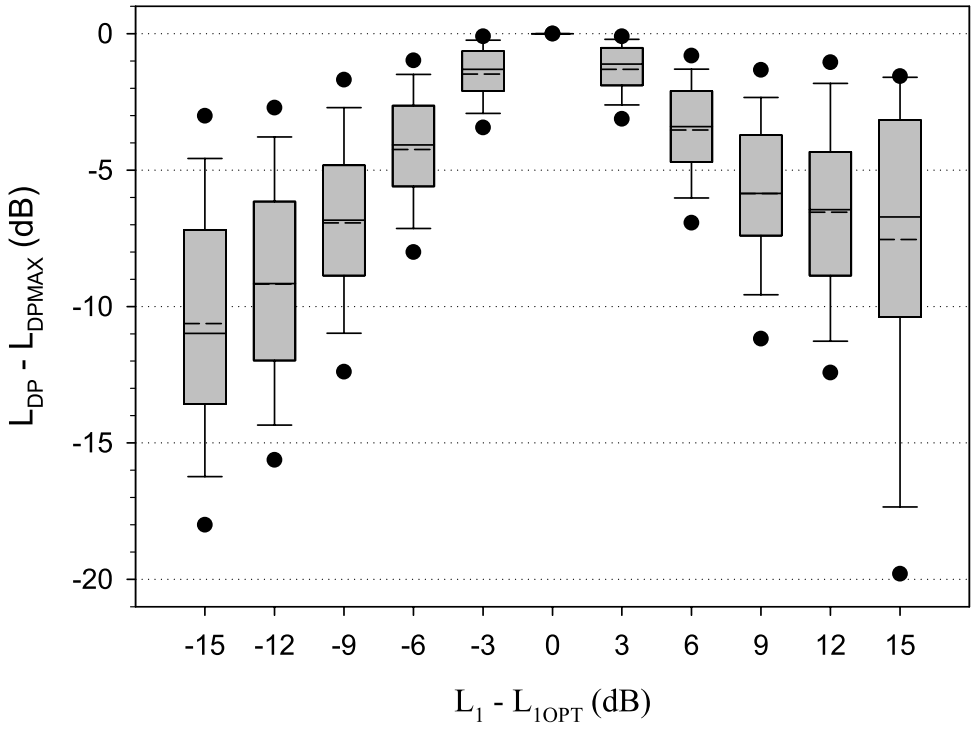


Figure 3.3: Distribution of L_{DP} reduction by L_{1ERROR}. L_{1ERROR} has been grouped in 3 dB steps and collapsed across frequency. Dashed lines represent arithmetic means. Filled circles represent 5^{th} (lower) and 95^{th} (upper) percentiles. Whiskers represent 10^{th} (lower) and 90^{th} (upper) percentiles. Solid box lines represent 25^{th} (lower), 50^{th} (in-between), and 75^{th} (upper) percentiles.

potentially more detrimental to L_{DP} than overestimating. This is perhaps due to a sort of saturation effect along the basilar membrane beyond the optimal L_1 value. The regression parameters were additionally assessed for effects of frequency using one-way ANOVA, revealing no significant effect on regression slope, $F(4, 262) = 1.38$, $p = 0.24$.

Univariate L_1 optimization models require the assumption that filtering of primary tone levels by the middle ear is either identical across ears or so minor as to be irrelevant. Neither of these assumptions can be reasonably accepted, as significant variations in middle ear energy transmission can be identified in even non-pathological ears (see figure 3.1). Ears demonstrating clinical degrees of conductive hearing loss violate this assumption further still. A multivariable model was developed in this study, which attempts to individualize L_1 recommendations by accounting for ear-specific immittance characteristics. Parameters found to significantly contribute ($p < 0.05$) to L_{1OPT} prediction accuracy are displayed in table 3.2. Of the variables directly-related to middle ear energy transmission, only energy absorbance statistically significantly improved the L_1 optimization model; its mean magnitude being 2.4 times the absorbance value. Ear-specific L_1 recommendations can be generated using the multivariable model using the following formula:

$$L_1 = 0.47L_2 + 2.40\text{EA} + f_{2param} + 38 \text{ [dB SPL]}, \qquad \text{(Eq. 3.1)}$$

where L_2 is the level of the f_2 primary tone, EA is the mean energy absorbance for the frequency band encompassing f_1 and f_2 within a given ear, and f_{2param} is a parameter determined by the frequency of f_2. For example, L_{1OPT}, given $L_2 =$ 55 dB SPL, EA = 0.45, and $f_2 = 4$ kHz, is given by $L_1 = 0.47(55) + 2.40(0.45) +$

2.36 + 38 [dB SPL].

Variable	**Estimate**	**95% CI**	**p-value**
L_2	0.47	[0.44, 0.49]	<0.0001
EA	2.40	[0.83, 3.98]	0.0028
Intercept	38	[36, 39]	<0.0001
1 kHz	reference	-	-
2 kHz	2.92	[2.25, 3.59]	<0.0001
3 kHz	3.57	[2.85, 4.29]	<0.0001
4 kHz	2.36	[1.69, 3.03]	<0.0001
6 kHz	5.59	[4.52, 6.66]	<0.0001

Table 3.2: Coefficients of the primary tone level optimization model developed in this study. Means and confidence intervals (CI) were calculated separately for all significant model parameters. For any given L_2, f_2, and frequency-specific energy absorbance value, L_{1OPT} can be estimated by $L_1 = 0.47L_2 + 2.40\text{EA} + f_{2param}$ + 38 [dB SPL]

Figure 3.4 displays the difference in recommended L_1 between $L_1 = 0.49L_2 +$ 41 [dB SPL] and this study's frequency-specific, multivariable model by L_2 for each f_2. It was reported in Chapter 2 that the precision of primary tone stimulation for the equipment used in this study was approximately 2 dB. For 2, 3, and 4 kHz, the difference between univariate and multivariable L_1 recommendations did not

exceed 2 dB for any L_2 between 20 and 75 dB SPL. This finding suggests that, within this frequency range, the differences between the two models are too small to be actionable in a reliable fashion. The differences identified for 1 and 6 kHz, on the other hand, are larger than 2 dB and should be considered functionally distinct.

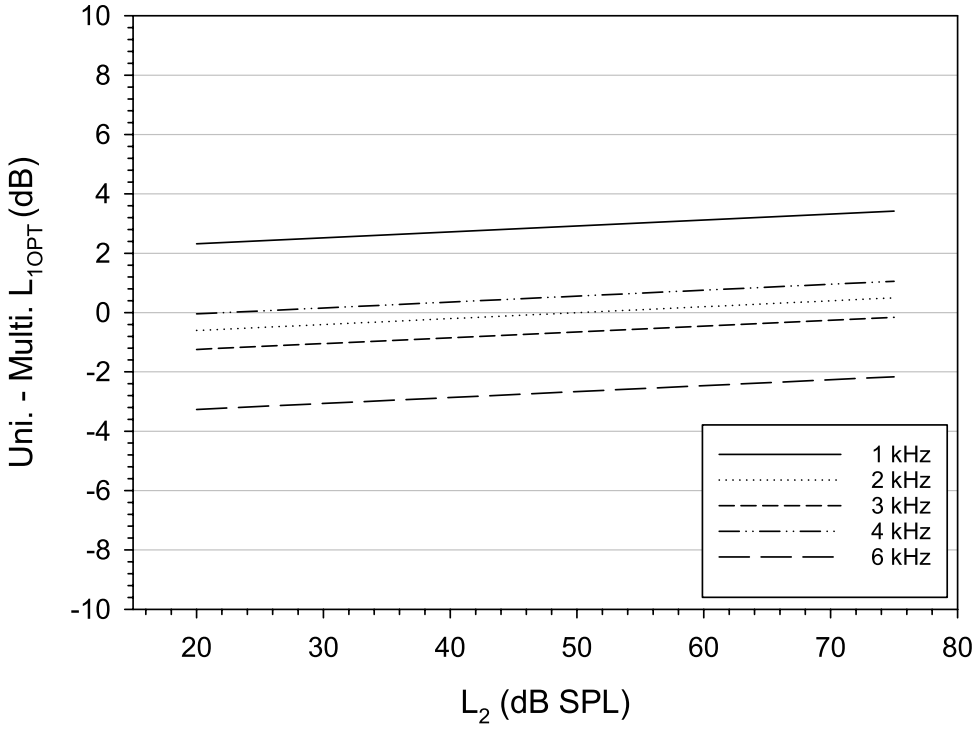


Figure 3.4: Differences in recommended L_1 between $L_1 = 0.49L_2 + 41$ [dB SPL] and this study's frequency-specific, multivariable model by L_2. For $25 \leq \text{L2} \leq 75$ [dB SPL], the difference between L_1 recommendation formulas was within 2 dB, except for $f_2 = 1$ and 6 kHz.

Figure 3.5 displays box and whisker plots for L_{1ERROR} by model and frequency. These results were obtained by subtracting the L_1 recommended by either the univariate or multivariable model by the L_1 found to have maximized L_{DP} for

a given frequency and L_2, or the L_{1OPT}. Across frequency, the multivariable model statistically significantly outperformed the univariate model ($p < 0.001$). Though differences are generally quite small, the multivariable model resulted in reduced L_{1ERROR} for every frequency tested, as compared to the univariate formula. However, the mean difference of 0.18 dB (SD = 1.54 dB, effect size = 0.12) is of questionable clinical meaning. As expected given the results in figure 3.4, the differences in L_{1ERROR} were largest for 1 kHz (M = 3 dB, SD = 0.43) and 6 kHz (mean = 1.4 dB, SD = 0.39). These results suggest that inclusion of ear- and frequency-specific energy absorbance parameters provides meaningful information for the prediction of L_{1OPT}, though improvements are generally small.

Reducing L_{1ERROR} is only significant inasmuch as it minimizes the associated reduction of L_{DP}. It is of interest then to compare the two models in terms of reductions in L_{DP} due to L_1 recommendation errors. Owing to L_1 having been stimulated in 3 dB steps above and below the Kummer et al. (1998) L_1 recommendation of $L_1 = 0.4L_2 + 39$ [dB SPL], not every possible L_1-L_2 combination was tested directly. To approximate the impact of every L_{1ERROR} within figure 3.5, the ear- and frequency-specific L_{1ERROR}/L_{DP} reduction functions developed previously (see Figure 3.2) were utilized. Figure 3.6 displays predicted reductions in L_{DP} due to L_{1ERROR} by model and frequency. Across frequency, the multivariable model again statistically significantly outperformed the univariate model ($p < 0.001$), demonstrating an average benefit of 0.15 dB (SD = 0.86, effect size = 0.18). Follow-up testing revealed significant outperformance of the multivariable model for 3 kHz (mean = 0.33 dB, SD = 0.54, effect size = 0.61) and 6 kHz (mean = 0.4 dB, SD = 1.14, effect size = 0.35). No other significant relationships were identified.

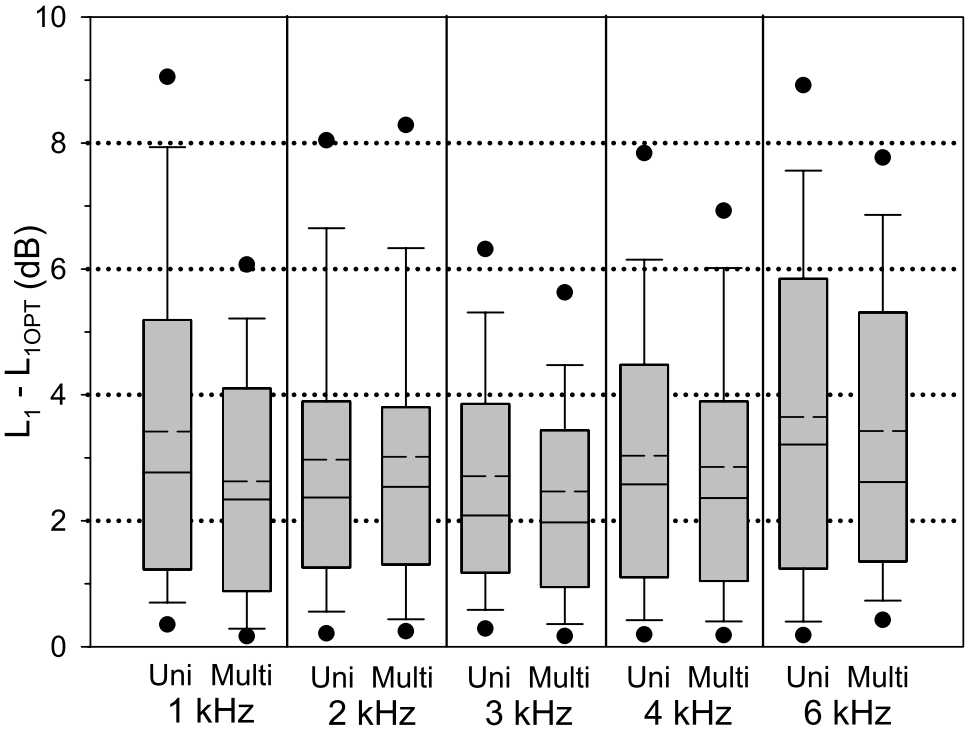


Figure 3.5: Differences between observed L_{1OPT} and its predicted levels using two optimization formulas: $L_1 = 0.49L_2 + 41$ [dB SPL] based on the findings in Chapter 2 and $L_1 = 0.47L_2 + 2.40\text{EA} + f_{2param} + 38$ [dB SPL] based on the current study. An explanation of box and whisker plot components can be found in the caption for Figure 3.3

3.4 Discussion

The inconsistency with which primary tone level optimization formulas predict L_{1OPT} in individual ears represents a significant threat to clinical utility. One factor which potentially contributes to the inaccuracy encountered when using current univariate methods is that ear-specific effects of middle ear sound energy transmission on primary tone levels are not accounted for. DPOAEs are believed

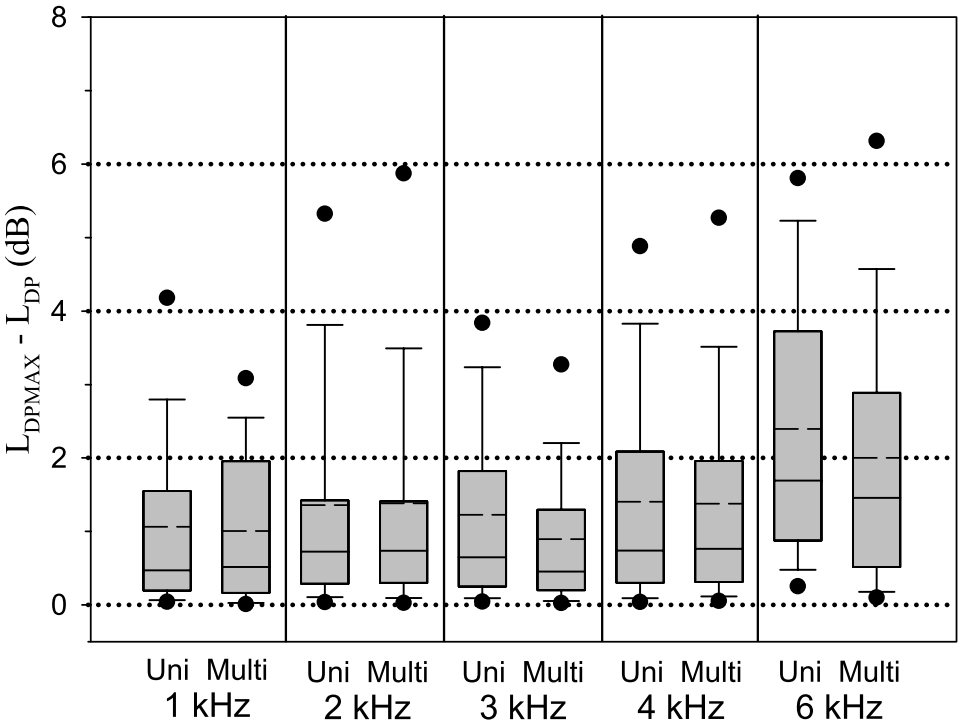


Figure 3.6: Reduction in DPOAE level due to deviation from L_{1OPT} for the optimization formulas included in the data of Figure 3.4. An explanation of box and whisker plot components can be found in the caption for Figure 3.3.

to result primarily from a non-linear interaction between traveling waves along the basilar membrane. The amplitude relationship of these traveling waves directly affects the quality of this interaction and is itself affected by attenuation of L_1 and L_2 within the middle ear. Specifically, because optimal level separation increases as L_2 decreases, an initially optimal level relationship will be rendered less than optimal if inefficient middle ear transmission results in a similar attenuation of both primary tones. The present study represents a first attempt to account for these middle ear effects using measures of aural acoustic immittance, resulting in an individualization of primary tone level separation recommendations on an ear-

and frequency-specific basis.

The normative tympanometric values obtained during this study are consistent with others reported in the literature. While variation across these healthy ears in terms of tympanometric features was considerable, neither V_{ea}, TPP, Y_{tm}, nor TW proved of significant utility for improving L_1 recommendations. However, the negative findings are likely due to limitations of 226-Hz tympanometry itself. Specifically, in addition to the limited appropriateness of assessing a frequency-specific system, such as the middle ear, with a single, low-frequency tone, it remains that tympanometry only describes the flow of energy into the middle ear. Energy flow through the middle ear and cochlea, which is of interest for OAE purposes, is not assessed. The present results suggest that tympanometric measures at 226 Hz do not reflect inter-individual differences in energy transmission in a manner which is of direct use for the adjustment of primary tone levels. While not investigated here, modern clinical adaptations of multi-frequency tympanometry exhibit many of the drawbacks of 226-Hz tympanometry and can be more difficult to interpret. Despite this, obtaining tympanometric results across a broader frequency range might provide a more detailed analysis of middle ear function and reveal yet unrecognized utility for use with DPOAEs.

The envelope of the normative energy absorbance response obtained in this study is similar to others previously reported. Specifically, due to the band-pass characteristic of the middle ear, absorbance of acoustic energy is reduced towards the frequency extremes, while a broad plateau exists for the middle frequency region around the resonance frequencies. Large inter-individual variations were additionally identified within this sample of young, healthy ears. The large range of EA values observed, though not optimal for the creation of clinically-useful normative limits, can be viewed positively in terms of the EA measure being sensitive

to frequency-specific differences in middle ear impedance between ears. Indeed, this feature can be conceived to have contributed to EA's significant influence on an optimization model.

Use of a multivariable formula, which attempts to account for ear-specific middle ear transmission characteristics through incorporation of an EA measure, resulted in statistically significantly improved L_1 prediction accuracy and a corresponding decline in the associated L_{DP} reduction. However, from a clinical perspective, mean improvements were negligible. Despite this, it remains that the multivariable model meaningfully improved DPOAE measurement results in certain ears. Specifically, the multivariable model reduced L_{1ERROR}, when compared to the univariate model, by more than 3 dB in 10% of ears. Decreasing sources of variance, such as the need for inserting separate ear probes for energy absorbance and DPOAE measures, may increase the proportion of ears benefitting from utilization of such a multivariable method further still.

Primary tone level optimization formulas which do not explicitly account for energy absorbance effects must nonetheless do so indirectly. This occurs because all L_{DP}, as measured within the ear canal, are shaped by the forward and reverse acoustic energy transfer functions of each distinct ear. The end result is an average energy absorbance effect being built in to each formula. In this way, the multivariable model developed here is not novel in that energy absorbance plays a role, but rather that its role is acknowledged and its value is individualized for each ear and frequency. It is possible that ears which diverge more strongly from the mean in terms of sound absorbance characteristics and exhibit steeper L_{1ERROR}/L_{DP} reduction functions might benefit disproportionately from use of this multivariable formula. Due to the fact that energy absorbance measures provide information distinct from all other tests in the standard audiological battery and the short

measurement time required, general clinical implementation of energy absorbance measures should be considered. However, further research evaluating the precise relationship between ear-specific EA characteristics and optimal primary tone levels in more diverse clinical populations is needed before a clinical recommendation can be made for this purpose.

3.4.1 Limitations

Several limitations may have unduly influenced this study's results. First, the immittance and DPOAE protocols implemented were completed within a given ear utilizing two separate ear probes. The need for ear probe replacement, therefore, represents a source of measurement variance. Though probe insertion depth is theorized to not be of great importance for energy absorbance measures, it has been shown to significantly affect tympanometry results. It is possible, then, that differing probe insertion depths influenced the relationship between tympanometric and DPOAE results. Second, response averaging during the energy absorbance measurements occurred for a fixed number of stimuli. Though an artifact rejection algorithm automatically removed noisy samples, additional independent control of measurement time would have been preferable. Halting the measurement based upon a response-based rule, such as the achievement of a minimal signal to noise ratio or criterion standard deviation of the response at key frequencies, for example, might have led to less variability in energy absorbance measures. Given the narrow range of possible EA values, the need for reliability cannot be overestimated. Third, similarities across participants in terms of multiple demographic characteristics might have served to lessen the utility of including immittance-related variables. Specifically, all participants in this study were of similar age, Caucasian, and demonstrated normal middle ear function. It is possible that the

impact of tympanometric and energy absorbance characteristics on optimal primary tone levels was underestimated, as these demographic factors, all of which are suspected to affect both energy absorbance and tympanometry results, were artificially constrained. Admitting participants of disparate ages and ethnicities or relaxing study admission requirements for middle ear function would have served to increase the range of immittance values obtained, potentially increasing measurement utility. Finally, the middle ear is known to filter forward-going signals, such as primary tones, significantly differently than it does backward-going signals, such as DPOAEs. EA measures only provide information relevant to forward-going signals. The development of a clinical measure for the assessment of a given ear's reverse middle ear transfer function might prove a useful addition to a multivariable primary tone level optimization formula.

3.4.2 Conclusions

Whereas DPOAEs are already an established part of the audiological test battery, energy absorbance measures are swiftly gaining in clinical significance. The findings of this study suggest that the incorporation of a frequency-specific energy absorbance measure into a primary tone level optimization formula does not improve mean recommendation accuracy over an L_2-based, univariate model in a clinically-meaningful way. However, significant improvements can be observed in individual ears.

4 Estimation of Minor Conductive Hearing Loss Using Distortion Product Otoacoustic Emissions

A version of the following chapter first appeared as the peer-reviewed article "Estimation of Minor Conductive Hearing Loss in Humans Using Distortion Product Otoacoustic Emissions,"S.C. Marcrum et al., 2017, [ePub ahead of print]. Ear Hear, p. 1–8. Copyright 2017, Wolters Kluwer Health.

4.1 Introduction

Distortion product otoacoustic emissions (DPOAEs) are an essential tool in the modern audiological test battery, in large part due to their sensitivity to the integrity of active cochlear mechanics. An indicator of peripheral auditory system function to the level of the outer hair cells, DPOAEs have been used for identifying normal and hearing impaired ears (Gorga et al., 1997; Musiek and Baran, 1997; Johnson et al., 2007, 2010; Kirby et al., 2011), differentiating sensorineural and

conductive hearing losses (CHL) (Gehr et al., 2004; Janssen et al., 2005; Janssen, 2013), objectively estimating hearing threshold (Boege and Janssen, 2002; Gorga et al., 2003; Oswald and Janssen, 2003; Janssen et al., 2005), and monitoring for deleterious side-effects of ototoxic medications (Reavis et al., 2011; Konrad-Martin et al., 2012), among other uses. Given their utility in diverse clinical and research applications, it is regrettable that DPOAEs are not robust in the presence of even relatively minor, subclinical middle ear dysfunction. Kummer et al. (2006), for example, reported simulations demonstrating that the presence of a 10 dB CHL is sufficient to reduce the prevalence of measurable DPOAEs in adults with normal cochlear function by 69%. Job and Nottet (2002) described the significantly reduced DPOAEs of patients with histories of otitis media and myringotomy, despite the lack of measureable CHL upon audiometric testing.

CHL affects DPOAE level (L_{DP}) via 3 primary mechanisms. The first mechanism is an inefficient transduction of primary tone energy through the middle ear, which results in decreased stimulation along the basilar membrane. As L_{DP} correlates positively with L_2 for an optimized L_1-L_2 relationship, reductions in L_2 via CHL lead to reductions in L_{DP}. The second mechanism is a decrease in the effectiveness of distortion-product generation within the cochlea due to a shift towards an L_1-L_2 relationship characterized by reduced travelling wave overlap near the f_2 place. For a given f_2/f_1 ratio and L_2, the degree of nonlinear distortion, and therefore the level of the DPOAE, is maximized in response to a certain optimal L_1 (L_{1OPT}). With f_2/f_1 fixed, L_{DP} is maximized when L_1-L_2 separation is set according to an optimization formula of the form: $L_1 = aL_2 + \text{b}$ [dB SPL] (Whitehead et al., 1995). Multiple authors have reported formula parameters for the prediction of average optimal L_1-L_2 relationships in both normal and hearing impaired ears (Whitehead et al., 1995; Kummer et al., 1998; Neely et al., 2005;

Johnson et al., 2006). General consensus indicates that below a certain high L_2, at which L_{DP} is maximized for $L_1 = L_2$, optimal L_1-L_2 separation increases as L_2 decreases (Gaskill and Brown, 1990; Whitehead et al., 1995). For example, Kummer et al. (1998) reported $L_1 = 0.4L_2 + 39$ [dB SPL] as being predictive of L_{1OPT} for f_2 = 1–6 kHz. According to this formula, maintenance of an optimal L_1-L_2 separation requires that L_1 change by 0.4 dB (parameter a) for every 1 dB change in L_2. A broadband CHL disturbs optimal L_1-L_2 separation by decreasing the effective levels of both primary tones at the rate of approximately 1:1. Utilizing the Kummer et al. (1998) formula, the level separation of the primary tones thus becomes 0.6 dB (1 - a) less optimal for every 1 dB of attenuation due to CHL. This excessive separation diminishes nonlinear distortion within the cochlea and results in decreased L_{DP}. The third mechanism is an attenuation of the evoked DPOAE as it travels through the inefficient middle ear towards the ear canal. The degree of this energy loss is sometimes modeled as being equal to that loss affecting the primary tones, though this is a convenient simplification and likely inaccurate (Kummer et al., 2006; Keefe and Abdala, 2007).

Figure 4.1 illustrates the effects of CHL on L_{DP}, which is displayed as a function of L_1 for an ear before and after experimental induction of CHL. The black line with squares represents DPOAE results without CHL, while the gray line with triangles represents results with CHL. The 9 dB CHL applied here reduces L_{DP} by more than 9 dB, indicative of the compounding effects of even mild CHL on L_{DP}. Of particular interest, the initially optimal L_1 of 62 dB SPL was rendered non-optimal by the CHL, as the effective L_2 had been decreased by the CHL from 55 to 46 dB SPL. Increasing L_1 to 65 dB SPL restored an optimal L_1-L_2 relationship. In this way, CHL served not only to attenuate signals within the middle ear, but also to lessen the degree of nonlinear distortion generation within

the cochlea.

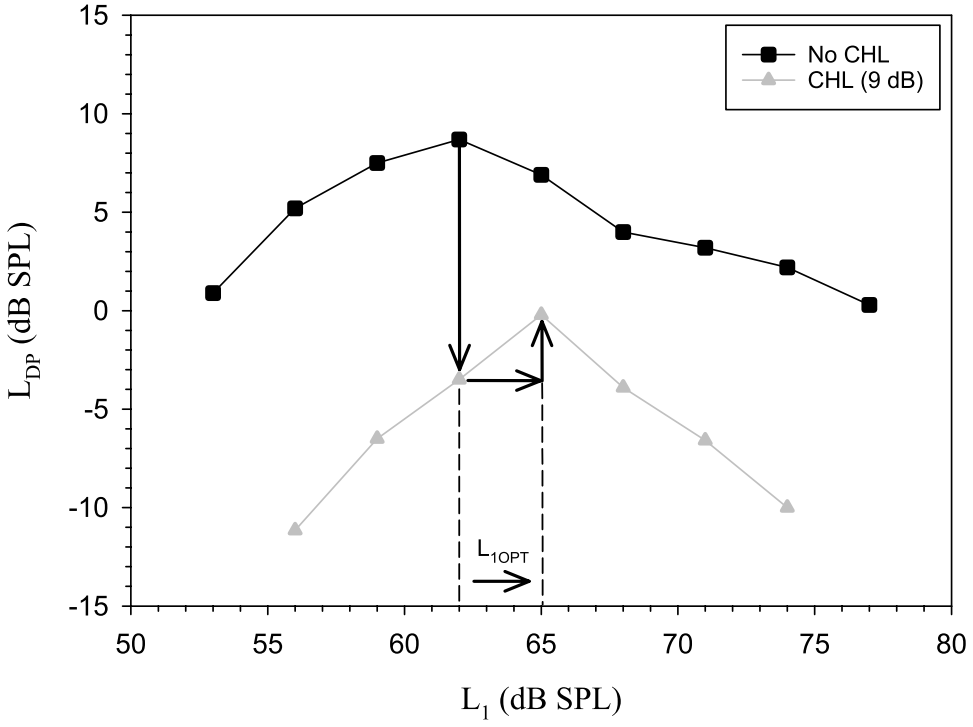


Figure 4.1: Effect of conductive hearing loss (CHL) on distortion product otoacoustic emission (DPOAE) level. For a constant L_2, DPOAE levels in an ear without (black squares) and with (gray triangles) a 9 dB CHL are plotted against L_1. The L_1 which maximizes DPOAE level (L_{1OPT}) without CHL is not optimal after CHL is induced. Even following L_1 optimization, maximal DPOAE level in the presence of CHL remains less than that with CHL absent. Reprinted from "Estimation of Minor Conductive Hearing Loss in Humans Using Distortion Product Otoacoustic Emissions,"S.C. Marcrum et al., 2017, [ePub ahead of print]. *Ear Hear*, p. 2. Copyright 2017, Wolters Kluwer Health.

Interest in objectively evaluating ears with potential CHL has increased in recent years, especially following the establishment of universal newborn hearing

screening programs. Acoustic immittance measures, auditory brainstem response (ABR), and otoacoustic emissions have all been implemented in the evaluation of ears with potential CHL, though with varying degrees of success. Wideband energy absorbance measures are simple to conduct and have been shown very effective in identifying ears with CHL (Ellison et al., 2012; Keefe et al., 2012; Prieve et al., 2013); however, large inter-subject variability in the absence of CHL appears to preclude a precise quantification of CHL (Keefe et al., 2012). On the other hand, diagnostic ABR testing allows for quantification of even mild CHL with reasonable accuracy (Conijn et al., 1989; Mackersie and Stapells, 1994), but the relative complexity of conducting the electrophysiological measure serves to limit its implementation in certain clinical environments. Several authors have reported using DPOAE characteristics to identify ears with mild CHL. Gehr et al. (2004), for example, compared the slope of DPOAE input-output (I/O) functions in guinea pigs after experimental induction of conductive and cochlear hearing losses. I/O functions obtained from ears with cochlear hearing loss exhibited significantly less compression than those from ears with CHL, enabling accurate differentiation. Janssen et al. (2005) compared extrapolated I/O function-based estimates of auditory threshold in neonates soon after birth and again after 4 weeks. Results indicated a significant reduction in estimated threshold after the 4 week period, providing evidence for the presence of a minor, temporary CHL in neonate ears.

Kummer et al. (2006) provided theoretical underpinnings and numeric simulation-based support for a method allowing not only for the detection, but also the quantification, of conductive hearing loss using DPOAEs. As previously mentioned, if an induced CHL attenuates both L_1 and L_2 to an equal extent, a less optimal L_1-L_2 separation results. The authors postulated that the increase in L_1 needed

to restore an optimal L_1-L_2 relationship (ΔL_{1OPT}) is related to the CHL by the formula CHL = (ΔL_{1OPT}) / (1 - a), where a is the slope of the optimization formula for the given ear in the absence of CHL. The term 1 - a, then, quantifies the rate of excessive reduction of L_1 due to CHL. In this way, the magnitude of CHL necessary for the observed change in L_{1OPT}, given the slope of the optimal L_1-L_2 relationship within a particular ear, can be calculated. Applying this method to previously obtained normative DPOAE data, simulated CHL of up to 20 dB were estimated with a median error of -1.7 dB and an interquartile range of -5 to 3.2 dB. Olzowy et al. (2010) applied the Kummer et al. (2006) method to guinea pigs with experimentally produced CHL (4–12 dB) and observed a mean error of 4.2 dB (SD = 2.6), when compared with CHL estimates based on compound action potential thresholds. To date, however, no study has assessed the feasibility of DPOAE-based quantification of experimentally-induced CHL in humans.

The ability to objectively quantify CHL using DPOAEs would represent a step forward in the clinical evaluation of patients for whom subjective methods are either inappropriate or impractical. For example, an accurate CHL quantification technique could prove useful for the correction of DPOAE-based estimates of hearing threshold in patients with special needs or in reducing false positive rates associated with universal newborn hearing screening programs. Independent of potential clinical utility, such a method would also provide further insight into the manner in which mild CHL affects the basic mechanisms of DPOAE function in humans.

This study was undertaken to assess the feasibility of objectively estimating experimentally-produced CHL in humans using DPOAEs by comparing CHL estimates resulting from DPOAE- and pure tone audiometry-based methods. A secondary aim was to compare the accuracy of DPOAE-based CHL estimates when

obtained using generic, as opposed to ear-specific, optimal primary tone level formula parameters.

4.2 Methods

4.2.1 Participants

Data were collected from 1 ear of 30 adult participants (27 females, 3 males) with normal hearing. Normal hearing was defined as air-conduction thresholds at or below 15 dB HL (IEC 60655, 1979) for audiometric test frequencies between 0.125 and 8 kHz, as measured with ER-3A insert earphones (Etymotic Research, Elk Grove, IL). No participant exhibited a significant air-bone gap, defined as a difference between air-conduction and bone-conduction thresholds exceeding 10 dB at any octave frequency between 0.5 and 4 kHz. Middle ear function was screened via 226-Hz tympanometry using an Interacoustics A/S Titan (Middelfart, Denmark). All participants passed the screen, exhibiting tympanometric peak pressure within the limits of -150 to +50 daPa (mean = -4 daPa, standard deviation (SD) = 16 daPa) and peak-compensated static acoustic admittance between 0.3 and 1.5 mmhos (mean = 0.81 mmhos, SD = 0.32 mmhos) (Roup et al., 1998). All participants denied a history of middle ear infection, otologic surgery, noise exposure, tinnitus, and any other otologic symptoms. Inclusion of a given participant's left or right ear was randomized and counter-balanced, resulting in groups of equal size. Participants ranged in age from 19 to 33 years (mean = 23.6 years, SD = 2.9 years) and were admitted to the study after providing informed consent in accordance with the regulations of the Institutional Review Board of the University Hospital Regensburg.

4.2.2 Equipment & calibration

The commercially available Sentiero Desktop (Path Medical, Germering, Germany) was used for DPOAE stimulus generation and calibration, DPOAE response recording and analysis, introduction and maintenance of a pressure gradient within the ear canal, and audiometric testing. The system consists of an interface which allows for measurement control and an ear level probe containing two receivers for stimuli presentation, a microphone for DPOAE recording, and a port connected via a tube to the system's tympanometer for pressure gradient maintenance.

For the majority of clinical DPOAE systems, primary tone calibration is conducted for each frequency in-situ at the plane of the probe in SPL using a broadband chirp stimulus. However, due to the possibility of complex acoustical interactions between forward-going stimuli and backward-going reflections from the ear drum, several authors have expressed concern regarding the use of SPL-based calibration methods (Gilman and Dirks, 1986; Siegel and Hirohata, 1994; Scheperle et al., 2008). To help mitigate the potential effects of standing waves on calibrated levels, the Sentiero Desktop utilizes a method in which the average RMS level of a chirp as measured within a given ear canal is compared to one as measured within an artificial ear simulator (Type IEC 60711). The overall level of the ear canal response is then adjusted until the level of the coupler response is matched. In this manner, the effects of any standing waves on the calibration process will be diluted across all test frequencies, as opposed to having a potentially more significant impact on a single frequency.

4.2.3 DPOAE stimuli

DPOAEs were recorded in response to 2 primary tones of differing frequency (f_1 and f_2) and level (L_1 and L_2), where f_2 = 1 kHz and f_2/f_1 = 1.22. The test frequency of 1 kHz was specified after pilot testing revealed CHL up to 10 dB could not be achieved reliably at higher frequencies using the experimental setup. L_2 was varied from 20 to 70 dB SPL in 5 dB steps. For each discrete L_2, L_1 was stimulated according to $L_1 = 0.49L_2 + 41$ [dB SPL], a relationship shown to have maximized L_{DP} for f_2 = 1–6 kHz in a sample of 57 normal-hearing ears (see Chapter 2). Additionally, L_1 was varied 15 dB above and below the formula-recommended L_1 in 3 dB steps. Measurements within an artificial ear simulator (Type IEC 60711) revealed no identifiable influence of system distortion for any stimulus pair with L_1 set to 90 dB SPL or below. Results were also visually inspected for the rapid growth associated with system distortion.

Stimulus pairs were presented for between 5 to 20 seconds each. Response averaging was discontinued at some time between these limits only if measurement characteristics satisfied a stop algorithm within the system. Briefly, a method was utilized to determine whether energy at the DPOAE frequency $f_{DP} = 2f_1$-f_2 exceeded a predetermined criterion limit. This criterion resulted in automatic measurement stoppage when SNR reached approximately 12 dB.

A minimum difference of 6 dB between the level of the DPOAE at $2f_1$-f_2 and that of the surrounding noise was required of any measurement to be included in the analysis. While it can be argued that a more stringent SNR requirement could have further decreased L_{DP} variability, it would also have significantly decreased the number of valid measurements, especially for instances in which lower primary tone levels were combined with higher degrees of CHL. 6 dB was identified as an appropriate compromise.

4.2.4 Procedures

Participants were seated in a reclining chair and the measurement probe was secured in the ear canal using a rubber eartip. A pressure of -350 daPa was built up within the ear canal and maintained for 30 seconds to verify an airtight seal. Multiple investigations have recognized negative middle ear pressure as a common characteristic of ears exhibiting various middle ear pathologies (Lildholdt et al., 1979; Bluestone and Klein, 2007; Nguyen et al., 2012). A negative ear canal pressure, which most naturally simulates a positive pressure buildup within the middle ear space, was used in this study because of incomplete sealing encountered when applying positive ear canal pressure of a similar magnitude. However, recent work demonstrates that positive and negative pressures applied within the ear canal exert similar influence on auditory thresholds and are similarly appropriate for the simulation of negative middle ear pressure for the frequency and pressure range of interest in this study (Sun, 2012; Feeney et al., 2014a). After confirmation of a hermetic seal, the ear probe was left in place for the duration of testing. All measurements were performed within a sound treated booth.

Estimation of CHL using pure tone audiometry

Auditory threshold for a 1 kHz sinusoid was determined using automated Bèkèsy audiometry. Specifically, the level of the sinusoid decreased in 2 dB steps from a starting level of 20 dB HL, as long as the participant indicated detection of the tone by depressing a handheld button. Once the tone became inaudible, the participant released the button and the tone began to increase in level. The mean level of 6 consecutive reversals was taken as an estimate of auditory threshold. Such estimates were obtained 3 times and, if the associated standard deviation was $\leq$ 1.5 dB, the mean was accepted as auditory threshold. If the observed standard

deviation exceeded the set criterion, the measurement process was repeated until the requirement was satisfied.

Auditory threshold was determined in this manner for 2 ear canal conditions. In the first condition, ear canal pressure was set to 0 daPa. In the second condition, negative ear canal pressure was increased until threshold estimates exceeded those found in the 0 daPa environment by between 3 to 10 dB. Though ear canal pressure was set individually for each ear, mean pressure utilized in this study was -255 daPa (SD = 93 daPa). CHL of less than 3 dB was excluded as it was deemed too small to be reliably quantified using subjective audiometry. CHL of more than 10 dB was excluded as it commonly led to absent DPOAE responses. An effort was made to induce CHL spanning the desired range by the individualization of applied ear canal pressures. The difference between auditory thresholds obtained for the two conditions was defined as the pure tone audiometry-based CHL estimate (CHL_{PT}) for that participant. A third auditory threshold measurement in the pressurized condition was obtained after DPOAE testing to verify stability of CHL_{PT}.

Estimation of CHL using DPOAEs

DPOAE measurements were conducted in each ear with ear canal pressure set to 0 daPa, as well as to the pressure utilized to induce CHL during audiometric testing. For each L_2 series, the L_1 found to have maximized L_{DP} was identified and defined as L_{1OPT}. All L_{1OPT} obtained within a given ear were plotted against their associated L_2 and a regression analysis was performed to determine the coefficients of the L_1 optimization formula, $L_1 = aL_2 + b$ [dB SPL].

CHL has the effect of making an initially optimal L_1-L_2 relationship less optimal. To again maximize L_{DP}, L_1 must be increased by an amount (ΔL_{1OPT}) related to the magnitude of the CHL by the slope of the ear-specific L_1 opti-

mization formula (1 - a). ΔL_{1OPT} can be quantified as the distance between the optimization formulas for a given ear with and without CHL [ΔL_{1OPT} = (a - aCHL)L_2 + (b - bCHL)]. The theoretical considerations of Kummer et al. (2006) assume no impact of CHL on basilar membrane mechanics. It should be expected then, that parameter a and aCHL are identical. However, to the extent that error exists in the DPOAE measurement process or that cochlear mechanics is in fact impacted, the difference between the two parameters will not equal 0. For these instances, a mean ΔL_{1OPT} across the measured L_2 range can be obtained. The DPOAE-based estimate of CHL magnitude (CHL_{DP}) is then given by the formula $CHL_{DP} = \Delta L_{1OPT}$ / (1 - a), where a is the slope of the optimization formula for a particular ear in the absence of CHL.

4.2.5 Data analyses

Significant differences between optimization formula parameters for the pressurized and non-pressurized ear canal conditions were evaluated using two-tailed paired-samples t tests. Pearson's r was used to evaluate the degree of linear dependence between CHL_{DP} and CHL_{PT}. The correlation was considered significant if $p <$ 0.05. Analysis of variance (ANOVA) was used to identify any significant differences in the accuracy with which various optimization formulas were able to predict CHL_{PT}. Pairwise comparisons were performed using Tukey's HSD. Statistical analyses were conducted using Sigmaplot 13 (Systat Software Inc., San Jose, CA).

4.3 Results

Of the 30 ears included in the present study, 21 provided data which could be utilized for the final analysis. Data from 7 ears were excluded due to absent

DPOAEs after the induction of CHL. In those ears, mean CHL_{PT} = 8.2 dB (SD = 1.0 dB). Data from 2 others were excluded because the ear probe did not sufficiently seal the ear canal in the pressurized condition. For the included ears, mean hearing threshold for a 1 kHz tone in the absence of CHL was 5.47 dB HL (SD = 0.58 dB). Mean hearing threshold after CHL induction was 12.95 dB HL (SD = 0.88 dB). Stability of the CHL throughout the DPOAE measurement process was verified via an additional hearing threshold measurement following the DPOAE protocol. Without ear probe repositioning or alteration of the applied ear canal pressure, mean hearing threshold was observed to be 13.54 dB HL (SD = 0.63 dB). A leaky seal could be expected to lead to a decrease in measured CHL_{PT} over time. With a mean test-retest difference of 0.59 dB, no such effect was observed for the present data set as a whole. Additionally, no difference in any given ear exceeded 2 dB.

Figure 4.2 displays DPOAE results for ear CK, which were typical of all ears. L_{DP} is plotted as a function of L_1 and L_2 both in the absence (black lines) and presence (gray lines) of CHL. Squares or triangles indicate the maximum L_{DP} values observed for each L_2 series and are projected to the L_1-L_2 plane. Dotted lines represent linear regressions through the maxima of the respective datasets. In this example, the formula for optimizing L_1 without CHL was $L_1 = 0.58L_2 + 32$ [dB SPL] (R = 0.96), while $L_1 = 0.56L_2 + 37$ [dB SPL] (R = 0.87) best predicted optimal L_1 levels in the presence of CHL. In contrast to results found in guinea pigs, notches, or steep, nonmonotonic declines in L_{DP}, were not observed at any given L_2 for a majority of the ears in the present study. As notches are theorized to alter both the amplitude and location of L_{DP} maxima, the relative absence of notches allowed for the use of a wider L_2 range than the 50–64 dB SPL used previously (Olzowy et al., 2010). Data for all L_2 were utilized in the generation of

CHL_{DP} estimates in the following manner: First, the distance between the two optimization formulas was calculated, ΔL_{1OPT} = (0.58 - 0.56) L_2 + (32 - 37) [dB SPL]. Then, ΔL_{1OPT} was calculated for each L_2 over the range of 20–70 dB SPL and the mean was obtained. Finally, using the slope of the optimization formula obtained in the absence of CHL and the ΔL_{1OPT} mean, CHL_{DP} was determined, CHL_{DP} = -4.1 / (1 - 0.58). For ear CK, this method resulted in a DPOAE-based CHL estimate of 9.76 dB, while the audiometry-based estimate was 8.66 dB. This process was repeated for each ear included in the study.

4.3.1 Effect of CHL on optimization formula parameters

Theoretical considerations for the calculation of CHL_{DP}, as laid out in Kummer et al. (2006), require that CHL has no meaningful impact on basilar membrane mechanics, and therefore, on optimization formula slope. Mean change in slope across ears due to CHL was found to be -0.08 dB/dB (SD = 0.14 dB/dB). Statistical analysis revealed no significant difference in terms of mean slope between the no-CHL and CHL coefficient groups, $t(40) = 1.73$, $p = 0.09$. Figure 4.3 displays the change in slope after CHL induction as a function of CHL_{PT} for each ear in the present study. The non-significant correlation result, $r(19)$ = -0.42; $p = 0.06$, suggests that stretching of the ossicular chain due to negative ear canal pressure does not systematically alter the slope of the ear-specific L_1 optimization formula for f_2 = 1 kHz, at least for the mild degrees of CHL_{PT} observed here. However, the arbitrary origins of the 0.05 significance cutoff should be borne in mind.

Though slope values were shown to remain relatively constant, a significant change in optimization formula parameter b is needed to compensate for the presence of CHL, the magnitude of this change increasing with CHL_{PT}. If the slope

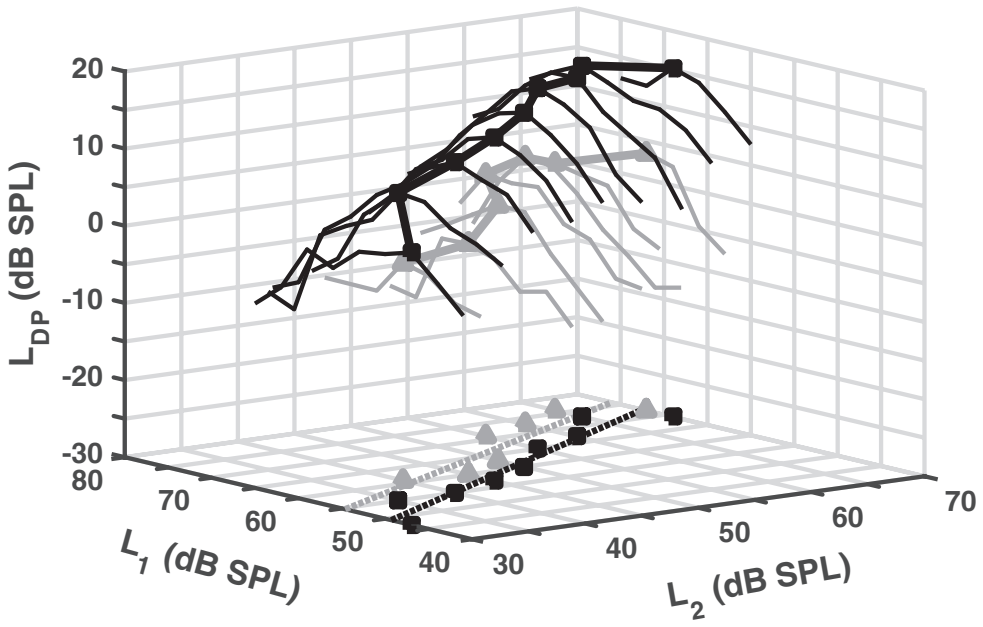


Figure 4.2: DPOAE levels for ear CK both without (black lines) and with (gray lines) CHL plotted against L_2 and L_1. For each L_2, maximal DPOAE level was identified with either a square (without CHL) or triangle (with CHL) and projected to the L_1/L_2-plane. Dotted regression lines mark the paths of the optimal L_1-L_2 relationships for the two conditions. Note the approximately parallel slope of the two dotted lines. Reprinted from "Estimation of Minor Conductive Hearing Loss in Humans Using Distortion Product Otoacoustic Emissions,"S.C. Marcrum et al., 2017, [ePub ahead of print]. *Ear Hear*, p. 4. Copyright 2017, Wolters Kluwer Health.

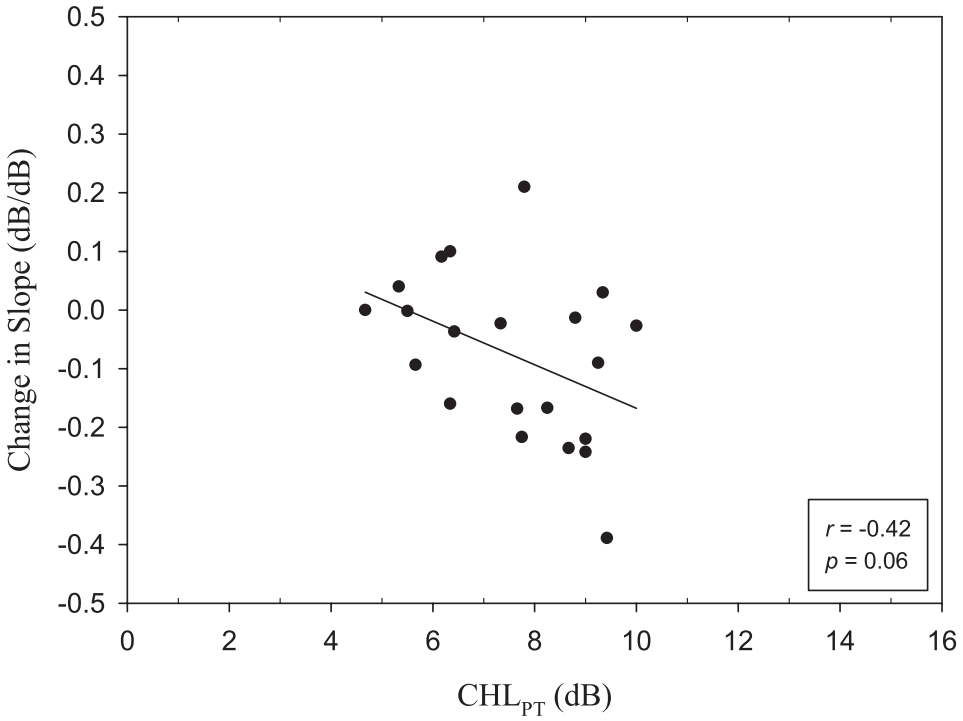


Figure 4.3: Change in optimization formula slope (parameter a) following induction of CHL plotted against a pure tone audiometry-based estimate of CHL (CHL_{PT}). Reprinted from "Estimation of Minor Conductive Hearing Loss in Humans Using Distortion Product Otoacoustic Emissions,"S.C. Marcrum et al., 2017, [ePub ahead of print]. *Ear Hear*, p. 5. Copyright 2017, Wolters Kluwer Health.

coefficient a is independent of the presence of CHL, the change in parameter b following CHL induction should be roughly proportional to CHL. The mean change in b due to CHL was found to be 7.9 dB (SD = 8.0 dB). Statistical analysis revealed a significant difference in terms of mean b values between the no-CHL and CHL coefficient groups, $t(40) = 3.49$, $p < 0.001$. Figure 4.4 presents the change in b as a function of CHL_{PT} after CHL induction. A significant linear dependence of change in b on CHL_{PT} was observed, $r(19) = .5$, $p = 0.02$. Specifically, as CHL_{PT}

increased, parameter b had to be increased to recover an optimal excitation within the cochlea.

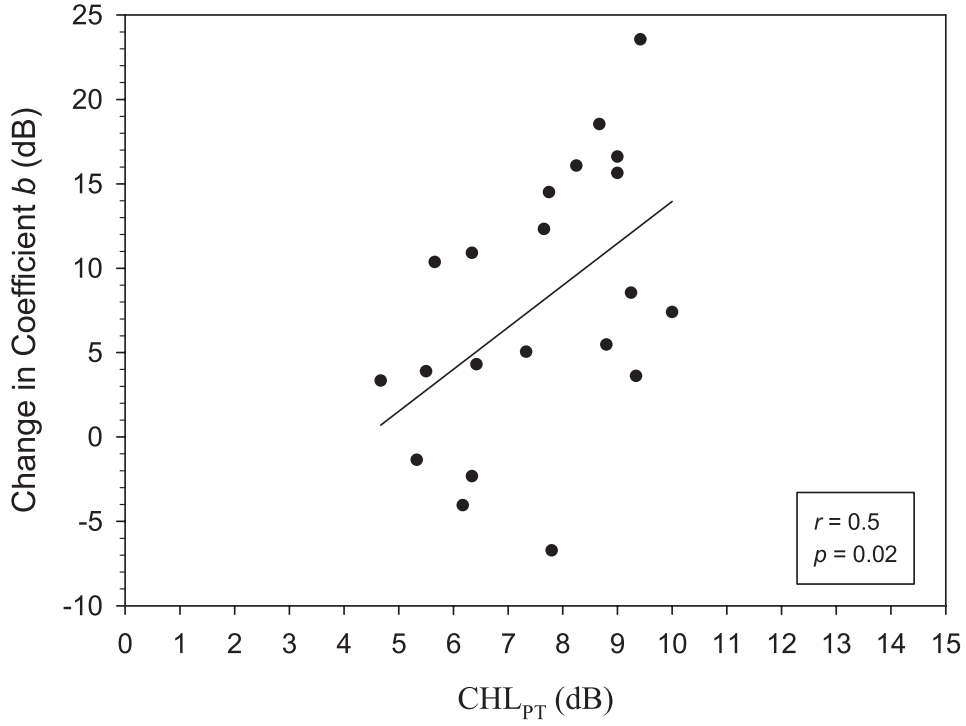


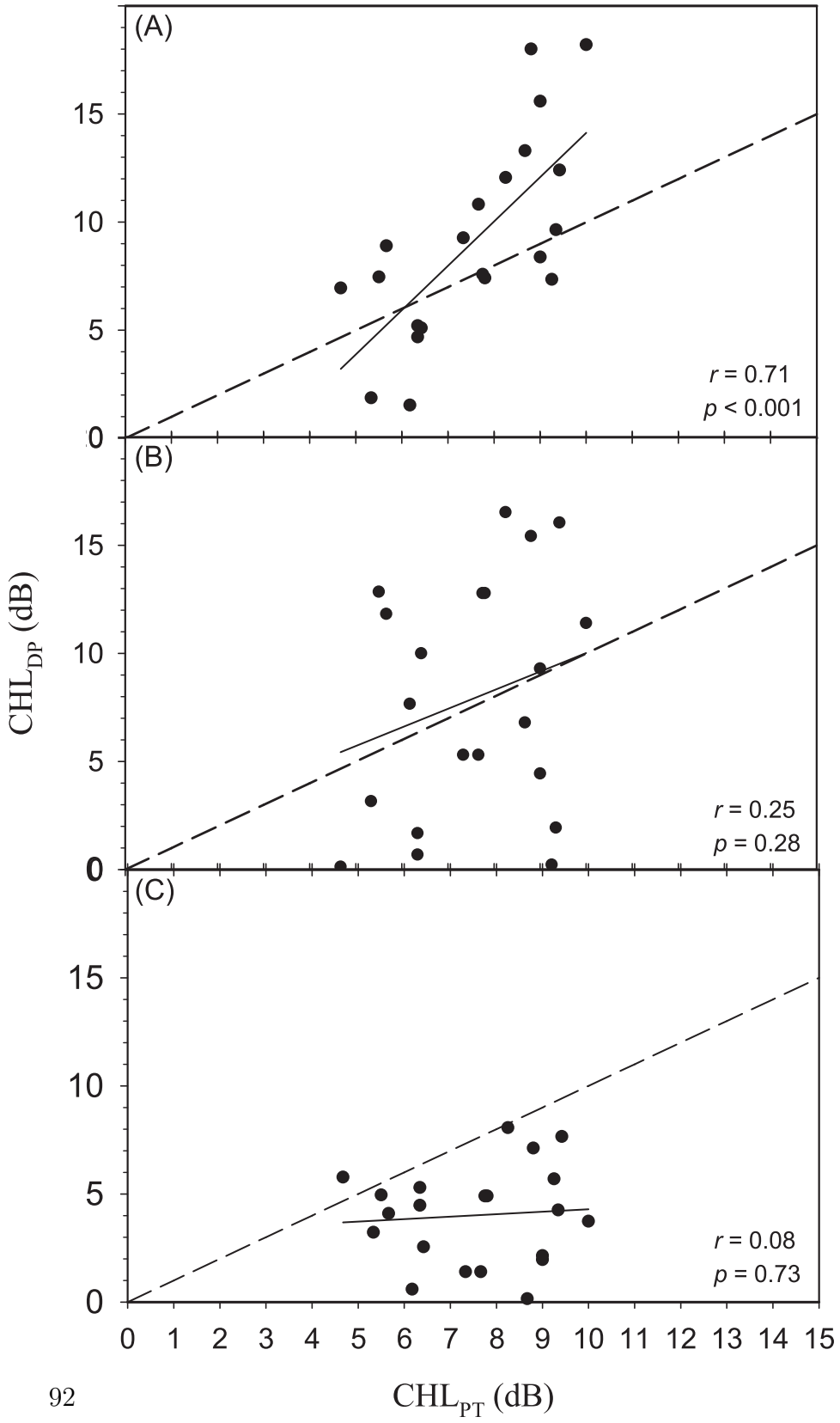
Figure 4.4: Change in optimization formula parameter b following induction of CHL plotted against a pure tone audiometry-based estimate of CHL (CHL_{PT}). Reprinted from "Estimation of Minor Conductive Hearing Loss in Humans Using Distortion Product Otoacoustic Emissions,"S.C. Marcrum et al., 2017, [ePub ahead of print]. *Ear Hear*, p. 5. Copyright 2017, Wolters Kluwer Health.

4.3.2 Accuracy of CHL_{DP} estimates

Calculation of CHL_{DP} requires the input of optimization formula parameter values for a given ear in both a pathological and non-pathological state. While parameters describing the pathological state can generally be obtained via diagnostic

evaluation within the clinic, those describing the non-pathological state must be estimated. The accuracy with which the estimated parameters describe the cochlear mechanics of each individual ear is therefore critical to determining utility. Several generic optimization formulas have been developed, which purport to predict the average optimal L_1-L_2 separation in non-pathological, adult ears. For example, $L_1 = 0.57L_2 + 34$ [dB SPL] has been suggested as optimal for evoking DPOAEs at 1 kHz specifically, while $L_1 = 0.49L_2 + 41$ [dB SPL] has been shown to optimally evoke DPOAEs for frequencies ranging from 1–6 kHz (see Chapter 2). In Figure 4.5, parameter values from three optimization formulas are compared in terms of their utility in estimating CHL_{PT}. In panel A, CHL_{DP} calculations were based on the ear-specific optimization formula parameters obtained in this study. In panels B and C, CHL_{DP} was calculated using parameters from $L_1 = 0.57L_2 + 34$ [dB SPL] and $L_1 = 0.49L_2 + 41$ [dB SPL], respectively. In this way, estimates of optimization formula parameters for the non-pathological state became decreasingly ear- and frequency-specific, while those for the pathological state remained specific to each ear.

When ear-specific optimization parameters for both the CHL and non-CHL conditions were utilized, a highly significant linear dependence was observed between DPOAE-based and pure tone audiometry-based estimates of CHL magnitude at 1 kHz, $r(19) = 0.71$, $p < 0.001$. Replacement of the ear-specific parameters obtained in the absence of CHL with generic parameters resulted in non-significant correlations with CHL_{PT}. Correlation results were found to be $r(19) = 0.25$, $p = 0.28$ and $r(19) = 0.08$, $p = 0.73$, when using the frequency-specific and frequency-nonspecific generic parameters, respectively. These results highlight the fact that generic optimization formulas, though descriptive of average optimal L_1-L_2 primary tone levels in normal hearing adults, are less accurate in individual ears.


(A)
r = 0.71
p < 0.001
(B)
r = 0.25
p = 0.28
(C)
r = 0.08
p = 0.73
CHL_DP (dB)
CHL_PT (dB)
0
5
10
15
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

4.4 Discussion

Conductive hearing loss alters DPOAE amplitude via attenuation of primary tone and evoked response levels as they are filtered by the middle ear, as well as through modification of the effective L_1-L_2 separation within the cochlea. This study is significant in that it provides empirical support for a theory regarding the manner in which these multiple mechanisms combine to influence DPOAE measurements (Kummer et al., 2006). Results of the present study also provide support for the feasibility of exploiting the systematic nature of these mechanisms to objectively estimate mild degrees of CHL in humans, at least for f_2= 1 kHz. Specifically, CHL_{PT} was predicted with a mean absolute error of 3 dB (SD = 2.48 dB), when optimal primary tone level relationships for both the CHL and non-CHL conditions were known. Due to this restriction, however, clinical utility appears limited.

The theory investigated in this study stipulates that the stiffening, slackening, or weighing-down of the ossicular chain that can arise from middle ear pathol-

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Figure 4.5 *(preceding page)*: Correlation of CHL_{DP} with CHL_{PT} as determined using three distinct sets of optimization formula parameters. In panel A, ear-specific parameters obtained in this study were utilized. In panel B, a generic, frequency-specific (1 kHz) optimization formula was used. In panel C, a generic, frequency-nonspecific optimization formula provided parameter values. The dashed line in each panel indicates y = x, which allows for a visual assessment of CHL estimate accuracy. Reprinted from "Estimation of Minor Conductive Hearing Loss in Humans Using Distortion Product Otoacoustic Emissions,"S.C. Marcrum et al., 2017, [ePub ahead of print]. *Ear Hear*, p. 6. Copyright 2017, Wolters Kluwer Health.

ogy exerts no influence on the compressive nature of basilar membrane mechanics. Specifically, the slopes of L_1-L_2 optimization formulas are theorized to be identical in both the presence and absence of CHL. While this assumption is unlikely to be perfectly fulfilled in clinically pathological ears, the present results demonstrate it to be approximated, if only in the instance of air pressurization. Additionally, it is encouraging that Olzowy et al. (2010) observed a strong relationship between compound action potential-based CHL estimates and CHL_{DP} in guinea pigs, as they induced CHL through the partial filling of the middle ear space and tympanomeatal angle with saline solution. This result implies that the current results might not be specific to CHL induced through pressurization. However, as the effects of ear canal pressurization on ossicular coupling to the cochlea diverge in many respects to those of clinical conditions such as otitis media with effusion, a definitive statement to the validity of the slope independence assumption should be withheld until the method can be tested in clinically pathological ears.

Previous authors have suggested that steep or nonmonotonic DPOAE growth behavior can significantly affect the accuracy of CHL estimates by shifting the location of the maximum L_{DP} response in the L_1-L_2 plane (Deppe et al., 2013). It could be expected then, that the accuracy of CHL_{DP} estimates should decrease with increasing L_1-L_2 optimization formula slope. However, no significant correlation could be identified between error in CHL_{DP} estimates and slope (parameter a), $r(19) = 0.26$, $p = 0.26$. This finding suggests that the impact of optimization formula slope on CHL estimate accuracy might not be as considerable as theorized. An alternative interpretation is that the use of a broad range of L_2 values might have served to minimize effects of irregular growth at individual L_2 values.

A distinction must be made between methods shown to be beneficial within a research setting and those appropriate for application within the clinic. For

the former, optimal L_1-L_2 function parameters can be determined for individual ears both before and after experimental induction of CHL. In the clinical setting, however, a potentially pathological ear is presented and optimal parameters for the non-pathological state must be estimated. One estimation method is the use of generic formulas, which have been shown on average to maximize L_{DP} in non-pathological ears. In the present study, the relationship between CHL_{DP} and CHL_{PT} was satisfying only when ear-specific optimization parameters were available. Estimating parameters for the non-CHL condition through the use of generic formulas, whether frequency-specific or not, decreased the degree of predictive accuracy below the level of usability. While the correlation between CHL_{PT} and CHL_{DP} was higher for generic, 1 kHz-specific parameters than for generic, frequency-nonspecific values, both resulted in non-significant correlations. These results stand in contrast to those of Olzowy et al. (2010), who found significant correlations when applying both frequency-specific and nonspecific, generic parameters in guinea pigs. Possible explanations could be a difference between guinea pigs and humans in terms of inter-ear variability of optimization formula parameters, a fundamental difference in the validity of the proposed method for 1 kHz DPOAEs, as opposed to those obtained at 8 kHz, or the narrower L_2 range incorporated into the calculations of Olzowy et al. (2010), as compared to the current investigation.

Given the large differences in optimization formula parameters found across individual ears, it is not possible to use the Kummer et al. (2006) method to definitively diagnose CHL. For example, a large ΔL_{1OPT} observed in an individual ear might result either from a CHL or an inaccurate L_1 estimate generated by a generic optimization formula. However, when included as part of a clinical test battery including tympanometry and stapedius reflex testing, this method may

serve not only to strengthen the CHL diagnosis, but also to provide unique information in the form of a CHL estimate. It is also possible that future studies into optimal DPOAE stimulus characteristics could yield results which demonstrate significantly reduced inter-individual variability. However, much work is needed before the proposed method should be considered for any role in a clinical routine.

4.4.1 Limitations

Several important limitations of the present study warrant mention. First, induced CHL was mild ($\leq$ 10 dB) and restricted to 1 kHz. Kummer et al. (2006), however, suggested that the investigated method is appropriate for all f_2 and for CHL up to 20 dB. To better evaluate this theory, larger CHL across a broader frequency range should be included. Given that the pattern of increasing optimal L_1-L_2 separation with deceasing L_2 has been identified in humans for at least f_2 = 1–8 kHz, the investigated method might be reasonably expected to function at higher frequencies. For example, though Olzowy et al. (2010) evaluated guinea pigs, the method was shown to be appropriate for f_2 = 8 kHz. Obtaining magnitude estimates for CHL up to 20 dB presents a more difficult challenge, however, as the present data indicate that even a 10 dB CHL is sufficient to reduce SNR below 6 dB for 7 out of the 30 ears tested. Evaluating CHL up to 20 dB would require either significantly increasing average L_{DP} or reducing measurement background noise beyond that which was achieved in this study.

Second, the method must be evaluated in clinical cases of middle ear pathology. As the effects of true CHL on the middle ear are only imperfectly simulated by the alteration of ear canal pressure alone, the method should be evaluated in ears exhibiting a variety of clinical symptoms. The results from Olzowy et al. (2010) are encouraging, as the experimental CHL utilized for the study was not induced

via ear canal pressurization, but rather through application of saline solution. Though also not fully representative of clinical pathology, CHL due to fluid within the middle ear is certainly a preferable approximation of clinical reality.

Third, the assumption that CHL attenuates both primary tones by the same amount requires additional investigation. For $f_2 = 1$ kHz and $f_2/f_1 = 1.22$, the difference between the primary tones is approximately 120 Hz. For $f_2 = 6$ kHz, however, the difference is approximately 1082 Hz. As CHL due to middle ear pressurization has been shown to decrease with increasing frequency (Cooper et al., 1977), it could be expected that attenuation provided by the CHL should be more consistent across low-frequency, as opposed to high-frequency, primary tones. Should future studies reveal that DPOAE-based estimates of CHL decrease in accuracy as f_2 rises, the assumption of equal attenuation across primary tones might need to be reassessed.

4.4.2 Conclusions

This study represents an initial investigation into the use of DPOAEs for the quantification of experimentally-induced CHL in humans. Though CHL_{DP} was shown to be significantly predictive of CHL_{PT} when optimization formula parameters for a given ear, both with and without mild CHL, were known, the lack of a significant relationship when using generic primary tone level formula parameters limits clinical utility.

5 Conclusions

Conductive hearing loss is defined clinically as a difference between air- and bone-conduction thresholds in excess of 10 dB, with lesser differences being considered of questionable significance. While perhaps a reasonable working definition in the broad sense, CHL of less than 10 dB has been shown to significantly impair the detectability of DPOAEs specifically (Job and Nottet, 2002; Kummer et al., 2006). A more appropriate and inclusive conception of CHL in regard to DPOAEs, therefore, would be any reduction in the energy applied to the cochlea due to inefficiencies in middle ear transmission. When viewed in this light, there is no longer a dichotomy between healthy ears and those with CHL, but rather a CHL continuum upon which all ears are placed. As each middle ear is uniquely inefficient and each inefficiency systematically affects DPOAE amplitude through alteration of effective primary tone levels, increasing knowledge of a given middle ear's mechanoacoustical properties might provide a mechanism through which DPOAE stimulation, and thereby DPOAE amplitude, can potentially be optimized. The preceding investigations centered on an effort to improve understanding of the role of ear-specific middle ear energy transmission characteristics in the evoking of distortion product otoacoustic emissions. To that end, traditional L_2-based univariate models, as well as multivariable models incorporating additional aural acoustic immittance features, were developed for the prediction of optimal primary tone level separa-

tions in ears lacking clinical signs of middle ear pathology. The impact of more sizable inefficiencies in energy transmission on optimal L_1-L_2 separations was additionally assessed via evaluation in ears with experimentally-induced CHL (3-10 dB).

The equipment used in the preceding investigations to evoke and record DPOAEs, as well as the physiological mechanisms involved in DPOAE generation, are imperfect in terms of their reliability. Results from Chapter 2 suggest that, although the utilized DPOAE measurement system exhibited a high degree of precision in the frequency domain and excellent test-retest reliability in terms of level, targeted sound pressure levels could only be approximated within 2 dB in the average ear canal. This limit can be viewed as a useful indicator of whether differences in recommended stimulation levels between optimization formulas can be acted upon in a reliable fashion. For example, while multiple reports suggest significantly different optimal primary tone level separations for higher-frequency ($f_2 = > 6$ kHz) (Neely et al., 2005; Johnson et al., 2006), as opposed to lower-frequency, f_2, this work's findings suggest that these differences are generally below the precision limit of 2 dB and therefore too small to be consistently actionable. This conclusion serves not only to provide support for the continued clinical use of frequency-nonspecific primary tone level optimization formulas, but also to underline the importance of acknowledging the technical limitations of measurement equipment.

Significant variability can be recognized across individual ears in terms of the primary tone level separations found to maximize DPOAE level (see Table 2.2). One factor theorized to contribute to this variability is differences in middle ear energy transmission characteristics. In Chapter 2, primary tone level optimization formulas were created, which did not specifically account for the effects of a given middle ear. In Chapter 3, a clinical wideband energy absorbance measure

was incorporated into a multivariable L_1-L_2 optimization formula. A comparison of results obtained when utilizing both methods revealed a general pattern of statistically-significant, yet clinically non-meaningful, improvement with the multivariable model, though significant improvements were identified within individual ears. These results likely stem from two sources: First, wideband energy absorbance is an indirect measure of the acoustic energy absorbed through the tympanic membrane during forward transmission. It is not, however, capable of describing energy absorbance through the oval window and into the cochlea or through the middle ear during reverse transmission of the DPOAE. In this way, it provides only an incomplete assessment of a given middle ear's impact. Second, as all participants were required to pass a clinical middle ear screening as a condition of enrollment, an artificially narrow range of middle ear statuses, as compared to the much broader range observed in the general population, was created. This factor might have served to mitigate the potential impact of the absorbance measure's inclusion, as well as to limit generalizability of the results. Taken together, these findings suggest that, while inclusion of ear-specific energy absorbance characteristics can lead to significant improvements in optimal primary tone level recommendation accuracy in specific ears, differences in EA is not a primary contributor to the variability observed across ears exhibiting clinically normal middle ear function. Despite this, an EA measure should nonetheless be considered for inclusion in a clinical test battery due to the unique nature of the information it provides.

Though generally weak in the absence of measurable CHL, a stronger relationship between middle ear function and optimal primary tone levels can be identified in the presence of mild CHL. Kummer et al. (2006) postulated that, if optimal primary tone level relationships for an ear without CHL are known or can be es-

timated accurately and a CHL can be presumed to attenuate both primary tones to a similar extent, the adjustment to L_1 required to restore an optimal L_1-L_2 separation following CHL induction can be utilized to estimate CHL magnitude objectively. This postulation is founded on knowledge of the compressive nature of basilar membrane mechanics and has found support in subsequent studies (Olzowy et al., 2010; Deppe et al., 2013). The present work extends previous findings to humans and provides empirical support for the supposition that CHL systematically affects DPOAE amplitude through a combination of middle ear filtering and alteration of effective primary tone level relationships within the cochlea. However, DPOAE-based CHL estimates were shown to be significantly predictive of puretone audiometry-based estimates only when optimization formula parameters for a given ear, both with and without CHL, were known. Additionally, due to the low-level nature of DPOAE responses and the time investment required to reduce background noise levels sufficiently using traditional signal averaging techniques, the method currently appears useful for only mild (3-10 dB) degrees of CHL. Utility is limited further still in the case of low-frequency DPOAEs, for which background noise levels and CHL are frequently greatest. This combination of the lack of a meaningful predictive relationship when using generic primary tone level formula parameters and the mild nature of CHL able to be assessed significantly limits the method's potential for clinical utility. Future work towards the development of superior generic primary tone level optimization formulas and alternative background noise reduction methods, however, could go a long way towards overcoming current limitations.

Viewed together, the preceding studies suggest that, for ears presenting clinically normal middle ear function, differences in middle ear energy transmission, as quantified using 226-Hz tympanometry and wideband energy absorbance, do not

meaningfully influence optimal DPOAE primary tone level separations on average. However, significant effects can occur in individual ears. Mild conductive hearing loss, on the other hand, has a significant effect on optimal separations, which can largely be explained by basilar membrane compression. Further, this effect can be exploited under certain conditions, providing objective information regarding middle ear health.

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List of Figures

List of Tables