



Diagnosis of Mechanical Ear Pathologies Using Structure-Based Modeling and Machine Learning Techniques

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Automatic diagnosis of mechanical ear pathologies using structure-based modeling and machine learning techniques

A dissertation presented

by

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to

The Division of Medical Sciences

in partial fulfillment of the requirements

for the degree of

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in the subject of

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*Automatic diagnosis of mechanical ear pathologies using structure-based modeling and machine learning techniques***Abstract**

Abnormal macro-mechanics of the ear such as otosclerosis, ossicular discontinuity and superior canal dehiscence (SCD) can result in a variety of debilitating auditory and vestibular symptoms such as hearing loss, blocked sensation of the ear, hyperacusis and dizziness. The mechanisms by which some mechanical pathologies cause such symptoms are not well understood, and these pathologies are difficult to diagnose and treat. To address these challenges, we set out to improve our knowledge of the mechano-acoustic mechanisms in the normal and abnormal ear, enabling us to develop advanced diagnostic methods. We focus on improving the diagnostic capability of wideband acoustic immittance (WAI), an acoustic measurement in the ear-canal that assess the transfer of stimulus sound energy into the middle ear. WAI is a non-invasive, inexpensive approach with the potential to differentiate the various middle ear and inner ear pathologies that interfere with sound-energy transfer. To automatically detect abnormal macro-mechanics with WAI, we develop a structure-based ear model that simulates pathological WAI patterns in individual ears and utilize machine learning methods to automatically detect mechanical differences between normal and pathological ears. In the first computational modeling study, we evaluate the utility of a structure-based model to simulate changes in mechanics of an SCD ear before and after surgical repair. Next, we modify the same structure-based model to simulate other pathologies of the ear and develop a classifier to differentiate among various pathologies including SCD, ossicular fixation and ossicular discontinuity. Finally, by using partial least squares discriminant analysis to select important WAI features, and a Random Forest

classifier to categorize normal-hearing and SCD ears, we develop a systematic method to improve classification accuracy for future larger sample sizes. The application of pattern recognition methods to WAI measurements offers the potential for automatic detection of various mechanical pathologies of the ear. Our developments aim to improve patient care through improved diagnosis to enable proper and fast treatment, better preparedness for surgery, and monitoring of mechanical changes postoperatively.

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Dedication

To my parents:

Thank you for your support and endless love

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CHAPTER 1. Introduction

I. OBJECTIVE

Hearing loss affects an estimated 28 million adults in the United States (Hoffman, Dobie, Losonczy, Katalin, Themann, & Flamme, 2016). A significant proportion of these individuals suffer conductive hearing loss (CHL) that results from pathologies within the external, middle and inner ear that interfere with the conduction of sound to the sensory structures in the inner ear (what we call macro-mechanical pathologies). In a study by Frear et al. (2019), 60% of patients at a single institution (data collected between 2015-2018 at Mass Eye and Ear) with hearing loss were diagnosed with a conductive pathology which included acute otitis media (19%), earwax impaction (25%) and surgical CHL (16%) (i.e. rupture of tympanic membrane, middle ear disorders, cholesteatomas, otosclerosis, superior canal dehiscence and external ear atresia). Since the neurosensory system is generally intact in patients with CHL, and conductive pathologies are generally amenable to surgical treatment, the potential for treatment is high. Various macro-mechanical lesions can result in similar CHL, but standard diagnostic tests such as audiometry often cannot distinguish among them. Although standard tympanometry in conjunction with an otologic exam can usually determine tympanic membrane perforation and middle-ear fluid, it is very difficult to identify the etiology of a CHL in the presence of a normal otologic exam (intact tympanic membrane without evidence of middle-ear fluid). The main objective of this dissertation is to develop structure-based model methods and explore machine learning techniques to automate detection of various macro-mechanical pathologies of the ear using wideband acoustic immittance (WAI), a cost-effective and non-invasive mechano-acoustic measurement taken in the ear canal. This may prevent unnecessary surgery, improve surgical preparation, better inform patients of prognosis, and enable monitoring of mechanical changes after surgery.

II. CHARACTERISTICS OF MACRO-MECHANICAL PATHOLOGIES

a. Ossicular fixation.

A very common presumptive diagnosis for mechanical hearing loss with a normal tympanic membrane is ossicular fixation of the malleus, incus and/or stapes. The etiology is often isolated stapes fixation associated with otosclerosis but can also be a consequence of past middle-ear infection causing extensive tympanosclerosis of the middle ear, ossicular scarring in the setting of trauma, or isolated fixation of the malleus head to the epitympanum. In a previous study, the reported clinical prevalence of otosclerosis with stapes fixation was 0.99 to 1.2% (Declau et al., 2001). Malleus fixation is considered rarer than stapes fixation, where in a retrospective study of 363 otosclerotic ears, only 19 were reported to have a malleus fixation (Seidman et al., 2004).

Unfortunately, standard 226 Hz-tympanometry cannot reliably differentiate the fixed malleus and fixed stapes from normal, as was shown clinically (Margolis et al. 1999), and in controlled experiments in cadaveric middle ears, what is often referred to as a temporal bone preparation (Nakajima et al. 2005). In skilled hands, pneumatic otoscopy can preoperatively distinguish malleus and stapes fixation, but the test is qualitative and heavily dependent on the training of the observer. In most cases, the final differentiation of malleus and stapes fixation is made only after intraoperative manual palpation by the surgeon, and even this direct assessment suffers from subjectivity. The importance of an accurate diagnosis of malleus from stapes fixation is particularly evident in stapes surgery for otosclerosis. A fixed malleus may be overlooked as the cause of a conductive hearing loss, which may be wrongly attributed to a fixed stapes. A fixed malleus may also coexist with a fixed stapes (Huber et al., 2003; Mehta et al., 2002; Schuknecht, 1993). In either case, overlooking a fixed malleus results in failure of stapes

surgery. Likewise, the conductive hearing loss produced by a bony defect of the superior canal, either trauma-induced or spontaneous, can mimic the loss produced by stapes fixation and be similarly missed.

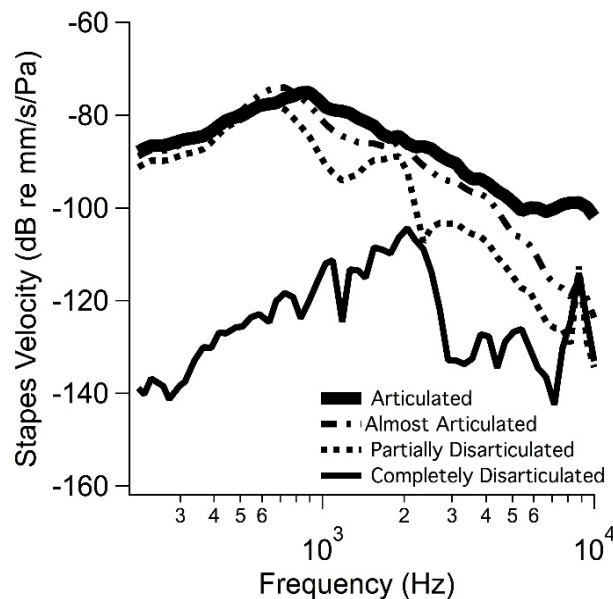


Figure 1.1 Sound-induced stapes velocity for normal and disarticulated middle ear. “Articulated” condition is shown in thick solid line. Partial disarticulation “Almost Articulated” (small compliance introduced into the ossicular chain) results in high-frequency hearing loss (above 5 kHz). The more compliant (looser) ossicular chain results in more hearing loss towards lower frequencies. Figure from Farahmand et al. (2016).

b. Ossicular Discontinuity

The second class of pathology we investigate is ossicular discontinuity that can may result from chronic otitis media with or without cholesteatoma, or trauma.

Exact incidence and prevalence of ossicular discontinuity are not known.

Total, or near-total ossicular discontinuity

can exhibit conductive hearing loss

similar to ossicular fixation. Standard

tympanometry is again not a reliable

means for differentiating ossicular

discontinuity from ossicular fixation (or

even a normal ossicular chain). *Partial*

ossicular discontinuity, where normal contact at an ossicular joint or along a continuous bony

segment of an ossicle is replaced by soft tissue or simply by contact of opposing bones (such as

in an opposed fracture) is often misdiagnosed. Clinical studies have shown that partial ossicular

discontinuity can result in *high-frequency conductive hearing loss*, although these findings are

often assumed to arise from audiometric errors (Anderson and Barr, 1971; Chien et al., 2008; Farahmand et al., 2016; Marshall et al., 1983; Merchant et al., 2010; Mustain and Hasseltine, 1981; Sim et al., 2013).

In the controlled experimental environment using animals or cadaveric ears, the introduction of a compliant link in the ossicular chain to mimic partial ossicular discontinuity produces loss of stapes motion at high frequencies (representing high-frequency hearing loss), which systematically progresses to lower frequencies as the compliance of the link is increased (made looser) (Farahmand et al., 2016). High-frequency hearing loss due to partial discontinuity is shown in Fig. 1.1, where the “Almost Articulated” discontinuity (with slightly more compliant middle-ear chain than normal “Articulated”) results in hearing loss only above 5 kHz. With a more compliant middle-ear chain, “Partially Disarticulated”, the hearing loss is increased and includes lower frequencies (down to 1 kHz). “Completely Disarticulated” has a large hearing loss over a broad frequency.

Note that because standard audiometric procedures only identify the conductive components of hearing losses at frequencies of 4 kHz and below, the predicted hearing loss in the “Almost Articulated” case in Figure 1.1 would be mistaken for a sensorineural hearing loss. Due to this deficiency in standard testing, a number of patients diagnosed with high-frequency sensorineural hearing loss could actually have a conductive loss or a mixed loss with a significant macro-mechanical component caused by partial ossicular discontinuity. Such mechanical losses would not be expected to improve with proposed new pharmacologic or genetic treatments targeting sensorineural hearing loss. Improved diagnostic methods for these mechanical lesions are necessary to enable appropriate treatment, especially because there is potential to surgically treat partial ossicular discontinuity.

c. Superior Canal Dehiscence (SCD)

A third mechanical pathology that yields similar symptoms and can present after trauma or blast injury is superior canal dehiscence (SCD). “Third window” lesions such as SCD are characterized by a mechanical defect of the bone surrounding the inner ear resulting in a variety of symptoms that mimic other otologic pathologies, making diagnosis challenging. SCD syndrome is associated with a bony defect of the superior semicircular canal, but other fistulas of the inner ear (involving the posterior canal, horizontal canal, or stapes footplate) can also present with similar symptoms and pathophysiology. In addition to hearing loss, canal dehiscence can produce debilitating auditory symptoms such as hyperacusis, hypersensitivity to self-generated sounds by the voice or body motion (footfalls, eye movements, hair or teeth brushing), aural fullness, vascular pulsations, as well as debilitating vestibular symptoms, such as Tullio sign (sound-induced vertigo) and Hennebert sign (nystagmus produced by pressure in the ear canal) (Minor et al., 1998; Niesten et al., 2014). As noted above, SCD symptoms mimic other otologic conditions, contributing to the lack of understanding and frequent misdiagnosis of this disease. Consequently, there is a misperception among many general clinicians that SCD is rare, leaving several patients with debilitating symptoms who undergo inappropriate treatments, including psychological evaluations and unnecessary middle ear surgery in some cases.

III. CURRENT CHALLENGES IN DIAGNOSIS OF MECHANICAL PATHOLOGIES

Patients with macro-mechanical pathologies involving the middle and inner ear experience a variety of auditory symptoms. Often, but not always, macro-mechanical auditory pathologies produce hearing loss as well as the other auditory symptoms.

Because all of the noted symptoms are common to various otologic pathologies, the differential diagnosis is complicated and therefore standard clinical practices often result in misdiagnosis and incorrect treatment. Patients with a normal physical exam showing an intact tympanic membrane and aerated middle ear can have a variety of mechanical pathologies yielding some set of aforementioned symptoms, including various types of ossicular fixation, partial or complete ossicular discontinuity, Eustachian tube dysfunction, patulous Eustachian tube, and pathological bony defects of the otic capsule such as superior canal dehiscence (SCD). Presently, there is limited ability to differentiate these possibilities without surgery or CT scan. This thesis will focus on three classes of mechanical pathologies of the middle and inner ear with overlapping symptoms that may be misdiagnosed: ossicular discontinuity, ossicular fixation and superior canal dehiscence.

Among the classes of pathologies described above, SCD poses particular challenges for diagnosis. *This arises, in part, because SCD is far more common than often perceived.* Over a million people are affected by SCD in the U.S. alone. Prevalence of SCD is reported to be 0.7% to 1.9% (Carey, Minor, & Nager, 2000; Crovetto et al., 2010). Thin bone over the semicircular canal with prevalence of 1.3% to 15.6% (Carey et al., 2000; Crovetto et al., 2010; Jackson et al., 2015) can also produce significant SCD symptoms (perhaps due to multiple micro-perforations), and thin bone also appears to be a risk factor for trauma-induced SCD (e.g. child birth, head trauma, high pressure, blasts) (Teixido et al., 2012).

A second aspect of the challenge associated with SCD is that it is easily and frequently misdiagnosed. Because SCD symptoms vary and often mimic other otologic pathologies, misdiagnosis in favor of more “common-place” etiologies is understandable. Particularly troubling, however, is that many of these patients undergo wrong treatments: (e.g. stapedectomy

surgery, gentamicin for Meniere's, years of psychiatric medication) that can result in worsening of symptoms and permanent harmful effects. In a recent survey at Massachusetts Eye and Ear, more than two hundred individuals reported an average of 50 months between initial symptoms and a correct diagnosis of SCD. Patients who are finally correctly diagnosed typically do not inform the prior clinicians of the earlier misdiagnoses, feeding the misperception that SCD is uncommon.

IV. OBJECTIVE MEASURE TO IMPROVE DIFFERENTIAL DIAGNOSIS: WIDEBAND ACOUSTIC IMMITTANCE

Non-invasive mechano-acoustic measurements recorded at the ear canal show great potential for diagnosis but are not generally used in the clinic today. Wideband acoustic immittance is a mechano-acoustic measurement made in the ear canal that measures the fraction of the stimulus sound reflected by the eardrum. WAI is a non-invasive, inexpensive approach with the potential to differentiate among middle-ear and inner-ear pathologies that cause similar symptoms.

Though there have been research advancements enabling the diagnosis of pathologies such as tympanic-membrane perforation and middle-ear effusion with WAI (Hunter & Margolis, 1997; Hunter et al., 2013; Voss et al., 2001), the use of WAI for diagnosis of various macro-mechanical pathologies with normal otologic exams still needs improvement. Present analytical techniques do not take advantage of the extremely rich broadband information in WAI. A technique for analyzing WAI measurements (using lumped-element model fits to the WAI data) that separates the various pathologies (Merchant et al., 2019). We hypothesize that such advanced analytical techniques can overcome previous limitations and allow objective separation and automatic diagnosis of multiple macro-mechanical disorders. To test this hypothesis, we develop a structure-based mechano-acoustic model consisting of the external, middle and inner

ear structures, and we apply new computational-modeling analyses techniques to WAI measurements in patients with surgically-confirmed middle ear, or CT-confirmed inner ear pathologies. In this dissertation, we show that WAI offers the potential for automatic detection of macro-mechanical lesions of the ear such as superior canal dehiscence, ossicular fixation, and ossicular discontinuity.

V. SUMMARY OF THESIS

This thesis is divided into three sections. Section 1 consists of four chapters that aim to automate the detection of abnormal macro-mechanics of the ear with WAI. In Section 2, we experimentally explore the effect of superior canal dehiscence and middle ear cavity on WAI in cadaveric human temporal bones. And finally, Section 3 consists of 2 chapters that are clinical studies that explore the use of mechano-acoustic ear canal measurements such as WAI and umbo velocity to compare SCD vs. thin bone overlying the superior semicircular canal, and a case study exploring the use of WAI to detect a rare incus fracture.

In Chapter 2, we test three previously published middle-ear models: Rosowski and Merchant (1995), O'Connor and Puria (2008) and Liu and Neely (2010), and determine how well the models adapt to ear-canal measurements such as WAI, and umbo velocity (V_u) via laser Doppler vibrometry obtained in live humans. By testing different configurations and parameter values from previously published models, we determine which model best adapts to actual data obtained from live patients with mechanical lesions such as stapes fixation (SF) and ossicular disarticulation (OD) as well as normal-hearing individuals. The goal of this chapter is to find a previously published middle ear model that can successfully follow the trends of ear canal measures in patients with middle ear disorders. WAI and V_u data were collected retrospectively

from our lab's mechanical measurements database of pathological and non-pathological data from 2009 to 2017. Several lab members throughout time including myself made both WAI and V_u measurements in pathological ears to add to our lab's mechanical measurements database. I personally collected data from 2015 to 2018 in over 50 pathological ears. Please see Table 1.1 for an explanation of where data originated from for each of the chapters.

In Chapter 3, we develop a structure-based model consisting of external, middle and inner ear structures designed to differentiate between pathological and non-pathological ears. The middle ear model is similar to that developed in Rosowski and Merchant (1995), which is carefully studied in Chapter 2. Specifically, we fit the model to WAI data measured from individual ears before and after SCD surgical repair to determine whether expected SCD model parameters change after surgery, and whether these parameters have a potential to measure the extent of surgical repair using WAI. WAI data from these SCD patients were measured before and after surgical repair between the years 2010 and 2017.

In Chapter 4, the structure-based acoustic circuit model of the ear developed in Chapter 3 is used to simulate WAI measurements in pathological human ears. Pathological models are fit to WAI measures of individual ears to determine which pathological model fits best to actual pathological WAI data. In combination with ABG information, we use the fitted model parameters to develop a single decision tree to separate ossicular discontinuity (OD), stapes fixation (SF) and superior semi-circular canal dehiscence (SCD). The goal of this chapter is to develop an automated procedure using WAI and ABG information to differentiate mechanical lesions of the ear that are difficult to diagnose in the clinic. WAI data of patients with OD and SF were collected retrospectively from our lab's mechanical measurements database from 2009 to 2017. WAI data

of patients with SCD were the same from Chapter 3 (pre-operative SCD condition), and were collected retrospectively between 2010 and 2017.

In Chapter 5, we establish machine learning methods to automatically detect abnormal macro-mechanics with WAI in patients with SCD. We determine critical SCD markers from power reflectance (extracted from WAI) information over a wide range of frequencies. By using partial least squares discriminant analysis to select important features, and a Random Forest classifier to categorize Normal and SCD ears, we develop a systematic method to improve classification accuracy for future larger sample sizes. The application of pattern recognition methods to WAI offers the potential for automatic detection of superior canal dehiscence and other mechanical lesions of the middle and inner ear. WAI data of patients with confirmed SCD were collected prospectively from our lab's mechanical measurements database from 2010 to 2017.

In Chapter 6, we use fresh cadaveric human temporal bones to assess the effect of SCD on power reflectance (PR, a derivative of WAI). Part of the challenge in quantifying SCD-induced effects in human temporal bones is that temporal bone experiments often require an open middle-ear cavity (MEC), and the MEC can have significant effects on PR. Here, we directly compare our experimental results in temporal bone to clinical PR data (before and after SCD surgery). We also study the effects of the middle ear cavity (MEC) on PR measurements in temporal bone, and determine the isolated effects of SCD in an estimated condition with an intact MEC. All experiments were performed jointly by myself and Stefan Raufer.

In Chapter 7, we carefully determine the differences between ears with SCD and with thin bone (near-dehiscence) overlying the superior semicircular canal. In the clinic, patients with near-dehiscence and frank dehiscence may exhibit similar symptoms. We highlight the difficulty in diagnosing thin bone cases using high-resolution CT by comparing CT readings performed by two

neuro-radiologists at the same institution. Since a dehiscence of the SSC is an anatomical defect leading to mechanical changes of the ear (Songer & Rosowski, 2007a), we use non-invasive mechanical measures such as WAI and umbo velocity via laser Doppler vibrometry to differentiate SCD, thin bone and a normal control group from each other. WAI data of patients with confirmed SCD and Thin Bone were collected prospectively from our lab's mechanical measurements database from 2010 to 2018.

In Chapter 8, we describe the first reported case of a fracture of the long process of the *incus* due to digital manipulation of the ear canal. The patient was previously treated for presumptive diagnosis of sensorineural hearing loss with intratympanic steroid injections. Here, we carefully discuss diagnostic markers for ossicular fractures, and show that PR can accurately diagnose an ossicular fracture.

Table 1.1: Data obtained for dissertation versus obtained from previous studies

Chapter Number	Data collected for particular study (not published elsewhere)	Data obtained from previous studies	Years of Data Collection
2	WAI and V_U measurements: 1. OD: 10 ears 2. SF: 6 ears	WAI and V_U measurements: 1. OD: 4 ears from Nakajima et al., 2013 2. SF: 10 ears from Nakajima et al., 2013. 3. Normal Hearing: 56 ears from Rosowski et al., 2012	2009-2017
3	WAI measurements: 1. SCD: 22 ears	WAI measurements: 1. SCD: 3 ears from Nakajima et al., 2013	2010-2017
4	WAI and V_U measurements: 1. OD: 10 ears 2. SF: 6 ears 3. SCD: 22 ears	WAI and V_U measurements: 1. OD: 4 ears from Nakajima et al., 2013 2. SF: 10 ears from Nakajima et al., 2013. 3. SCD: 3 ears from Nakajima et al., 2013	2009-2017

5	WAI measurements 1. SCD: 68 ears 2. Normal Hearing: 12 ears from unaffected side of SCD patients	WAI measurements 1. SCD: 17 ears overlap with Merchant et al., 2015 2. Normal Hearing: 58 ears from Rosowski et al., 2012	2010-2018
6	WAI measurements in 6 human temporal bones		2016-2017
7	WAI measurements 1. SCD: 68 ears 2. Thin Bone ears: 39 2. Normal Hearing: 15 ears from unaffected side of SCD patients	WAI measurements 1. SCD: 17 ears overlap with Merchant et al., 2015 2. Age-matched Control 1: 26 ears from Rosowski et al., 2012 3. Age-matched Control 2: 42 ears from Noij et al., 2018	2010-2018
8	WAI and UV measurements in 1 patient with incus fracture		2017

**CHAPTER 2. Comparisons of middle-ear structure-based models to simulate wideband
acoustic immittance and umbo velocity measurements**

1. Introduction

In the early sixties, detailed measurements of middle ear mechanics of normal and pathological ears facilitated the design of the first anatomical structure-based network models of middle ear structure and function (Matthews, 1983; Moller, 1965; Onchi, 1961; Siebert, 1973; Zwislocki, 1963; Zwislocki, 1962). Since then, network models (also known as lumped-element models) have provided quantitative descriptions of the mechanics of the ear. Each lumped element parameter (resistance, mass, or compliance) or a combination of parameters of a network model represents an anatomical structure of the ear and contributes to the overall acoustic input impedance of the ear, where input impedance is a measure that quantifies of how the ear moves in response to sound.

Included in these structure-based network models are elements representing the ear canal, the tympanic membrane, the ossicles, the middle ear cavities, the flexible round and oval windows, the load of the fluid-filled inner ear structures, and the ossicular joints. The parameter values in each of these models were selected to fit experimental data measuring various aspects of sound transmission from the ear canal to the inner ear (i.e. acoustic impedance at the eardrum, stapes velocity, umbo velocity, etc.). Changes in particular model parameters can simulate pathologies that occur in live human ears, such as stapes fixation or ossicular disarticulation. For example, Kringlebotn (1988) developed a structure-based model of the human middle ear that simulated acoustic impedance at the eardrum for a normal ear, otosclerotic ear, and an ear with an ossicular disruption of the incudo-stapedial joint (Kringlebotn, 1988).

Present-day modelers have further developed structure-based models to understand the underlying mechanics of normal ears as well as pathological ears, make improvements in middle ear reconstructive surgeries, and establish an inner ear model to successfully simulate clinical measures such as wideband acoustic immittance (WAI), distortion product otoacoustic emissions

(DPOAE) or bone conduction stimulation responses (Guan & Puria, 2017; Liu & Neely, 2010; O'Connor & Puria, 2008; Rosowski & Merchant, 1995; Voss, Merchant, & Horton, 2012).

Voss et al., (2012) determined the effects of middle-ear disorders on acoustic ear-canal measurements known as WAI in human cadaveric ears. This study modified the Kringlebotn middle-ear model to represent manipulations made in the middle ear of cadaveric specimens that mimicked conductive pathologies such as stapes fixation and incudo-stapedial joint disarticulation. Rosowski and Merchant (1995) also modified the Kringlebotn model to analytically study middle ear reconstructive procedures such as stapedectomy and tympanomastoid surgery. Their model produced estimates of acoustic input impedance and air-bone gap, and used these measures to study the required diameter of the ossicular prosthesis in stapedectomy that would optimize transmission of sound. They also determined the necessary volume of the middle-ear air space in a tympanomastoid surgery to achieve the best acoustic results. In an effort to improve previous structure-based models, O'Connor and Puria (2008) carefully modeled the human tympanic membrane, ossicular chain (ossicles and joints), and cochlea by manually fitting lumped-element model parameters based on 16 measurements of stapes velocity transfer function (stapes velocity normalized by the pressure difference between the ear canal and middle ear cavities) obtained from human temporal bone specimens. Their model predictions and measurements of stapes velocity (re: ear canal pressure) in living ears measured intraoperatively were comparable (i.e. in Chien et al. 2006; Huber et al. 2001). More recently, Liu and Neely (2010) used a structure-based middle ear model to simulate distortion product (DP) ototacoustic emissions (OAEs), an ear-canal acoustic measure commonly used to test the integrity of outer hair cells in the inner ear (measurable only in the living). OAEs can also assess the function of the middle ear since the middle ear conducts sound to the inner ear

and then conducts the secondary vibrations (known as OAEs) from the inner ear to the ear canal. The middle-ear model used in Liu and Neely (2010) was adapted from a previous middle ear model developed for cat by Matthews (1983), and the model effectively reproduced results from human cadaveric specimens published in Puria (2003) and Nakajima et al. (2009)

Although each aforementioned model had different applications for their structure-based ear model and simulated different measurements (i.e. WAI, air-bone gap, stapes velocity, DPOAE), there were many similarities, and all studies used similar methods (minimization of the difference between predictions and measurements) to fit the model to measurements made in cadaveric specimens. Since the mechanical contribution of the middle-ear and inner-ear to the overall acoustic input impedance is mainly passive, the parameter values calculated for these studies can apply to live human ears (O'Connor & Puria 2008; Chien et al., 2009). O'Connor and Puria (2008) showed that their model, optimized to measurements made in cadaveric specimens, effectively simulated stapes velocity measurements made intraoperatively in human ears, suggesting that their model may be applicable to living ears in addition to cadaveric ears. Chien et al. (2009) showed that the mean stapes velocity measurements on 14 live patients (measured intraoperatively) were comparable to mean stapes velocity measurements in cadaveric ears and concluded that middle-ear mechanics were similar in live and cadaveric ears. Their results were similar to the model calculations by O'Connor and Puria (2008). Earlier studies have also shown that ear canal measurements of acoustic impedance and umbo velocity show no noticeable differences between averages found in a population of cadaveric ears versus a population of live ears (Goode, Ball, and Nishihara 1993; Rosowski et al. 1990).

In this chapter, we compare and test three previously published middle-ear models: Rosowski and Merchant (1995), O'Connor and Puria (2008) and Liu and Neely (2010), and

determine how well the models fit ear-canal measurements such as wideband acoustic immittance, and umbo velocity via laser Doppler vibrometry obtained in live humans. By testing different configurations and parameter values from previously published models, we can determine which model best adapts to actual data obtained from live patients with mechanical lesions such as stapes fixation (SF) and ossicular disarticulation (OD) as well as normal-hearing individuals. The goal of this chapter is to find a previously published middle ear model that successfully predicts the trends of ear canal measurements in patients with middle ear disorders.

2. Methods

2.1 Subjects and Data Collection

Wideband acoustic immittance (WAI) and umbo velocity (V_u) data collected from sixteen patients with *stapes fixation* (SF) were used in this study. Their age ranged from 29 to 65 years with an average of 45 years (standard deviation = 11.4 years). The male to female ratio was 1:3. Ten out of 16 SF patients were previously collected for the Nakajima et al., 2013 study. Measurements from fifteen patients with *ossicular discontinuity* (OD) were collected. Their age ranged from 16 to 57 years, with an average age of 39 (standard deviation = 13.3 years). The male to female ratio was 8:7. Four out of these 15 OD patients overlapped with the Nakajima et al., 2013 study. According to the surgical reports, seven out of the 15 OD patients had a complete disarticulation, where there was no contact between the two ends of the disarticulation. Eight out of 15 OD patients had a partial discontinuity. Partial OD was defined as a loose ossicular chain either due to an incomplete fracture of an ossicle or injury to a joint, and where normal contact in the ossicular chain was replaced with fibrous tissue or a loose contact of opposing ends (as defined in Farahmand et al. 2016).

All pathological ears satisfied the following criteria prior to measurement: 1) no history of middle-ear surgeries, 2) a normal 226 Hz admittance tympanogram, and 3) a normal otoscopic exam of the external ear and tympanic membrane. Confirmation of middle-ear diagnosis was made after exploratory surgery. WAI and V_u data of 56 healthy, normal-hearing (NH) ears from (John J Rosowski, Nakajima, & Hamade, 2012) were used to define the normal response. WAI was measured with the Mimosa Hear ID System, and V_u was measured with the Polytec HLV-1000 laser Doppler vibrometer (Rosowski et al. 2012). This study was completed with the approval of the Massachusetts Eye and Ear Institutional Review Board

2.2 Anatomical structure-based network models of the ear

The previously developed middle ear models found in O'Connor and Puria (2008), Rosowski and Merchant (1995) and Liu and Neely (2010) were compared to each other. The three models have the same series circuit model topology, where the impedance at the tympanic membrane (TM) was equal to the sum of the impedance of the middle ear cavities (Z_{MEC}) and the impedance of the TM, ossicles and cochlea (Z_{TOC}) (See Figure 2.1). The impedance blocks in Figure 2.2 consist of a combination of lumped element parameters (R = Resistance, L = Mass, K = Stiffness or C = Compliance) that represent a mathematical description of the function of the anatomical structures contained in that block. Detailed structure-based circuit models are shown in Figure 2.3. The values of each parameter labeled in Figure 2.3 are located in Table 1 of Appendix A2. In Liu and Neely (2010), the model topology and parameter values were only provided for the ossicular chain, thus we included a tympanic membrane model (from Rosowski and Merchant, 1995), middle ear cavity model (from Voss et al. 2000) and an inner ear model which included the impedance of the cochlea and round window (from Frear et al. 2018). The combination of other models and the Liu and Neely (2010) middle ear model will be known as

the “hybrid” model in this chapter and denoted by LNH. The Rosowski and Merchant (1995) and O’Connor and Puria (2008) models of the ear were left unchanged and are referred to as RM and OP, respectively. One of the goals of this chapter was to find a previously published middle-ear model that best simulates wideband acoustic immittance (WAI) measurements in normal and pathological ears. Thus we incorporated an ear canal model to compute the input impedance at the location of the WAI probe in the ear canal (Z_{in}). The tested structure-based models simulate measurements of input impedance (Z_{in}) magnitude and phase, absorbance and power reflectance. Ear-canal pressure reflectance (ECR) was computed from Z_{in} and the estimated characteristic impedance of the ear canal (Z_0) using the following equation:

$$ECR = \frac{Z_{in} - Z_0}{Z_{in} + Z_0} \quad (1)$$

where Z_0 equals the product of the density (ρ) and speed of sound in air (c) divided by the cross-sectional area of the ear canal, A_{EC} (i.e. $Z_0 = \rho c / A_{EC}$). Power reflectance (PR) was calculated by taking the square magnitude of ECR. The dB level of the Absorbance, the arithmetic complement of PR, was defined by the following equation:

$$\text{Absorbance Level} = 10 * \log_{10}|1 - PR| \quad (2)$$

The translational velocities of the umbo (V_u) were also calculated from model equations in order to make comparisons to actual V_u data in live humans. This value as a function of frequency depended on the topology of each of the tested circuit models and is well-explained in their respective publications.

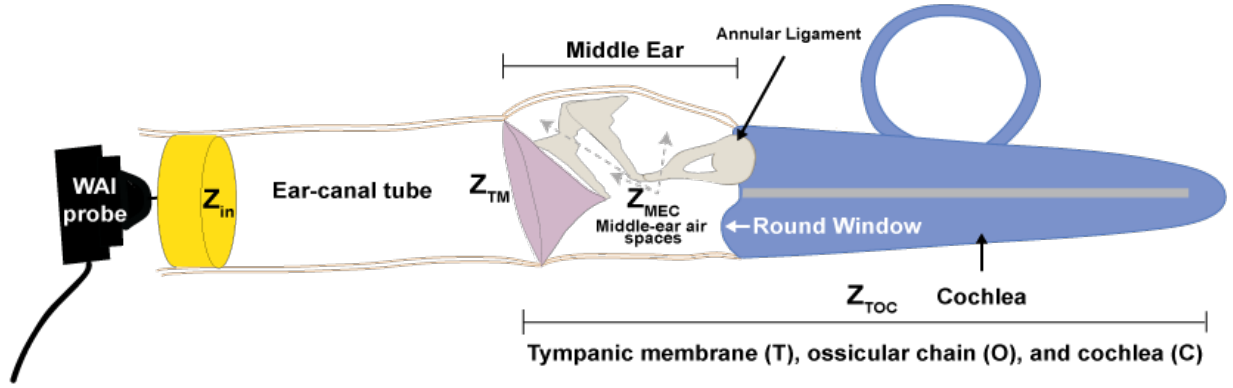
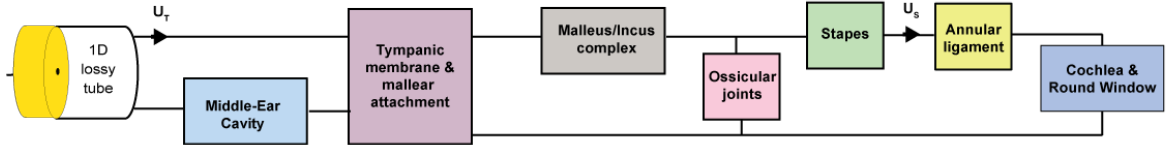
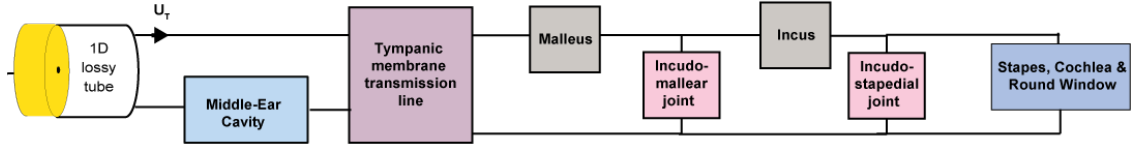


Figure 2.1: Simplified anatomical representation of middle ear and inner ear. The stimulus is introduced using a WAI probe sealed in the ear canal. Z_{MEC} represents the impedance of the middle ear air spaces and Z_{TOC} represents the impedance of the tympanic membrane, ossicular chain and cochlea. Z_{TM} is the sum of Z_{MEC} and Z_{TOC} , and Z_{IN} is the input impedance at the location of the WAI probe in the ear canal. The WAI probe consists of microphone and speaker to record sound pressure measurements in response to a chirp stimuli.

a. Rosowski and Merchant (1995)



b. O'Connor and Puria (2008)



b. Liu and Neely (2010)

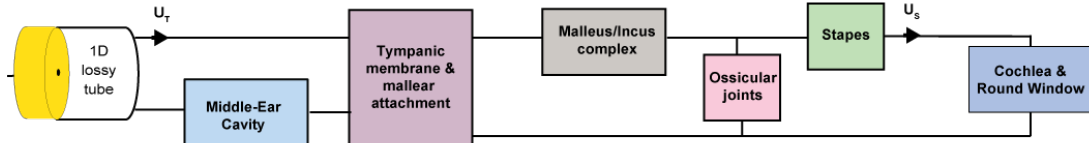
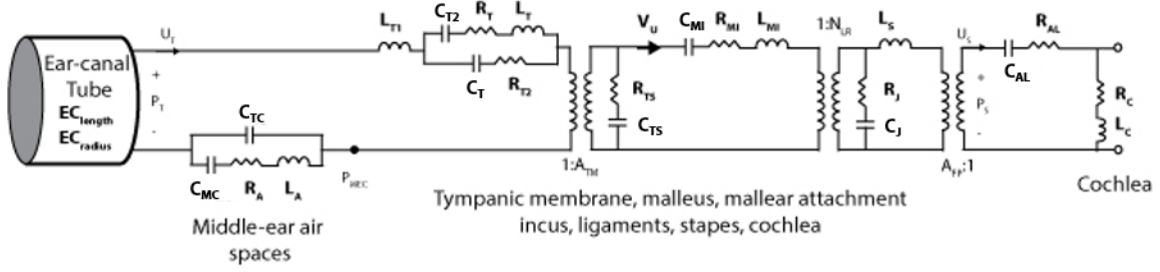
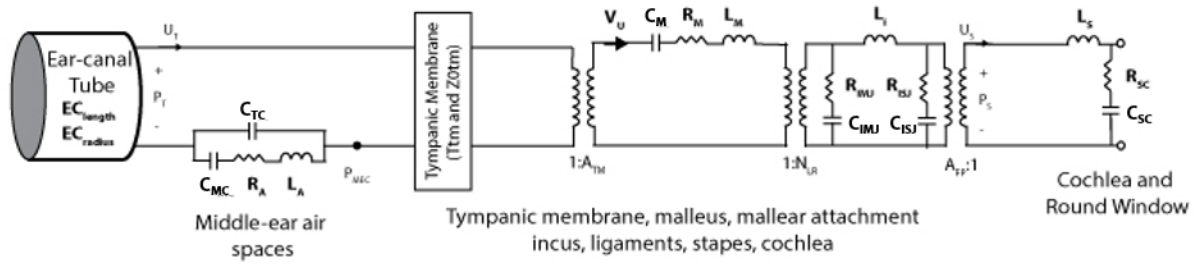


Figure 2.2: Comparisons of simplified anatomical circuit model of the ear in a) Rosowski and Merchant (1995), b) O'Connor and Puria (2008), and c) the Liu and Neely (2010) hybrid model.

A. Rosowski and Merchant (1995)



B. O'Connor and Puria (2008)



C. Liu and Neely (2010) Hybrid Model

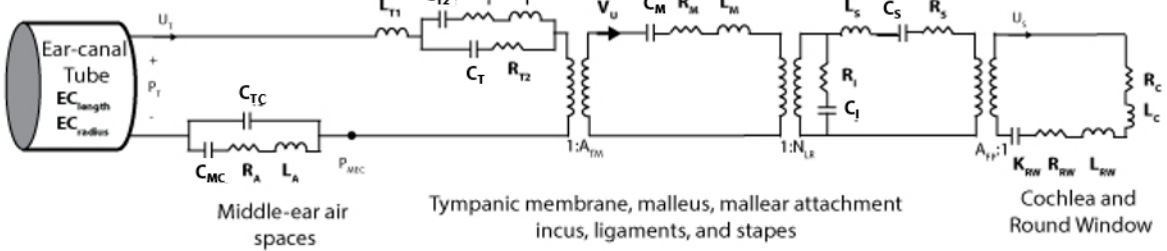


Figure 2.3: Detailed structure-based lumped element models in A) Rosowski and Merchant (1995), B) O'Connor and Puria (2008) and C) Liu and Neely (2010) Hybrid models. Each model mathematically models the human external, middle, and inner ear. Estimation of ear canal acoustics is made using a one-dimensional lossy transmission line. The ear-canal is coupled to a middle ear model consisting of: 1) middle ear air spaces, 2) tympanic membrane (TM), malleus, malleolar attachment, incus, ligaments and stapes. The inner ear model accounts for the impedance of the cochlea and round window. The parameter values and description of each model are located in Table 1 of Appendix A2.

Ear-canal modeled as a one-dimensional lossy tube

The ear canal model was necessary to simulate the input impedance at the WAI probe in live human ears. The ear canal was treated as a lossy one-dimensional tube using the lossy transmission-line models of tube segments that were first described by Egolf (1977) and neatly presented in Songer and Rosowski (2006). See Appendix A2 for the lossy transmission-line

model equations. The factors needed to calculate the input impedance at the location of the probe in the ear canal (Z_{in}) are the terminating impedance of the rest of the middle-ear system (Z_{TM}), the length of the ear canal (l_{EC}), and also the cross-sectional area of the ear canal (A_{EC}). The length of the ear canal was estimated for each patient from the one-quarter wavelength standing wave frequency. The standing wave frequency was determined from the reflectance phase information (derived from WAI). Near the standing-wave frequency, the reflectance phase rapidly transitions from negative to positive, and the frequency at zero phase corresponds to the one-quarter wavelength standing wave frequency (swf) resonance. The estimated length of the ear canal is $c/(4 \cdot \text{swf})$, where c is the speed of sound in air. The length of the ear canal was estimated for each subject, and then the average of all ear canal lengths was used as the ear-canal length parameter (l_{EC}) value for each model. The cross-sectional area of the ear canal was assumed to be 44.2 mm^2 with a diameter 7.5 mm.

Middle-ear cavity model topology

A circuit model of the middle-ear cavity describes the combined air spaces of the tympanic cavity, the aditus ad antrum, the tympanic antrum and the mastoid air cells. The volume of this air-filled space varies greatly among individuals, where Molvaer, Vallersnes, and Kringlebotn (1978) measured volumes ranging from 2 to 22 cm^3 across 55 human temporal bone specimens. Stepp and Voss (2005) developed a middle-ear cavity model to predict the effects of modifying the volume of the air-filled cavities on quantities such as the admittance at the tympanic membrane and stapes velocity measured in human cadaveric specimens. Similar to Kringlebotn's middle ear cavity model, the circuit model of the middle ear cavity in Stepp and Voss (2005) consists of two branches in parallel, one branch consisting of the compliance of the

tympanic cavity air space (C_{TC}), and the second branch with a series mass (M_A) and resistance (R_A) representing the tube-like aditus ad antrum air space, and the compliance of the mastoid air cells and tympanic antrum air space (C_{MC}). The values of these parameters are listed in Table 1 of Voss et al. (2000) for the “Bone 24L” model, and can also be found in the Appendix of this chapter. This middle-ear cavity model is placed in series with the impedance of the rest of the middle-ear system for both LNH and OP ear models. The parameter values of the middle ear cavity used in the original RM model were left unchanged and are listed in Table 1 of the Appendix. The RM middle ear cavity circuit model has the same topology as Stepp and Voss (2005).

Tympanic membrane, ossicles and cochlea model topology

The OP model treats the tympanic membrane as a one-dimensional cylindrical lossless transmission line. The two parameters, characteristic impedance (Z_{0tm}) and the wave propagation delay (T_{tm}), are used to calculate the input impedance of the transmission line (the ratio of the pressure at the input of the transmission line and the volume velocity entering the transmission line). In both the RM model and the LNH model, the model topology of the eardrum and the malleal attachment is the same as that in Kringlebotn (1988) where there are six elements in one branch ($RLC \parallel RC$ in series with L). In the RM model, there is also a parallel branch with two elements (RC) that represents the motion of the uncoupled eardrum from the malleus.

In all three models, the ossicular chain model accounts for the motion of the ossicles (malleus, incus and stapes) and ossicular joints (incudo-stapedial and incudo-malleal joints). In the RM and LNH models, there is only a single parallel branch that represents the loss of motion due to the joints. In OP, there are two parallel RC branches, one for each ossicular joint. The

placement of the mechanical elements of the ossicular model differ across the three models as is shown in Figure 2.3. Parameters representing the annular ligament (acoustic compliance and resistance) were specified in the RM and OP models.

The inner ear is simplified in all three models where the cochlea behaves mostly as a resistive load. The inner ear model of the LNH model was modeled using data from cadaveric specimens in Frear et al. (2018). The series inner ear model incorporated an RLC circuit to describe the motion of the round window and an RL circuit to represent the cochlea. The values of these parameters are included in Appendix A2.

2.3 Simulation of pathologies – Stapes Fixation and Ossicular Discontinuity

The parameters in each of the tested models (RM, OP, and LNH) were fit to normal cadaveric ears. These normal models were altered to mimic stapes fixation (SF) and ossicular discontinuity (OD), in a similar manner as Voss et al., (2012). To mimic SF in the RM and LNH models, the compliance of the stapes (C_s) or annular ligament (C_{AL}) was decreased ten-fold (Fig. 3 above). In the OP model, the authors combined the compliance of the annular ligament and the round window into a single element C_{SC} , and we decreased this combined compliance by 10 to simulate stapes fixation.

OD was modeled by increasing the compliance of the incudo-stapedial joint ten-fold and also by decreasing the joint resistance to zero. The altered parameters included: C_I and R_I in the LNH model; R_{ISJ} and C_{ISJ} in the OP model, and R_J and C_J in the RM model (Fig. 3).

2.4 Sensitivity Analysis

We first determine the error between the data and each of the models by taking the sum of 1) the root mean square error of the log impedance magnitude ($|Z_{in}|$) between the model and the actual median data, and 2) the root mean square error of the absorbance level between

the model and the actual median data for each of the pathological conditions (SF and OD). See Appendix A2 for the error function. After determining which model fits best to pathological and normal ears by comparing error between the model and the data, we performed a sensitivity analysis of the best model's parameters to evaluate which had the largest effect on WAI measures. We evaluated a range of values from one-tenth of the published value to up to 10 times the published value. A sensitivity analysis was performed for each parameter by multiplying the published parameter values by 0.1, 0.25, 0.5, 2, 4, 8 and 10, and quantifying the size of the changes in the computed Absorbance Level.

3. Results

3.1 Model predictions of WAI and UV in normal hearing ears

Figure 2.4 shows impedance magnitude (A) and phase (B) derived from WAI measurements in 56 normal hearing ears (Rosowski et al. 2012), along with the predictions of the three models. The input impedance (Z_{in}), as illustrated in Fig. 1, describes the ratio of sound pressure and volume velocity in the ear canal near the sound source. The normal data vary considerably from subject to subject (individual data are plotted with gray lines). The median of the data (black line) was used to gauge model performance. Input impedance magnitude derived from all 3 models (colored lines) showed general agreement with the median data in live humans. In general, the models' input impedance decreased as a function of frequency until 4 kHz, and slightly increased up to 6 kHz. For all models, the input impedance phase varied between -0.25 and 0.25 cycles similar to the median data. LNH model exhibited a local maxima in phase at 773 Hz. A local maxima in phase was also seen in the RM model at 1.1 kHz. All three models demonstrated a compliance-dominated system (magnitude decreases as a function of frequency

and an angle of ~ -0.25 cycles) at low frequencies up to about 3 kHz. With increasing frequency, the impedance phase of the models and the data shift to positive phase. The RM model provides a better qualitative fit to the median phase of the subjects at frequencies above 2 kHz.

Figures 2.4C and 2.4D plot absorbance level and power reflectance as a function of frequency. Absorbance and PR are compliments of each other that quantify the amount of sound power absorbed or reflected at the TM. These quantities are less sensitive to the space between the probe and the eardrum than the complex input impedance (Allen, 2005; Voss and Allen 1994; Rosowski, Stenfelt and Lilly 2013; Souza et al., 2014; Lewis and Neely, 2015). Figure 2.4C illustrates the measured Absorbance Level that varies between -20 and 0 dB, where 0 dB describes perfect absorbance. PR illustrated in Figure 2.4D is unitless and ranges from 0 to 1, where 0 indicates that all sound power is absorbed by the eardrum (matched middle ear impedance) and 1 indicates that all sound power is reflected off the eardrum. At frequencies below 0.6 kHz, the models are in general agreement with normal PR values in live humans, which decrease with frequency from near 1 to about 0.6, while the RM and OP models produce a better visual fit to the measured Absorbance Level. The LNH model, shows less absorbance (and higher PR) than the median of the normative data, and the OP model shows higher absorbance (and smaller PR) than the median. At frequencies, above 0.6 kHz, both the LNH and OP models predict lower values of Absorbance Level, and higher values of PR, than the median and the individual measurements from live humans. As in the comparison of predicted and measured impedance phase angle the RM middle-ear model best reproduces the median absorbance and PR data in these normal hearing subjects.

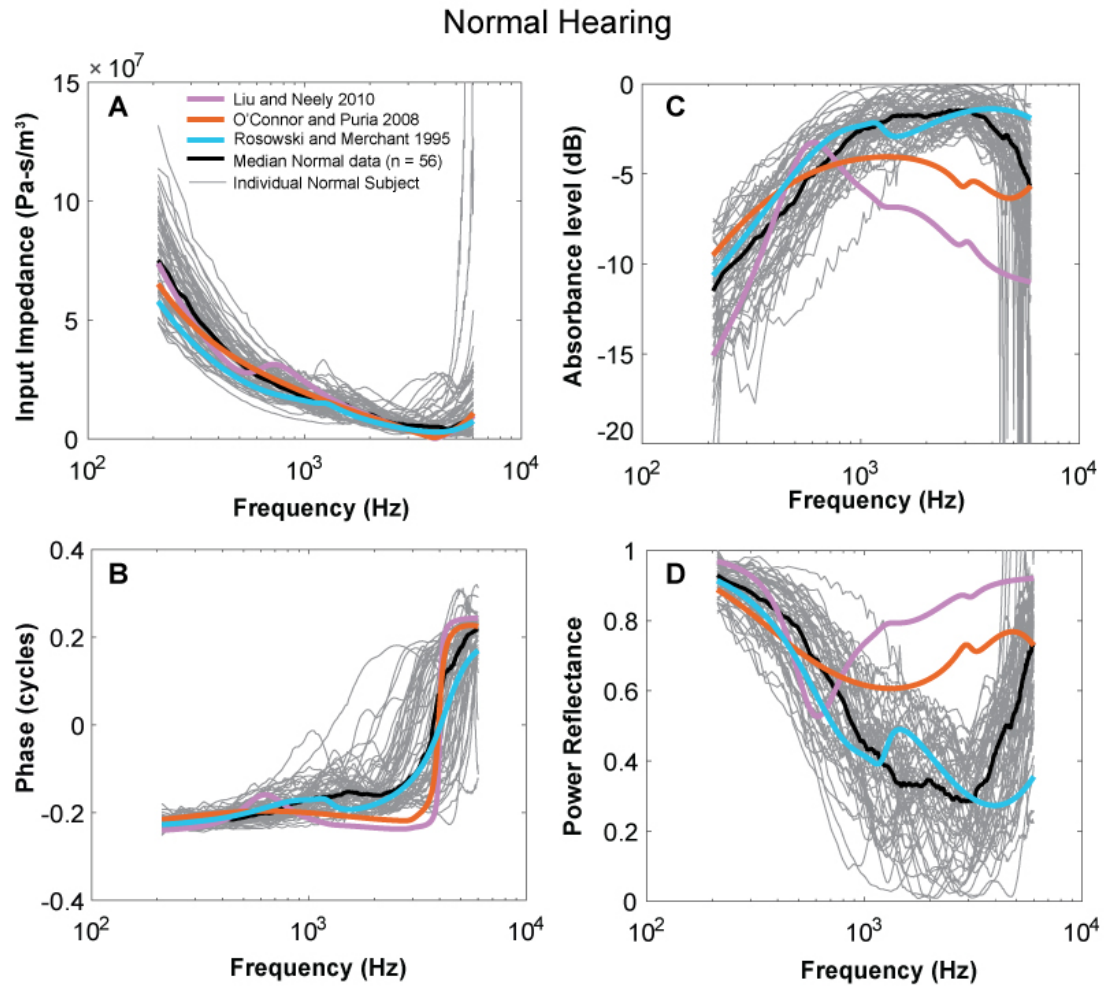


Figure 2.4: Wideband acoustic immittance normative model results (colored lines) compared to actual data in 56 normal hearing individuals (black and gray lines). A) Input Impedance magnitude ($\text{Pa}\cdot\text{s}/\text{m}^3$), B) Input Impedance phase. C) Absorbance level (dB) and D) Power Reflectance as a function of frequency computed from Rosowski and Merchant's model (blue line), Liu and Neely's hybrid model (lavender line) and O'Connor and Puria's model (orange line). The solid black line represents the median across 56 healthy ears, and gray lines are data from all of the individual subjects.

Umbo velocity (V_u) referenced to the input sound pressure in the ear canal was calculated from each circuit model and compared to normative V_u data (via laser Doppler vibrometry) in live humans. Figure 2.5 compares model predictions and live human V_u data. All model predictions of V_u magnitude and phase fall outside the range of the normal V_u data. The median of the normative data shows two local maxima in the magnitude, one occurring at 1

kHz (with magnitude 0.22 mm/(s-Pa)), and another between 3-4 kHz (0.29 mm/(s-Pa)). All three models were able to capture the first maxima with velocities that fell within the range of normal hearing data at frequencies below 2 kHz. After the first maxima, however, all models showed a decline in magnitude at higher frequencies. Both LMH and RM models fell outside the range of normal data above 3 kHz. The median phase of the normative data decreased from 0.16 cycles to -0.14 cycles as a function of frequency. The OP and LNP model predictions of V_u phase also showed a steady decline from ~ 0.2 to -0.2 . However, the RM model predicted a decrease in phase of up to -0.4 cycles at high frequencies. Phase curves for each of the model plots fell within range of patient V_u data. The model that best predicted the median V_u data and phase is the OP model. The RM model, however, better fit the maxima in V_u magnitude near 1 kHz.

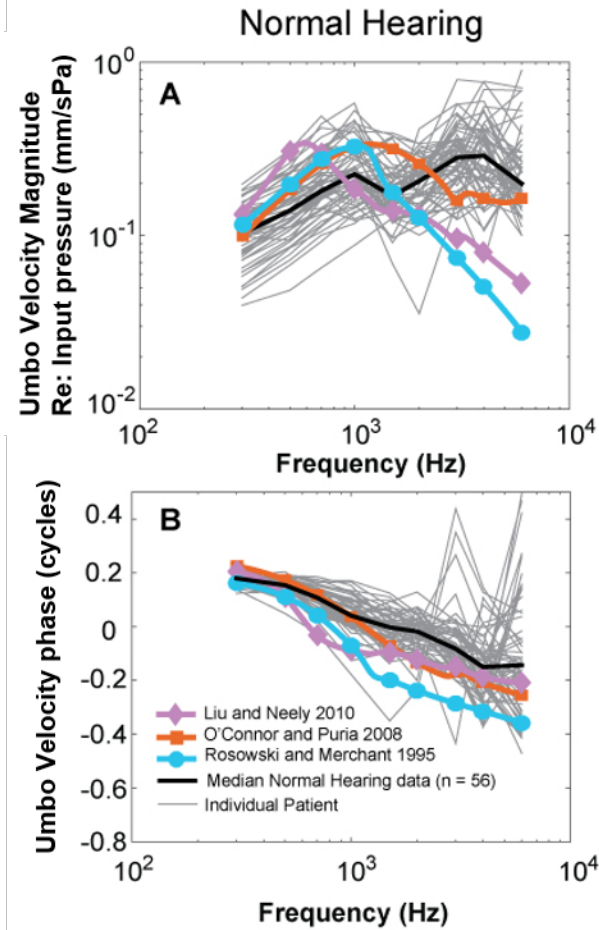


Figure 2.5: Umbo velocity normative model results. VU normalized by sound pressure in the ear canal: model predictions (colored lines) compared to actual data in 56 normal hearing individuals (black and gray lines). A) normalized umbo velocity magnitude (mm/(s-Pa)) and B) umbo velocity phase (cycles) as a function of frequency computed from Rosowski and Merchant's model (blue line), Liu and Neely's hybrid model (lavender line) and O'Connor and Puria's model (orange line). The solid black line represents the median across 56 healthy ears, and gray lines are data of individual subjects.

3.3 Model predictions of WAI and UV in ears with stapes fixation

Figures 2.6A and 2.6B plot the predicted input impedance magnitude and phase of the 3 models of stapes fixation along with measurements from 16 live patients with confirmed stapes fixation (SF). Overall the median impedance magnitude is slightly greater at low frequencies for patients with SF as compared to normal hearing subjects. The median impedance phase of patients with SF is lower than the median phase of normative data below

3 kHz. Patients with SF have an overall decrease in absorbance at frequencies below 1.3 kHz (ranges between -15 dB at 210 Hz to -2.6 dB at 1.3 kHz), and an increase in PR. These differences in WAI due to stapes fixation are modeled by increasing the stiffness of the annular ligament in each of the circuit models by a factor of 10. The OP model of stapes fixation shows a slight decrease in absorbance at low frequencies relative to the normal model, but overall behaves similar to the normal model. The LNH model successfully simulates the decrease in absorbance (as well as increase in input impedance and power reflectance) at low frequencies, but at frequencies above 1 kHz it predicts a decrease in absorbance that is not seen in patient population absorbance values measured in SF patients. The differences between the absorbance measured in the patient population and these two model predictions produce analogous differences in measured and predicted PR. The RM model produces a good visual fit to the median and falls within range of all the SF patient data. In Table 2.1, we provide the total error between the SF model fits and the median actual SF data, where the total error is the sum of the 1) root mean square error between model absorbance level and actual median absorbance level and the 2) root mean square error between model input impedance magnitude and actual input impedance magnitude. The RM SF model produced the least error with a total error of 3.439.

To illustrate the difference in WAI between SF patients and normal hearing subjects, the difference in the median absorbance level and the input impedance magnitudes ($|Z_{in}|$) values between the two subject groups are plotted in Figure 2.7. The median Absorbance Level is lower in SF patients at frequencies below 1 kHz as compared to normal hearing subjects, and about the same at higher frequencies (Fig. 2.7A). The RM model provides the best prediction of this change. However, in Fig. 2.7B which compares the difference between the median Z_{in}

magnitude in patients with stapes fixation and normal hearing subjects, the increase in impedance at low frequencies in SF patients is best estimated by the LNH model. The plot shows the predictions from the RM and OP models lie within the range of differences between individual SF ears and the median $|Z_{in}|$ values in normal hearing ears.

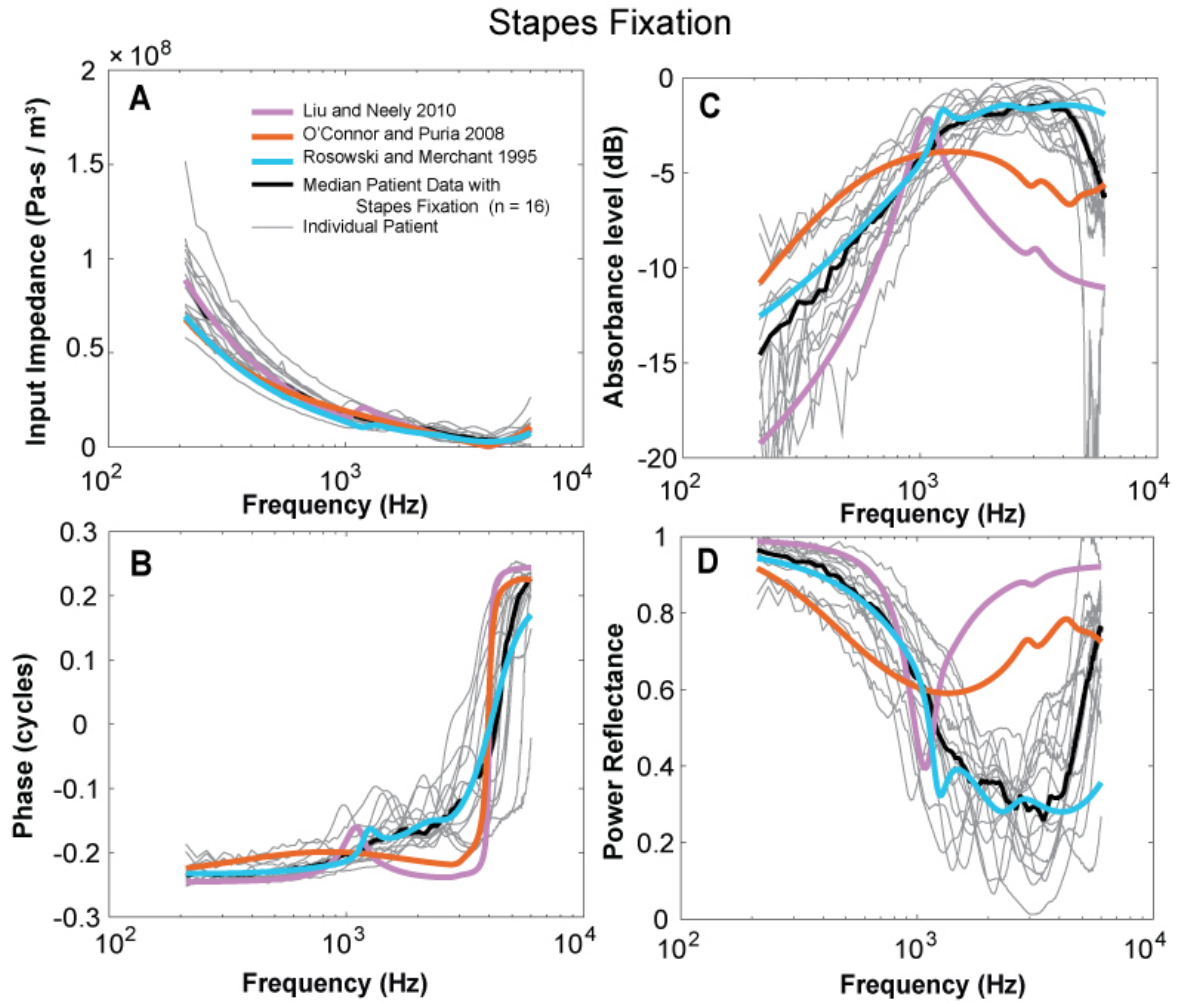


Figure 2.6: Wideband acoustic immittance stapes fixation model results (colored lines) compared to actual data in 16 patients with stapes fixation (black and gray lines). A) Input Impedance magnitude ($\text{Pa}\cdot\text{s}/\text{m}^3$), B) Input Impedance phase. C) Absorbance Level (dB) and D) Power Reflectance as a function of frequency computed from Rosowski and Merchant's model (blue line), Liu and Neely's hybrid model (lavender line) and O'Connor and Puria's model (orange line). The solid black line represents the median across 16 ears with stapes fixation, and gray lines represent data of individual subjects.

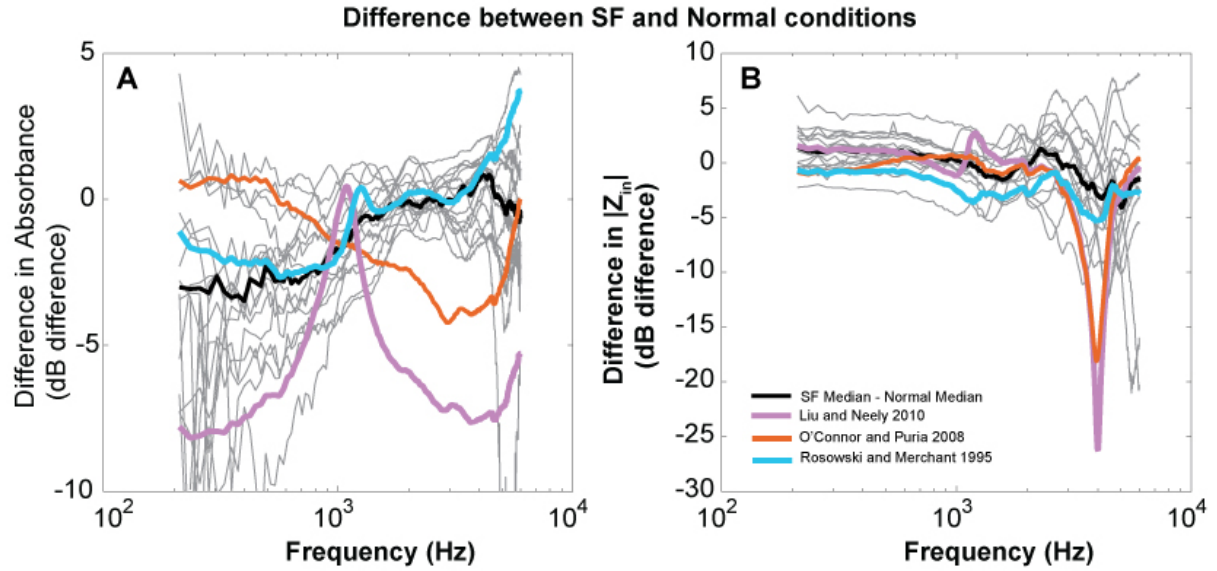


Figure 2.7: Difference between Stapes Fixation and Normal Conditions. A) The difference between stapes fixation absorbance measurements and the median across normal hearing ears. The solid black line represents the difference between actual measurements, whereas the colored lines represent the difference between the model estimate of absorbance of an ear with stapes fixation and the median absorbance in normal hearing ears. B) The difference between stapes fixation input impedance magnitude (dB) measurements and the median across normal hearing ears.

Figure 2.8 compares model predictions and actual V_u data in SF patients. The median of the SF V_u data has one maxima occurring at 3 kHz (0.382 mm/(s-Pa)). Compared to normative data, V_u measured in SF patients were lower in magnitude at frequencies below 1.5 kHz (SF: 0.045 mm/(s-Pa) to 0.13 mm/(s-Pa) ; NH: 0.10 to 0.23 mm/(s-Pa)). The median V_u magnitude in the SF group increases as a function of frequency up to 3 kHz and declines slightly up to the 6 kHz limit of the measurements. All model predictions also increase as a function of frequency until it reaches a peak. The OP and LNH models show a peak magnitude in V_u at around 1.1 kHz, whereas the RM model shows a peak magnitude at 2.6 kHz (similar to the median peak frequency of patients). Both OP and LNH models overestimate the magnitude of umbo velocity as compared to the patient median data, whereas the RM model shows lower mobility than the median patient data at all frequencies.

Overall V_u phase in SF patients shows a gradual decline as a function of frequency up until 1.5 kHz. At higher frequencies the phase drops off more steeply than normal hearing subject. The phase zero-crossing between 2-3 kHz in the SF group is higher than the 1-1.5 kHz zero-crossing range in normal hearing subjects. The LNH and OP models reproduce V_u curves similar to the SF median curve at frequencies below 1 kHz, but the phase zero-crossing falls is lower – between 1-1.2 kHz for both models (similar to Normal). V_u phase calculated from the RM model shows a lower phase at low frequencies as compared to the median SF data. Similar to median SF data, the RM phase prediction shows a gradual decline in phase for frequencies below 2 kHz and a zero-crossing which lies close to 2.2 kHz. In Table 2.2, we provide the total error between the SF model fits and the median actual SF data, where the total error is the sum of the 1) root mean square error between model umbo velocity magnitude and actual median umbo velocity magnitude and the 2) root mean square error between model umbo velocity phase and actual umbo velocity phase. The OP model produced the smallest total error with an error value of 6.272.

The difference in the median of V_u magnitude and phase between SF patients and normal hearing subjects are illustrated in Fig. 2.8C and 2.8D. The median V_u magnitude is lower in SF patients at low frequencies below 1 kHz as compared to the median of normal hearing subjects. The corresponding phase change at around 1 kHz is an increase in phase for SF patients. At around 3 kHz, there is an increase in V_u magnitude for SF patients as compared to the normal hearing subjects. This increase in V_u magnitude is due to the shift of resonance to higher frequencies in SF patients. Although all the models lie within the range of differences between individual SF ears and the median of normal hearing subjects (gray lines), they do not follow the same V_u magnitude and phase patterns as the median

differences between SF patients and normal hearing subjects. Unlike the LNH and OP models, the RM model successfully estimates the decrease in V_u magnitude at low frequencies and an increase in phase near 1 kHz. However, at higher frequencies, the simulated magnitude maxima is lower than the median V_u magnitude for normal hearing subjects, which is not observed in the actual V_u magnitude data.

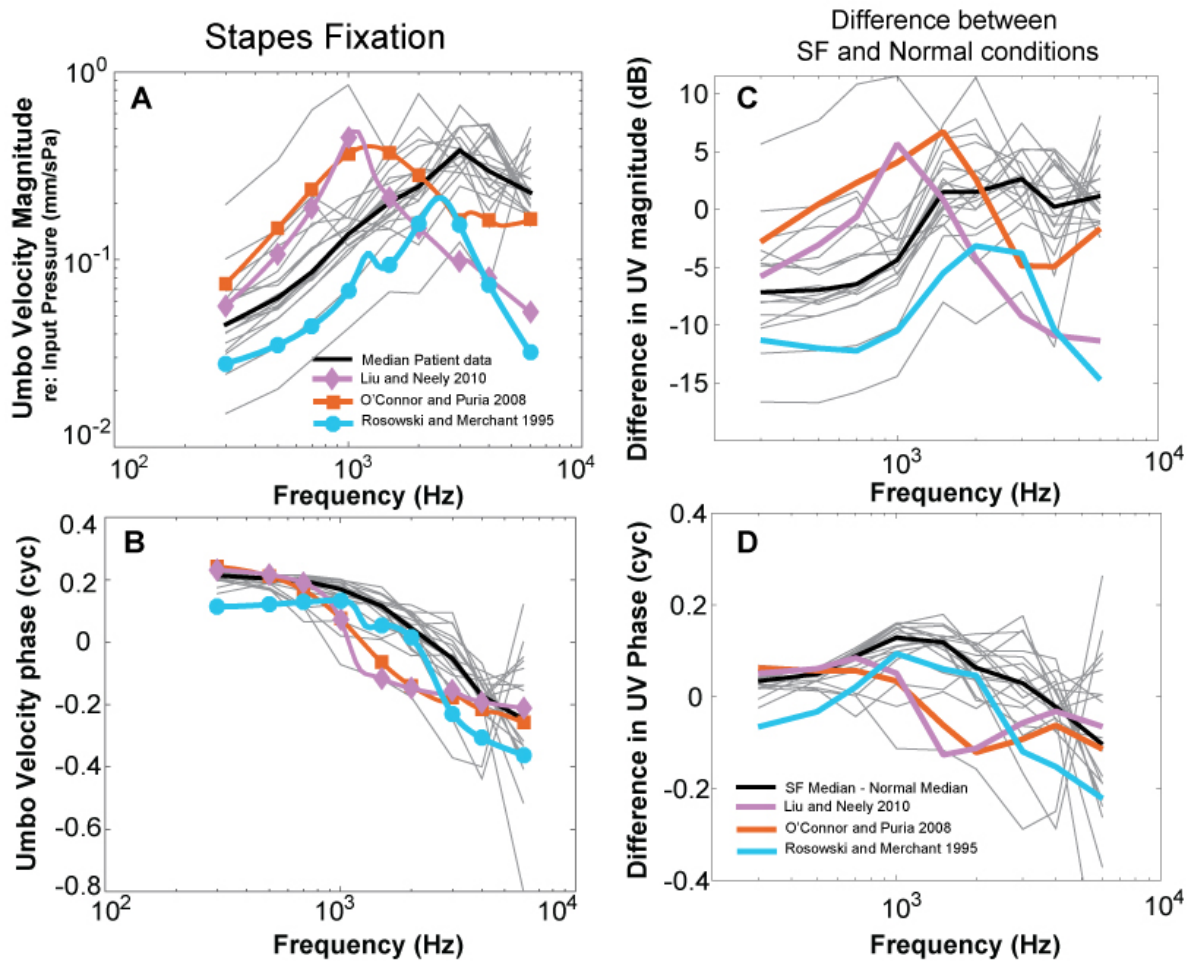


Figure 2.8: Umbo velocity Stapes Fixation model results. VU model results (colored lines) compared to actual data in 16 patients with stapes fixation (black and gray lines). A) Normalized umbo velocity magnitude (mm/s-Pa) and B) umbo velocity phase (cycles) as a function of frequency were computed from Rosowski and Merchant's model (blue line + circles), Liu and Neely's hybrid model (lavender line + diamonds) and O'Connor and Puria's model (orange line + squares). The solid black line represents the median across 16 individuals with stapes fixation C) The change in UV magnitude between SF models (colored lines) relative to the median of normal hearing subjects. The black line represents the difference between the median of UV magnitude in patients with SF and the median of UV magnitude in normal hearing subjects. D) The change in UV phase between SF cases and normal hearing subjects.

3.3 Model predictions of WAI and UV in ears with ossicular discontinuity

Figures 2.9A and 2.9B plot the input impedance magnitude and phase predicted by models simulating ossicular discontinuity at the incudo-stapedial joint and also data from live patients with ossicular discontinuity (OD). As compared to normal hearing subjects, the median impedance magnitude is slightly lower at low frequencies for patients with OD as compared to normal hearing subjects, and there is an increase in magnitude (that can be seen as a sharp peak in many cases) between 600 to 1200 Hz. The peak is more pronounced in some subjects than others and does not depend on whether the fracture was partial or complete. The impedance phase of patients with OD shows a pronounced peak in phase between 600 – 800 Hz. This phase peak is nonexistent in normative impedance phase data and is most clear in the cases with a sharp magnitude peak. The median curve washes out these peaks that occur at different frequencies and describes instead a narrowband increase in impedance magnitude between 600 to 800 Hz; a near 0 dB absorbance level (absorbance value near 1) (Figure 2.9C) and a notch-like decrease in power reflectance to near 0 are seen in the same frequency range (Figure 2.9D). These distinct patterns in WAI data are seen in patients with both incomplete and complete ossicular disarticulation, and the medians of the 4 WAI parameters from the two subgroups are nearly indistinguishable. Because of this similarity between the two groups, subsequent analyses will ignore this distinction.

These changes in WAI due to ossicular discontinuity are modeled by decreasing the stiffness (or increasing the compliance) of the incudo-stapedial joint in each of the circuit models by a factor of 10. The RM and LNP predictions show a new peak in impedance magnitude and phase angle, much like that observed in the OD patients; the OP predictions do not show such peaks (Figure 2.9A&B). The OP model predicts a very slight decrease in

absorbance level at low frequencies relative to the normal model, but again behaves similar to the normal model (Figure 2.9C). The LNH model successfully simulates the narrowband increase in absorbance level (as well as the peak in input impedance phase and notch in power reflectance at around 0.9 kHz) at low frequencies, but also predicts a significant decrease in absorbance level at frequencies above 1 kHz that falls out of range of the absorbance levels measured in OD patients. The RM model predictions generally fit all of the WAI components across the measured frequency range, and show peaks and valleys features similar to some of the individual data. However, there are differences between the RM predictions and the data, e.g. the predicted peak in absorbance level occurs at 1 kHz as compared to around 0.7 kHz in actual data.

The difference between OD patients and normal hearing subjects in the median of absorbance level and the input impedance magnitude ($|Z_{in}|$) values are shown in Figure 2.10. The median absorbance values are 4 dB greater in OD patients near 600 Hz as compared to normal hearing subjects, and the median absorbance of the two groups (OD and Normal) are about the same at frequencies greater than 1 kHz (Fig. 2.10A). The model that best predicts this difference is the RM model, though it predicts an OD associated increase in absorbance level at frequencies above 3 kHz that is not seen in the patient data. When comparing $|Z_{in}|$ median differences between patients with ossicular discontinuity and normal hearing subjects, OD causes a decrease in impedance magnitude at frequencies below 0.7 kHz. The difference between the medians of the two groups is near 0 at higher frequencies. The RM model and the LNH model successfully predict the decrease in impedance magnitude at low frequencies, but also show a narrowband increase at around 1 kHz. This peak does not occur in the difference between the medians but does occur in several individual OD ears (gray

lines). This peak occurs at different frequencies in individual ears (between 600-1500 Hz), and the median across ears does not show the peak.

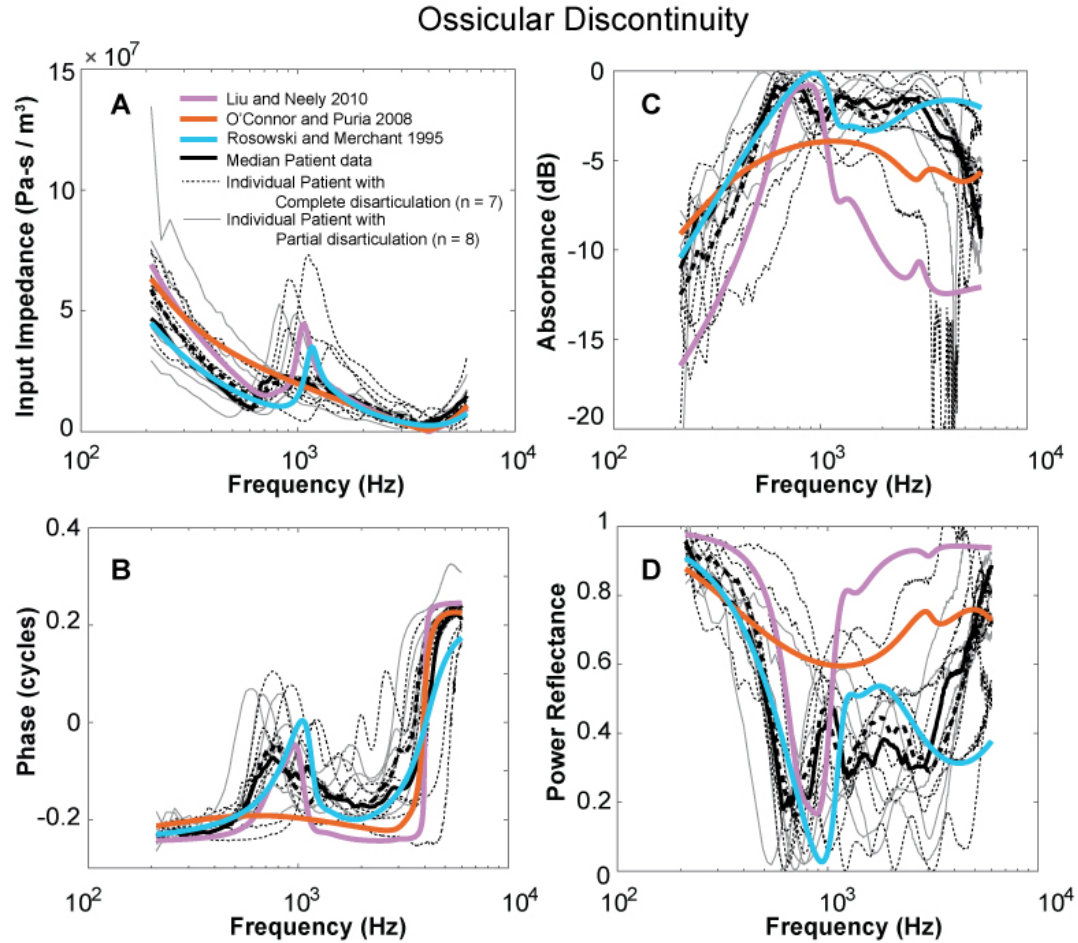


Figure 2.9: Wideband acoustic immittance Ossicular Discontinuity model results (colored lines) compared to actual data in 15 patients with ossicular discontinuity (black and gray lines). The dotted lines represent individuals with partial OD, whereas the solid gray lines represent patients with complete OD. The median of each of these groups is shown in either solid black line (complete OD median) or dotted black line (partial OD median). A) Input impedance magnitude ($\text{Pa-s}/\text{m}^3$), B) Input impedance phase. C) Absorbance (dB) and D) Power Reflectance as a function of frequency were computed from Rosowski and Merchant's model (blue line), Liu and Neely's hybrid model (lavender line) and O'Connor and Puria's model (orange line). The solid black line represents the median across 56 healthy ears, and gray lines are data of individual subjects.

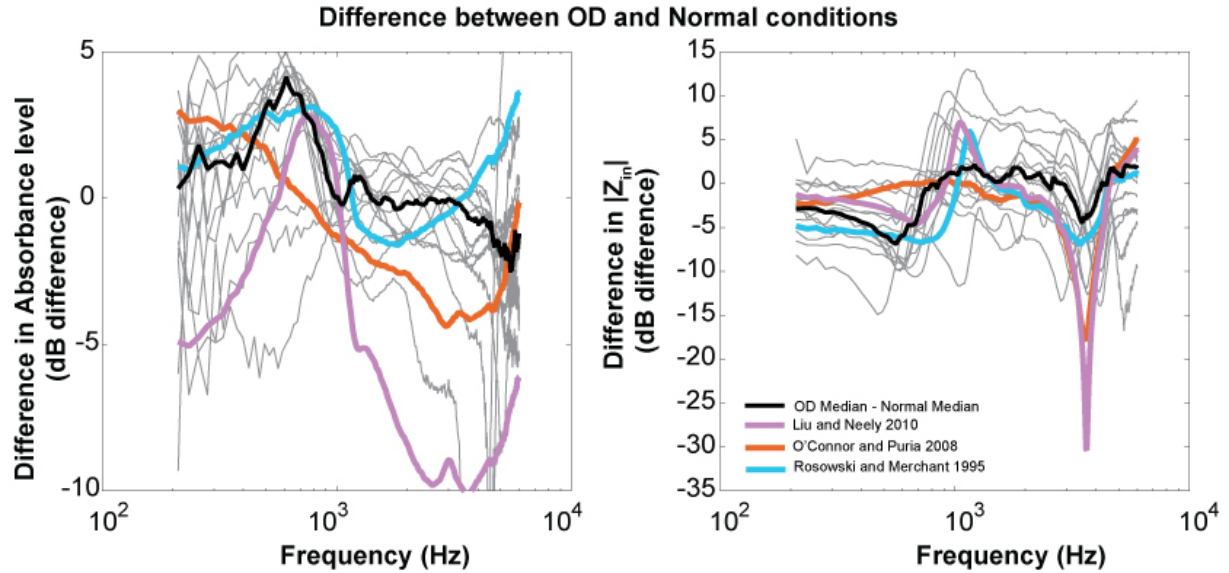


Figure 2.10: Difference between Ossicular Discontinuity and Normal Conditions A) The difference between ossicular disarticulation absorbance measurements and the median across normal hearing ears. The solid black line represents the difference between actual measurements, whereas the colored lines represent the difference between the model estimate of absorbance of an ear with ossicular disarticulation and the median absorbance in normal hearing ears. B) The difference between ossicular disarticulation input impedance magnitude measurements and the median across normal hearing ears.

Figure 2.11 illustrates model predictions and V_u measurements in OD patients (both complete and partial). The median of the OD V_u data shows one maximum occurring at 0.7 kHz (0.803 mm/(s-Pa)) which is higher in magnitude and lower in frequency than the first maxima in the normal data (0.23 mm/(s-Pa) and 1 kHz, see Figure 2.5). As compared to normative data, V_u measured in OD patients showed an overall increase in umbo velocity magnitude at frequencies below 2 kHz (OD: ranging between 0.26 mm/(s-Pa) to 0.80 mm/(s-Pa); NH: 0.10 to 0.23 mm/(s-Pa)). At frequencies above 1.5 kHz, the median magnitude gradually declines, and there is no distinct second peak as seen in normal hearing subjects at higher frequencies. Near the frequency of the magnitude peak in OD patients, there is a sharp decline in the median V_u phase, where the zero-crossing is close to 0.7 kHz. After the decline, the median V_u phase angle increases slightly up to 3 kHz, and then exhibits a second

smaller step change. All 3 models predict an increase in umbo velocity magnitude at low frequencies, however only the RM and LNH models predict a significant peak in umbo velocity magnitude where the peak of the RM model is around 1.5 mm/(s-Pa), and the peak of the LNH model is 0.86 mm/(s-Pa). The OP and LNH predictions fall within the range of the measured umbo velocity magnitude and phase data, while the RM magnitude is just above that range between 0.5 and 2 kHz. The steep slope of the phase near the location of the magnitude peak is successfully predicted by both the RM and LNH models, and the zero-crossing predicted by these models are also near 0.7 kHz. The difference between OD patients and normal hearing subjects in median UV magnitude and phase are illustrated in Fig. 2.11C and 2.11D. As expected, the median V_u magnitude is higher in OD patients at frequencies below 1 kHz as compared to the median of normal hearing subjects. There is a corresponding decrease in phase relative to the normal value between 0.7 to 1 kHz for OD patients. Although all the model predictions generally lie within the range of differences between individual OD ears and the median of normal hearing subjects (gray lines), the best model that simulates the differences in the median V_u magnitude and phase is the LNH model. The overall error between model and actual median data was calculated for each model in Table 2.2. The model that produced the least error was the OP model (error = 3.772), however the errors of the RM (error = 4.598) and LNH (error = 4.444) models were similar to that of the OP model.

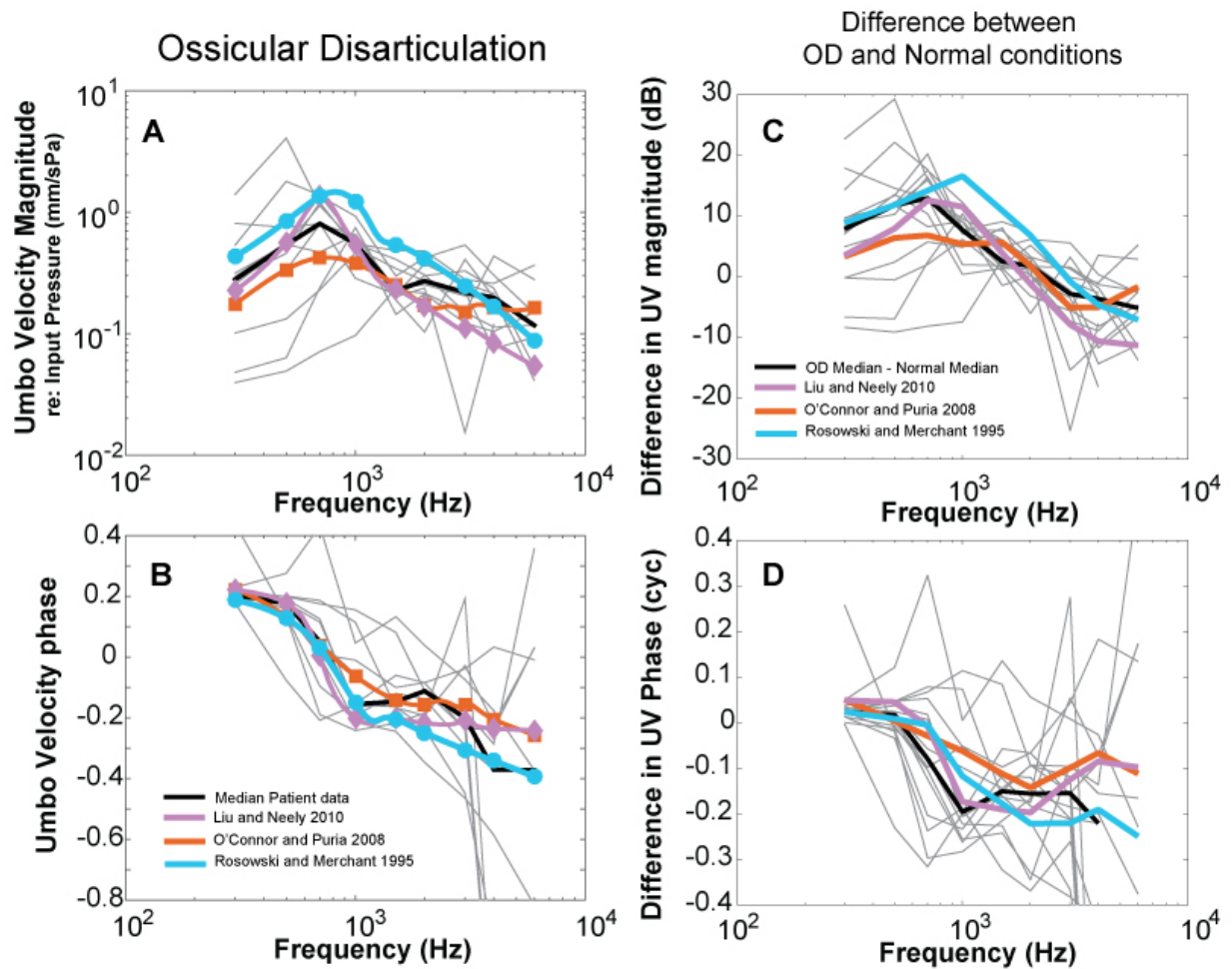


Figure 2.11: Umbo velocity Ossicular Discontinuity model results. VU model results (colored lines) compared to actual data in 15 patients with ossicular discontinuity (black and gray lines): No distinction is made between partial and complete disarticulation. A) Normalized umbo velocity magnitude (mm/s-Pa) and B) umbo velocity phase (cycles) as a function of frequency were computed from Rosowski and Merchant's model (blue line), Liu and Neely's hybrid model (lavender line) and O'Connor and Puria's model (orange line). The solid black line represents the median across 15 individuals with ossicular discontinuity. C) The change in UV magnitude between OD models (colored lines) relative to the median of normal hearing subjects. The black line represents the difference between the median of UV magnitude in patients with OD and the median of UV magnitude in normal hearing subjects. D) The change in UV phase between OD cases and normal hearing subjects.

Table 2.1: Sum of the Root-mean-square errors between model and actual median data of absorbance level and impedance magnitude are calculated for each model for the Stapes Fixation and Ossicular Disarticulation data

Models	Error between SF model and data	Error between OD model and data
RM	3.439	5.078
OP	8.032	7.747
LNH	12.394	13.619

Table 2.2: Sum of the Root-mean-square errors between model and actual median data of umbo velocity magnitude and phase are calculated for each model for the Stapes Fixation and Ossicular Disarticulation data

Models	Error between SF model and data	Error between OD model and data
RM	8.195	4.598
OP	6.272	3.772
LNH	8.323	4.444

3.4 Sensitivity Analysis of the RM Model

The goal of the sensitivity analysis was to find parameters that largely affected the predictions of WAI, to learn what contributes to the significant variations in normal ears. We chose to perform the sensitivity analysis using the RM model because it simulated WAI measured in SF and OD patients with the least error (Table 2.1). The first step of the sensitivity analysis procedure was to vary each parameter in the RM model one at a time and observe the effect of these changes on the model predictions of the absorbance level. Parameter values were decreased and increased by one order of magnitude above their published value (PV).

Such alterations determined that model predictions of the Absorbance Level were not sensitive to very large changes in C_{MC} , C_{TC} , R_A , C_{MI} , R_T , R_{AL} , L_S , R_J , C_J and R_{MI} , where there

were no noticeable differences between the absorbance level at $10 \times PV$ and the absorbance level at $0.1 \times PV$.

Changes in the other model parameters produce changes in absorbance level that were larger than 1 dB over some frequency range (Figure 2.12). For each parameter, effects of a range of parameter values ($0.1 \times PV$ to $10 \times PV$) on absorbance (dB) were computed. Large absorbance level changes at low frequencies (below 1 kHz) were observed if the compliance of the tympanic membrane (C_{T2}) or annular ligament (C_{AL}) were altered. For both of these parameters, the absorbance level decreased as the compliance decreased. Parameters that affected only a narrow mid-frequency range were the mass of the malleus and incus complex (L_{MI}), the mass of the cochlea (L_C) and the resistance of the cochlea (R_C). When the mass of the malleus-incus complex decreased, a slight increase in absorbance is observed at around 1 kHz. As the cochlear resistance parameter (R_C) decreased, there was an increase in absorbance level at around 900 Hz, and a decrease in Absorbance Level at around 1400 Hz. Decreasing the cochlear mass parameter (L_C) to $0.25 \times L_C$ produced a noticeable peak in absorbance around 1.1 kHz. Mid to high-frequency absorbance (above 1 kHz) was affected by several eardrum parameters such as the acoustic resistance of the tympanic membrane (R_{T2}), the acoustic compliance of the tympanic membrane (C_T , C_{T2}), the mass of the tympanic membrane (L_T , L_{T1}) and the mechanical resistance (R_{TS}) and compliance (C_{TS}) of the uncoupled tympanic membrane. The largest changes in absorbance were observed when varying the C_{TS} parameter, where decreasing the compliance of the suspended eardrum decreased absorbance values at high frequencies between 1 kHz and 5 kHz. The largest change in absorbance were produced by small variation in the compliance of the tympanic membrane (C_{T2}) and the compliance of the annular ligament (C_{AL}).

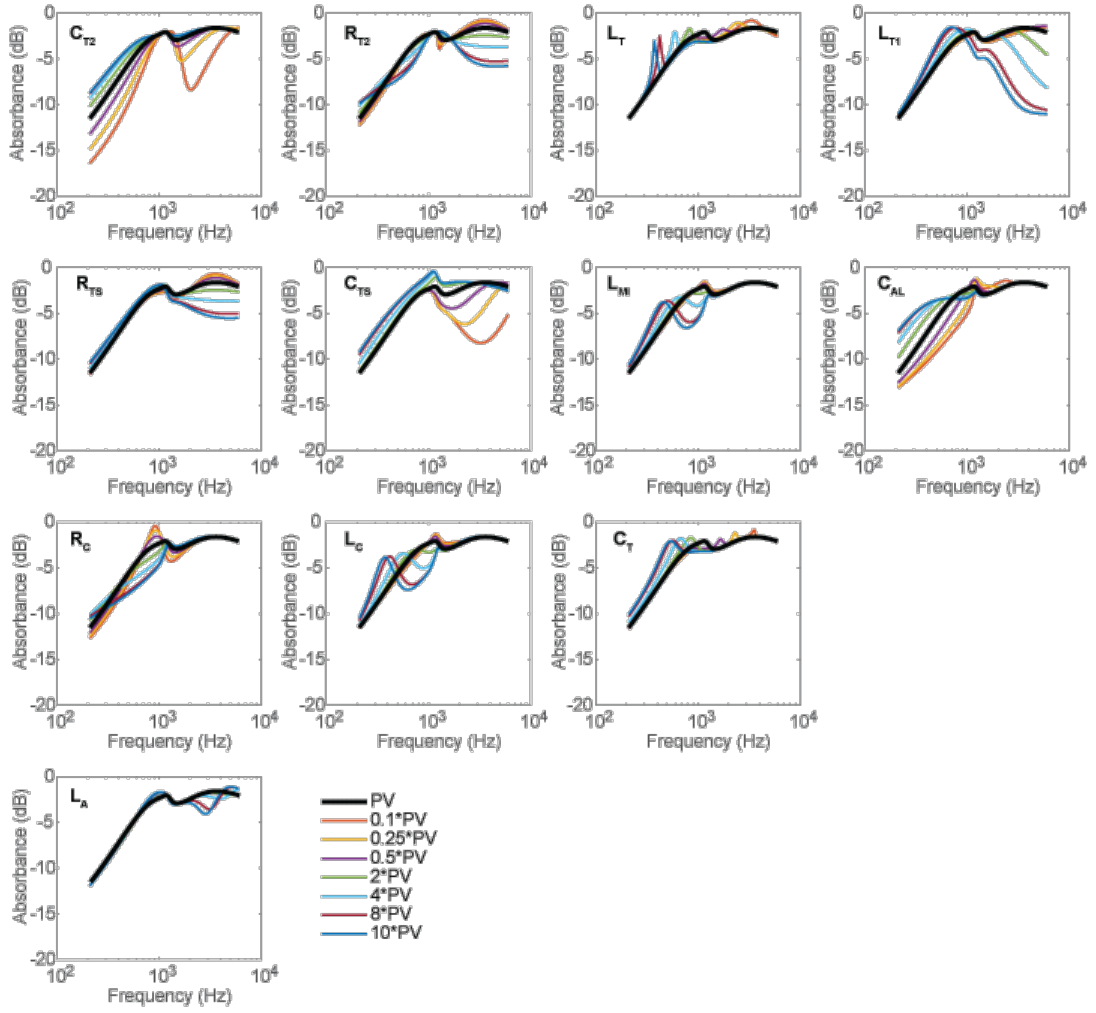


Figure 2.12: Sensitivity analysis for RM model parameters that noticeably affect absorbance level.

4. Discussion

4.1. Comparison of models

In this chapter, we show that we can apply previously published structure-based models, where parameters are optimized by temporal bone measurements, to our live human measurements. We also demonstrate that these models can predict measurements of WAI and V_u data from live pathological ears by simply changing model parameters in manners that fit the pathological anatomy (i.e. decrease the stiffness and resistance of the ISJ to model OD and increase the stiffness of the annular ligament to model SF). We did not aim to optimize the previously

published models to our current data in live humans, but instead used the given parameters in the publications to determine how well the previous middle ear models could simulate live human measurements in normal and pathological ears.

Overall, the Rosowski and Merchant (1995) model was similar if not better than the other models in predicting WAI and V_U measurements in patients with stapes fixation and ossicular discontinuity. In stapes fixation (Figures 2.6-2.8), where the models' element associated with the stiffness of the annular ligament was increased by 10, the RM model successfully captures the decrease in absorbance at low frequencies, as well as the decrease in umbo velocity magnitude at low frequencies. The RM model also successfully predicted the shift to higher frequencies of the resonance or peak in umbo velocity magnitude and the corresponding zero-crossing in phase. A tenfold decrease in the compliance of the annular ligament in the OP model has little effect on the absorbance at low frequencies, where significant alterations are seen in SF patient data. The altered LNH model predicts increased stiffness and decreased absorbance level at low frequencies, but also predicts low absorbance at high frequencies that is inconsistent with absorbance data in SF patients.

Using the RM model, the combination of changing both the resistance and the compliance parameters of the incudo-stapedial joint replicated the effect of ossicular discontinuity (OD) on our mechanical measurements (WAI (Figures 2.9 & 2.10) and V_U (Figure 2.12)). Typically, in OD patients, we see a significant narrowband peak in absorbance (or a large decrease in power reflectance as shown in Masud et al., 2019 and Chapter 8) between 600-800 Hz. The middle ear models that captured this peak were the RM and LNH models. The OP model was not greatly affected by large changes in the parameters of the incudo-stapedial joint. The OP model includes parallel branches for both the incudo-stapedial (IS) and incudo-malleal

joints (IM), whereas the other two models combine the effect of the two joints into a single branch. Even if we increased the compliance (by a factor of 10) and the resistance (to 0) parameters of both the IS and IM joints, the OP model was not able to predict the narrowband increase in absorbance (not shown). However, all three ossicular discontinuity models were able to reproduce the increase in umbo velocity magnitude and the shift of the resonance of the normal ear to a lower frequency.

4.2 Sensitivity analysis of WAI data

The goal of the sensitivity analysis was to find how each parameter value of the TM model affected WAI measurements, and ultimately define the parameters responsible for the large variation in WAI seen in normal ears. The parameter values were varied from a quarter to twice the published value. We selected this parameter range because it was similar to that used by O'Connor and Puria (2008). We used alterations in the predicted change in absorbance level as a measure of the sensitivity of the model parameters.

The largest changes in absorbance level (Figure 2.12) were due to alterations in the compliance of the annular ligament (C_{AL}), and the coupled and uncoupled tympanic membrane (C_{TS} , C_{T2}). In each of these cases, a decrease in compliance produces a larger change than an increase in compliance. Stiffening of the eardrum may occur due to age, or changes attributed to past ear infections (e.g. myringosclerosis or tympanosclerosis). Thus, the structure-based model supports the notion that age as well as a history of ear infections may play a large role in the variability of WAI measurements across normal ears.

By learning which parameters affect absorbance values and at what frequencies, we can develop a structure-based model that can be optimized for each individual patient or normal-hearing subject. WAI measurements are sensitive to certain parameters, and not sensitive to

others, thus it is not necessary to optimize all parameters, but instead only select parameters that have a significant effect on WAI. In the next chapter, we will develop an optimized structure-based model to fit to individual WAI data. The sensitivity analysis performed in this chapter will help define the parameters for optimization in order to fit the model to each individual dataset.

4.3 Improving diagnostics of mechanical pathologies

Differences in particular parameter values can give us intuition of the type of pathology a patient may have. Here, we simply changed one or two parameters of the structure-based model to simulate well-known middle ear lesions. If instead these parameters were optimized to fit individual data, we hypothesize that differences in parameter values across individual ears would automatically differentiate normal hearing ears from pathological ears. We will test this hypothesis in the next chapter by fitting a structure-based model to WAI data measured in patients with superior canal dehiscence before and after surgical repair. In the future, we aim to improve diagnostics of conductive, macro-mechanical pathologies (i.e. ossicular discontinuity, otosclerosis and superior canal dehiscence) through an optimized structure-based model, where large differences in certain parameter values (i.e. C_{ISJ} , R_{ISJ} , C_{AL}) may point to a particular mechanical lesion of the ear.

5. Conclusions

To summarize, we compared three structure-based models in order to determine whether they could simulate non-invasive ear-canal measurements such as WAI and V_U in live humans. These previous published models had been optimized to fit human temporal bone data, so we aimed to study how well these models could fit to our mechanical measurements in live humans. By incorporating similar methods used in Voss et al. (2012), where they established different model configurations for ossicular discontinuity and stapes fixation, we were able to compare model predictions to the median WAI and V_U data collected in pathological ears. Overall, the RM model best replicated our mechanical measurements in normal hearing subjects as well as patients with stapes fixation and ossicular discontinuity. Thus, there is great potential in using this structure-based approach in differentiating various mechanical lesions of the ear.

**CHAPTER 3. Structure-based model development and model testing on superior canal
dehiscence measurements**

1. Introduction

For more than five decades, structure-based network models have provided a quantitative description of the mechanics and acoustics from the ear canal to the inner ear (Kringelbotn, 1988; Y.-W. Liu & Neely, 2010; Moller, 1965; O'Connor & Puria, 2008; Onchi, 1961; J J Rosowski & Merchant, 1995; Susan E. Voss, Merchant, & Horton, 2012; J. Zwislocki, 1963; J. J. Zwislocki, 1962). Each lumped element (resistance, mass, or compliance) or combination of elements within these structure-based networks represents an anatomical structure of the ear, which contributes to the overall acoustic input impedance of the ear, where input impedance is a measure that quantifies how the ear receives sound. Simple manipulations of a structure-based network model can simulate the effect of conductive ear pathologies such as stapes fixation (a decrease in the compliance of the annular ligament) and ossicular disarticulation (short-circuiting the connection between ossicles and the cochlea) on ear-canal based measures such as the input impedance, absorbance and umbo velocity (Kringelbotn 1988; Zwislocki 1962, 63; Susan E. Voss, Merchant, and Horton 2012).

Previous middle-ear modelers have shown that changes to particular model parameters that simulate middle ear pathology can predict the effect of structural changes made in cadaveric ears on acoustic measurements in those ears (Voss et al., 2012; O'Connor and Puria, 2008). For example, recent studies have described mechano-acoustic models of the cochlea that accurately predict the effect of superior canal dehiscence (SCD) on acousto-mechanical measurements in human temporal bones (Frear et al., 2018; Raufer, Masud, & Nakajima, 2018) and in live chinchillas (Songer & Rosowski, 2006, 2007a). SCD, an opening of the bone overlying the superior semicircular canal, decreases cochlear input drive (the difference in sound pressure across the base of the cochlear partition that starts the traveling wave) and increases air-conducted

audiometric thresholds at low frequencies (S. N. Merchant, Rosowski, & McKenna, 2007; M. E. Niesten et al., 2015; D V Pisano, Niesten, Merchant, & Nakajima, 2012; Ward, Carey, & Minor, 2017). An SCD acts as an acoustic leak that allows some of the volume velocity produced by stapes motion to exit the inner ear vestibule and enter the middle cranial fossa. Due to this leak, the path of volume velocity is split between (i) the combined impedance of the cochlea and round window and (ii) the dehiscent superior semicircular canal and its terminating impedance (see Figure 1 in Raufer et al., 2018). The use of network models to predict non-invasive clinical ear-canal measures such as wideband acoustic immittance in pathological ears, shows great promise for diagnosing various mechanical lesions of the ear (Merchant, Siegel, et al., 2015; Voss, Merchant, and Horton 2012; Merchant et al. 2019). In this study, we combine previous mechano-acoustic structure-based models to carefully study the effects of SCD on ear-canal measurements of wideband acoustic immittance in live humans before and after SCD-surgical repair.

Wideband acoustic immittance (WAI) is an umbrella term that includes measures such as acoustic input impedance, absorbance, and power reflectance—where all of these measures are related to each other (Rosowski, Stenfelt, & Lilly, 2013). Previously, it has been shown that SCD induces a sharp decrease (a notch) in power reflectance at frequencies around 0.8 kHz, where this notch is consistent with the sharpening of a 0.8 kHz middle-ear resonance by the SCD related decrease in the cochlear input impedance (Nakajima et al. 2012b). The notch is reduced after surgical repair (Masud et al. 2018). Merchant et al. (2015a) developed an SCD detection algorithm to sense this narrowband notch in power reflectance. Further evidence of an SCD induced sharpening of a resonance in middle-ear mechanics has been shown in laser Doppler vibrometry measurements of sound-induced umbo velocity in SCD ears of patients (Rosowski et al. 2008). WAI measurements in cadaveric ears are similarly altered by opening a dehiscence in the superior

semicircular canal, and this change is reversed by patching the dehiscence with a stiff, non-porous material (Masud et al., 2018, Chapter 6).

These previous clinical studies and temporal bone experiments demonstrate the potential utility of WAI to identify SCD in patients in the clinic. To aid the development of WAI based clinical tools, we investigated a diagnostic method utilizing a structure-based model of the ear fitted to WAI in normal and pathological ears, where changes in the fitted parameters could be of diagnostic value. Here, we apply this method to study WAI measurements in SCD ears before and after surgical repair of SCD, where the post-SCD-repair measurements define our baseline data and are considered approximations of the WAI in normal individuals. Utilizing a structure-based model to simulate WAI across a wide range of frequencies we quantify objective parameters to both detect SCD and track the ear's condition after surgical repair.

Objectively determining the efficacy of SCD surgical repair is necessary because SCD symptoms are often similar to other common otologic diseases, and while successful SCD surgery reduces or eliminates the myriad symptoms of this disorder, these symptoms may recur after a time. When they do recur, it is difficult to determine whether the returning symptoms are due to incomplete repair, post-surgical changes at the SCD repair site, or another otologic pathology.

Various measures are available to assess the surgical repair of SCD; however, all have limitations. If preoperative vestibular evoked myogenic potentials (VEMP) testing (with low threshold values) and audiograms were consistent with SCD, and then normalized after surgery (Janky et al., 2013), post-operative VEMP and audiometric measurements could help track the condition of the repair. However, SCD repair can compromise the vestibular and cochlear

sensory mechanism causing abnormally high VEMP thresholds and sensorineural hearing loss, and thereby confuse the use of VEMP and audiometry as a measure of surgical efficacy.

While SCD audiograms can show increased low-frequency air-conduction (AC) thresholds and hypersensitive low-frequency bone-conduction (BC) in pre-operative SCD cases (Reference), SCD has its largest effect on low frequency (< 0.25 kHz) hearing thresholds, and these affects are most apparent at frequencies below the normal hearing testing range (Cheng et al., *in press*). Also some SCD ears do not show a hypersensitive BC thresholds or increased AC thresholds (Noij et al. 2018, & Chapter 7). A recent study of only a few examples suggested that the extent of the superior semicircular canal occlusion after surgical repair of the dehiscence can be determined by superimposing a preoperative computed tomography (CT) scan and postoperative magnetic resonance imaging (MRI) (Chemtob et al., 2019). However, this technique involves manually co-registering the CT and MRI scans by a neuroradiologist, who subjectively determined the existence of a residual leak or SCD defect.

The goal of the present study is to develop a structure-based modeling approach that can differentiate between pathological and non-pathological ears. Here, we fit the model to WAI data measured from individual ears before and after SCD surgical repair to determine whether expected SCD model parameters change after surgery, and whether the changes in parameters can accurately assess the extent of surgical repair immediately post-surgery and at later times.

2. Methods

2.1 Patient Demographics and Data Collection

This study was completed with the approval of the Massachusetts Eye and Ear Institutional Review Board. Wideband acoustic immittance (WAI) was collected from 24 patients (25 ears) with superior semicircular canal dehiscence (SCD). All ears had a

minimum visible dehiscence of 1.9 mm long on high-resolution computed tomography (CT) imaging and then had surgical repair of the dehiscence via a middle fossa craniotomy by the same surgeon (DJL). Age of the subjects ranged from 25 to 66 years old with an average age of 49.4 years (standard deviation = 10.6 years). There were 9 males and 15 females in the study, with 13 left ears and 12 right ears. All ears satisfied the following criteria prior to the initial measurement and surgery: 1) no previous history of middle-ear surgeries, 2) a normal 226 Hz tympanogram, 3) a normal otoscopic exam of the external ear and tympanic membrane, and 4) every patient had WAI measurements before and after surgical repair. The post-surgical WAI measurements were made at least three months after SCD surgery.

Detailed methods for WAI measurements have been described previously (Rosowski et al., (2012)). WAI is a non-invasive ear-canal measurement of the mobility of the tympanic membrane (TM) that can assess middle-ear mechanics. The term “immittance” encompasses impedance and admittance, either of which can be used to compute power reflectance and absorbance (see Rosowski et al. (2013) for an overview). WAI was measured with the Mimosa Acoustics HearID system using broadband (frequencies between 0.2 and 6 kHz) chirps at a stimulus level of 60 dB SPL. The Mimosa system includes a computer that controls and records from an ER-10C (Etymotic Research, Elk Grove, IL) probe that has two speakers (only one used in this study) and a microphone coupled to a foam probe tip. To make WAI measurements, the foam probe tip was sealed in the ear canal and wideband chirp sound stimuli were presented to the subject. Two measurements were taken and averaged together for each ear. For the purpose of this study, complex acoustic impedance, power reflectance, and absorbance level (in dB) were quantified and compared.

The acoustic input impedance is defined by the complex ratio (with magnitude and phase angle) of the sound pressure at the ear canal to the volume velocity at the location of the probe tip within the ear canal. The acoustic input impedance measured at the probe tip (Z_{in}) is computed from sound pressure measurements in the ear canal (P_{in}), and the Thevenin equivalent source characteristics (P_{source} and Z_{source}) estimated using published calibration procedures (e.g.: J. B. Allen 1986; D H Keefe et al. 1993, G. R. Merchant et al. 2016), where:

$$Z_{in} = \frac{Z_{source} P_{in}}{P_{source} - P_{in}} \quad (1)$$

Ear canal reflectance (ECR) is the complex ratio of the reflected sound pressure and the forward pressure (Equation 2). ECR is computed from Z_{in} and the estimated characteristic impedance (Z_0) of the ear canal at the probe tip using the following equation:

$$ECR = \frac{P_{Reflected}}{P_{Forward}} = \frac{Z_{in} - Z_0}{Z_{in} + Z_0} \quad (2)$$

Z_0 depends on the density of air (ρ), velocity of sound propagation (c) and cross-sectional area of the ear canal (A) at the probe tip:

$$Z_0 = \frac{\rho c}{A} \quad (3)$$

Power reflectance (PR) is the squared magnitude of ECR:

$$PR = |ECR|^2 \quad (4)$$

PR ranges from 0 to 1, where 1 indicates that all power from the forward going sound wave in the ear canal was reflected and 0 indicates that all power was absorbed. Absorbance Level is the arithmetic complement of PR scaled in dB:

$$\text{Absorbance Level (dB)} = 10 \times \log_{10} (1 - \text{PR}) .$$

(5)

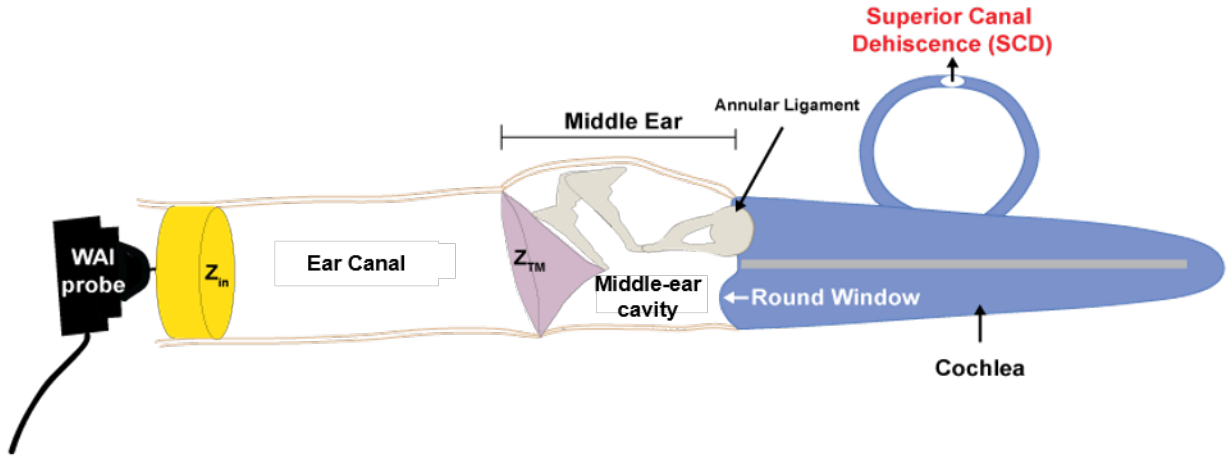


Figure 3.1: Anatomical representation of superior semicircular canal dehiscence. WAI is computed from the sound pressure in the ear canal that is produced by the sound source in the WAI probe.

2.2 Statistical comparison of surgically-repaired and normal ears, and SCD vs. surgically-repaired ears

To determine the validity of using surgically-repaired ears as our baseline, “normal” measurements, we compared the average of our WAI measurements in surgically-repaired ears ($n = 25$) to previously published measurements in normal, healthy ears ($n = 56$) (Rosowski et al., 2012). First, we compare the mean and standard error of $|Z_{in}|$, $\angle Z_{in}$, PR and Absorbance Level in both populations. We then test whether there are any significant difference between the measurements made within 1/3 octave frequency bands in the two populations. Non-parametric statistical tests such as Kruskal Wallis and post-hoc Mann-Whitney U were used to compare

these unbalanced groups. Multiple Mann-Whitney U tests were used to compare the results within the individual frequency bands. Significance level was set at 0.05.

The difference between measurements made with an open SCD and the baseline surgically-repaired measurements, for each ear, was calculated for $|Z_{in}|$, $\angle Z_{in}$, PR and Absorbance Level using the following formulas:

$$\Delta|Z_{in}| = 20 * \log_{10} \frac{|Z_{in_{pre}}|}{|Z_{in_{post}}|} \quad (7)$$

$$\Delta\angle Z_{in} = \angle Z_{in_{pre}} - \angle Z_{in_{post}} \quad (8)$$

$$\Delta PR = PR_{pre} - PR_{post} \quad (9)$$

$$\Delta Absorbance = 10 * \log_{10} \frac{1-PR_{pre}}{1-PR_{post}} \quad (10)$$

The individual difference in WAI calculated in equations 7-10 for all 25 ears (between pre and post-surgical repair measurements) and the mean of these differences were plotted for comparison. The individual differences can show more pronounced effects of SCD than does the mean. These computed changes in impedance magnitude, impedance phase, PR and absorbance level were also averaged across each one-third octave frequency bands. The Wilcoxon signed-ranks test, a non-parameteric test for two populations when the samples are paired, was used to determine whether the changes in any frequency band were significant at 0.05 level.

2.3 A structure-based network model of the ear

Our baseline structure-based network model of the ear (Figure 3.2) contains a model of the ear canal, the middle-ear model of Rosowski and Merchant (1995), and a new inner ear model. The complete model was fit to individual WAI measurements made before and after SCD surgical repair in the 25 ears. The ear canal was modeled by an impedance that includes contributions from 1) the tympanic membrane and ossicular chain model of Rosowski and Merchant (1995), 2) the middle ear cavity model of Voss et al., (2000), and 3) an inner ear model

with explicit impedances of the round window, cochlea and superior semicircular canal (SSC) (Frear et al., 2018; Raufer, Masud and Nakajima, 2018).

Ear-canal model:

The ear canal compliance is modeled as a lossy one-dimensional tube using the transmission-line models of tube segments described by Egolf (1977). Figure 3.1 points out (i) the WAI probe measures the acoustic impedance at the location of the probe tip in the ear canal (Z_{in}) some distance from the TM, and (ii) the impedance of the middle-ear and inner-ear system (Z_{TM}) terminates the ear canal. The baseline length of the ear canal between the probe tip and the TM (the length of the canal) was estimated from the one-quarter wavelength standing wave frequency (SWF) determined from WAI measurements in each individual patient. The SWF was determined from the reflectance phase information (derived from WAI). In the frequency domain, the reflectance phase rapidly transitions from negative to positive, crossing zero at the one-quarter wavelength SWF resonance frequency (Whitnell and Gowdy, 2013). The estimated length of the ear canal (l_{EC}) is $c/(4 * SWF)$. The cross-sectional area of the ear canal in the base-line model was assumed to be 44.2 mm^2 (diameter of 7.5 mm) in all patients (Allen et al., 2016).

Middle-ear model:

The middle-ear model includes the middle-ear cavity, tympanic membrane, ossicles, and ossicular chain ligaments and joints. The model of the middle-ear cavity (Figure 3.2b highlighted in light blue) was adapted from Voss et al., (2000). The circuit consists of two branches in parallel: one branch consists of the compliance of the air within the tympanic cavity (C_{tc}); the other branch is the series combination of the compliance of the air within the mastoid antrum and other air spaces (C_A) and the mass

(M_A) and resistance (R_A) of the air-filled tube-like aditus that connects the air-filled masotid antrum to the tympanic cavity. The initial baseline values of these parameters are in Appendix A2. The middle-ear cavity model is placed in series with the impedance of the rest of the middle and inner-ear components because the volume velocity flowing through the tympanic membrane and malleal attachment needs to overcome the impedance of the middle-ear cavity.

The baseline TM and ossicular model is adapted from Rosowski and Merchant (1995). Fig. 3.2b models the TM, ossicles and inner ear in terms of 3 transformers and 21 elements (values in Appendix A2 and A3). The first transformer is the tympanic membrane transformer, $1/A_{TM}$, that converts the tympanic membrane volume velocity to malleus velocity. The second is the ossicular chain transformer, $l_I:l_M$, that accounts for the mechanical transformation of force and velocity resulting from the rotation of the ossicular chain. The third is the stapes footplate transformer, $A_{FP}/1$, that converts the velocities and forces acting on the stapes footplate into a sound pressure and volume velocity at the entrance to the inner ear. The topology of the eardrum and the malleal attachment is described by six elements (an RLC || RC in series with L; Fig. 3.2b the purple box). There is also a parallel branch with two elements (RC) that represents the motion of the uncoupled eardrum. The ossicular chain model accounts for the motion of the ossicles (Fig. 3.2b gray and green boxes which include malleus, incus and stapes) and ossicular joints (pink box), where a single parallel branch accounts for motion losses due to both the incudo-malleal and incudo-stapedial joints. The impedance of the stapes mass is represented by an inductor (green box), and the impedance of the annular ligament is

modeled as a series compliance and resistance (yellow box). The baseline element values are described in Table A3.1 in Appendix A3.

Inner-ear model:

Our baseline values of inner ear model parameters (the brown box of Fig. 3.2b) were derived from Frear et al. (2018) and Raufer et al. (2018), who estimated parameter values from a controlled set of temporal bone experiments. Values of L_{RW} , C_{RW} , R_{RW} , R_c and L_c are from Frear et al., (2018). The cochlea was modeled as a resistor and a mass in series, the round window (RW) as a resistor, compliance and a mass in series, and the superior canal as a mass and a resistor in series. The parallel placement of the superior canal branch and the baseline values of its elements (R_{SCD} and L_{SCD}) come from Raufer et al. (2018). The baseline parameter values of the inner ear model parameters are listed in Table A3.1 in Appendix 3.

2.4 Procedure to fit the baseline model to individual WAI measurements in the surgically-repaired dataset

The baseline mechano-acoustic model shown in Fig. 3.2b was fit to individual WAI measurements from the surgically-repaired data set by allowing a selected set of model parameters to vary. We assumed that if the surgically-repaired ears had WAI measurements that were similar to those in normal ears (as investigated in the initial Results section below), then the middle and inner-ear processes were similar and could be described by normal model parameters. To improve the fits to individual rather than mean data, we varied nine parameters, including: the length and radius of the ear canal (l_{EC} and r_{EC}), the compliance due to the total air volume of the middle ear cavity ($C_A + C_{TC}$), and C_{T2} , C_{AL} , L_{RW} , C_{RW} , R_{SCD} ,

L_{SCD} . Optimal values of these nine parameters were determined in a three-step procedure similar to Withnell and Gowdy (2013). Each step constrained the number of parameters that were free to vary. The goal was to find parameter values that minimized the cost function (the sum of the root mean square errors of log magnitude of Z_{in} , reflectance magnitude and phase ($|R|$ and $\angle R$), and power reflectance), and thereby reduced the difference between the model predictions and the measured data (See Appendix A3). The MATLAB function *fminsearch* was used to determine the parameter values that minimized the cost function. In the first step of the fitting procedure, the compliance due to the total air volume within the middle ear cavities ($C_{TC} + C_A$), where $C = \text{Volume}/(\text{adiabatic compressibility of air})$, was estimated by optimally fitting the model to individual data restricted to frequencies below 1 kHz. C_{TC} was set to 0.0625 times the optimum total middle-ear cavity compliance ($C_{TC} = 0.0625 \times (C_{TC} + C_A)$), where the initial parameter values set the total middle-ear cavity volume to 8 cc. The summed compliance was chosen for optimization because the volume (and compliance) of the middle ear air spaces in adult humans can span a large range—anywhere between 2 and 20 cc (Molvaer et al., 1978; Voss et al., 2012), and its compliance contributes to the low-frequency behavior of the middle ear.

In the second step, six of the middle-ear and inner-ear parameters were free to vary: C_{T2} , C_{AL} , L_{RW} , C_{RW} , R_{SCD} , L_{SCD} in order to ‘best fit’ the measurements made at frequencies above 600 Hz. This frequency range was selected because we know SCD effects on reflectance are more pronounced at frequencies between 600-1800 Hz (Merchant et al., 2015). Parameters C_{T2} and C_{AL} were selected for optimization because a small change in these parameters produces a large change in predicted absorbance values (Chapter 2). Parameters L_{RW} and C_{RW} were included to improve the fit of the cochlear model to patient data.

The last step was to estimate the length and radius of the ear canal by fitting the model to the individual data for frequencies above 1500 Hz, where the ear canal acts like an acoustic transmission line (e.g. Wiener and Ross 1946; Withnell and Gowdy 2013). The ear canal length was estimated from the SWF, and the initial radius was assumed to be 3.8 mm.

In summary, when fitting the baseline model to WAI measurements in the baseline surgically-repaired dataset, only nine model parameters varied from patient to patient. These nine parameters were carefully hand-selected to reduce the error calculated by the cost function (Appendix A3). The initial and bounded values of these parameters are listed in Table 1. The values of each parameter were constrained between a lower and upper bound limit to avoid illogical parameter values (i.e. negative values). The upper and lower limit values provided a range of what the fitted value can be. In some cases, this range was manually determined in order to avoid the situation when all cases had a parameter value of one of the bounds (for C_{RW} and C_{AL}). In most cases, the lower bound is $1/16^{\text{th}}$ of the initial value, and the upper bound is 16 times the initial value. The upper limits of both SCD parameters were set to be extremely large (orders of 10^{20}) to be able to simulate a normal ear (no dehiscence) condition. The length of the ear canal ranged between 1 and 3 cm which was a range that we calculated from our population of ears. Bounds of the ear-canal radius were selected manually, choosing values close to an ear-canal radius of 0.37 cm. Note the ear canal length represents the distance between the probe tip to the eardrum, thus a lower band value of 1 cm is possible. The foam ear tip attached to the probe is approximately 1 cm. The middle ear cavity volume ranged between 2 cc to 20 cc, a range noted in Molvaer et al., 1978 and Voss et al., 2012.

2.5 Procedure to fit the baseline model to individual WAI measurements in the SCD dataset

After optimizing the baseline model to post-surgical WAI measurements in each of the 25 ears, we fit the individual optimized baseline models to the pre-surgical (SCD state) WAI measurements made in each ear. In this fitting stage only 4 parameters were free to vary: l_{EC} , r_{EC} , R_{SCD} and L_{SCD} . Optimal values of these four parameters were determined in a two-step procedure. In the first step, two parameters R_{SCD} and L_{SCD} were fit to WAI data at frequencies above 600 Hz, where SCD effects are most apparent in reflectance. In the second step, only the ear canal parameters were free to vary. We chose to vary the ear canal parameters in the SCD case because the insertion of the foam ear tip may differ, altering the computed acoustic length of the ear canal. The initial and bounded values of these 4 parameters are listed in Table 3.1.

Table 3.1: Initial, lower bound and upper bound values for each parameter that is free to vary in post-surgical repair model and SCD model. IV = initial value

Model Condition	Parameter free to vary	Units	Initial Value (IV)	Lower Bound	Upper Bound
Post-surgical repair model (no SCD)	C_{AL}	m^5/N	8.28×10^{-16}	$0.0625*IV$	$2*IV$
	C_{RW}	m^5/N	9.57×10^{-14}	4×10^{-16}	9.57×10^{-8}
	L_{RW}	Kg/m^4	5.42×10^5	$0.0625*IV$	$16*IV$
	L_{SCD}	Kg/m^4	1×10^7	5×10^8	2×10^{20}
	R_{SCD}	$Pa-s/m^3$	2.5×10^{10}	1.88×10^9	2×10^{20}
	C_{T2}	m^5/N	1.3×10^{-11}	$0.0625*IV$	$16*IV$
	V_{total}	m^3	8×10^{-6}	0.7×10^{-6}	20×10^{-6}
	l_{EC}	m	$1/(4 * swf/c)$ MEASURED FOR EACH PATIENT	0.01	0.03
	r_{EC}	m	0.0037	0.002	0.005
	L_{SCD}	Kg/m^4	1×10^7	$0.0625*IV$	2×10^{20}

SCD model	R_{SCD}	Pa-s/m ³	2.5×10^{10}	$0.0625 \cdot IV$	2×10^{20}
	l_{EC}	m	$1/(4 * swf/c)$ MEASURED FOR EACH PATIENT	0.01	0.03
	r_{EC}	m	0.0037	0.002	0.005

2.6 Comparison of parameter values of SCD vs. surgically-repaired cases

The R_{SCD} and L_{SCD} values that best fit the individual SCD and surgically-repaired data sets were compared. By plotting the R_{SCD} and L_{SCD} values in a two dimensional scatter plot, we attempted to visually separate the SCD cases from the post-operative surgically-repaired cases.

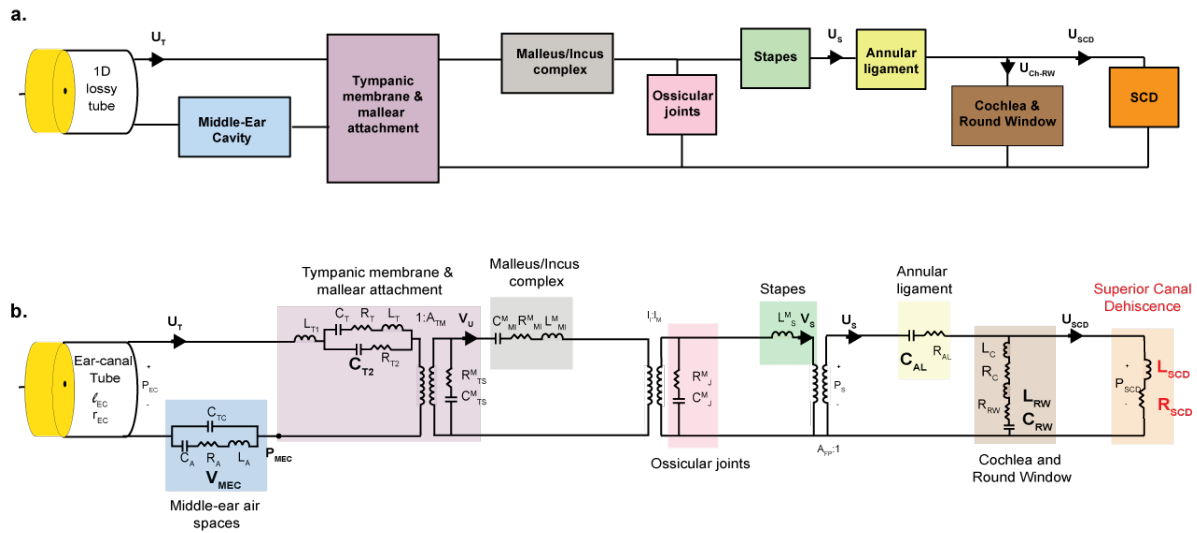


Figure 3.2: a) A simplified structure-based circuit model of the ear. b) A detailed lumped-element circuit of the human external, middle, and inner ear. The model structures and parameter values are closely related to those of Voss et al. (2000), Rosowski and Merchant (1995), Raufer, Masud and Nakajima (2018). Estimation of ear canal acoustics is made using a one-dimensional lossy transmission line. The ear-canal is coupled to a middle ear model consisting of multiple anatomical structure including: middle ear air spaces, tympanic membrane (TM), malleus, incus, stapes, and the annular ligament. The inner ear model accounts for the impedance of the cochlea, round window, and the superior canal dehiscence. U_T , U_S , U_{Ch-RW} and U_{SCD} represent the volume velocities of the tympanic membrane, stapes, cochlea+round window, and within the dehiscent canal. P_{EC} , P_{MEC} , P_S , P_C and P_{SCD} represent the sound pressures at the entrance to the ear canal, within the middle ear cavity, produced by the stapes at the oval window, at the entrance to the cochlea and the dehiscent canal. The lumped elements in red (L_{SCD} and R_{SCD}) are parameters that we allow to vary between the SCD and SCD-repaired cases.

3. Results

3.1 Post-operative WAI measures are similar to previous measurements in normal ears

The frequency dependent acoustic input impedance measured in the ear canal (Z_{in} magnitude and phase) of our 25 surgically-repaired ears are similar to Z_{in} measured in normal ears in earlier studies (J.J. Rosowski et al. 2012; Shahnaz et al. 2009; Withnell and Gowdy 2013). Figure 3.3 a & b shows the mean and standard error of Z_{in} for the surgically repaired cases are similar to those from 56 normal subjects (Rosowski et al., 2012). A Kruskal-Wallis test comparing absorbance level between these two groups, found no statistical difference (Chi square = 1.47, $p = 0.22$, $df = 1$). Additionally, multiple Mann-Whitney U tests comparing absorbance level in the two groups within each of 15 $1/3$ octave bands showed no significant differences between groups at all bands; all the calculated p-values were greater than 0.05.

At frequencies less than 0.6 kHz in both groups, the impedance magnitude decreases as frequency increases, and the phase is near -0.25 cycles, consistent with a stiffness-dominant system. At frequencies above 2 kHz, the impedance phase rapidly changes from negative to positive; the average zero-crossing frequency is 3.8 kHz (standard deviation = 0.87 kHz).

As shown in Fig. 3.3 c & d, the mean (+/- standard error) of the surgically-repaired PR and absorbance level (in dB magnitude) is statistically indistinguishable ($p > 0.05$ using multiple Mann-Whitney U tests to compare 15 frequency bands between the two groups) from that measured in normal subjects by Rosowski et al. (2012). In both surgically-repaired and normal ears, at frequencies below 0.3 kHz, the mean PR (Fig. 3.3c) is ~ 0.9 and the mean absorbance level (Fig. 3.3d) lies between -13 to -10 dB indicating that most of the forward acoustic sound wave is reflected back by the eardrum, and less than 0.1 of the available sound power is absorbed. As frequency increases, PR decreases and reaches a minimum of around 0.25 near 3-4

kHz; over the same frequency range, the Absorbance Level increases and reaches a maxima near -1 dB. The coincident minimum in PR and maximum in Absorbance Level suggest a maximum in sound energy reception by the middle ear at these mid-frequencies. At frequencies above 4 kHz, the mean PR quickly increases with frequency to almost 0.75 at 6 kHz, and the mean Absorbance Level falls to -7 dB consistent with poor absorbance of sound energy above 5 kHz.

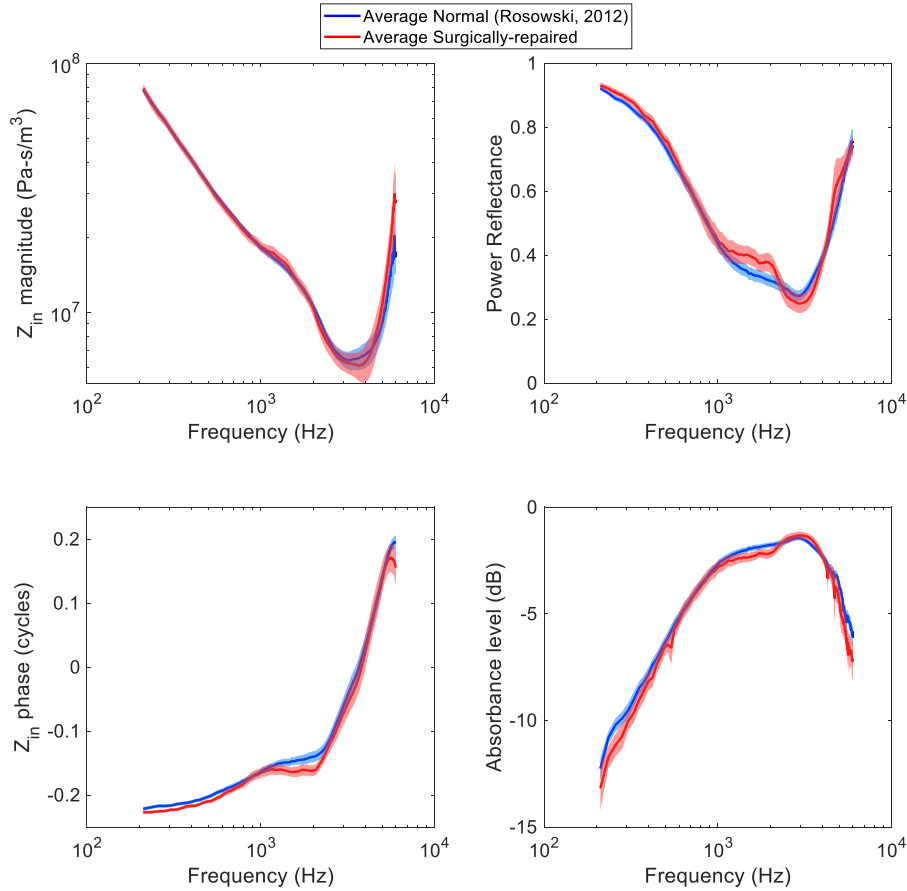


Figure 3.3: Mean and Standard Error of WAI measures in normal and surgically-repaired SCD cases: a) acoustic input impedance (Z_{in}) magnitude, b) Z_{in} phase, c) power reflectance and d) Absorbance Level. Shading represents bootstrapped standard error of the mean. WAI measures of surgically-repaired ($n = 25$; red) and normal ($n = 56$; blue) ears (Rosowski et al., 2012) are similar.

3.2 Effect of SCD on WAI in patients

To determine the effect of SCD on WAI measures, we compare WAI measured in the SCD and surgically-repaired states in each ear. Because of the similarity between surgically-

repaired and normal (Fig. 3.3), we assume that WAI and the mechanisms that produce it are similar between the surgically-repaired and normal ear conditions.

The SCD conditions and the surgically-repaired conditions show noticeable differences in each of the WAI related measurements. Figure 3.4 plots the SCD-related changes in impedance magnitude $\Delta|Z_{in}|$ (Fig 3.4a) and impedance phase $\Delta\angle Z_{in}$ (Fig 3.4b) for all of the individual ears (colored lines). The largest changes observed in individual ears occur at frequencies between 3.3-6 kHz but those changes include both increases and decreases and the mean is generally close to 0. Paired non-parametric tests (Wilcoxon signed-ranks test) on the data averaged in 15 octave bands found significant differences in impedance magnitude between SCD state and surgically-repaired state only in bands centered at 0.644 kHz and 0.785 kHz (signed-rank: $z = -2.60$, $p = 0.009$ and $z = -2.65$, $p = 0.008$). Significant changes in impedance phase only occurred at one-third octave bands centered at 0.785 kHz and 0.996 kHz (signed-rank: $z = 2.43$, $p = 0.015$ and $z = 2.94$, $p = 0.003$). The directions of the significant changes near 0.8 kHz (a decrease magnitude and an increase in phase) are consistent with the hypothesized change in middle ear resonance near that frequency suggested by Merchant et al., 2015.

Fig. 3.5 plots the effect of SCD associated ΔPR (Fig 3.5a) and Δ Absorbance Level (Fig 3.5b) in individual ears. Regular SCD induced differences in mean PR and mean Absorbance Level are noticeable in frequency regions where the SCD had its largest effect on Z_{in} . These changes include a statistically significant decrease in PR at one-third octave frequency bands centered at 0.785 kHz and 0.996 kHz (at 0.785 kHz: $z = -2.46$, $p = 0.01$, at 0.996 kHz: $z = -2.68$, $p = 0.0074$) and an increase in Absorbance Level in the same frequency bins (at 0.785 kHz: $z = 2.13$, $p = 0.03$, at 0.996 kHz: $z = 2.73$, $p = 0.0063$). This SCD related decrease in PR has been reported by Merchant et al. (2015) in human SCD patients, and by Masud et al. (2018) in

controlled human temporal bone experiments (see Section 2 of dissertation). The significant ΔPR and $\Delta \text{Absorbance Level}$ near 0.8 kHz are consistent with the change in middle-ear impedance suggested by $\Delta |Z_{in}|$ and $\Delta \angle Z_{in}$. While the mean ΔPR reaches its most negative value of -0.11, and the $\Delta \text{Absorbance Level}$ reaches its most positive value of 1 dB at 0.8 kHz, SCD effects in individual ears are generally larger. Some peaks in the individual $\Delta \text{Absorbance Level}$ point to as much as a 5 dB change at around 800 Hz; however, the peak $\Delta \text{Absorbance Level}$ occurs at different frequencies in different individuals, and the averaging process smooths out the differences and reduces the peak change in magnitude. Averaging similarly reduces the mean reduction in ΔPR which can be as large as -0.45 in individual ears.

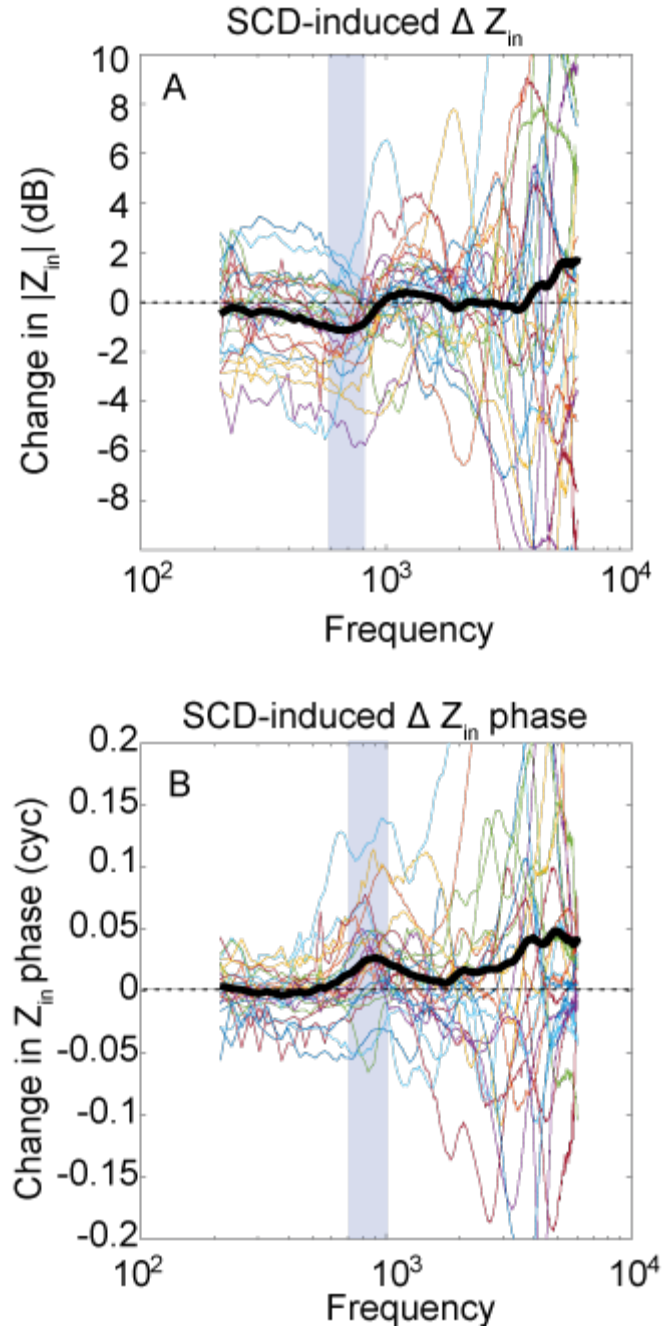


Figure 3.4: The mean and individual SCD-induced changes in acoustic input impedance a) magnitude $|Z_{in}|$ and b) phase $\angle Z_{in}$. The solid black line represents the median change across 25 ears. The blue transparent region represents where the average across ears at particular one-third octave frequency bands were significantly different from 0.

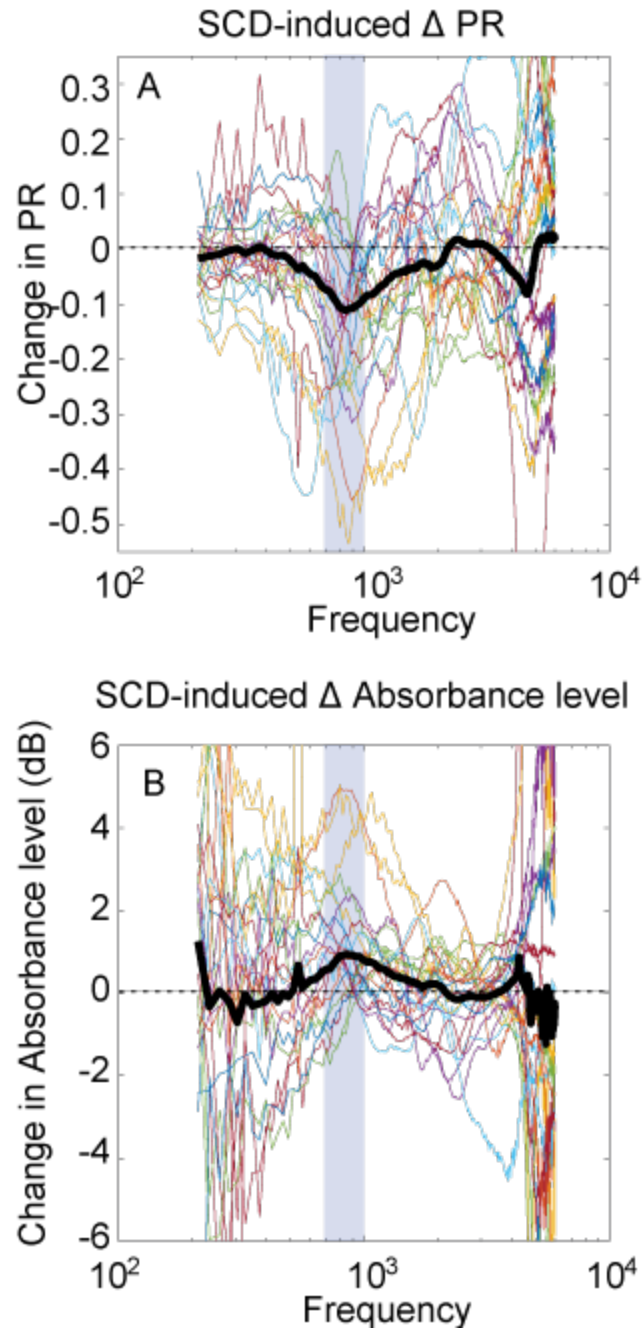


Figure 3.5: The mean and individual SCD-induced changes of a) power reflectance (PR) and b) absorbance level. The solid black line represents the mean change across 25 ears. The blue transparent region represents frequency bands that displayed significant change between SCD and surgically-repaired WAI data for all 25 ears.

3.3 Model predictions of the effect of SCD on WAI

The structure-based computational model in Figure 3.2, was fit to individual WAI data measured from SCD and surgically-repaired ears using the techniques described in the Methods.

Example model fits of $|Z_{in}|$, $\angle Z_{in}$, PR, and Absorbance Level for both ear states are plotted for 6 representative ears in Figure 3.6. The measurements in patients are plotted with solid lines while the modeling results are plotted with dashed lines. Data and predictions for the SCD state are in red, while the surgically-repaired baseline state is plotted in black/gray. As described above, the only differences between the SCD and surgically-repaired models are the parameter values for ear-canal length (l_{EC}), ear-canal radius (r_{EC}), the resistance of the dehiscence (R_{SCD}) and the mass of the fluid displaced by sound due to the dehiscence (L_{SCD}). Individual measurements were modeled, enabling the model to simulate the SCD-induced narrow-band peak in absorbance or notch in power reflectance (see Figure 3.5). The surgically-repaired model results (gray dashed line) and the actual measurements in surgically-repaired ears (black solid line) are generally in agreement. In all SCD and surgically-repaired cases, the predicted $|Z_{in}|$ decreases as a function of frequency at $f < 1\text{ kHz}$ (with a decrease in magnitude of a factor of 2 for a doubling of frequency), and $\angle Z_{in}$ is near -0.25 cycles, where both are indicative of a stiffness-dominated system. As frequency increases the slope of the measured and simulated $|Z_{in}|$ gradually decreases. At frequencies above 4 kHz, the measured and simulated acoustic input impedance magnitude increases and the phase reaches +0.25 cycles in both pre-operative and post-operative cases, consistent with a mass-dominated Z_{in} at high frequencies.

PR and Absorbance Level are plotted in Fig. 3.6 cn & dn ($n = 1:6$). The individually-tailored model fits generally agree with the individual measurements for the surgically-repaired conditions (solid black, dashed gray), as well as the SCD conditions (solid red, dashed red). The

later condition generally shows the characteristic notch or decrease in PR (or local peak in absorbance level) at around 1 kHz. The difference between the PR in the SCD and surgically-repaired states (ΔPR) was computed for the 25 individual measurements and the 25 fitted models. Fig. 3.7 plots the median and the 25-75% interquartile range of ΔPR from the measurements (black solid line and gray shaded region) and the models (dark blue line and lighter shaded region). The figure demonstrates the median of the model has a PR notch at a slightly higher frequency than is observed in the patient measurements, though the cause for this shift is not clear.

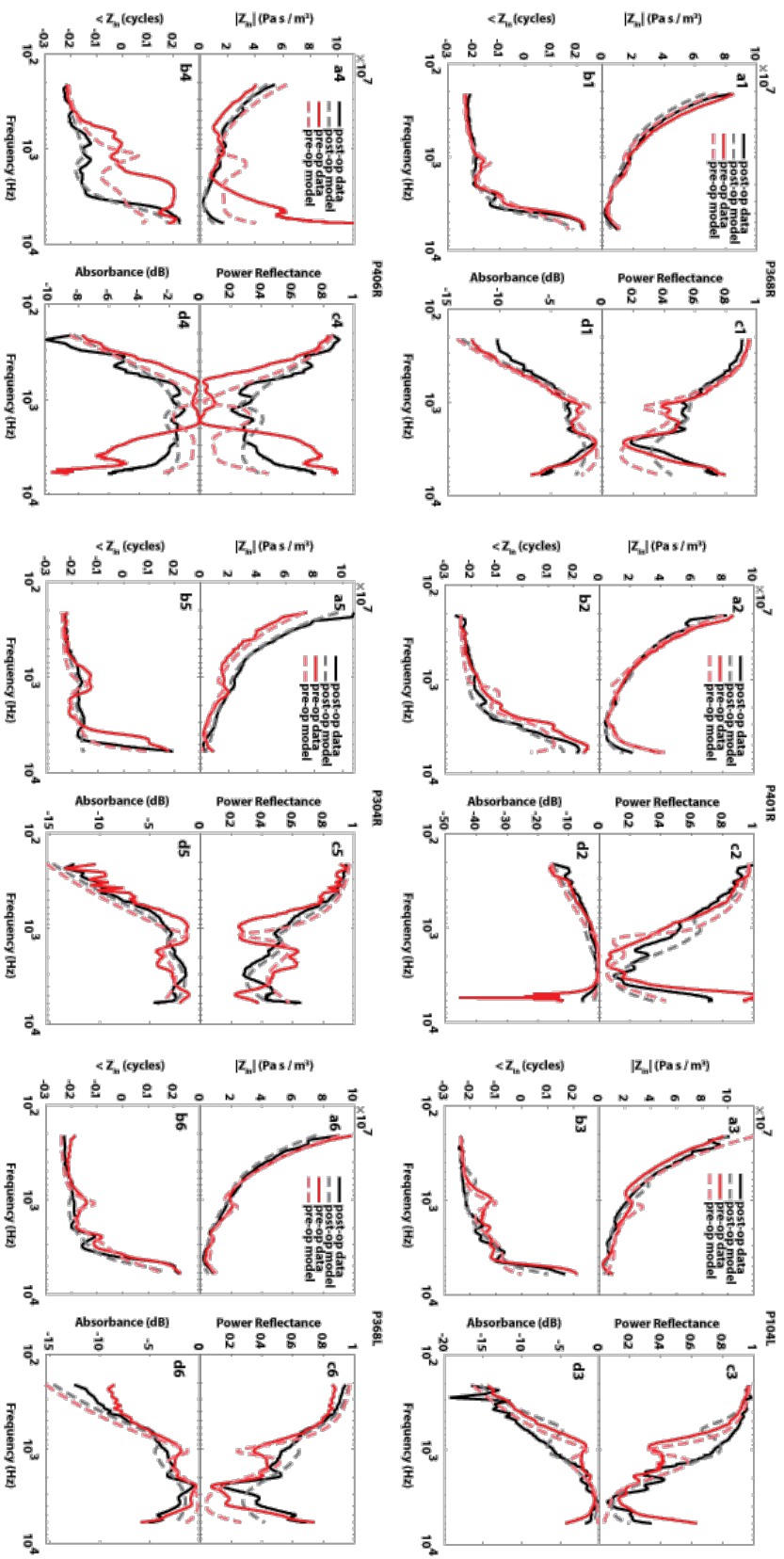


Figure 3.6: Model fits to WAI measurements from six patients. a) Impedance magnitude ($|Z_m|$), b) impedance phase ($\angle Z_m$), c) power reflectance (PR) and d) absorbance level (A) are plotted. For each ear, the model was fit to the patient measurement data for the SCD state and the surgically-repaired state. These six ears are representative of the range of model fits to the data.

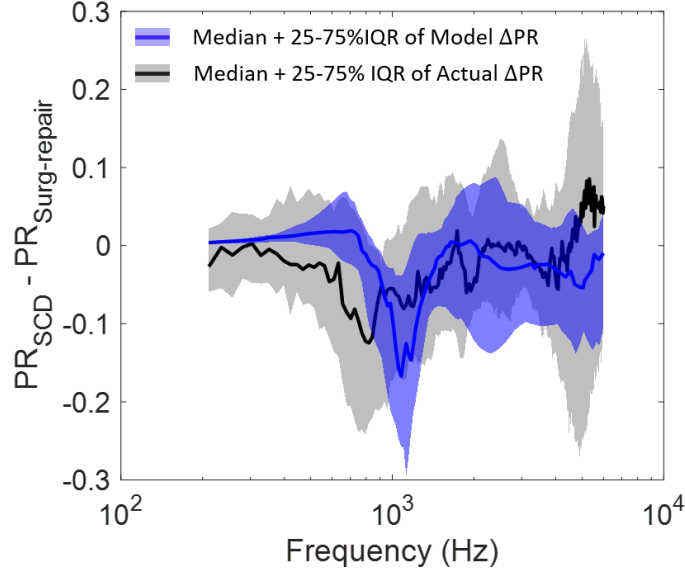


Figure 3.7: Comparison of the median (+/- 25-75% IQR) ΔPR between the SCD and post surgically-repaired states as estimated by the structure-based model (blue) and the actual individual data (black and gray shading).

3.4 Separation of SCD and surgically-repaired measurements

We introduced two parameters: L_{SCD} and R_{SCD} into the model to help fit the WAI measurements in either the open or surgically-repaired SCD cases (see Fig. 3.2b). Prior to optimization in both states, the initial value of these parameter values were set to $R_{SCD} = 2.5 \times 10^{10} \text{ Nsm}^{-5}$ and $L_{SCD} = 1 \times 10^7 \text{ Ns}^2\text{m}^{-5}$. During the data fitting process, these parameter values were optimized to minimize the error between the model and actual WAI measures. The possible ranges of these parameter values for each state are noted in Table 3.1.

Figure 3.8 demonstrates that the fitted values of these parameters differ greatly between the SCD and surgically-repaired states. For each model fit ($n=2$) to each patient ear ($n=25$), the parameter values of $\log_{10} L_{SCD}$ are plotted against $\log_{10} R_{SCD}$. The element values fit to the SCD conditions are plotted with red data points while the element values fit to the surgically-repaired conditions are plotted with cyan points. Note that the median fitted values in the SCD and post-

operative state differ by about 10 orders of magnitude. In general, the pre-surgical (SCD) parameters were much lower in magnitude than the fitted post-surgery parameters; however, two of the pre-surgery measurements yielded fitted R_{SCD} and L_{SCD} parameters that were similar to the post-surgery parameters. This misclassification of 2 cases out of 50 L_{SCD} and R_{SCD} fits suggests a classification error rate of 4%. Given this low error in separation and the large magnitude of the differences between the two groups, it was not surprising that Wilcoxon signed-rank tests confirmed that the R_{SCD} values fit to the surgically-repaired measurements (median = $6.14 \times 10^{19} \text{ Nsm}^{-5}$) are significantly greater than R_{SCD} values fit to the SCD measurements (median = $2.88 \times 10^9 \text{ Nsm}^{-5}$) (Wilcoxon: $Z = 4.02$, $p = 5.76 \times 10^{-5}$), and similarly, the surgically-repaired model parameter values of L_{SCD} (median = $5.84 \times 10^{18} \text{ Ns}^2\text{m}^{-5}$) are significantly greater than the pre-operative model parameter values of L_{SCD} (median = $3.83 \times 10^6 \text{ Ns}^2\text{m}^{-5}$) (Wilcoxon: $Z = 3.08$, $p = 0.0021$).

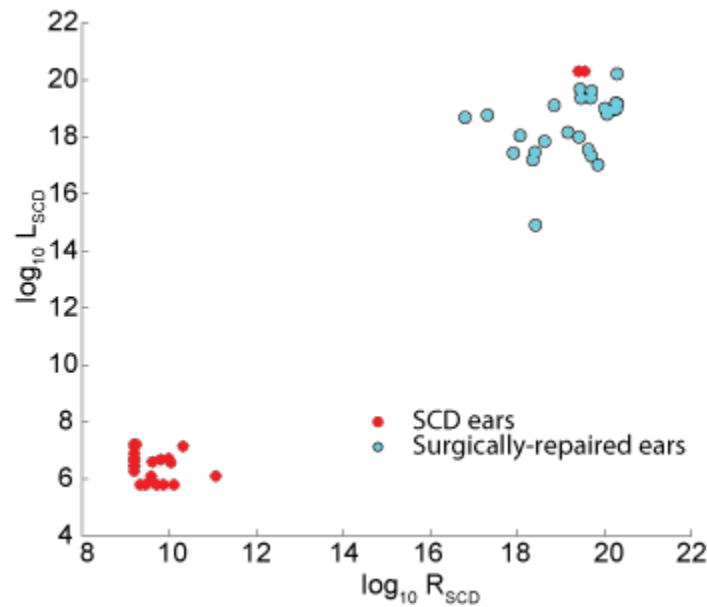


Figure 3.8: Comparison of model parameters between the two states: SCD vs. Surgically-repaired. L_{SCD} is plotted against R_{SCD} for SCD ears (red diamonds) and surgically-repaired ears (blue circles).

4. Discussion

4.1 WAI measures of SCD and surgically-repaired conditions.

WAI, a simple and non-invasive ear-canal measurement, is a promising tool to measure the mechano-acoustic effects of SCD. SCD has been found to introduce a narrow band decrease into PR measurements, derived from WAI, at around 0.8 kHz (Merchant et al., 2015). Furthermore, our finding that WAI in surgically-repaired and normal ears were statistically the same, suggests that the surgery has normalized the mechanical processes that contribute to WAI in the surgically-repaired ears.

4.2 Structure-based computational model to capture the effect of SCD

We use a structure-based mechano-acoustic model that includes important details of the outer, middle and inner ear (Figure 3.2) to predict WAI measurements in the normal (surgically-repaired) and SCD condition. An SCD impedance branch is introduced parallel to the cochlea and round window impedance, to simulate the split of the stapes volume velocity U_S that enter the vestibule into a volume-velocity in two branches: one describing the impedance of the cochlea and round window U_{Ch-RW} , and an SCD branch SCD U_{SCD} (Figure 3.2). For the normal or surgically-repaired condition the SCD impedance is very high and could be replaced by an open circuit (with little or no volume velocity flowing through the SCD impedance block in Fig. 3.2). We demonstrate that the introduction of lower values for SCD elements can successfully model the decrease in PR (increase in absorbance) around 0.8 kHz as well as the SCD-related changes we observe in the input impedance, Z_{in} .

Our choice to fit to individual data rather than averages is significant because the averaged data (with its smeared-out representation of the narrow-band changes introduced by SCD) is not representative of any clinical WAI measurement. Averaging across multiple ears smooths out the

defining pattern of a consistent but frequency-varying narrow-band local minima and maxima in WAI measurements. To fit the surgically-repaired condition (our best-estimate of the normal condition) we fix twenty parameters of the model of Figure 3.2 using values from the literature and allow nine model parameters (the length and radius of the ear canal (l_{EC} and r_{EC}), total compliance of the middle ear cavity ($C_{TC} + C_A$), and C_{T2} , C_{AL} , L_{RW} , C_{RW} , R_{SCD} , L_{SCD}) to vary to get the best fit to the individual ear's dataset. Once these parameters are set by the surgically-repaired data, the only parameters that are varied to model the SCD condition are L_{SCD} , R_{SCD} , and the radius and length of the model ear canal. The latter two are included because the location of the measurement probe tip in the ear canal and the ear canal radius at that location can vary between two different measurements.

The optimization procedure outlined here is a generalizable algorithm to automatically detect mechanical differences in pathological and non-pathological ears. The presence or absence of SCD generally produced easily differentiable results in two parameters, where for all models fit to surgically-repaired ears, the SCD impedance branch acts as an open circuit with L_{SCD} and R_{SCD} fixed at very large values (on the order of 10^{16} to 10^{21} mks acoustic ohms or inductance units). When fitting the model to WAI measured in SCD ears, the median values of L_{SCD} and R_{SCD} were $2.88 \times 10^9 \text{ Nsm}^{-5}$ and $3.83 \times 10^6 \text{ Ns}^2\text{m}^{-5}$ respectively, and generally close to those determined in Raufer et al. (2018) and Cheng et al. (2019) in cadaveric human specimens with an induced SCD. There were exceptions; measurements in two SCD ears were fit with values of L_{SCD} and R_{SCD} that were similar to those seen post-surgery. Because of the lack of effect of SCD on these elements in two ears (Figure 3.9), estimations of L_{SCD} and R_{SCD} only correctly defined the presence of an SCD in 23 of 25 ears but did correctly define normality in all of the 25 post-surgical ears. Therefore, the error rate for classifying SCD vs. surgically-repaired ears was 4%

(2/50). This error is much lower than the 21% error rate produced by the notch detection algorithm developed by Merchant et al., 2015 to differentiate pathological SCD ears and non-pathological ears.

Close inspection of the data and model fits in the two misclassified cases shed little light on the reason for the error. Some of the data is noisy at frequencies below 0.6 kHz, but that data is not used in the fit of the two SCD elements. Both measurement sets do show differences in Z_{in} and PR near 0.6 kHz that would indicate the presence of an SCD, but these differences are not repeated in the model fits. Indeed, the predictions of the SCD and Post-surgery models hardly differ, as might be expected for the large values of R_{SCD} and L_{SCD} introduced by the SCD fitting procedure, and any difference that occur must be due to differences in the models' ear canal length and radius (Case 1: $l_{ec} = 0.0198$ m, $r_{ec} = 0.0037$ m; Case 2: $l_{ec} = 0.0272$ m, $r_{ec} = 0.0040$ m). We then closely looked at each of the patients' medical notes to find whether their symptoms may explain inaccurate diagnosis using WAI. In Case 1, it was found that acoustic reflexes were absent in both ears after surgery. This may indicate that the patient could also have a middle-ear pathology such as ossicular fixation or discontinuity. In Case 2, we found that one of the patient's 226 Hz tympanograms after surgery showed a highly mobile tympanic membrane. This mechanical change of the eardrum can affect WAI measures. These two cases show that there are potential limitations in using WAI as a stand-alone device to detect SCD. Since we are evaluating the motion of the eardrum, the eardrum and the ossicles attached to the eardrum, must be normal in order for WAI to detect SCD patterns.

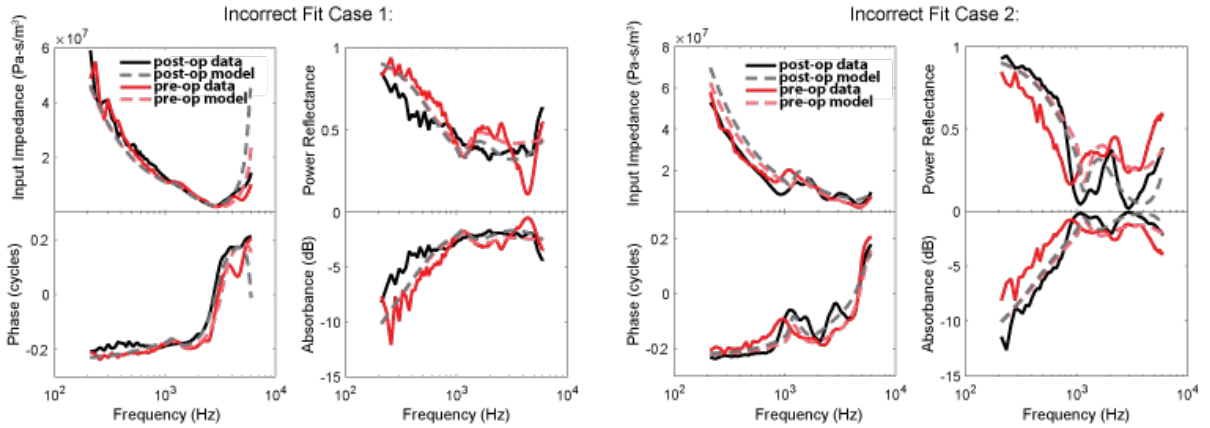


Figure 3.9: In two cases, the model is unable to fit the SCD and surgically-repaired data well. Some potential reasons are described in the text

5. Summary

We adapted several mechano-acoustic structure-based models so that we could simulate WAI measurements in normal and pathological ears. We demonstrated that WAI measured in ears after successful surgical repair of SCD was similar to normal WAI measurements, which allowed us to use the variations from the normal model to compare WAI in pre- and post- SCD surgery conditions. A fitting procedure was used to describe individual sets of model parameters that fit individual post-surgical WAI measurements. A smaller set of these individual parameters were then fit to pre-surgical measurements. Comparison of the parameters that varied in the pre and post-surgical cases showed large easily recognizable differences that allowed separation of the pre- and post-surgical WAI measurements with a very low (4%) error rate. The results suggest the use of structure-based models to fit individual WAI responses shows promise in diagnosing mechanical lesions of the ear in the clinic. Another application of this modeling approach can be to study the efficacy of surgical repair of SCD and to monitor the mechanics after surgical repair. In the next chapter, we use the same structure-based model to differentiate

SCD from two known middle-ear pathologies that produce similar auditory symptoms: stapes fixation and ossicular discontinuity.

**CHAPTER 4. Further development of structure-based model to automatically differentiate
mechanical pathologies of the ear**

1. Introduction

Sound transmission to the sensory cells of the inner ear is affected by a variety of passive macro-mechanical processes within the outer, middle and inner ear. Relevant to the latter are the bony and soft-tissue surrounding structures (e.g. the aqueducts to the cranial cavity, the round-window membrane, etc). Otologic pathologies such as ossicular fixation, ossicular discontinuity and superior canal dehiscence (SCD) result from abnormal macro-mechanics. The symptoms and hearing results produced by the different pathologies can be very similar (e.g., SCD can cause a variety of symptoms including: hearing loss, hyperacusis, autophony, dizziness induced by sound and static pressures, and the sensation of intolerably loud sounds transmitted through the body with varied expression across different patients). The mechanisms by which some mechanical pathologies cause such symptoms are not always understood and differentiating pathologies with overlapping symptoms is challenging.

For example, in a patient presenting with conductive hearing loss with a normal appearing clear tympanic membrane without evidence of middle-ear fluid the presumptive diagnosis is usually stapes fixation due to otosclerosis, and often, the patient undergoes surgical middle-ear exploration followed by stapedotomy. However, the etiology of the conductive hearing loss can be fixation of a different ossicle, ossicular interruption, or an inner-ear lesion such as superior canal dehiscence (SCD). These other conditions are not always easily assessed during surgical exploration, e.g. a hairline fracture of an ossicle at a visually inaccessible location or a fixation of the malleus hidden within the epitympanic space may be missed. In their observations, surgeons rely on “palpating” the ossicles with a surgical pick and use subjective tactile and visual cues to assess ossicular mobility. The accuracy of these assessments depend on the skill and experience of the surgeon (Linder et al., 2015) and such palpations introduce the risk of trauma (e.g., it is easy to loosen the very delicate incudo-stapedial joint) (Chien et al. 2009; Nakajima et al., 2005).

Previously, non-invasive ear-canal measurements of umbo velocity with laser Doppler vibrometry have been used to differentiate various etiologies responsible for conductive hearing loss (Goode et al., 1993; Huber et al., 2001; Nakajima et al., 2012a; Nakajima et al., 2005b; Nakajima et al., 2005; Rosowski et al., 2003; Rosowski et al., 2004). Wideband acoustic immittance (WAI) is quicker, easier, and less expensive than umbo velocity measurements, and is sensitive to several different middle-ear lesions (Allen, Jeng, and Levitt 2005; Feeney, Grant, and Marryott 2003; Keefe, Ling, and Bulen 1992; Nakajima et al. 2012b, 2013a; Shahnaz et al. 2009; Stinson 1990; Voss and Allen 1994). Nakajima et al., 2013 developed a simple method to separate three conductive pathologies: stapes fixation, SCD, and ossicular discontinuity. This method consisted of gathering a preliminary dataset of WAI measures from pathological ears and plotted average absorbance level (between 0.6 kHz to 1 kHz) as a function of average air bone gap (between 1-4 kHz). The sensitivity and specificity for each pathology were high and ranged between 83% and 100%. However, the boundaries to separate pathologies were manually optimized for this small dataset. The purpose of this study was to develop a more robust method to classify these three conductive pathologies. We determine how well a combination of audiometry, objective WAI measurements and model analyses, can automatically separate three different macro-mechanical pathologies, and thereby be used to prevent unnecessary surgery, better prepare surgeons and patients for specific surgical procedures, and provide improved prognostic abilities.

WAI includes measurements of acoustic admittance and impedance as well as the related quantities of sound pressure and power reflectance and absorbance. The sensitivity and selectivity of a combination of WAI and other clinical assessments to different mechanical disorders has been quantified (Nakajima et al., 2012, 2013) by using WAI measurements in patients with conductive hearing loss and confirming the diagnosis by surgical finding (for all middle-ear pathologies)

and/or CT (for inner-ear pathology). This preliminary study used a simple classification algorithm that combined information from absorbance level (derived from WAI) between 600-1000 Hz and audiometric air-bone gap (ABG) between 1 – 4 kHz to separate stapes fixation, ossicular discontinuity, and SCD from each other with a sensitivity and specificity between 83% and 100%. Merchant et al., 2015 investigated the ability of WAI measurements alone to differentiate SCD from normal ears and developed an algorithm to detect an SCD-associated sharp decrease (or notch) in power reflectance near 1 kHz. The Merchant et al. study achieved a sensitivity between 80-93%. However, the presence of a notch in PR in some normal ears led to a moderate specificity near 70%. In the present study, we utilize a wider frequency range of WAI information in combination with ABG measurements in an effort to improve the sensitivity and specificity of WAI measurements to various mechanical lesions of the ear such as stapes fixation, SCD and ossicular discontinuity.

A structure-based acoustic circuit model of the ear developed in Chapter 3 to simulate WAI in normal ears could simulate WAI measurements in individual pathological human ears. These simulations resulted in a small collection of fitted parameters (see Chapter 3). We used a combination of these fitted model parameters and audiometric measurements of ABG to define a single decision tree that separates ossicular discontinuity (OD), stapes fixation (SF) and superior semi-circular canal dehiscence (SCD). This study quantifies the ability of this automated procedure to separate these difficult to diagnose macro-mechanical lesions of the auditory periphery.

2. Methods

2.1 Wideband acoustic immittance and audiometric air-bone gap measured in pathological ears

WAI measurements and audiometric thresholds were collected from patients with confirmed SF, OD and SCD. ABG was calculated from the audiometric air conduction (AC) and bone conduction (BC) thresholds ($ABG = AC - BC$).

Our study population included 16 patients with SF (all due to otosclerosis) with ages of 29 to 65 (average = 45, standard deviation = 11.4 years), and male to female ratio of 1:3. Ten out of 16 SF patients were from the Nakajima et al., 2013 study. There were fourteen patients with OD with ages of 16 to 57 (average = 37.4, standard deviation = 12.3 years) and male to female ratio of 5:2. Four out of these 14 OD patients overlapped with the Nakajima et al., 2013 study. According to surgical report, six out of 14 OD patients had a “complete disarticulation,” where presumably there was no contact between the disconnected ends. Eight out of 14 OD patients had a “partial discontinuity” with a loose ossicular chain either due to an “in-place” fracture of an ossicle (where the opposing fractured components were in contact with each other), a less than total injury to a joint, or where normal contact in the ossicular chain was replaced with fibrous tissue or (Farahmand et al. 2016).

For SCD, WAI measures and audiometric thresholds were collected from 24 patients (25 ears). All patients had a frank dehiscence (at least about 1.9 mm length dehiscence) seen on high-resolution CT imaging. Subjects ages ranged from 25 to 66 years (average = 49.4, standard deviation = 10.6 years) and male to female ratio was 3:5. Only 3 out of these 25 SCD ears were included in the Nakajima et al., 2013 study.

All pathological ears satisfied the following criteria: 1) no history of prior middle-ear surgery, 2) a normal standard 226 Hz tympanogram, and 3) a normal otoscopic exam of the external ear and tympanic membrane performed by an otologist. Confirmation of middle-ear diagnosis was made after exploratory surgery or via high-resolution CT-scan and surgery in the

case of SCD. WAI was measured with the Mimosa Hear ID System following the methods described by Rosowski et al., 2013. Audiometric thresholds were measured by clinical audiologists using standard clinical practices at the Massachusetts Eye and Ear. This study was approved by the Massachusetts Eye and Ear Institutional Review Board.

2.2 Air-bone gap (ABG) grouping

ABGs were quantified by audiometry at 5 frequencies: 250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Conductive hearing loss was defined as an ABG of 20 dB and greater at one or more frequencies. Frequencies at and below 1000 Hz were considered low-frequency (LF). Frequencies above 1000 Hz were considered high-frequency (HF). Four groups were formed based on whether a conductive hearing loss existed at: 1) LF and HF 2) HF only, 3) LF only, or 4) no conductive hearing loss.

2.3 Structure-based models to simulate WAI in pathological ears

Our structure-based circuit model of the human external, middle and inner ear is shown in Fig. 4.1 and described in Chapter 3. This model can simulate WAI measures from individual ears of various conditions (Chapter 3). The representative normal-ear model parameter values obtained from averaged data are described in the Appendix A4. In chapter 3, nine model parameters were varied to obtain the best fit between individual WAI measurements in normal-like ears that were successfully treated for SCD, these included: 1) the length of the ear canal, 2) the radius of the ear canal, 3) the volume of the middle ear cavity space, 4) the compliance of the tympanic membrane C_{T2} , 5) the compliance of the annular ligament C_{AL} , 6) the inductance of the round window L_{RW} , 7) the compliance of the round window C_{RW} , 8) the resistance of the superior canal dehiscence R_{SCD} , 9) and the inductance of the superior canal dehiscence L_{SCD} . Because the model was fit to ‘normal-like’ ears (Chapter 3), the values of R_{SCD} and L_{SCD} (Fig. 4.1) were

extremely large, and the SCD branch acted as an open circuit. The values of the nine parameters fit the individual data in Chapter 3 varied across the 25 ears. In the present study, we used a baseline model where the values of the formerly 9 variable parameters are the average of the parameters fit to the 25 ears (Chapter 4, Appendix A4). Several of the baseline-element values of this ‘normal’ ear model were altered to define separate models of SF, OD and SCD ears. Variations in several parameters of the different models were used to fit individual WAI measurements from patients with known conductive hearing loss, and the best-fit model was used to classify the ears into one of the three pathologies.

To simulate each pathology (SF, OD and SCD), one or two baseline model parameter values were varied as follows: SF was simulated by decreasing the baseline compliance of the annular ligament (C_{AL}) by an order of magnitude while all other model elements were fixed to the baseline state (similar to Voss et al., 2012). To fit the model to WAI data from individual pathologic ears, the decreased C_{AL} was optimized to find the local minimum of a cost function by using the *fminsearch* function in MATLAB. The cost function was previously defined in the appendix of Chapter 3. To simulate OD, two parameters were varied: the compliance and the resistance of the ossicular joints (C^{M_J} and R^{M_J}) while all others were fixed. The initial OD model increased the baseline compliance of the joints C^{M_J} by 10 and decreased the baseline value of resistance R^{M_J} to zero. As the compliance increases and the resistance decreases, the impedance at the joint branch decreases toward 0, approximating a short circuit (Voss et al., 2012). The two altered element values were then optimized to fit WAI data from individual pathologic ears using the same cost-function. SCD was modeled by altering 2 baseline parameters: the mass and the resistance of the superior semicircular canal dehiscence (L_{SCD} and R_{SCD}) while all others were fixed. The initial values of these SCD parameters were derived by Raufer et al. (2018), where

R_{SCD} is 1×10^{10} Pa-s/m³ and L_{SCD} is 1×10^6 Kg/m⁴. These two element values were then optimized to fit WAI data from individual pathologic ears.

2.4 Decision tree for classification of pathologies

To classify patient data into one of the three mechanical pathologies, a decision tree with the initial step based only on audiometric ABG was used (Figure 4.2), where each ABG-based category led to no more than two suspected conditions. If both LF and HF ABG exist, either OD or SF is suspected. If only a HF ABG exists, an OD is suspected, while if only a LF ABG exist, either SCD or SF are suspected. If ABGs are less than 20 dB (clinically insignificant CHL), an SCD or normal ear is suspected.

At the second level of the decision tree, differentiation between two suspected conductive pathologies is performed with our structure-based modeling approach. For example, in the case where both LF and HF ABG exists, a choice between OD and SF is made by optimally fitting the patient's WAI measurements to the OD model with variable C^M_J and R^M_J and the SF model with variable C_{AL} . The model that produces the lesser error (or better fit) determines whether the patient is categorized as OD or SF. Parameter values obtained in the fitting procedure are not used to separate the pathologies. The same method is applied for the patients in the LF ABG only and No ABG groups.

Structure-based model manipulations

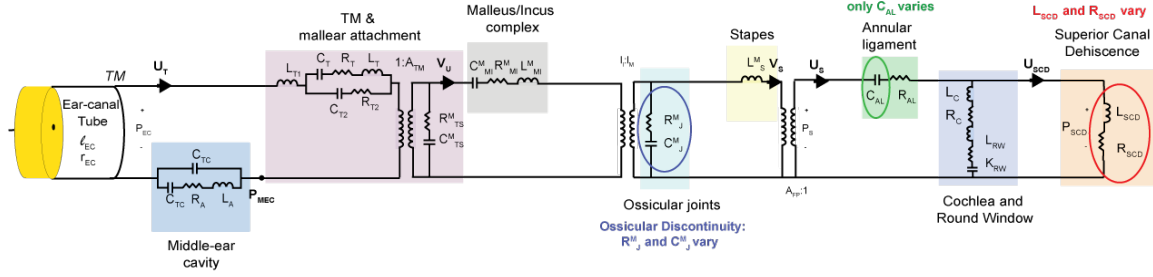


Figure 4.1: A structure-based circuit model of the human external, middle, and inner ear to simulate wideband acoustic immittance data (detailed in Chapter 3), built upon aspects of Stepp and Voss (2005), Rosowski and Merchant (1995), Rauber, Masud and Nakajima (2018). Specific model parameters (indicated by oval outlines) are modified to simulate pathologies such as ossicular discontinuity, stapes fixation, and superior canal dehiscence (SCD). Ear canal acoustics is estimated by a one-dimensional lossy transmission line. The ear-canal is coupled to a middle and inner ear model consisting of 8 blocks: 1) middle ear air spaces, 2) tympanic membrane (TM) and malleolar attachment, and 3) the malleus and incus complex, 4) ossicular joints, 5) stapes, 6) annular ligament, 7) cochlea and round window and 8) superior canal dehiscence. U_T , U_S , and U_{SCD} represent the volume velocities of the tympanic membrane, stapes and through a dehiscence canal. P_{EC} , P_{MEC} , P_S , P_C and P_{SCD} represent the sound pressures of the ear canal, middle ear cavity, stapes, cochlea and at the dehiscence canal.

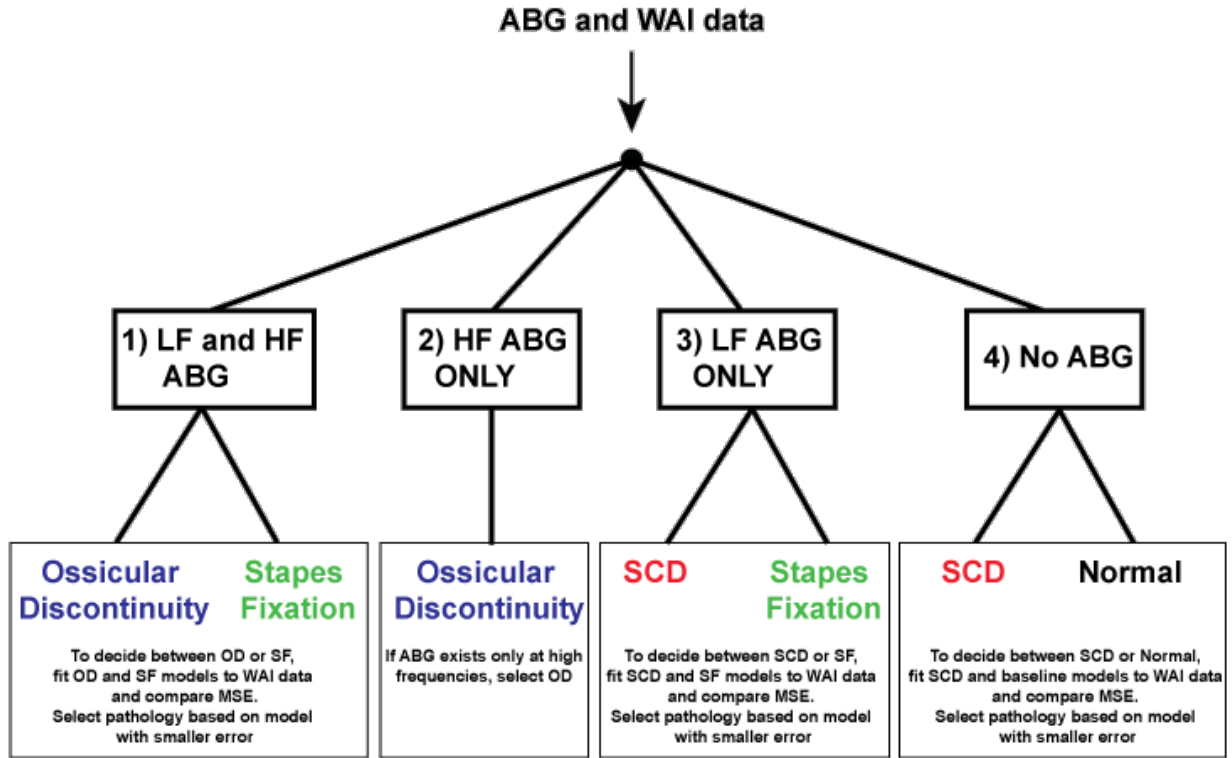


Figure 4.2: Decision tree to classify into pathologic groups. The first level of the decision tree separates patients based on ABG groups. A significant ABG exists if $ABG \geq 20$ dB. LF ABG represents an ABG at

1000 Hz or any lower frequency. HF ABG means a significant ABG exists at any frequency above 1000 Hz. The second level of the decision tree shows pathologies that are possible under each ABG group. After narrowing possible pathologies to no more than two types per group, our structure-based model is used to determine the pathology.

3. Results

3.1 Classification based on ABG and WAI information

The decision-tree divided fifty-five patients into 4 ABG groups: (1) 25 patients in the LF and HF ABG group, (2) one patient in the HF ABG only, (3) 21 patients in the LF ABG only, and (4) 8 patients in the no ABG group. In the LF and HF ABG group (group 1), the SF and OD structure-based models were fit to all 25 ears, and the model that produced the least squared error (between model and data) predicted the pathology for each patient. This approach predicted the 25 LF and HF ears contained 12 OD and 13 SF patients. The prediction of OD was correct in 11 of 13 ears with OD, and SF was correctly identified in all 11 ears with SF. One of the predicted OD ears actually had SCD. Since group 1's correct confirmed diagnoses were 1 SCD, 13 OD, and 11 ears, the ABG grouping was inaccurate for one ear with SCD which had both LF and HF ABG (which is unusual), and the modeling wrongly predicted two ears as SF when they were actually OD. The accuracy of the classifier incorporating both the ABG and modeling fit for group 1 of LF and HF ABG was 88%.

Ears with HF ABG only (group 2) were classified as having OD since it was rare and unexpected to see SF and SCD patients with an ABG only at high frequencies. All SF and SCD patients in this study did not exhibit an ABG at high frequencies only. The one patient with HF ABG only did indeed have surgically-confirmed OD. Group 3 consisted of 21 ears with LF ABG only. SCD was classified correctly in 15 out of 16 SCD ears (one SCD patient was incorrectly identified as SF), and all 5 SF patients were correctly identified. The accuracy of the classifier in this group was 95.2%. Group 4 consisted of 8 ears with no ABG. Seven out of 8 SCD patients

were correctly identified as having SCD (1 ear was wrongly classified as a normal). The accuracy of the classifier in this group 4 was 87.5%. Table 4.1 summarizes the number of ears in each ABG group and how they were diagnosed with the decision tree classifier.

3.2 Overall evaluation of diagnostic classifier (ABG + model)

Table 4.2 provides the performance measures of the diagnostic classifier using ABG and structure-based modeling. The evaluation metrics are sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and F1 score. The sensitivities to the three pathologies were over 86%. The specificities (the ability of the classifier to correctly classify an individual as not having the particular pathology) range between 92-100%.

Table 4.1: Diagnosis for individual ear

ABG group	Number of patients in each group	Actual number of patients for each pathology	Diagnosis for each pathology
Group 1: LF and HF ABG	25	OD: 13	OD: 11, SF: 2
		SF: 11	SF: 11
		SCD: 1	OD: 1
Group 2: HF ABG only	1	OD: 1	OD: 1
Group 3: LF ABG only	21	SCD: 16	SCD: 15, SF: 1
		SF: 5	SF: 5
Group 4: No ABG	8	SCD: 8	SCD: 7, Normal: 1

The Positive Predictive Value (PPV) is the percentage of patients with a positive test result who actually have the disease, and the Negative Predictive Value (NPV) is the percentage of patients with a negative test who do not have the disease. The PPV on average was 92% and the NPV on average was 95.3%. The accuracy of the diagnostic classifier was overall 91% (50/55). The average F1 score (the harmonic average of sensitivity and PPV, which can vary between 0 and 1, where 1 indicates perfect sensitivity and PPV) is 0.913.

Table 4.2: Evaluation of performance measures for decision tree classifier

Pathology	PPV	NPV	F1 Score	Sensitivity	Specificity
Ossicular Discontinuity (<i>this study</i> n = 14)	92%	95%	0.89	86%	98%
Stapes Fixation (<i>this study</i> n = 16)	84%	91%	0.91	100%	92%
Superior Canal Dehiscence (<i>this study</i> n = 25)	100%	100%	0.94	88%	100%

4. Discussion

In this study, we aimed to make a robust, objective classifier that automatically separates mechanical pathologies of aerated adult middle ears with normal tympanic membranes, where the possible pathologies include SF, OD, and SCD. By using both ABGs and the structure-based models fit to individual wideband acoustic immittance measurements (impedance, impedance phase, power reflectance, and power absorbance), we correctly diagnosed the 55 ears 91% of the

time. A simple method that separated the three pathologies by average absorbance level and air-bone-gap described by Nakajima et al., 2013, produced similar accuracy (89%) but utilized a smaller dataset. In Figure 4.3, we repeat the same approach with our larger dataset and find that the classification boundaries differ greatly from that found in Figure 9 of Nakajima et al., 2013. In this previous study, the boundaries were selected manually to separate preliminary pathological data. We used their approach and selected boundaries that optimized the performance of the classifier. For the boundaries drawn in Figure 4.3, the sensitivities to determine the pathological condition among the 3 conditions were over 78.5% (average 91.5%), and the specificities were over 95% (average 97%). Using the previous boundaries drawn in Nakajima et al., 2013 would significantly reduce these sensitivities and specificities due to smaller border regions for each pathology. Although this simple method produced high specificity and moderate to high sensitivity, the boundaries are optimized and fitted to this particular dataset and may not be robust to new additional data.

Similarly, in Merchant et al., 2015, they used a simple narrowband of WAI information to determine whether an SCD patient had a characteristic SCD power reflectance notch at around 1 kHz. If a notch existed, the classifier would diagnose SCD, if not, the ear would be classified as normal. The characteristics of the notch (height, depth and frequency range) was optimized so that the performance of the notch detection classifier was maximized. The sensitivity and specificity of the notch detection classifier was 93% and 69%. In Chapter 5, we show that the notch detector classifier applied to a larger SCD dataset produces a lower sensitivity (76.5%). Thus, the notch detector algorithm performed well with the data it was fit to, but did not perform well with new, unseen data. The goal of this chapter was to improve automation of diagnosis using a combination of ABG information and structure-based modeling techniques and develop

methods to successfully classify new, individual ears without needing to readjust classification parameters.

In the first step of our decision tree classifier, we grouped the patients by ABG characteristics into four categories (Figure 4.2). This enabled classification in the next step to decide between at most two pathologies. To distinguish between the two second-step pathologies, two pathological models were fit to the individual WAI measures and the errors calculated between each model and actual data. The model that better fit the data indicated the presumed diagnostic category. Figure 4.3 shows examples where the better fitting pathology-adjusted structural models correctly identified the actual pathology. Ears with OD showed a distinct notch in PR at frequencies between 0.6 and 1 kHz (Fig. 4.4a) that have been associated with an increase in the sharpness and change in frequency of the middle-ear resonance (Merchant et al. 2016). Individual SF ears showed increased reflectance and decreased absorbance at low frequencies as well as a shift of the middle ear resonance to higher frequencies (Fig. 4.4 b & c); changes consistent with an increased stiffness. Ears with SCD typically produced less prominent transitions in impedance magnitude and angle and notches in PR near 1 kHz (Fig. 4.4 d & e); however, some SCD WAI measures were normal-like and did not produce a notch in PR.

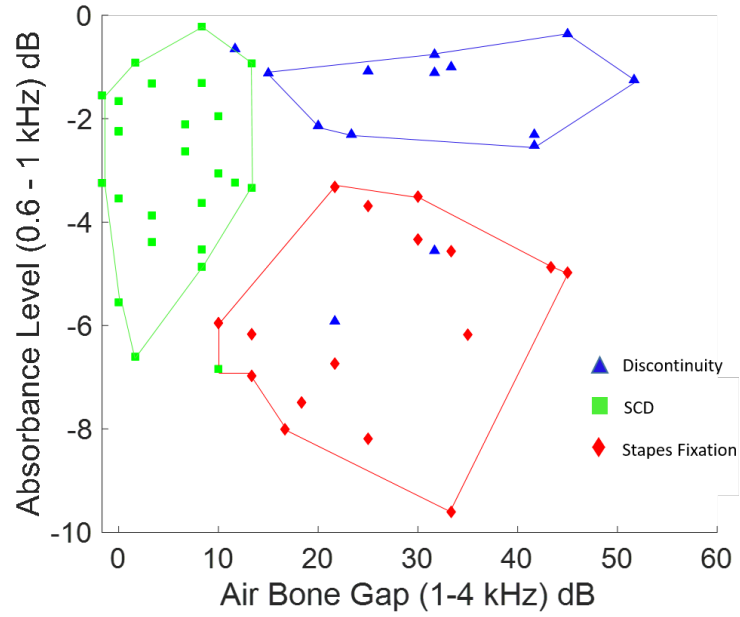


Figure 4.3: Absorbance level (dB) averaged between 0.6 – 1 kHz plotted against air-bone gap averaged between 1-4 kHz, similar to Figure 9 of Nakajima et al., 2013. The red boundaries enclose all 16 cases of stapes fixation. The blue boundaries consist of 11 out of 14 cases with ossicular discontinuity. The green boundaries enclose 24 out of 25 SCD cases. A total of 4 ears were misclassified. Absorbance level is calculated as $10 \times \log_{10}[1 - \text{PR}]$.

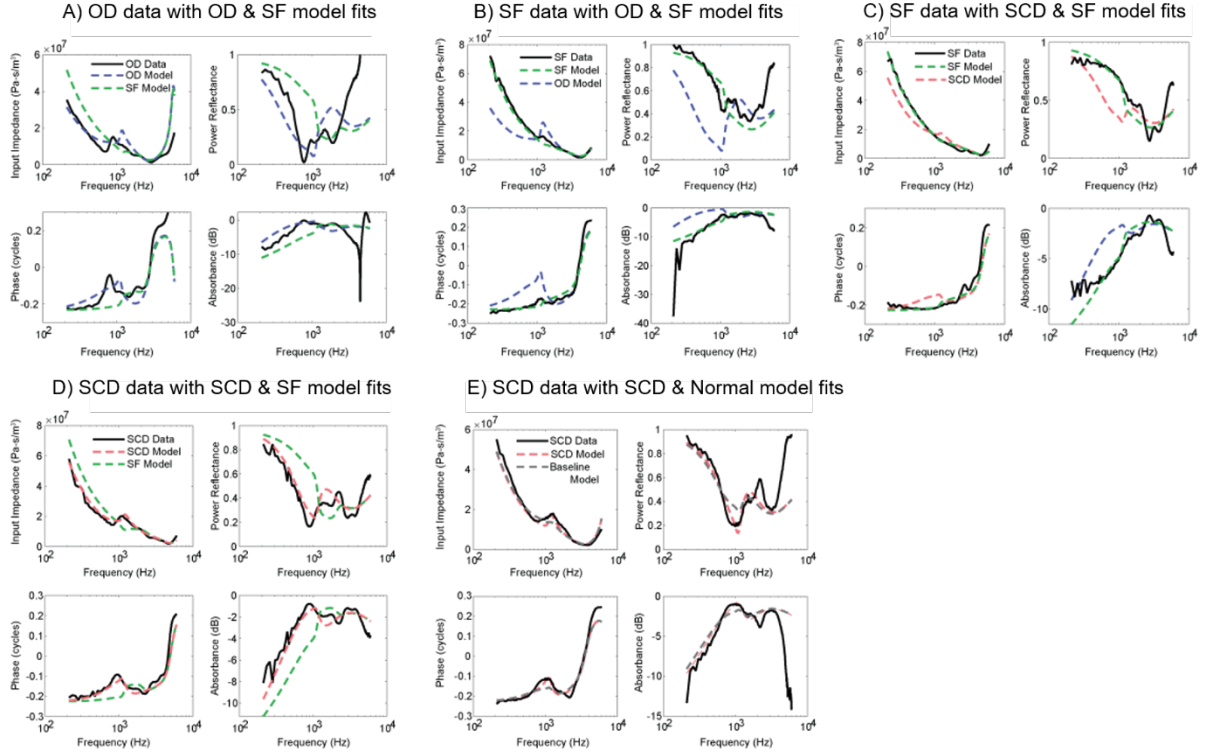


Figure 4.4: Correct identification of pathology occurred for 91% of patients. Examples of correct classification based on minimal error between the correct pathological model and data are shown here. A) OD and SF models were fit to WAI measures of a single OD patient. B) OD and SF models were fit to WAI measures of a single SF patient. C) SCD and SF models were fit to WAI measures of a single SF patient. D) SCD and SF models were fit to WAI measures of an SCD patient. E) SCD and Normal models were fit to WAI measures of an SCD patient.

According to our decision tree, when a patient had significant ABG (≥ 20 dB) that was restricted to frequencies of 1000 Hz or less, the ear would be classified as either SCD or stapes fixation. Patients with partial or complete disarticulation had either high-frequency ABG only, or a significant ABG at both low-frequencies and high-frequencies. Only a single ear experienced high-frequency conductive hearing loss, and, similar to findings in Farahmand et al. (2016) and Masud et al. (2019), that patient had a confirmed partial ossicular discontinuity (in this case there was a fracture of the anterior and posterior crus of the stapes). Temporal bone experiments have shown that partial discontinuity results in loss of stapes velocity at high frequencies, and as the ossicular chain becomes completely disarticulated, significant losses in stapes velocity occur at

all frequencies (Farahmand et al., 2016). However, WAI measures are not significantly different between partial and complete disarticulations, and in this study we do not differentiate between partial and complete disarticulations.

All 16 of our patients with confirmed stapes fixation had ABGs at frequencies of 1000 Hz or less, and 11 of 16 had ABGs in both the low and high frequency range (250 Hz – 4000 Hz). Sixteen of the 25 SCD ears exhibited ABGs at low frequencies only, while 8 had audiometric thresholds that were within normal limits. One unusual SCD ear had significant ABG at both low and high frequencies. This is also rare in our larger SCD database where only 4 out of 85 (4%) of SCD ears had significant ABG at both low and high frequencies (Chapter 7). The classifier incorrectly classified the 1 SCD ear as an OD ear (Figure 4.4, Panel A). The WAI data of SCD ears and OD ears were similar, where noticeable changes in impedance magnitude and phase as well as absorbance are seen at frequencies between 600 to 1000 Hz. The contribution of the suspected resonance is more pronounced and at lower frequencies in the OD cases as compared to the SCD cases.

When separating SF and SCD ears, the classifier performed well and only misclassified one SCD ear as a SF ear. The reason for this error is that the WAI measurements in this particular ear did not have characteristic SCD or SF patterns—there was increased absorbance across all frequencies below 2 kHz; there may have been an air-leak when fitting the probe into the ear canal as indicated by the increased absorbance at 400 Hz due to the increased impedance phase below 400 Hz (Figure 4.5, Panel B). Both models produced large errors when fit to this patient's measurements and neither model accurately captured the atypical WAI patterns. Perhaps it would be better to have the model classifier identify “neither case” if the errors are over a certain amount for both model fits.

Lastly, a normal-ear model and SCD model were fit to 8 individual SCD ears. The error was similar but generally smaller for the SCD model, except for one ear where both the SCD and normal-ear models generated the same WAI results (Figure 4.5, Panel C). The next chapter (Chapter 5) aims to improve classification between normal and SCD ears, where we utilize a Random Forest classifier to classify a larger database of normal and SCD ears.

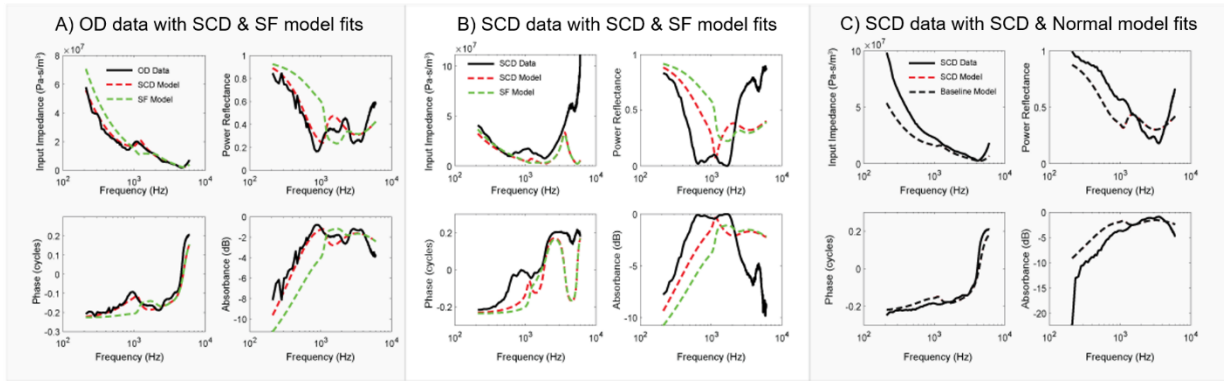


Figure 4.5: Examples of incorrect model fits to data. A) OD and SF model fits to WAI of an ear with SCD. The classifier incorrectly selected OD. B) SCD and SF model fits to WAI of an ear with SCD. The classifier incorrectly selected SF. C) Normal-ear and SCD model fits to WAI of an ear with SCD. The decision tree classifier incorrectly selected Normal for this ear.

5. Conclusion

The goal of this study was to automate the classification of mechanical middle ear and inner pathologies that are commonly misdiagnosed in the clinic. By combining audiometric threshold information and structure-based model fitting to WAI data, mechanical pathologies such as SF, OD and SCD were successfully identified more than 90% of the time. This approach can be extended to include other abnormalities of the ear such as malleus fixation, TM perforation, and middle ear effusion. Here, we chose to differentiate three mechanical pathologies that were difficult to diagnose in the clinic because 1) the auditory symptoms can be similar across these pathologies, 2) clinical otoscopy shows normal middle ear and tympanic membrane, and 3) CT scans cannot always detect very small lesions such as a fracture of an ossicle or a small SCD. To

prevent error, it is important to keep these factors in mind when collecting WAI data. Here, we fit specific model parameters linked to pathology to individual ears instead of to an average of ears. Fits to individual WAI data allows for models to simulate specific resonances at particular frequencies. Here we show that we can differentiate pathologies by simply comparing the errors between the pathological models and the actual data. The SCD and OD models are successful in simulating the modified middle ear resonance whereas the SF model simulates increased stiffness of the middle ear system. Using a structure-based modeling approach allows us to manipulate the model by changing just a few parameters that are anatomically relevant in the pathology.

CHAPTER 5. Machine learning techniques to detect superior canal dehiscence

Abstract

Objective: Superior canal dehiscence (SCD), an acousto-mechanical lesion is often initially misdiagnosed. Wideband acoustic immittance (WAI) measures the mechanics of the ear and differs between SCD and Normal ears. The main goals of this study are to 1) develop a machine learning algorithm based on WAI measurements that accurately distinguishes SCD from Normal ears and 2) evaluate the accuracy of this classification.

Methods & Results: Power reflectance was calculated from WAI measurements in 85 symptomatic SCD ears that showed a frank dehiscence by high-resolution computed tomography (CT), and 69 Normal ears. A previously developed algorithm that detects a narrow-band decrease in power reflectance (notch detector) for SCD (Merchant et al., *Otology and Neurotology*, 2015) was tested on the whole dataset—this classifier produced an area under the Receiver Operating Characteristic (ROC) curve of 0.72 and an accuracy rate of 72%. In an attempt to improve on this result, we developed an algorithm that utilizes more information from WAI measurements and new classification techniques.

We used modern machine learning techniques to develop a novel diagnostic procedure from power reflectance. Multiple classification models were first trained and optimized with a “cross-validation” dataset. We used a 10-fold cross validation procedure for training and validation. We found that important features to train the algorithm were the responses at three frequencies over a wide bandwidth between 700 Hz – 5000 Hz. We also used parameters extracted from the previously developed classifier (notch detector) as features in our analysis. Our results show that using a repeated 10-fold cross-validation procedure, a Random Forest classifier produced the best results.

We then evaluated the optimized classification methods on a separate test dataset. The average sensitivity and specificity of the RF classifier on several test sets were 0.91 and 0.87, respectively. The average accuracy was 0.88.

Conclusion: WAI shows promise as a diagnostic detector for SCD if appropriate analyses and classification methods are used. These methods have diagnostic potential for detecting SCD as well as other mechanical pathologies, especially when the WAI features are altered by pathology, such as in otosclerosis and ossicular disarticulation.

1. Introduction

Wideband acoustic immittance (WAI) measurements have been widely studied as a tool to differentially diagnose macro-mechanical pathologies of the ear in infants, children and adults (Nakajima 2012, 2013, Keefe et al., 2017, Sanford and Brockett., 2014, Merchant et al., 2015, Merchant et al., 2019, Feeney et al., 2003). This non-invasive, ear-canal measurement of the mobility of the tympanic membrane (TM) assesses middle-ear function. The term “immittance” encompasses several acoustic measures of TM mobility such as impedance, admittance, pressure reflectance and power absorbance where each measure is related to one another (see John J Rosowski, Stenfelt, and Lilly 2013 for review). Pressure reflectance (R), a measure derived from WAI, is defined as the ratio of the reverse sound pressure wave that originates at the TM to the forward pressure wave, and the square magnitude of R is known as power reflectance (PR). PR (or its complement—absorbance) has been widely studied as a potential diagnostic tool in live humans because it is relatively insensitive to the probe position in the ear canal, whereas acoustic impedance and its inverse, admittance, are sensitive to the probe’s location (Stinson, 1990; Voss et al., 2008). Moreover, PR values are easy to interpret: a PR value of 1 indicates that all power

is reflected by the tympanic membrane (representing a very stiff middle-ear system), and 0 indicates that all power is absorbed (representing a matched middle-ear impedance).

While mechanical lesions of the middle ear such as otitis media, otosclerosis and ossicular discontinuity have been previously studied and characterized by WAI (Ellison et al., 2012; Hunter, Bagger-Sjöbäck, & Lundberg, 2008; Keefe et al., 2017; Masud et al., 2019; Shahnaz et al., 2009; Voss et al., 2012), our understanding of inner ear lesions and their effects on WAI measures are less known. Recently, we discovered a characteristic pattern in PR in both fresh human cadaveric temporal bones and live humans with an inner ear lesion known as superior semicircular canal dehiscence (SCD) (Masud et al. 2018; Merchant et al. 2019). SCD is a mechanical disorder where an opening of the bony wall of the superior semicircular canal changes sound transmission within the inner ear and can produce debilitating auditory and/or vestibular symptoms such as hearing loss, autophony, hyperacusis, sound-induced and pressure-induced vertigo, and imbalance (Mikulec, Poe, & McKenna, 2005; Niesten et al., 2014; Ward et al., 2017; Zhou, Gopen, & Poe, 2007).

Clinicians have difficulty diagnosing SCD because its symptoms are similar to other pathologies (e.g. eustachian tube dysfunction, otosclerosis, Meniere's disease). To further complicate diagnosis, symptoms across SCD patients vary considerably (Merchant et al., 2007; Ward et al., 2017; Zhou et al., 2007). Currently in the clinic, an SCD is generally confirmed through computerized tomography (CT) imaging, a diagnostic that is not typically performed on patients presenting with conductive hearing loss due to cost and radiation exposure. Pure-tone audiometry and cervical vestibular evoked myogenic potentials (cVEMP) are useful diagnostic tests if SCD is suspected, but results of these measures are not consistent across patients with SCD and institutions (see Chapter 7). WAI, a simple objective measure of mechanics, shows

promise in detecting SCD early in the diagnostic work-up thereby preventing misdiagnosis and avoiding wrong and unnecessary treatment.

The first study to explore the potential of WAI to detect SCD was published in 2015 by Merchant and colleagues. In several SCD patients, Merchant et al. found a distinct narrow-band decrease (a notch) in PR at around 1 kHz. They used this characteristic notch as a method to differentiate normal hearing subjects from patients with SCD. The notch-detecting algorithm is a promising screening procedure for SCD with high sensitivity (80-93%) but moderate specificity (69-72%; Merchant et al. 2015) that can help determine whether imaging is warranted. However, the moderate specificity of the algorithm limits its use as a complete diagnostic tool.

In this current study, we determine if the notch-detecting algorithm of Merchant et al. (2015) produces similar results in a larger cohort of SCD subjects. Additionally, we use modern pattern recognition tools to improve diagnosis. For example, we determine critical markers for SCD from power reflectance information over a wide range of frequencies. By using partial least squares discriminant analysis to select important features, and a Random Forest classifier to categorize Normal and SCD ears, we develop a systematic method to improve classification accuracy for future larger sample sizes. The application of pattern recognition methods to WAI can potentially automate detection of SCD and other acoustic-mechanical lesions of the middle and inner ear.

2. Methods

Subjects

Superior Canal Dehiscence Group:

We prospectively collected WAI data from 85 patients with SCD that met the following inclusion criteria: 1) a visible SCD on CT scan, 2) absence of any middle ear pathology such as otitis media or tympanic membrane lesions, 3) no prior history of ear surgery, 4) normal 226 Hz tympanometry, and 5) absence of an ear-canal sound leak in WAI measurements. Additionally, these patients underwent audiometry and cVEMP.

Normal Group:

For the normal group of ears, WAI measurements of 58 normal hearing subjects were obtained from Rosowski et al. (2012) as well as 12 additional normal ears from patients with unilateral SCD. In these 12 ears, we confirmed by CT scan that there was bone overlying the superior semicircular canal (no evidence of thinning or dehiscence). These ears met the criteria defined in Rosowski et al. (2012). The criteria is as follows: 1) No history of significant middle-ear disease, 2) no history of otologic surgery, 3) normal tympanic membrane (TM) on otoscopy, 4) pure-tone audiometric thresholds of 20 dB HL or better for 0.25 – 8 kHz, 5) air-bone gaps (ABG) no greater than 15 dB at 0.25 kHz and 10 dB for 0.5 – 4 kHz and (6) normal, type-A peaked tympanograms. A total of 69 ears were used in this study where we excluded ears due to a sound leak in WAI measurements.

Wideband Acoustic Immittance

WAI was measured with an FDA-approved Mimosa Acoustics HearID system (Champaign, IL USA). A foam tip with inner tubing coupled to the sound source and microphone was inserted into the sealed ear canal. A broadband (210 Hz - 6000 Hz) chirp stimulus of 60 dB SPL was presented at 24 Hz intervals for the duration of 3 seconds. WAI was recorded with an Etymotic ER-10C microphone. Ear-canal Pressure Reflectance (R) as well as impedance (or admittance) magnitude and phase measurement were analyzed. Pressure reflectance is the complex ratio of the reflected sound pressure to the forward sound pressure (which includes all of the secondary reflections from the plane of the probe). PR, the focus of this study, is the square magnitude of the ear-canal reflectance. Post-processing of data was done in MATLAB.

Sound-Leak Detection

The presence of an sound-leak due to incorrect insertion of the foam ear tip was determined using methods similar to Groon et al. (2015). In our study, a sound-leak was defined as an average admittance phase between 200 and 500 Hz that was less than or equal to 50 degrees. The 50 degrees threshold was selected because there is a clear separation between ears with admittance phase below 50 degrees, which we suspected may have a leak, and ears with low-frequency admittance phase that ranged between 65 to 90 degrees (Figure 5.1).

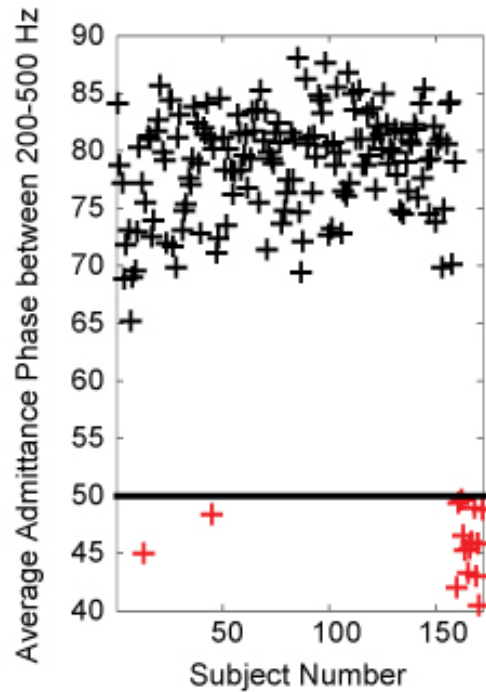


Figure 5.1: Detecting a sound-leak. An average admittance phase between 200-500 Hz of below 50 degrees was an indicator of a leak. Each of the red markers represents a subject that may not have had a complete seal of the ear tip thus producing an air-leak capable of affecting ear-canal measurements.

Audiometry and Tympanometry

All subjects underwent an audiogram as well as 226 Hz tympanometry by an audiologist. The audiogram included air- and bone-conduction thresholds. Bone-conduction thresholds were masked if the difference between air- and unmasked bone-conduction thresholds exceeded 10 dB HL. Because an ABG at low frequencies (i.e. at 250 Hz) is commonly observed in patients with SCD, ABGs were calculated at 250 Hz for both normal and SCD subjects. We only included ears with normal tympanograms because WAI are sensitive to abnormal tympanic membrane mechanics.

Notch Detection Algorithm

G. R. Merchant, et al. (2015) described a simple algorithm to detect SCD by finding a characteristic decrease (notch) in the difference between the power reflectance (PR) measured in each patient and the average PR in normal ears. The presence of a notch indicated the ear had SCD, whereas the absence of a notch indicated a normal ear. The notch-detection algorithm relied on three variables: the notch depth, notch size, and the notch frequency range (described in Figure 5.2). These three variables were optimized in order to improve detection of SCD. The minimum PR notch size for detecting a notch was 0.05, the minimum notch depth was 0.097, and the frequency range to detect a notch was between 550 Hz and 1845 Hz. For a more detailed description of these variables, see Merchant et al., 2015. In the current study, we use the presence of a notch, its frequency, size and notch as features or input variables for the machine learning classifier.

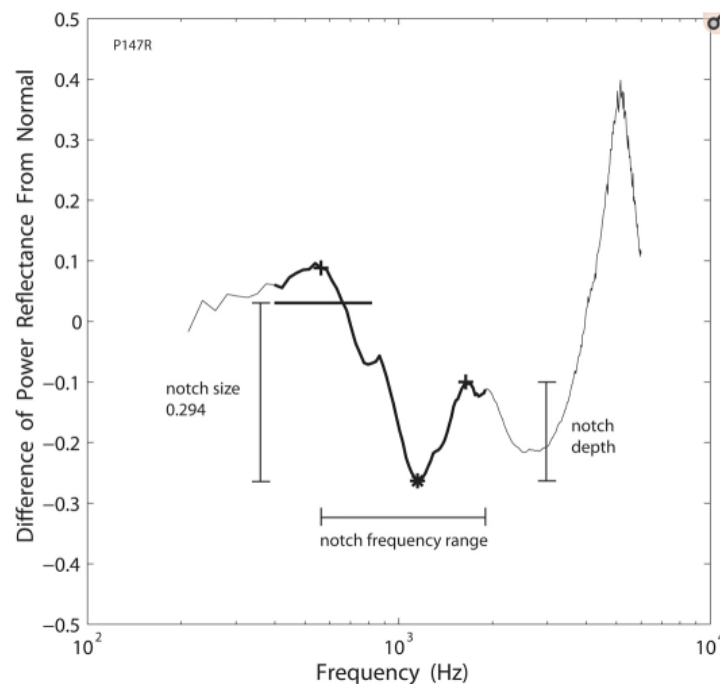


Figure 5.2: Figure from Merchant et al., 2015 illustrating notch frequency range, notch size and notch depth. These features are derived from the difference in PR between an individual SCD ear and normal mean.

Classification Method

The large dataset containing 85 SCD ears and 69 Normal ears was randomly split into two datasets: one to train the classifier, and another to test the classifier. We split the entire dataset, which contained both types of ears. Eighty percent of the data was used to train the predictive model (cross-validation set), and 20% of the data was used to test the model (test set). See Figure 5.3 for an illustrative summary of the classification procedure. The caret package in the R programming language, which provides a set of functions to streamline the process of designing predictive models for classification and regression problems, was used for 1) feature selection, 2) splitting the dataset (80/20), 3) classifier tuning, 4) classifier selection, and 5) classifier validation.

Missing data were replaced by using the k-nearest neighbor, where the weighted average of the values of the neighbors replaced the missing values. The only input variable with missing data was air-bone gap information at 250 Hz where 9 out of 85 SCD patients did not have air-bone gap information at 250 Hz. The weights are the exponential of the Euclidean distance between the missing case and the neighbor, k . The total number of neighbors was selected to be 3. This imputation was performed by using the DMwR package in the R language. The DMwR package consists of a set of functions found in the book Data Mining with R, learning with case studies (Torgo, 2017).

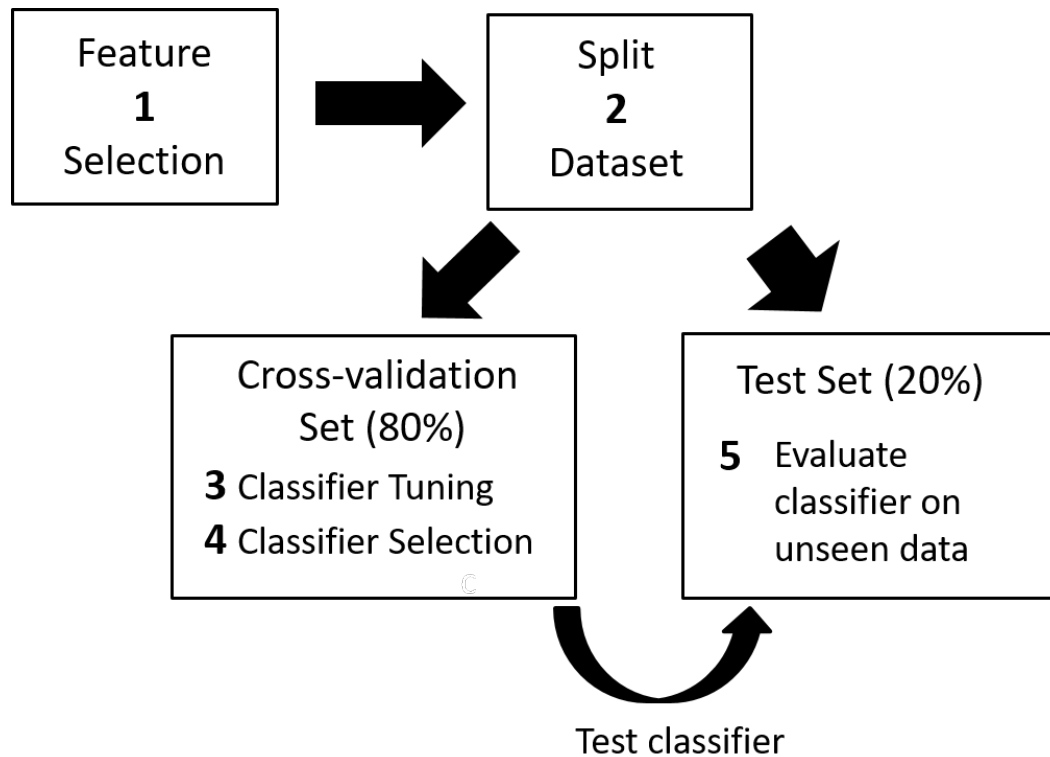


Figure 5.3: Classification Procedure

Dimension Reduction and Feature Selection:

Each WAI measurement consisted of a total of 248 frequency points. To determine which frequencies were important features in distinguishing SCD from Normal, the number of frequency points were reduced to 15 by calculating the average across every one-third octave band. Dimension reduction is necessary in this case because the number of features should be less than the number of samples (i.e. number of individuals with WAI measurements) for the classifier to work effectively. Partial least squares discriminant analysis (PLS-DA) was used to further reduce the number of features. PLS-DA is a dimensionality reduction method commonly used in classification or when the response variable is categorical (Y. Liu & Rayens, 2007; Rosipal & Krämer, 2006). PLS-DA takes into account the two classes (SCD and Normal) and reduces the dimension of the feature matrix while maximizing the separation of classes. PLS-DA

was used to determine which of the 15 frequency bands were important to classify SCD and Normal ears. For this step, the entire dataset was used, and a repeated cross-validation method was implemented where 5 repeats of a 10-fold cross-validation procedure was used. Other features that were selected were notch size and notch depth determined by the notch-detection algorithm

Classifier Selection:

Using the caret package in R, the ROC values (or area under the Response Operator Curves) of five binary classifiers were compared to determine how best to detect SCD. Random Forest, Logistic Regression, Naïve Bayes', PLS-DA and K-nearest Neighbors classifiers were trained. All models were trained with the larger cross-validation data set. The features (or predictor variables) in the cross-validation set were centered (mean subtracted from each value) and scaled (values divided by the standard deviation). The predictive models were tuned and evaluated using 5 repeats of 10-fold cross-validation to reduce over-fitting on the cross-validation dataset. This allowed a comparison of ROC value distributions (50 values) between the models, where for each iteration, the model was trained and tuned using the training set, and predictions were made on a validation set (unseen data that was not used to train the model). This dataset was used to calculate the ROC value of all predictive models.

Algorithm Tuning:

After evaluating various classifiers, we tuned the parameters of the best performing model: Random Forest (RF). First described by Breiman (2001), RF is an ensemble algorithm that takes a subset of features (PR at critical WAI frequencies, ABG at 250 Hz, notch size, and notch

depth) and a subset of observations (SCD or Normal) to construct decision trees. Multiple decision trees are combined to get a more accurate and consistent prediction. Majority voting or an average of predictions from multiple decision trees are used to classify each patient. For example, if three out of four decision trees predict SCD for a single patient, the patient would be classified as SCD. Here, variables that were tuned to improve the ROC of the classifier were 1) the number of decision trees to construct before evaluating the maximum voting value, and 2) the maximum number of randomly selected features the RF model is allowed to use in an individual tree.

Model Performance

A nested cross-validation approach was applied in order to simultaneously perform model tuning and model evaluation of the RF classifier. The steps in a nested cross-validation are: 1) split the data into a cross-validation and test set, 2) optimize model parameters using cross-validation (10-fold, 5 repeats) on the cross-validation data set but not the test set, 3) select the best model parameters based on which produced the highest ROC value, and 4) test the performance of the optimized model on the test set. These steps were repeated 25 times to find the average sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the RF classifier.

3. Results

Results:

Subject groups:

Superior Canal Dehiscence Group:

From our large database of SCD patients, we determined 85 ears (41 females and 38 males) SCD that met our inclusion criteria: 1) a visible SCD on CT scan (greater than 1.9 mm in size), 2)

absence of any middle ear pathology such as otitis media or tympanic membrane lesions, 3) no prior history of ear surgery, 4) normal 226 Hz tympanometry and 5) an absence of a measurable air-leak in ear-canal WAI measurements. The age range of SCD patients were 17 to 70 years, with an average age of 49.5 years (± 10.4).

Normal Hearing Group:

Wideband acoustic immittance measurements of 55 ears from normal hearing subjects were acquired from Rosowski et al., 2012. These normal ears were from 28 different patients, 12 males and 16 females with age ranging from 22-64 years with a mean age of 33 years. An additional 14 ears (of the unaffected side of unilateral SCD patients which were confirmed normal via CT and audiograms) with a mean age of 47.3 ± 10.0 (range 29-67) years (9 female, 5 male) were included. A total number of 69 normal ears were used in this study.

Notch-detection algorithm:

The simple algorithm designed by Merchant et al. (2015) was used to classify our cohort of 85 SCD ears and 69 Normal ears. This cohort of patients was larger than that used in Merchant et al. (2015) (40 SCD ears and 58 normal hearing ears). The notch-detection algorithm on our cohort resulted in classification accuracy of 71%. The sensitivity was 0.765 and the specificity was 0.643. Classification of predictions by the notch-detection test produced an area under the Receiver Operating Curve (ROC) of 0.704. The negative predictive value and positive predictive value were 0.692 and 0.722, respectively.

Classification:

Feature Selection

Using partial least squares discriminant analysis, the most important frequencies of PR values measured were determined and selected as features in the classification analysis. Out of the 15 frequency bands (averaged across every 1/3 octave band), three most important frequencies were 790 Hz, 1000 Hz and 5070 Hz. (Figure 5.4). These three features had an importance factor greater than 80%. In addition to PR values at these three frequencies, the air-bone gap (ABG) at 250 Hz, and the notch size and notch depth computed from Merchant and colleagues' notch-detection algorithm were included as features.

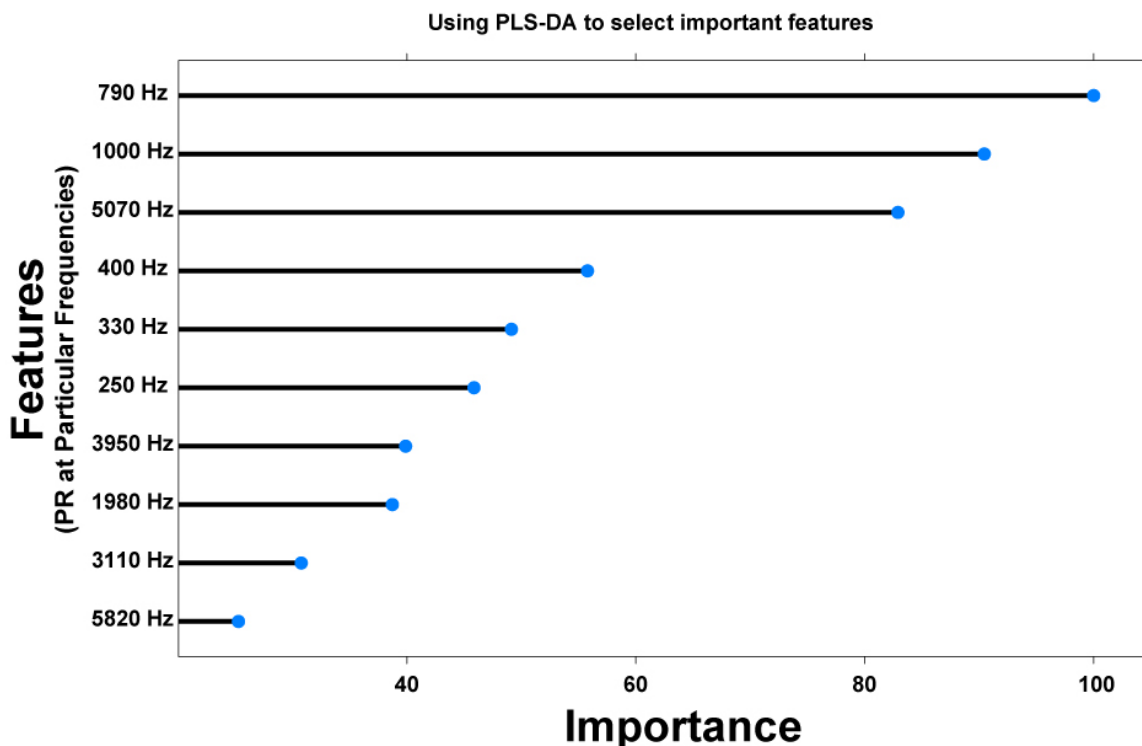


Figure 5.4: Partial least squares discriminant analysis determines which frequencies (averaged across 1/3 octave bands) are important in differentiating SCD ears from Normal ears.

Classifier Selection

Five potential classification models were assessed and compared. The area under the ROC curve was the main metric used to evaluate the classification models (built with the cross-validation data $n = 124$). The trained predictive model that produced the highest average ROC value was

the RF classifier (0.943), followed by the logistic regression classifier (0.933). The average ROC values for K-Nearest Neighbors, PLS-DA and Naïve Bayes were 0.897, 0.923, and 0.921 respectively (Figure 5.5). Although RF and Logistic Regression models performed similarly on the cross-validation set, we selected the RF classifier because it consistently produced the highest average ROC value on the cross-validation set with different splits of the data (i.e. data randomly split into cross-validation and test sets by selecting different random seeds in R).

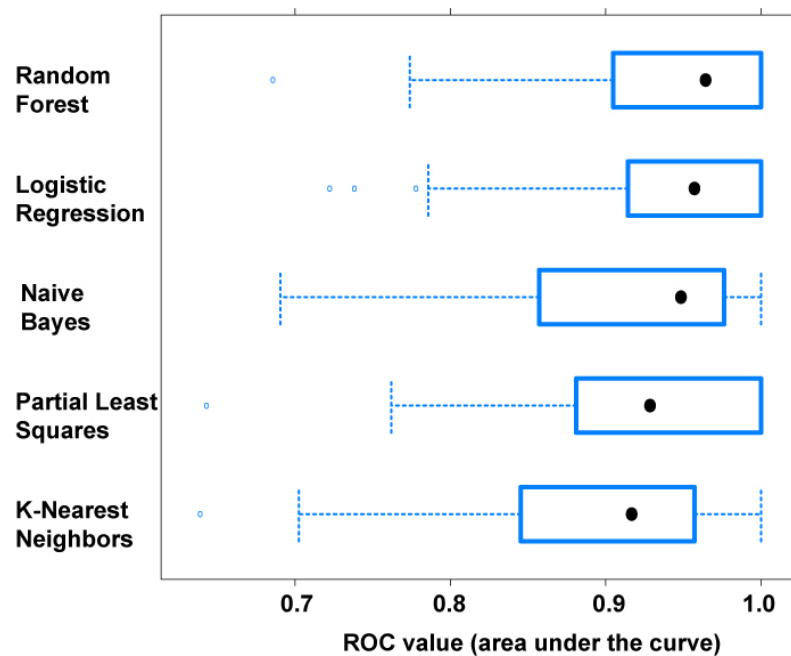


Figure 5.5: Area under the ROC curve values for 5 different classification models in order of highest average ROC value Random Forest, Logistic Regression, Naïve Bayes, Partial Least Squares discriminant analysis, and K-nearest neighbors.

Algorithm Tuning and Model Validation:

The RF classifier was tuned to improve model results. The two parameters that were optimized for the RF classifier was the total number of decision trees and the maximum number of randomly selected features for an individual tree. These parameters were selected based on which produced the highest ROC value. An example of parameter tuning is shown in Figure 5.6,

where for a particular RF classifier, the highest ROC value was obtained when the total number of decision trees was 2500 and the maximum number of randomly selected features used in an individual tree was 3. Although the ROC values were very close for each of the tested total number of decision trees (500, 1000, 1500, 2000, and 2500), the caret package in R (see Methods) automatically selects the number of decision trees based on the highest average ROC value calculated from the cross-validation set.

After training a RF model with tuned parameters (trees = 2500, randomly selected features or predictors for each tree = 3), we tested the model on our test set (unseen data of $n=31$). To ensure a robust and reproducible estimate of generalization performance, the tuning step (Step 3 in Diagram) and model evaluation step (Step 5 in Diagram) was repeated 25 times on different cross-validation and test sets. This is known as a nested-cross validation procedure as described earlier in the methods.

Nested cross-validation was implemented to simultaneously tune the model and estimate performance. At each iteration the model parameters may differ. We evaluated the RF model on 25 different test sets (unseen data). Figure 5.7 shows that the average sensitivity across these test sets was 0.91 and the specificity was 0.87. The average positive predictive value was 0.85 and the average negative predictive value was 0.93. Table 5.1 gives a summary of model performance on unseen data.

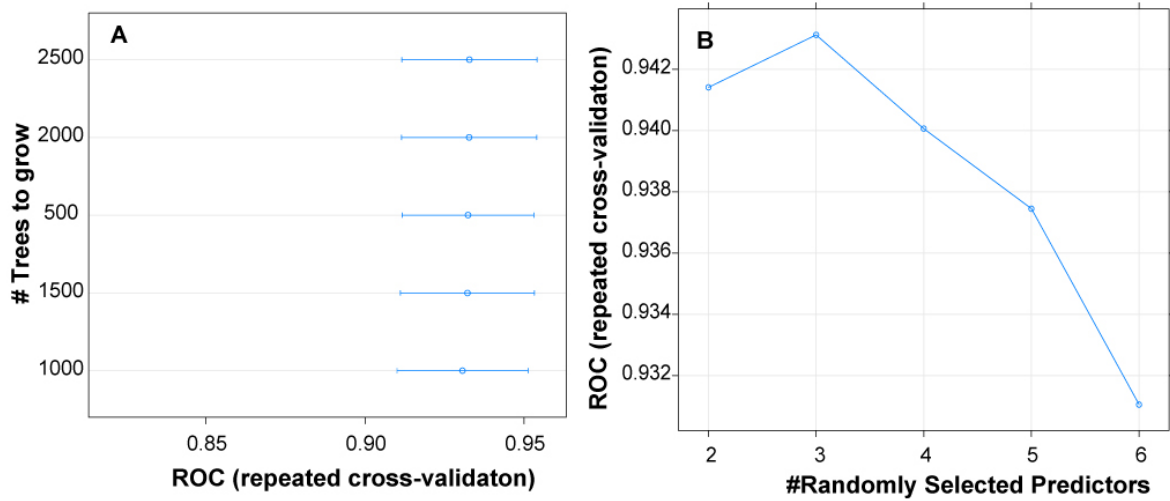


Figure 5.6: Model tuning results. A) Number of trees to grow as a function of ROC value. Error bars represent 95% confidence interval. For this particular iteration, 2500 trees produced the highest average ROC value. B) ROC values as a function of the number of randomly selected predictors. Three randomly selected predictors sampled as candidates at each split produced the highest ROC value. The caret package in R was used to tune these two RF parameters.

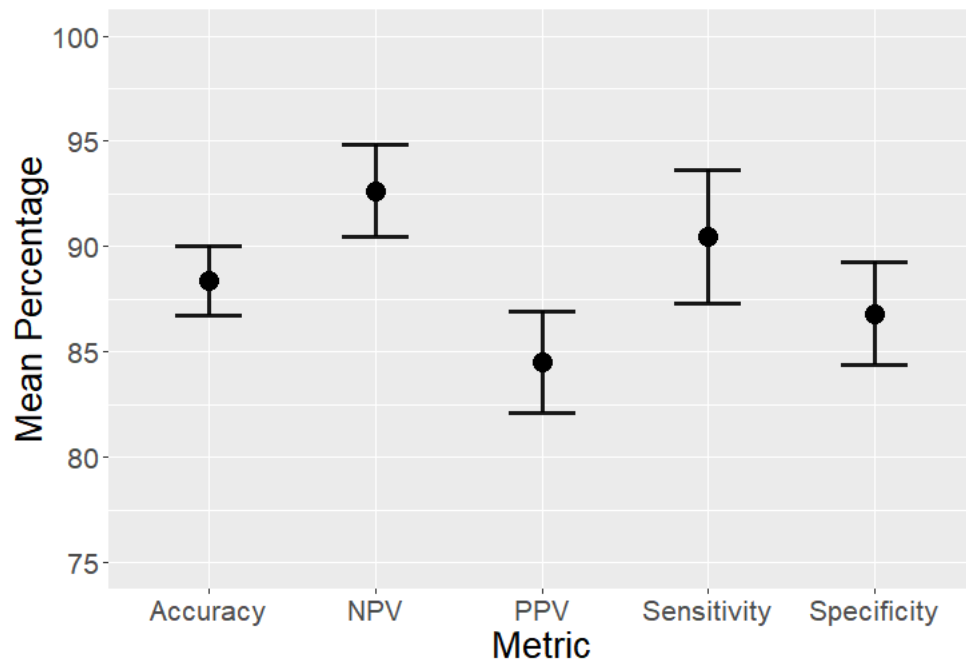


Figure 5.7: Metric mean values of 25 different test sets. Metrics to evaluate the RF classifier include accuracy, negative predictive value (NPV), positive predictive value (PPV), sensitivity and specificity.

Table 5.1: Metric statistics for RF model evaluation on 25 test sets

	Average	95% CI	Minimum	Maximum
Accuracy	0.88	0.87 – 0.90	0.80	0.97
NPV	0.93	0.91 - 0.94	0.80	1
PPV	0.85	0.82 – 0.87	0.73	0.93
Sensitivity	0.91	0.87 - 0.94	0.77	1
Specificity	0.87	0.84 – 0.89	0.69	0.94

4. Discussion

In this study, we aimed to improve a simple notch-detection algorithm designed by Merchant et al. (2015), by incorporating common pattern recognition methods. When we only used the notch-detection algorithm of Merchant et al. (2015) on our dataset of 85 SCD ears and 69 Normal ears (larger set than used by Merchant et al.), the sensitivity and specificity of the classifier was 0.765 and 0.643. Whereas previously, Merchant et al. (2015) reported sensitivity and specificity values of 0.93 and 0.69, respectively. The sensitivity of the classifier dropped by approximately 18% with new unseen PR data from SCD patients. The specificity of the classifier was similar, as we used a similar population of Normal ears from the Merchant et al. paper.

To improve upon the earlier notch detection algorithm, we used parameter values generated by the algorithm as features (input variables) in our predictive models. The following parameter values were computed for each subject: notch size, and notch depth. Next, we included the ABG measure at 250 Hz for each patient. As compared to Normal ears, SCD ears exhibit low frequency ABG, where supra-threshold bone-conduction and higher than average air-conduction thresholds occur at low frequencies range (Y. Song Cheng et al., *in press*).

To determine whether PR values at other frequencies (outside of the notch frequency range in the notch-detection algorithm) were important in differentiating SCD and Normal ears,

we used PLS-DA analysis. The number of frequency points in our raw dataset was 248 points. Generally, classification is more efficient when the number of samples is much greater than the number of features. However, our number of samples ($n = 154$), was far less than the number of features ($p = 248$), so we used a dimension reduction procedure to reduce covariate dimensions and select critical features. The first step we took to reduce the number of frequency points was taking the average PR value across each one-third octave band. This reduced the number of frequency points from 248 to 15. Next, by using PLS-DA, we aimed to reduce the number of 15 features by selecting the three most important variables that separated SCD from Normal ears. Like principal components analysis for regression problems, PLS-DA is a popular method for dimension reduction for classification (Fort and Lambert-Lacroix, 2005; Ruiz-Perez and Narasimhan, 2017), when the response variable is categorical. With PLS-DA, we determined that there were two frequency regions that may play an important role in differentiating SCD and Normal ears. The discriminant analysis showed that important features that differentiated SCD and Normal ears were at around 800 Hz – 1000 Hz (within frequency range used by Merchant et al. (2015) notch detector, as well as 5000 Hz. The variable importance plot showed that PR values at 790 Hz, 1000 Hz and 5070 Hz were ranked the top 3 features, where the importance of these 3 features were similar (over 80%; See Figure 5.4). PR values computed at the other frequency bands were less important and thus not incorporated (below 60%) into our model.

After selecting important features, we trained several classification models to determine which would be best as a diagnostic test. Classifiers such as RF, Logistic Regression, and K-nearest neighbors are common classification algorithms used in medical diagnosis. Here, we used Receiver Operating Characteristic (ROC) values (area under the ROC curve) to determine the tradeoffs between sensitivity and specificity in each binary classifier. By optimizing ROC

values, we tuned classifier parameters (i.e. number of trees to grow for RF) to improve classification. In this study, we proposed that by recognizing critical features that can differentiate SCD and Normal ears, and optimizing binary classifiers, we could develop a robust method to improve classification for future larger datasets. This may allow us in the future to develop a stand-alone device with only wideband acoustic immittance information and no other data (i.e. air-bone gap, cVEMP) to accurately predict SCD.

The RF classifier performed the best in separating SCD and Normal ears. The RF classifier was selected because of its consistent performance and its simplicity. Generally, decision trees answer questions in succession which sends us down a particular path down a tree given the answer (i.e. SCD or Normal ear). The depth of the tree represents how many conditional questions are asked before we reach our predicted class. In medical diagnosis, decision trees could be used to pick out important patterns in the data that separates the two groups. RF is an ensemble learning method that reduces the chance of over-fitting (minimize error due to variance) by constructing several decision trees at training time and selecting the class that is the mode of the classes of individual trees. It is a powerful method in medical diagnosis because it is easy to interpret and visualize. This method improves upon the over-fitting problem of a single decision tree used in Merchant et al (2015).

After training the RF classifier with the cross-validation dataset, we evaluate the performance of the model on unseen data, which is known as our test set. To determine repeatability of the test results, we performed a nested cross-validation to simultaneously tune the parameters and evaluate the tuned model on unseen data. Metrics such as accuracy, sensitivity and specificity were evaluated on 25 different test sets. The RF classifier predicted SCD or Normal with 88% accuracy on the test sets. The average sensitivity and specificity

values calculated on the test set were high—91% and 87%. Because we had a disproportionate number of subjects (more SCD ears than Normal ears) and were interested in boosting the diagnostic ability of the classifier, we aimed to maximize the ROC value (area under the ROC curve) rather than the accuracy value. Overall, if the entire data set ($n = 154$; combining cross-validation and test sets) is classified through a tuned RF algorithm, the sensitivity and specificity increased to 0.98 and 0.96. The accuracy of classifying SCD and Normal for the entire set was 98% (95% CI: 0.943 to 0.996). These values are much greater than the test set results, which suggests that it is important to set aside data to accurately test your trained classifier. These high sensitivity and specificity results show great promise in using a RF learning algorithm to detect SCD with wideband acoustic immittance data.

As we collect more data, we can improve our classifier and work towards WAI as a stand-alone measurement to detect SCD from Normal, as well as from other pathologies. Sharing data with other institutions would be helpful to gain more data. Already, Susan Voss and colleagues host an online database for the WAI measurements made on Normal ears of adult ages above 18 and above (<http://www.science.smith.edu/wai-database/home/about/>). In the future, using this database as well as more data from ears with mechanical pathologies (i.e. otosclerosis, ossicular disarticulation, SCD), will allow for improved development of powerful machine learning methods. Another method to improve classification accuracy would be to add various audiometric results (e.g. stapedial reflex, cVEMP thresholds) as features. Currently in the clinic, it is difficult to retrieve a complete diagnostic work-up from all patients; such as air-bone gap, acoustic reflex, tympanometry, and VEMP measurements. Lack of information likely contributes to misdiagnosis of SCD. WAI measurements could be performed with standard

audiometric tests, improving on diagnostic accuracy, especially at the early stages of diagnostic work-up, to enable clinicians to suspect SCD as a differential.

A mechanical measure is powerful because it has the potential to differentiate mechanical pathologies of the middle and inner ear that are misdiagnosed in the clinic. Modern machine learning tools, as used in this study, show great promise in detecting useful patterns in WAI that could improve classification performance. With more WAI data, we can develop better classifiers. Also, by using acoustic modeling techniques (described in Chapters 3), we can better understand the underlying mechanisms of the pathologies. In the future this computational modeling technique described in Chapter 3 could be combined with the machine-learning technique describe here. Incorporating machine-learning techniques to a diagnostic algorithm can improve clinical care by preventing misdiagnoses and inappropriate treatments.

**CHAPTER 6. The Effect of Middle Ear Cavity and Superior Canal Dehiscence on
Wideband Acoustic Immittance in Fresh Human Cadaveric Specimens**

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ABSTRACT

Superior canal dehiscence (SCD) is a hole in the bony wall of the superior semicircular canal, which can cause various auditory and/or vestibular symptoms and can result in wrong and/or delayed diagnosis. Wideband acoustic immittance (WAI) can potentially distinguish various mechanical middle-ear pathologies as well as inner-ear pathologies non-invasively. We found that in patients, SCD was commonly associated with a narrow-band decrease in power reflectance (PR, derived from WAI) near 1 kHz. Because clinical data has large variation across individual ears and because we do not know the individual “normal” state prior to SCD, we measured WAI in five fresh temporal bone specimens to determine the effects of SCD with respect to the normal state. In temporal bone, we measured PR to assess mechanical changes before and after SCD, as well as to assess the effect of an open or closed middle-ear cavity. After SCD, PR had a consistent decrease between 0.48 and 0.76 kHz, and a slight increase between 1.04 and 1.4 kHz in the open cavity condition. However, in several experiments, we observed low PR around 1 kHz in the normal state before SCD, likely due to the specimen’s open middle ear cavity (MEC). Because we see effects of both SCD and open MEC around 1 kHz, some of the SCD effect can be masked by the effect of the MEC in the temporal bone specimens. To compensate for this MEC effect, we estimated the effect of

SCD in a closed MEC case, but the effect did not differ significantly from the measured open MEC. This study demonstrates the limitation of temporal bone experiments with open MEC when studying inner-ear lesions with WAI.

1. Introduction

Superior canal dehiscence (SCD), a hole in the bony structure of the superior semicircular canal, currently affects 0.5-0.6% of American adults (J P Carey et al., 2000). Clinicians face several challenges in diagnosing SCD because its symptoms are similar to other conductive pathologies, and to further complicate diagnosis, symptoms across SCD patients vary considerably. Currently in the clinic, an SCD is only confirmed after a computerized tomography (CT) scan, a diagnostic that is not often performed on patients with conductive hearing loss owing to cost and radiation risk. Audiograms and vestibular evoked myogenic potentials (VEMP) are useful diagnostic tests if SCD is suspected but these measures are not consistent across patients with SCD. There is a clear need for an *objective* non-invasive measure of mechanical dynamics to effectively detect SCD, a mechanical lesion in the inner-ear, to prevent misdiagnosis and avoid wrong and unnecessary treatment.

Non-invasive mechano-acoustic measurements recorded at the ear canal show great promise for diagnosis. Previous studies have shown that wideband acoustic immittance (WAI), in conjunction with audiometric data, can differentiate among middle-ear lesions (e.g. ossicular fixation and disarticulation) and inner-ear lesions (e.g. SCD) (Hideko Heidi Nakajima et al., 2012b; Hideko Heidi Nakajima, Rosowski, Shahnaz, & Voss, 2013b). WAI recordings stimulates the ear with wideband sound and measures how much sound energy is reflected by the eardrum. Though there has been some research advancements enabling the diagnosis of pediatric

pathologies such as eardrum perforation and middle-ear effusion with WAI (Holte, Margolish, & Cavanaugh, 1991; D H Keefe et al., 1993), the use of WAI for diagnosis of SCD and other macro-mechanical pathologies with normal otologic exams still needs clarification.

In this study, we use fresh cadaveric human temporal bones to assess the effect of SCD on power reflectance (PR, a derivative of WAI). PR is the square of the magnitude of the ratio between the sound pressure reflected at the eardrum to the forward sound pressure. Unlike the input impedance at the eardrum, PR is less sensitive to probe placement and the length of the residual ear canal (Susan E Voss, Horton, Woodbury, & Sheffield, 2008). Here, we measure PR over a wide frequency range (20 Hz to 20 kHz) to improve analysis. Neely et al. (Neely, Stenfelt, & Schairer, 2013) theorized that the time domain analysis of WAI measurements over this wide frequency range could improve diagnosis of macro-mechanical pathologies of the ear. Part of the challenge in quantifying SCD-induced effects in human temporal bones is that temporal bone experiments often require an open middle-ear cavity (MEC), and the MEC can have significant effects on PR. Here, we directly compare our experimental results in temporal bone to clinical PR data (before and after SCD surgery). We also study the effects of the middle ear cavity (MEC) on PR measurements in temporal bone, and determine the isolated effects of SCD in an estimated condition with an intact MEC.

2. Methods

2. a. Temporal Bone Preparation

Six fresh human temporal bones were prepared to study WAI measured at the ear canal at frequencies between 20 Hz to 20 kHz. An extended facial recess approach was used to access the middle ear cavity. The lateral aspect of the superior semicircular canal was exposed at the epitympanic space. Initial stapes velocity and round window velocity were measured with laser

Doppler vibrometry on each specimen in the normal state to determine whether there were any abnormal inner-ear air leaks, or middle-ear or inner-ear lesions (i.e. fixation or discontinuity). Techniques quantifying stapes and round window velocity were described previously (Hideko Heidi Nakajima, Ravicz, Merchant, Peake, & Rosowski, 2005b; Hideko Heidi Nakajima, Ravicz, Rosowski, et al., 2005). If the phase of the stapes velocity to round window velocity ratio deviated from a half cycle at low frequencies in the initial condition or after repairing the SCD, the experiment was not included in the study (Hideko Heidi Nakajima, Ravicz, Merchant, Peake, & Rosowski, 2005b). Only 6 out of 20 specimens were included in the study because several had pre-existing abnormalities or air entered the inner ear at some point during the experiment. Out of the six fresh human temporal bone experiments, five were used to study only the effect of the SCD, where four of those five were used to study the effect of the MEC (sfm016, sfm017, sfm019, sfm020), and three of the five were used to study both the effect of the MEC and the SCD (sfm017, sfm019, and sfm020).

2. b. Non-invasive Assessment of Middle-ear Function

In the current study, we analyze PR to study the effects of SCD and MEC. PR is the square of the magnitude of the ear-canal reflectance ($PR=|ECR|^2$). Ear-canal reflectance (ECR) is the complex ratio of the reflected pressure wave to forward pressure wave (which includes all of the secondary reflections from the plane of the probe) in an ear canal, and is related to the impedance measured in the ear canal (Z_{EC}) by the following equation:

$$ECR = \frac{Z_{EC} - Z_0}{Z_{EC} + Z_0} \quad (1)$$

where Z_0 is the initial characteristic impedance of the residual ear canal ($\rho_0 c/A$; ρ_0 = density of air, c = speed of sound, A = cross-sectional area of the ear canal). ECR is then transformed to the time domain, and Z_0 is re-estimated by determining the value of Z_0 that minimizes the absolute value of the time-domain reflectance (TDR) when time is 0 (Lewis & Neely, 2015; Rasetshwane & Neely, 2011). The impedance measured at the ear canal is computed from the pressure measurement in the ear canal (P_{EC}) and the Thevenin equivalent source characteristics P_{source} and Z_{source} which were computed using the calibration procedures proposed by Allen 1986 and Keefe et al., 1992 (J. B. Allen, 1986; Douglas H Keefe, Ling, & Bulen, 1992).

$$Z_{EC} = \frac{Z_{Source} P_{EC}}{P_{Source} - P_{EC}} \quad (2)$$

For our measurement, we shortened the bony ear canal to a length of 5-8 mm, and sealed a 35 mm long 8 mm diameter cylindrical brass tube at the entrance of the shortened ear-canal. Into the brass tube, we placed a foam ear tip coupled to the sound source and microphone. The acoustic length from the end of the ear tip to the umbo ranged from 29 mm to 35 mm for all experiments. The characteristic impedance in Equation 1 is estimated using the dimensions of the cylindrical brass tube. The acoustic length is estimated by determining the time at which the TDR reaches a peak (Lewis & Neely, 2015). The peak time (t_{ec}) is the time required for the stimulus to travel from the probe to the eardrum and back. The acoustic length (l_{ec}) is the product of t_{ec} and the speed of sound divided by 2 ($l_{ec} = t_{ec} * c/2$). Sound was delivered by a custom built sound source (the HARP system designed by J.H. Siegel) and the ear-canal sound pressure was measured from 0.02 to 20 kHz with an ER10B+ probe microphone tube integrated into the foam ear tip (Etymotic Research, Elk Grove Village, IL).

2. c. Temporal Bone Manipulations

PR measurements were made on each bone in a) the initial normal state with open cavity (OC), b) normal state with closed cavity (CC), c) pathological state with OC and SCD and d) reversal of SCD with OC. We placed silicone impression material (Westone Laboratories, Inc. Colorado Springs, CO) over the MEC opening to seal the MEC. To simulate SCD, we drilled a hole into the lateral wall of the superior semicircular canal. The size of the hole was approximately 1 mm long and 0.6 to 0.8 mm wide. The hole was drilled while the semicircular canal was immersed in saline to prevent air from entering into the inner ear. Reversal of SCD was accomplished by carefully covering the dehiscence with a piece of paper and then covering with Jeltrate, a dental impression material (Dentsply International, Philadelphia, PA). The paper prevented the Jeltrate from entering the lumen of the canal, and the Jeltrate hermetically sealed the SCD. After repairing the SCD, reversal of the velocity and WAI measurements ensured that the effects measured were solely due to SCD. Estimation of the input impedance (Z_{ED}) for the pathological state with closed cavity and SCD was estimated using the following formula:

$$Z_{ED}^{CC+SCD} = Z_{ED}^{OC+SCD} + Z_{ED}^{CC+normal} - Z_{ED}^{OC+normal} \quad (3)$$

The ear-canal reflectance for the estimated (CC + SCD) state was computed using Equation 1. Equation 3 is only valid if we assume that the input impedance is measured at the eardrum and does not include contributions of the residual ear-canal space. That way we can assume a series impedance middle-ear model similar to Zwislocki's model (J. J. Zwislocki, 1962), where the impedance at the eardrum, impedance of the middle-ear cavities, and the impedance of the tympanic membrane, ossicles and cochlea are all in series. We correct for the ear-canal space and

estimate the impedance at the eardrum by assuming the ear-canal is a lossless, uniform cylindrical tube (Rabinowitz, 1981; Withnell & Gowdy, 2013). Each of the experimentally measured impedances on the right side of Equation 3 is transformed to the plane of the eardrum. The equation to transform the impedance at the ear-canal (Z_{EC}) to the impedance at the eardrum (Z_{ED}) is:

$$Z_{ED} = Z_0 \left(\frac{Z_{EC} - jZ_0 \tan(kl_{ec})}{Z_0 - jZ_{EC} \tan(kl_{ec})} \right) \quad (4)$$

3 Results

3. a. Effect of Middle-Ear Cavity

Figure 6.1 shows PR measured in four ears for both the open (black solid line) and the closed (gray dotted line) cavity conditions. Each experiment shows a noticeable reduction in PR at around 1 kHz with open MEC (exposed to ambient air) as compared to closed MEC. At higher frequencies between 1.5 kHz and 3 kHz, there is a slight increase in PR with open versus closed. Figure 6.1E summarizes the difference in PR between the open and closed cavities for each experiment (colored lines) and the average across all experiments (black solid line). The summary plot shows that when the cavity is open there is a consistent decrease in PR at around 1 kHz and a slight increase in PR between 1.5 and 3 kHz. For all four experiments, the frequency range for the decrease due to the MEC lies between 0.9 kHz and 1.120 kHz.

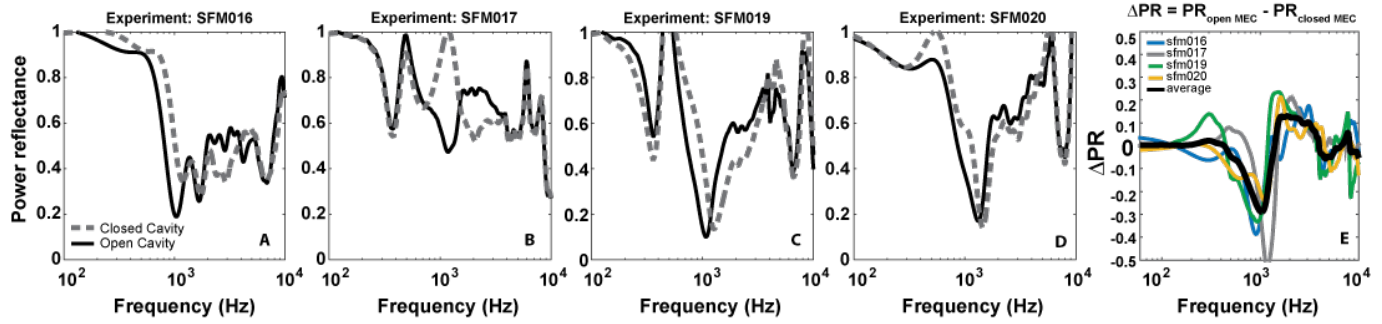


Figure 6.1: A-D) The effect of middle-ear cavity (MEC) on power reflectance in temporal bone specimens in the closed cavity condition (gray dotted line) and open cavity condition (black solid line). Each plot represents a single experiment. E) The summary plot displays the difference in PR between open and closed cavity conditions ($\Delta PR = PR_{\text{open MEC}} - PR_{\text{closed MEC}}$). The solid black line is the average difference across experiments, and the colored lines represent the difference in PR for each experiment.

3. b. Effect of Superior Canal Dehiscence with Open Cavity

Figure 6.2 shows the effect of SCD on PR in three open cavity (OC) experiments. Each experiment produces different patterns in PR. With SCD, all ears consistently show a change in PR ($\Delta PR = PR_{\text{SCD}} - PR_{\text{Normal}}$) of a narrow-band decrease (average 0.2287) at 0.48-0.76 kHz, and a narrow-band increase (average 0.211) at 1.04-1.4 kHz. In Figure 6.2A-C, the gray dotted lines represent the condition after repairing the SCD, and is similar to that of the normal, baseline (black solid line) in all experiments.

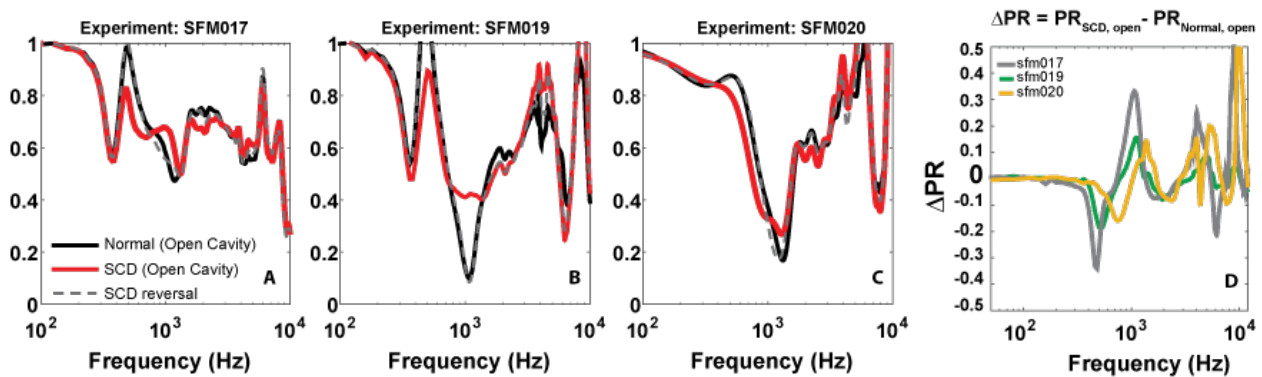


Figure 6.2: A-C) The effect of superior canal dehiscence (SCD) on power reflectance in temporal bone specimens. Plotted are the normal OC condition (black solid line), SCD + OC condition (red solid line) and SCD reversal + OC condition (gray dotted line). Each plot represents a single experiment. D) The summary plot displays the difference in PR between SCD and normal conditions ($\Delta PR = PR_{\text{SCD}+\text{open}} - PR_{\text{normal}+\text{open}}$) with colored lines representing individual experiments.

3. c. Estimating the Effect of Superior Canal Dehiscence with Closed Cavity

Figure 6.3 estimates the effect of the SCD when the cavity is closed for three experiments. Normal PR is plotted with dashed gray and SCD with red solid line (Fig 6.3A-C). This closed MEC condition was estimated using Equation 3. For the 3 experiments shown in Fig. 6.3D, there is a decrease (average 0.33) in PR between 0.46 and 0.54 kHz, and an increase (average 0.16) in PR between 0.84 and 1.44 kHz. Below 0.34 Hz, there is no change in PR between the normal and SCD conditions.

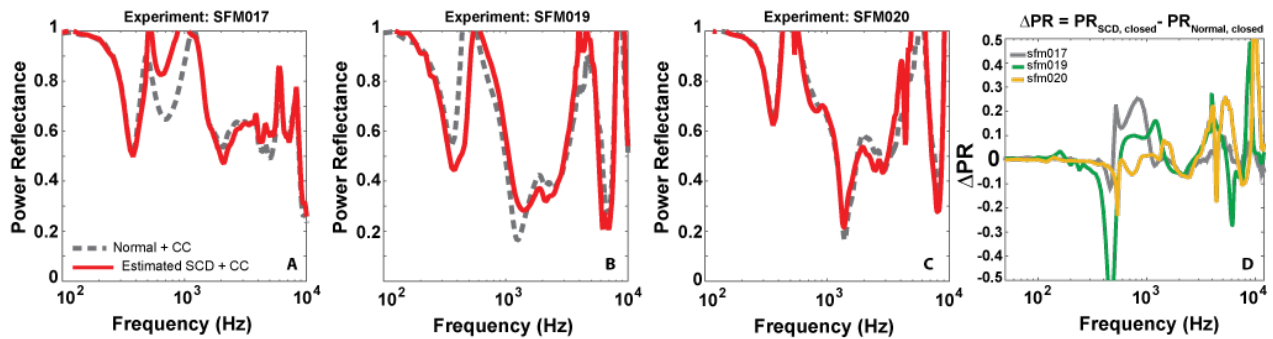


Figure 6.3: A-C: Estimating the power reflectance in temporal bone specimens with closed middle-ear cavity. Plotted are the normal + CC condition (gray dotted line), and SCD + CC condition (red solid line). Each plot represents a single experiment. D) The summary plots show the difference in PR between SCD and normal conditions ($\Delta PR = PR_{SCD+CC} - PR_{normal+CC}$) for each experiment.

3. d. Effect of Superior Canal Dehiscence on Power Reflectance in Patients

Figure 6.4 presents PR from 4 representative patients with SCD before surgery (red line) and after surgery (gray dotted line). Arrows represent the notch due to SCD. The summary plot in Figure 6.4E shows that the average decrease in PR (or notch) due to SCD is near 850 Hz across 20 patients. This average change shows a wider and shallower decrease than individual ears because the frequency of this notch varies across ears, ranging between 0.515 kHz and 1.172 kHz. The histogram in Figure 6.5 shows the distribution of the notch frequency across patients.

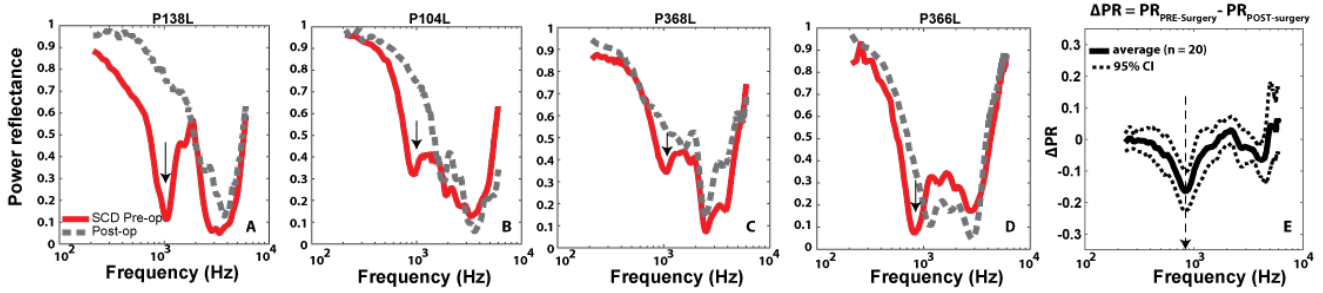


Figure 6.4: The effect of SCD on PR in live human patients with SCD before (red solid line) and after SCD repair (gray dotted line) with middle-fossa craniotomy surgery. Each plot represents a single patient. E) The summary plot displays the average difference in PR between pre-operative and post-operative measurements across 20 patients. The solid black line represents the average and the dotted lines represent the 95% confidence intervals of the mean.

4. Discussion

The effects of the MEC on ear-canal acoustic measurements in human-cadaveric specimens have been previously studied (Susan E Voss et al., 2008). These studies have suggested that the variation in MEC volume plays a role in the variability observed in wideband acoustic immittance measurements. Our results are similar to that of Voss et al. (Susan E Voss et al., 2008), where there is a decrease in PR at 1 kHz when the middle-ear cavity is open as compared to closed. A noticeable decrease (or notch) in reflectance at around 1 kHz is also seen in patients with superior canal dehiscence (G. R. Merchant, Rösli, Niesten, Hamade, et al., 2015b) as compared to normal. Because both decreases in PR are similar: one due to open middle-ear cavity, and the other due to SCD, it can be difficult to isolate the effect of SCD on PR with cadaveric specimens with open middle-ear cavity.

Therefore to estimate the effect of SCD in the closed cavity condition for our temporal bone experiments, we used the effect of closing the MEC and the effect of SCD in the open cavity case in our experiments (Equation 3). In temporal bone, our estimate of the effect of SCD in the closed cavity resulted in a decrease in PR at around 450 Hz and an increase around 800 Hz (Fig. 6.3D).

However, in the live patient recordings, the effect of SCD compared to surgically repaired SCD showed a significant decrease around 850 Hz without a higher frequency increase. Incidentally, the open cavity temporal bone results were more similar to the patient data than the estimated closed cavity results. Furthermore, the effects of SCD in both the temporal bone data and the patient data vary in frequency across ears, and some patient data matches considerably well with our temporal bone data. In Figure 6.6, we show an example of the difference in PR before and after surgery for a single patient (black line) which matches quite well with our experimental temporal bone results of Δ PR (open cavity condition) from experiment sfm020. This suggests that the variation in our temporal data is similar to the variation across patients (see Figure 6.6). Experimentally manipulating the inner-ear system with SCD allows for further development of phenomenological models to better understand the auditory and vestibular symptoms and to aid in SCD diagnosis.

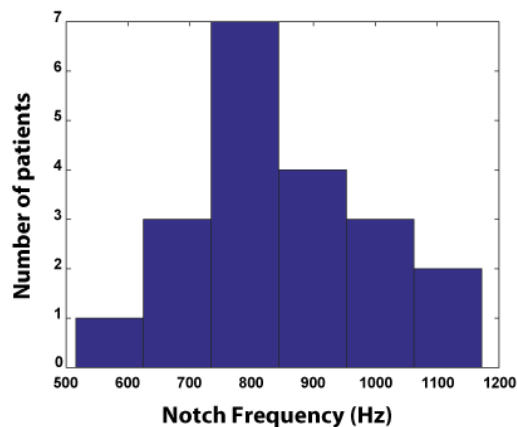


Figure 6.5: Histogram of notch frequencies for 20 patients

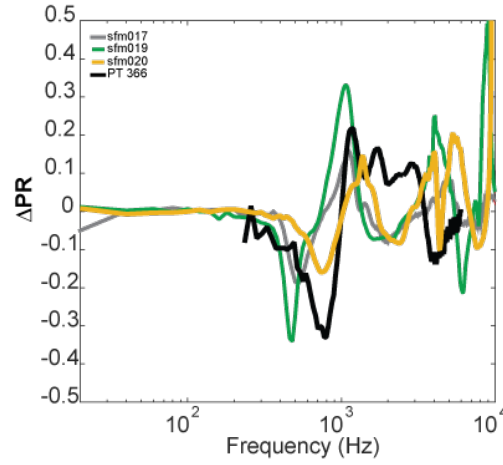


Figure 6.6: Difference in PR between SCD and normal conditions. The colored lines represent experimental temporal bone data for the open cavity condition, whereas the solid black line represents the difference in PR before and after SCD repair for Patient 366 (Figure 6.4D). This particular patient has similar SCD-induced effects to experiment sfm020 (yellow line).

CHAPTER 7. Thin bone versus frank dehiscence overlying the superior semicircular canal

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1. Introduction

Superior canal dehiscence (SCD) is an opening of the bone overlying the superior semicircular canal (SSC) (Minor et al., 1998, Minor et al., 2000, Carey, Hirvonen, Hullar, & Minor, 2004). The mechanical alteration by the dehiscence alters sound transmission of the inner ear by allowing acoustic volume velocity to flow abnormally through the SCD (Rosowski et al., 2004, Songer and Rosowski, 2007, Carey et al., 2007, Crane et al., 2008, Crane et al., 2010). This mechanical alteration can result in increased stimulation of the vestibular apparatus resulting in vestibular symptoms such as pressure or sound-induced vertigo. SCD also decreases low-frequency cochlear drive, the pressure difference across the cochlear partition at the base, consistent with hearing loss at low frequencies (Song et al. 2019, Raufer et al. 2018, Niesten et al. 2014, Pisano et al. 2012). Other SCD-induced symptoms include aural fullness, autophony, and hearing bodily-evoked sounds (eyeballs moving, heartbeat, footsteps) (Minor et al., 1998, Crane et al., 2008, Crane et al., 2010, Carey et al., 2007, Niesten et al., 2014; Ward et al., 2017; Zhou et al., 2007). These symptoms vary from patient to patient and may mimic middle ear pathologies such as ossicular fixation, ossicular discontinuity, and patulous Eustachian tube. SCD symptoms are similar to those of vestibular disorders such as Meniere's disease and vestibular migraine (Merchant & Rosowski, 2008; Zhou et al., 2007). Misdiagnosis is common. At our institution, we surveyed 230 SCD patients between 2001 and 2017, and found that the average time for SCD patients to be diagnosed correctly after the onset of symptoms was

approximately 50 months. Patients were often wrongly diagnosed for a number of other pathologies, and as a result underwent wrong treatments such as unnecessary middle-ear surgery and psychiatric medications (Merchant & Rosowski, 2008; Zhou et al., 2007).

SCD is diagnosed based on a combination of symptomatology, audiometric thresholds, vestibular evoked myogenic potentials (either ocular, oVEMP, or cervical, cVEMP), and high-resolution computed tomography (CT) imaging. On audiometric testing, SCD patients characteristically show low-frequency air-bone gap (ABG), caused by a combination of decreased bone-conduction thresholds (hyperacusis) and increased air-conduction thresholds. In some ears, the audiometric measurements may be within normal thresholds with SCD, particularly because clinical audiometry does not measure low enough in frequency for the low-frequency air-conduction hearing loss that increases with SCD size and is variable across ears (Cheng et al. 2019; Pisano et al. 2012; Niesten et al. 2014).

SCD patients have cVEMP and oVEMP with lower than normal thresholds (higher than normal amplitudes) because of the increased excitation of the saccule and utricle (Benamira, Alzahrani, & Saliba, 2014; Janky et al., 2013; Niesten, McKenna, Herrmann, Grolman, & Lee, 2013; Noij, Wong, et al., 2018; Welgampola, Myrie, Minor, & Carey, 2008). Generally, VEMPs are not measured unless SCD or vestibular dysfunction is specifically being diagnosed, and VEMPs have limitations such as variation in methodologies across centers, interpretation, and tolerance of patients (Rosengren et al., 2019).

High resolution CT imaging is most relied upon to diagnose SCD. However, CT is not standard of care for common problems such as conductive hearing loss or dizziness. CT imaging also increases medical expense and radiation exposure, and interpreting images can sometimes have uncertainty. Radiologists can find it difficult to distinguish between thin intact bone and

definitive SCD (Belden, Weg, Minor, & Zinreich, 2003; Sequeira, Whiting, Shimony, Vo, & Hullar, 2011). Patients with what appears to be thin bone covering the SSC on CT sometimes have symptoms consistent with SCD, resulting in uncertainty of whether these symptoms are the result of thin bone with similar mechanical abnormality to SCD or perhaps some other etiology.

Prior studies have explored improvements to interpret CT images to detect SCD. Thin-section temporal bone CT scans reformatted in the planes perpendicular to the SSC (Stenvers) and parallel to the SSC (Pöschl) are most useful to diagnose SCD (Belden et al., 2003; Sequeira et al., 2011; Sparacia & Iaia, 2017). To improve detection of SCD on high-resolution CT, Belden et al. (2003) showed that decreasing the slice thickness to 0.5 mm improves the positive predictive value by as much as 60% when compared to a slice thickness of 1 mm.

Previous studies have also shown that CT imaging cannot be exclusively relied upon for diagnosing SCD, especially when the dehiscence is small or the bone overlying the SSC is thin. Sequeira et al. (2011) showed that conventional clinical CT (0.5 mm thickness) may reduce diagnostic specificity by inaccurately showing a dehiscence when thin bone is actually present. In their human cadaveric study, clinical CT identified 7 out of 8 as dehiscent when there was thin bone. Ward et al. (2013) identified 11 thin bone ears (10 patients) at the time of surgery with SCD symptoms. Clinical CT incorrectly identified 4 out of 11 thin bone ears as having a frank dehiscence.

It is possible that patients with thin bone have SCD symptoms because there may be micro dehiscences. In temporal bone experiments, small pin-point (0.3-0.5 mm diameter) SCD decreased intracochlear pressures at mid frequencies in addition to low frequencies (Pisano et al., 2012). In these ears, enlarging the SCD from pinpoint to 1-2 mm long resulted in reversal of this mid-frequency pressure decrease to normal pressure while the low frequency pressures continued

to decrease further. Repairing the SCD reversed the pressures at all frequencies to their initial state of normal SSC. It is possible that such a pinpoint dehiscence is similar to thin bone that may have multiple micro-dehiscences. SCD repair surgery has also been shown in some cases to improve some SCD symptoms in patients with thin bone over the SSC (Ward et al., 2013). These studies question thin bone diagnosed with CT, and it continues to be a dilemma whether patients with SCD-type symptoms and thin bone actually have mechanical perturbation in sound transmission similar to SCD and are indeed affected by SCD syndrome. Because of this existing uncertainty, it is important to determine whether patients with thin bone (diagnosed with CT as well as direct visualization during surgery) should undergo surgery to actually open a hole at the thin SSC bone, then conventionally repair the opening (Ward et al., 2013).

In this study, we determined if there were similarities or differences between ears with definitive SCD (frank dehiscence) and ears with thin bone over the SSC, where both groups have SCD-type symptoms. Comparison was also made against controls with normal ears. We studied whether similarities or differences exist in symptoms, cVEMPs, and audiograms between different states of the SSC. We also determined whether measurements that are affected by the mechanical perturbation induced by SCD are also affected by thin SSC. These measurements included the wideband acoustic immittance (WAI) and the umbo velocity (UV), both measured non-invasively at the ear canal.

2. Methods:

2.1 Description of the study population

This work was approved by the institutional review board of the Massachusetts Eye and Ear (MEE). This retrospective study drew subjects that consulted otologists at MEE for symptoms consistent with SCD between 2010 –2018. These patients reported at least one of the following

symptoms: autophony, hyperacusis, aural fullness, unusually audible bodily-evoked sounds (e.g. hearing eyeballs move, footsteps, or loud sounds due to shaving or brushing one's hair), Tullio phenomenon, and Hennebert sign. These subjects had CT scans with either "Frank-Dehiscence" or "Thin-Bone" overlying a SSC (definitions of the two groups are detailed in a section below). A total of 85 ears had "Frank-Dehiscence" from 79 individuals (41 female, 38 male) that ranged in age from 17-70 years, with average age of 49.5 +/-10.4 (standard deviation) years. The definition of "Thin-Bone" relied on a radiologist report that described uncertainty of SCD due to "thin bone", "near dehiscence", "possible SCD", etc. This study had 39 ears in the Thin-Bone group from 35 individuals (24 female, 11 male), with a mean age of 46.6 +/- 10.9 (range 17-65) years. Patients who had prior ear surgery and/or other existing middle or inner ear pathology (i.e. abnormal tympanograms and/or absent acoustic reflexes), were excluded.

For comparison, asymptomatic "normal" ears were included in this study with the following criteria: (1) No history of significant ear disease, (2) no history of otologic surgery, (3) normal TM on otoscopy, (4) pure-tone air conduction thresholds of 20 dB HL or better for 0.25 – 8 kHz, (5) air-bone gaps (ABG) no greater than 15 dB at 0.25 kHz and 10 dB for 0.5 – 4 kHz, and (6) normal type-A peaked tympanograms. The normal groups were made up of various types of "normal" ears depending on the measurement. The normal groups were: (1) Rosowski-Normal group with 26 ears (14 subjects), previously obtained by Rosowski et al. (2012) in a study involving mechano-acoustical measurements at the ear canal; (2) Contra-Normal group of 15 ears, where CT showed normal thicknesses of bone overlying the SSC and were the contralateral side of the affected ears of patients with unilateral SCD or unilateral Thin-Bone; (3) Noij-Normal group of 42 ears (21 subjects), previously obtained by Noij et al. (2018) in a study involving cVEMP measurements. The Noij-Normal group consisted of healthy ears that met the

above criteria, with an ABG < 15 dB in combination with normal tympanograms and/or present reflexes, and also no history of hearing loss, vertigo, balance problems, neurological disorders and musculoskeletal disease. Information about the control groups are shown in Table 7.1.

For each type of measurement, in addition to comparing Frank-Dehiscence and Thin-Bone groups, we also compared to control groups. The control groups were made of different combinations of normal groups. The control group to study cVEMPs was a combination of Noij-Normal and Contra-Normal groups. The control group to study WAI, UV and audiometry thresholds was a combination of the Rosowski-Normal and the Contra-Normal groups.

Table 7.1: Information of Frank-Dehiscence, Thin-Bone, and Normal groups.

	Frank-Dehiscence	Thin-Bone	Rosowski-Normal	Contra-Normal	Noij-Normal
Number of ears (number of subjects)	85 (79)	39 (35)	26 (14)	15 (15)	42 (21)
Mean age in years (SD)	49.5 (10.4)	46.6 (10.9)	43.7 (10.7)	47.3 (10.0)	48.9 (11.8)
Age range, years	17-70	17-65	22-64	29-67	32-68
Female sex, %	51.9%	68.6%	78.6%	66.7%	57.1%
Number of ears with VEMP testing	66	32	0	15	42
Number of ears with Audiometric data	76	36	26	15	42
Number of ears with WAI	84	36	26	15	0
Number of ears with UV	75	28	26	15	0
Number of ears with CT scans	85	39	0	15	0

2.2 Frank-Dehiscence group and Thin-Bone group determined by CT

This study included CT images of ears from symptomatic patients described as SCD, question of SCD, or thin bone over the SSC in the original radiology report of the patient medical record. The majority of CT images were obtained at MEE with either a multi-detector row CT scanner (Somatom Sensation 40 before 2014, or Discovery CT750 HD after 2014) or a cone beam CT scanner (3D Accuitimo 170). The Somatom Sensation 40 and Discovery CT750 HD scanner both have a slice thickness of 0.63 mm and the 3D Accuitimo 170 scanner has a slice thickness of 0.5 mm. Scans obtained from other hospitals varied in slice thickness of 0.6-1.0 mm.

CT images were inspected to distinguish “Frank-Dehiscence” ears from “Thin-Bone” ears. The Frank-Dehiscence group included dehiscences with lengths of at least 2 mm. The size of the dehiscence was measured in the Pöschl view using the angle and ruler tool on Synapse PACS (Fujifilm Corp, Japan). The diameter of the canal was measured in millimeters and the size of the dehiscence was calculated using the formula for arc length b ;

$$b = \frac{\alpha}{360} 2\pi$$

where α is the central angle in degrees. Figure 7.1 provides examples of CT images of Frank-Dehiscence, Thin-Bone and normal SSC in the Poschl and Stenvers view. The Thin-Bone ears were categorized if the original radiology report described the SSC bone as abnormally thin or if there was uncertainly whether an SCD existed due to thin bone.

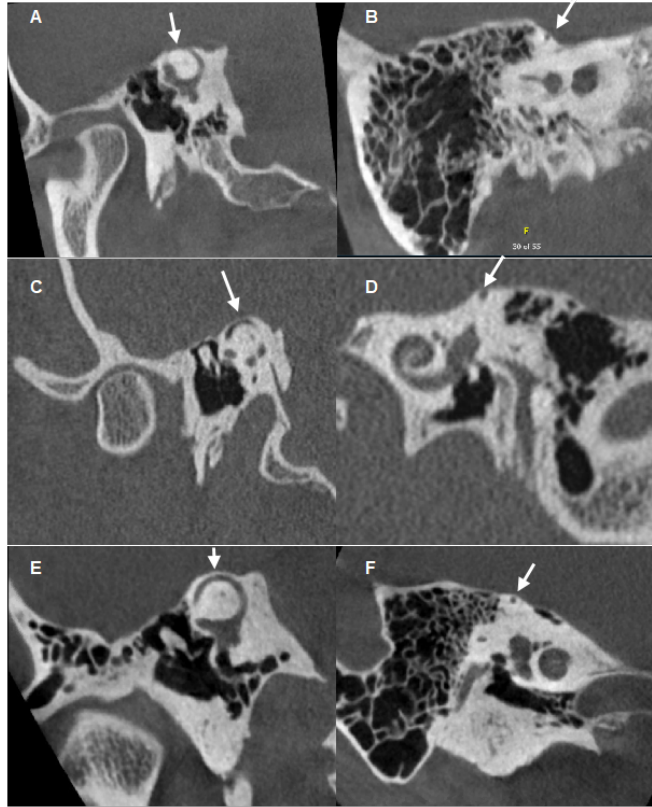


Figure 7.1: CT images of the superior semicircular canal (SSC) in Poschl (left column A, C, E) and Stenvers (right column B, D, F) view. Each row represents a different ear: Frank-Dehiscence (A and B), Thin-Bone (C and D) and a normal covering of bone (E and F).

2.3 SCD symptoms

Auditory and vestibular symptoms consistent with SCD were compared between patients grouped as Frank-Dehiscence and Thin-Bone. Symptoms were obtained from the medical records where information from a questionnaire was recorded. The auditory symptoms studied included autophony, hyperacusis, aural fullness and unusually audible bodily-evoked sounds (i.e. eyeball motion, footsteps, bowel movements, shaving or brushing one's hair). The vestibular symptoms included Tullio phenomenon, Hennebert sign, as well as imbalance.

2.4 Comparison of symptoms between Frank-Dehiscence and Thin-Bone groups

The occurrence of SCD symptoms were compared between 85 Frank-Dehiscence ears and 39 Thin-Bone ears. Additionally, we compared these symptoms across two different subgroups of patients: 21 unilateral Frank-Dehiscence patients and 11 unilateral Thin-Bone patients. The unaffected ears of these unilateral cases were confirmed to have normal thicknesses of bone over the SSC with CT. To compare symptoms between the Frank-Dehiscence and Thin-Bone groups statistically, a Fisher's exact test was used and a p-value of < 0.05 was considered to be statistically significant.

2.5 Grading within the Thin-Bone group

The Thin-Bone group mentioned above was categorized on the assessments of CT scans in the medical records by various radiologists. To have consistency of the radiologic assessment and to rate the extent of bone over the SSC, two neuro-radiologists with extensive experience in diagnosing SCD in our institution developed a grading system for the Thin-Bone group. The two radiologists adopted a Likert scale (Likert, 1932) of grade 1 to 5 to assess the Thin-Bone group from reformatted CT images in the Pöschl and Stenvers views of the SSC. The two neuro-radiologists assessed the CT images independently of each other while blinded to: the original CT report, all clinical information, and all measurements and assessments made by others. Grade 1 was assigned when a frank lucency was observed for at least two consecutive frames on both Pöschl and Stenvers views. Grade 1 was considered definitive SCD by our two neuro-radiologists (although the original radiologists reported thin bone or uncertainty in the medical record). Grade 2 was assigned if a small punctuate lucency was seen in one frame on both views or two consecutive frames in one view; this was considered "probable" SCD. Grade 3 was

assigned when a small punctuate lucency was seen on one slice of one view; this was considered “possible” SCD. Grade 4 was assigned when there was thin but present bone covering the superior semicircular canal; this was considered “unlikely” SCD. Grade 5 was assigned when a definitive normal layer of bone, not thin bone, overlay the SSC on both views (although the original radiologists had described as thin bone in the medical records).

2.6 cVEMP for diagnosing SCD

The methods used for measuring cVEMPs are detailed in Noij et al. (2018). Briefly, 500 Hz tone bursts were presented monaurally with supra-aural headphones (Telephonics TDH-49) at a repetition rate of 13/s. Duration of the time burst was a 4 ms rise and 4 ms fall time with no plateau. Tone bursts were presented at 93-, 103-, 113- and 123-dB peak-equivalent sound pressure level (peSPL). The level of sound is reported in peSPL because the peak that is reached in the stimulus is instantaneous and no plateau is reached. Previous reports describe and details this stimulus and its unit (Noij et al. 2018, 2019).

2.7 Audiograms for diagnosing SCD

Hearing thresholds were obtained using air-conducted (AC) pure-tone stimuli at 250-, 500-, 1000-, 2000-, 4000- and 8000-Hz, and bone-conducted (BC) sound stimuli at 250-, 500-, 1000-, 2000- and 4000-Hz. ABG was calculated at each frequency by subtracting BC from AC threshold levels. The two most distinguishable frequencies measured clinically for differentiating SCD from healthy ears have been found to be 250 and 500 Hz (Benamira et al., 2014, Niesten et al., 2014), hence ABG was extracted and analyzed for these two frequencies.

2.8 Power reflectance (PR), a mechanical measure of the ear

WAI is a non-invasive ear-canal measurement used to assess middle-ear mechanics. Sound is presented at the ear canal, and the sound reflected from the tympanic membrane is measured. This measurement allows for various immittance calculations such as impedance, admittance, power reflectance (PR) and absorbance, detailed in Rosowski et al.'s (2013) overview. Here, WAI was measured using the Mimosa Acoustics HearID system for frequencies between 0.2 and 6.0 kHz at 60 dB SPL. PR, the relative magnitude of the power of sound reflected by the TM with respect to the forward stimulus sound, was calculated from the WAI. We compared the PR frequency responses across Frank-Dehiscence, Thin-Bone and normal control ears. Merchant et al. (2015) found that SCD decreased PR at a narrow frequency band, resulting in a “notch” of the frequency response. The “notch frequency range” was found to be between 600-1800 Hz. To quantify this SCD notch, the *notch size* and *notch depth* was calculated from the frequency response of the PR normalized by the average PR across normal hearing individuals (detailed in Merchant et al. 2015). The difference between the magnitudes of the higher-frequency maxima and the notch minima determined the *notch depth*. The lower-frequency maxima was defined as the average value of the normalized PR magnitude computed for low frequencies 1.5 to 0.5 octaves below the notch frequency. The difference between the lower-frequency maxima and the notch minima determined the *notch size*. The notch size and notch depth were compared across the three groups: Frank-Dehiscence, Thin-Bone and healthy control.

2.9 Umbo Velocity (UV), a mechanical measure of the ear

UVs were measured in a subset of the WAI subjects in the manner detailed in Rosowski et al. (2012). UV was measured with laser Doppler vibrometry (Polytec, Inc.) while the stimulus sound pressure near the TM at the ear canal was measured. Frequency responses of UV magnitude and phase with respect to ear-canal pressure provided information regarding the acoustic input admittance of the middle and inner ear.

2.10 Statistical analysis for clinical measures

We studied clinical measures – cVEMPs, ABGs, PR and UV – to determine if for each measurement, there were differences between the Frank-Dehiscence group, the Thin-Bone group, and the control group relevant for each measure. None of these measurements resulted in normal distribution, as demonstrated by a Kolmogorov-Smirnov test. Therefore, for each clinical measurement, a non-parametric Kruskal-Wallis (KW) test, was used to determine if there were significant differences (p-values of <0.05) between the medians of any of the groups: Frank-Dehiscence, Thin-Bone, and control groups. Once we determined if differences existed among the medians of the groups with the KW test, then to determine which groups statistically differed, post-hoc pairwise comparisons using a Mann-Whitney U (MW-U) test were performed with Bonferroni correction for multiple comparisons. The p-value was adjusted by dividing the p-value of 0.05 by the number of comparisons. Statistical analyses were performed using MATLAB.

3. Results

3.1 Symptoms of Frank-Dehiscence and Thin-Bone groups

Some patients present to the clinic complaining of SCD symptoms, and their CT images show thin bone over the SSC. We tested the hypothesis that the patients in the Frank-Dehiscence group and the Thin-Bone group will report similar symptoms with similar rates. (Note, all patients in the Frank-Dehiscence or Thin-Bone groups had at least one symptom.) With CT, the Frank-Dehiscence group was measured to have an SCD at least 2 mm long as detailed in the Methods section, and the Thin-Bone group was described as such in the original radiologist report in the medical records.

We first compared symptoms between the patient groups with Frank-Dehiscence (79 patients, 85 ears) and Thin-Bone (26 patients, 29 ears). In this comparison, each group could have either unilateral or bilateral pathology. For example, all patients in the Thin-Bone group have either bilateral Thin-Bone, or unilateral Thin-Bone with a normal contralateral ear. For auditory symptoms, patients clearly indicated which ear (or ears) suffered from a particular symptom. For vestibular symptoms, such as imbalance and Tulio's phenomenon, specification of side was not reported. Figure 7.2 plots the incidence of symptoms in both Frank-Dehiscence and Thin-Bone groups. As plotted in Fig. 7.2A, for the Frank-Dehiscence group, 82% (70/85) patients reported at least one auditory symptom (autophony, aural fullness, hyperacusis, and/or bodily-evoked sounds), and 80% (68/85) patients reported at least one vestibular symptom (Hennebert sign, Tulio's phenomenon, or imbalance). Similarly, in the Thin-Bone group, 86% (25/29) patients reported auditory symptoms, and 82% (23/28) patients reported vestibular symptoms. The incidences of all auditory symptom and all vestibular symptom between Frank-Dehiscence and Thin-Bone groups revealed no significant difference ($p > 0.05$) with the Fisher's

exact test. Figure 7.2 plots the incidence of each symptom for Frank-Dehiscence and Thin-Bone groups. The incidences of each symptom between Frank-Dehiscence and Thin-Bone groups revealed no significant difference ($p > 0.33$) with the Fisher's exact test.

Instead of lumping both bilateral and unilateral cases together, we next concentrated our study on only unilateral cases. We compared symptoms between 21 unilateral Frank-Dehiscence cases and 11 unilateral Thin-Bone cases. Figure 7.3A shows that for the unilateral Frank-Dehiscence group, approximately 80% (17/21) patients had at least one auditory symptom, and 76.2% (16/21) had at least one vestibular symptom. For the unilateral Thin-Bone group, all 11 patients had at least one auditory symptom and at least one vestibular symptom. The incidences of all auditory symptom and all vestibular symptom between unilateral Frank-Dehiscence and unilateral Thin-Bone groups revealed no significant difference ($p > 0.05$) with the Fisher's exact test. When comparison between the two groups was made for the presence of each symptom (Fig. 7.3B), no significant difference between the unilateral Frank-Dehiscence and unilateral Thin-Bone groups was found with a Fisher's exact test ($p > 0.13$). Although not statistically different, there was a reasonable percent difference in incidence of autophony between the two groups (Frank Dehiscence: 80% vs. Thin-Bone: 55%). Additional unilateral ears in both groups would be necessary to determine if there is statistical significance.

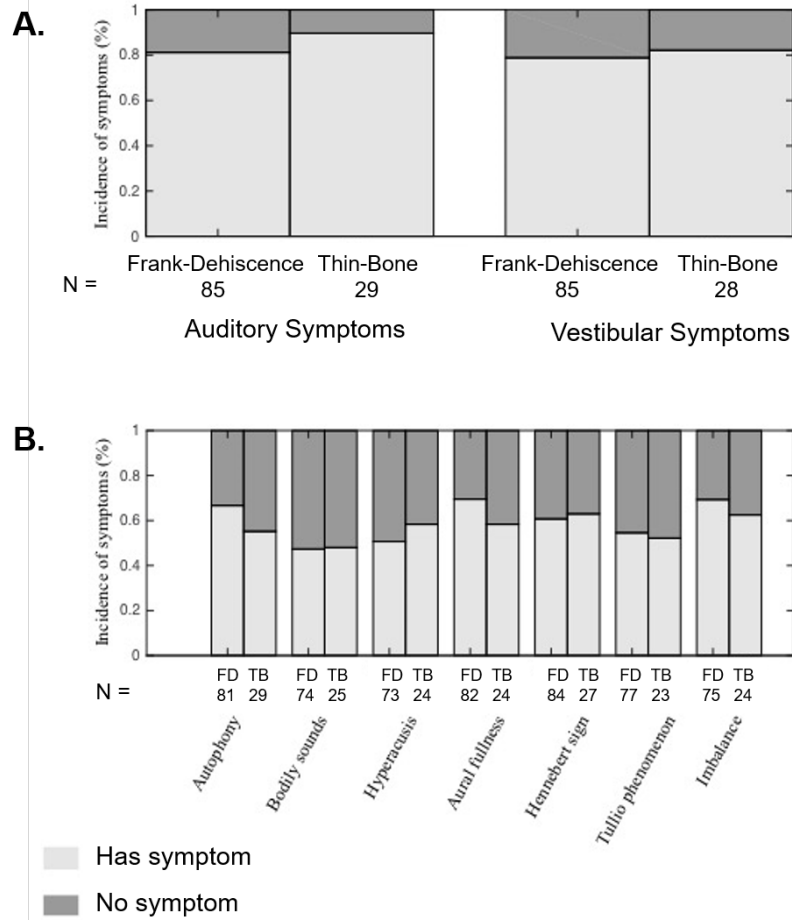


Figure 7.2: Comparison of symptoms between Frank-Dehiscence (FD) and Thin-Bone (TB) groups where the groups include bilateral cases. (A) Incidence of at least one auditory or one vestibular symptom in 85 ears (79 patients) with Frank-Dehiscence and 29 ears (26 patients) with Thin-Bone. (B) Incidence of each symptom between Frank-Dehiscence and Thin-Bone. Number of patients are at the bottom of the x-axis.

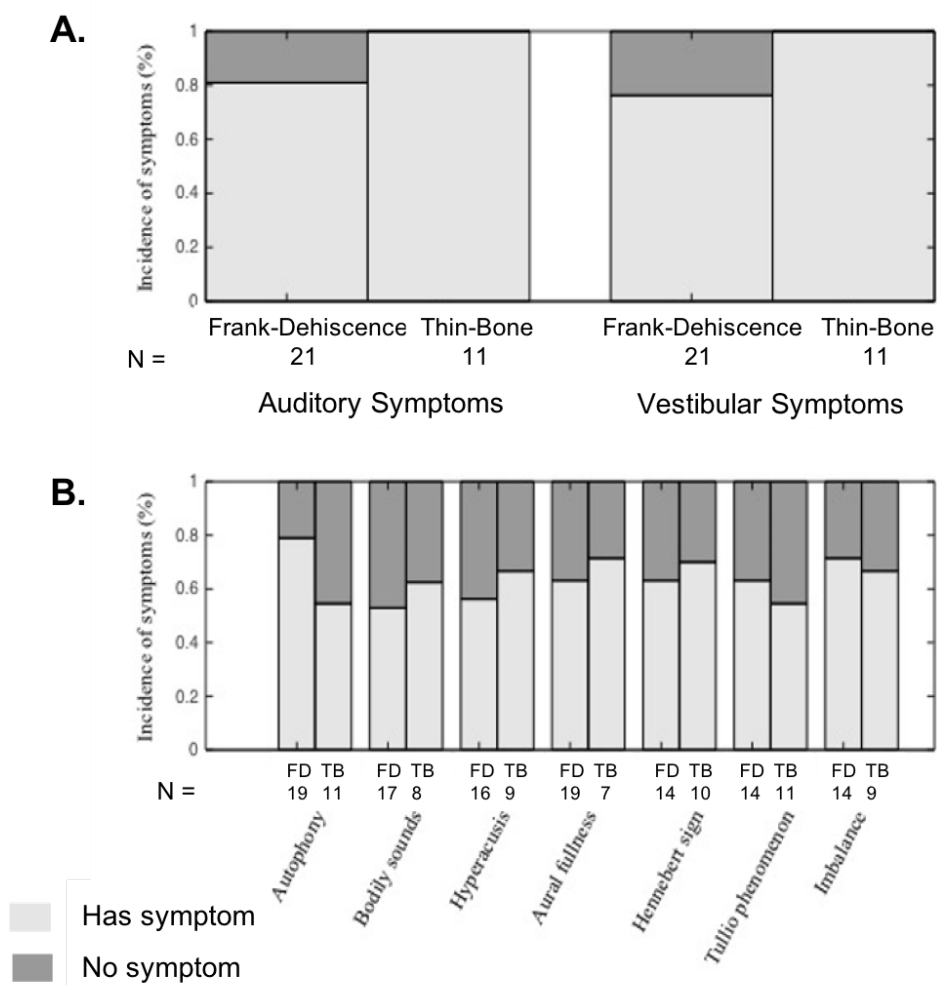


Figure 7.3: Incidence of symptoms in unilateral Frank-Dehiscence and unilateral Thin-Bone groups. (A) Incidence of at least one auditory symptom and at least one vestibular symptom. (B) Incidence of each symptom between unilateral Frank-Dehiscence and unilateral Thin-Bone groups. Number of patients (N) are at the bottom of the x axis.

3.2 Grading the extent of bone over the SSC in the Thin-Bone group

In the medical records, different radiologists reported their CT findings of thin bone over the SSC. These descriptions varied and often expressed uncertainty; it appeared that it was often difficult to know whether the bone was thin without dehiscence or thin with a small dehiscence. These original reports were composed by different radiologists using different diagnostic

methods, criteria, judgments and experiences. Therefore, in this study, two experienced neuro-radiologists were blinded to all clinical and previous diagnoses, and independently assessed all CT images in the Thin-Bone group and graded them in the manner described in the Methods section with a scale that ranged from 1 to 5. See Appendix for the number of patients and their demographics for each grade number. The inter-observer reliability between the two neuro-radiologists was calculated to be 45% (17 matches out of 38 ears). However, each time the grading differed, the observers differed by only one grading scale. Thus, it can be interpreted that there was general agreement in rating thin bone cases. The neuro-radiologists felt that grade 1 was considered an SCD, and a grade 2 may have had a pinpoint SCD. Grades 3 and 4 were considered thin bone from thinner to thicker. Grade 5 was believed to be normal thickness of bone overlying the SSC. Out of the 39 ears assessed, grades of 3 and 4 were given by the first radiologist to more than half of the Thin-Bone group (23/39 ears), while the second radiologist graded 3 and 4 to about half (19/39 ears). Grades 1 and 2 (the likelihood of having SCD) were given by the first radiologist in 8/39 ears, while the second radiologist in 13/39 ears. Grade 5 (normal bone overlying the SSC) was given to 8/39 by the first radiologist and 5/39 by the second radiologist.

3.3 cVEMP thresholds in Frank-Dehiscence, Thin-Bone and control groups

At our institution, patients suspected to have SCD usually had cVEMP testing to aid in diagnosis. Here we compared cVEMP thresholds among various groups: the Frank-Dehiscence group, the Thin-Bone group, and the control group for cVEMP. The control group for cVEMP consisted of Noij-Normal group and the Contra-Normal group (all groups are described in the Methods section and Table 7.1). Figure 7.4 displays a beeswarm plot of cVEMP thresholds at

500 Hz for each of the 3 groups: Frank-Dehiscence group, Thin-Bone group, and control group. We determined that cVEMP threshold median differences exist among the groups with the KW-test ($KW \chi^2 = 55.01$, $p = 1.1E-12$). Then to determine which groups' medians differ, post-hoc MW-U tests with Bonferroni correction for the 3 comparisons required a p-value of <0.0167 for significance. The post-hoc pairwise comparisons revealed that the Frank-Dehiscence group (median = 98 dB peSPL) had significantly lower thresholds than the Thin-Bone group (median = 113 dB peSPL, $U = 477$, $p = 1.9E-8$). The Frank-Dehiscence group also had significantly lower thresholds than the control group (median = 113 dB SPL, $U = 733$, $p = 6.8E-11$). The Thin-Bone group and the control group had no significant differences in cVEMP threshold ($U = 970.5$, $p = 0.77$).

Because the Thin-Bone group contained a variety of anatomy as observed by the two neuro-radiologists, we determined if cVEMPs from each grade (Grade 1-5 as defined in Methods) from the Thin-Bone group differed from Frank-Dehiscence group and from the control group. Figure 7.5 shows a boxplot comparing cVEMP thresholds at 500 Hz for the different grades of Thin-Bone (Grade 1-5) to both the Frank-Dehiscence group and control group. cVEMP thresholds at 500 Hz were statistically similar across the different Thin-Bone grades, and all Thin-Bone grades were similar to the control group. Even the Thin-Bone ears rated as grade 1 and believed to have a small SCD were similar to the control groups. However, the Frank-Dehiscence group differed from all the Thin-Bone grades as well as the control group. Further analysis with more samples in each grade is necessary to test for significance. We combined Grades 3 and 4 to statistically compare to Frank-Dehiscence and control groups. Statistical differences using MW-U tests were found between Frank-Dehiscence and Thin-Bone (Grades 3 and 4; median = 113 dB peSPL, $p <$

2.9E-6) and Frank-Dehiscence and control groups ($p = 6.8E-11$). Statistical analysis between groups can be found in the Appendix, section A7.1.

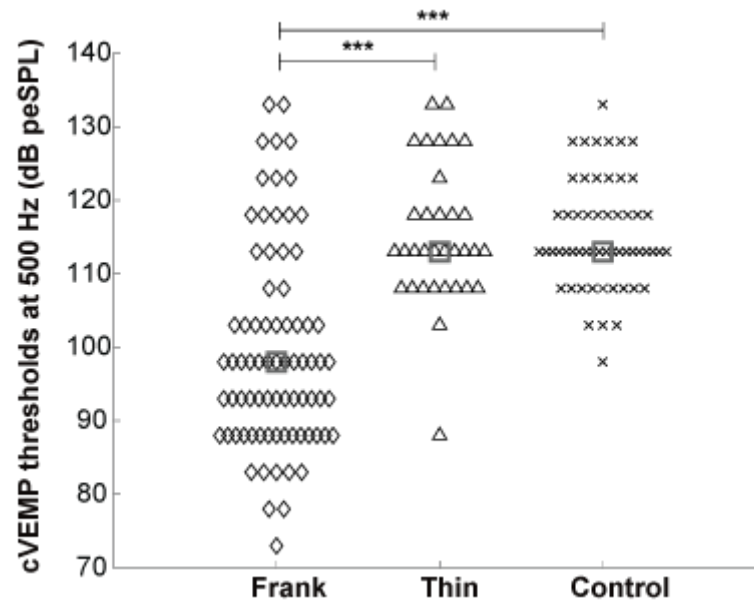


Figure 7.4: cVEMP thresholds (dB peSPL) at 500Hz are shown for each ear in all three groups. The gray boxes represent the median of the data. “***” indicates statistical significance of $p < 0.000167$ between the groups indicated.

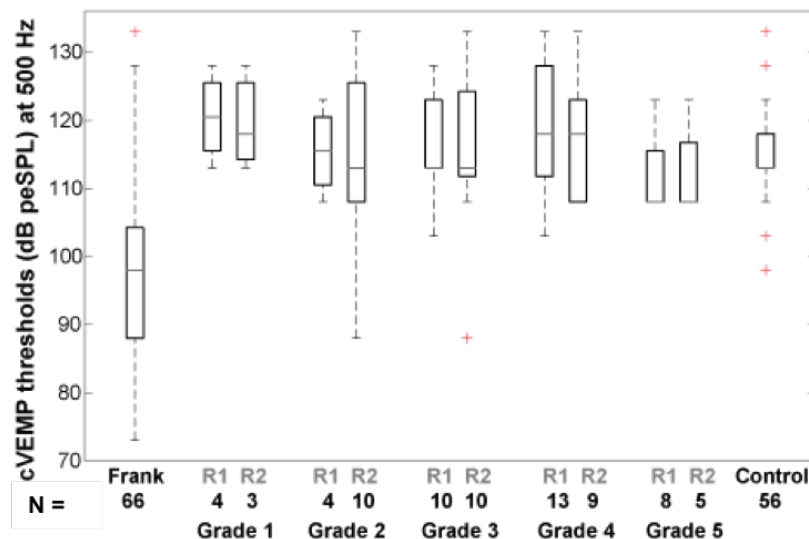


Figure 7.5: Boxplot of the cVEMP thresholds at 500 Hz of the different grades of Thin-Bone (Grades 1-5), the Frank-Dehiscence group, and the control group. The central gray horizontal mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points, and are not considered outliers, while the outliers are

plotted individually using the red '+' symbol. The number of ears (N) in each group is indicated at the x-axis. R1 and R2 indicate the two neuro-radiologists who determined the Thin-Bone grades.

3.4 Audiometric data in Frank-Dehiscence, Thin-Bone and control groups

Audiometric threshold measurements and ABG were compared between Frank-Dehiscence, Thin-Bone, and control groups for audiometry. The control groups for audiometry were combinations of the Rosowski-Normal and Contra-Normal groups (separate control groups for AC threshold, BC threshold, and ABG). Individual data points in each group are plotted for AC thresholds (Figure 7.6 A&B), BC thresholds (Figure 7.7 A&B) and ABG (Figure 7.8 A&B), for 250 and 500 Hz. Only low frequencies were compared across groups because SCD usually affected only the low frequency AC and BC thresholds and ABG (Cheng et al. 2019, Brantberg et al. 2016, Niesten et al., 2014; Noij et al., 2017). For example, only 4 out of 85 (4%) of Frank-Dehiscence ears had abnormal ABGs at mid or high frequencies in this study. To determine if any significant difference between the groups existed, the KW non-parametric test was used. MW-U Post-hoc pair-wise comparisons of AC threshold, BC threshold, and ABG revealed which comparisons between groups had statistical differences.

For AC thresholds, statistically significant differences were found among the groups at 250 Hz (KW $\chi^2 = 49$, $p < 0.001$) and at 500 Hz (KW $\chi^2 = 40$, $p < 0.001$). The Frank-Dehiscence group was significantly different from the Thin-Bone and control groups. Specifically, for AC thresholds at 250 Hz, the Frank-Dehiscence group had statistically higher thresholds (median = 20 dB HL for AC, $U = 708.5$ and $p = 2.5E-6$) compared to the Thin-Bone group and control group (both Thin-Bone and control groups had AC threshold medians of 10 dB HL for AC, $U = 558$, $p = 2.1E-10$). For AC thresholds at 500 Hz, the Frank-Dehiscence group had significantly higher threshold (median = 20 dB HL for AC) than the

Thin-Bone group threshold (median = 10 dB HL for AC), with pairwise comparison statistics of $U = 853.5$, $p = 1.1E-4$. The Frank-Dehiscence group had significantly higher AC threshold than the control group (median 10 dB HL for AC, $U = 631.5$, $p < 3.3E-9$). No other significant differences for AC thresholds at 250 Hz and 500 Hz were found across groups ($p > 0.017$).

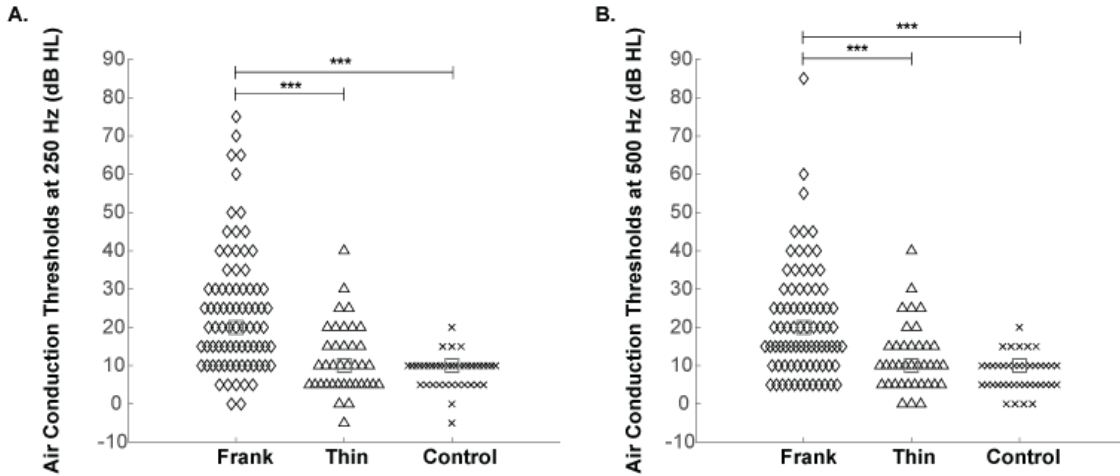


Figure 7.6: Air-conduction thresholds at 250 Hz (panel A) and 500 Hz (panel B) are shown for every ear in each group. *** indicates statistical significance of $p < 0.00017$ between the groups indicated.

For BC threshold, significant differences at 250 Hz was found between groups (KW $\chi^2 = 49$, $p = 0.004$). No significant difference was found between groups for BC thresholds at 500 Hz ($p > 0.1$). Post-hoc MW-U pairwise comparisons for BC thresholds revealed that at 250 Hz, Frank-Dehiscence thresholds (median = 0 dB HL for BC) had significantly lower thresholds compared to the Thin-Bone (median = 5 dB HL for BC) with $U = 804$, $p = 0.005$. Frank-Dehiscence BC thresholds (median = 0 dB HL for BC) also had significantly lower thresholds compared to the control (median = 5 dB HL for BC) with $U = 1186$, $p = 0.008$. The 250 Hz BC thresholds did not statistically differ between the Thin-Bone group and

control group. Analysis of BC threshold comparisons between groups at 500 Hz did not reveal statistically significant differences.

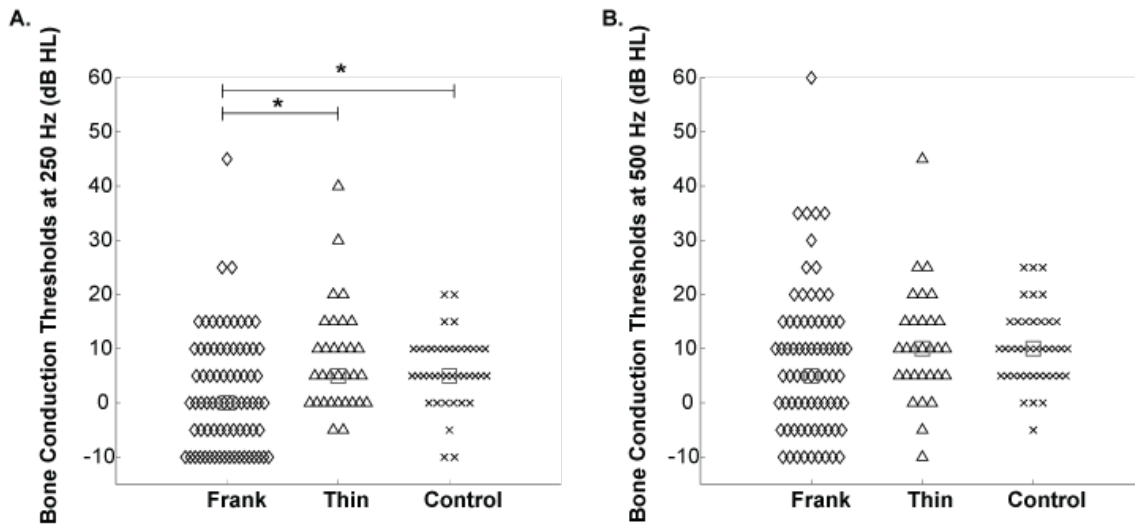


Figure 7.7: Bone- conduction thresholds at 250 Hz (panel A) and 500 Hz (panel B) shown for every ear in each group. * indicates a statistical significance of $p < 0.017$ between the groups indicated.

For ABG, statistically significant differences among groups were found at 250 Hz (KW $\chi^2 = 56$, $p < 0.001$) and at 500 Hz (KW $\chi^2 = 46$, $p < 0.001$). ABGs were larger for Frank-Dehiscence patients than the Thin-Bone and control groups. ABG at 250 Hz was significantly larger for the Frank-Dehiscence group (median = 20 dB) than the Thin-Bone group (median = 2.5 dB HL) with post-hoc MW-U results of $U = 422$, $p = 1.9E-10$. The ABG of the Frank-Dehiscence group (median = 20 dB) was also significantly larger than the control group (median = 2.5 dB) with HL, $U = 395$, $p = 1.4E-11$. At 500 Hz, the ABG of the Frank-Dehiscence group (median = 20 dB) was significantly larger compared to the Thin-Bone group (median = 2.5 dB HL) with $U = 370$, $p = 8.01E-8$. The Frank-Dehiscence group (median = 20 dB) also has a significantly larger ABG at 500 Hz than the control group ABG (median = 0 dB) with $U = 261$, $p = 2.01E-13$. No other significant differences in BC thresholds were found between groups at 250 and 500 Hz.

We then compared ABG for the different grades of Thin-Bone ears (as defined by the two radiologists), the Frank-Dehiscence group, and the control group. Figure 7.9 shows that ABG thresholds at 250 Hz are similar across the different Thin-Bone grades, and all Thin-Bone grades were similar to the control group. Further analysis with more samples in each grade is necessary to test for significance. We combined Grades 3 and 4 to statistically compare to Frank-Dehiscence and control groups. Statistical differences using MW-U tests were found between Frank-Dehiscence (median = 25 dB) and Thin-Bone (Grades 3 and 4; median = 5 dB, $p < 6.8E-7$) and Frank-Dehiscence and control groups ($p = 1.4E-11$). Details of the statistical analysis can be found in the Appendix, in section A7.2.

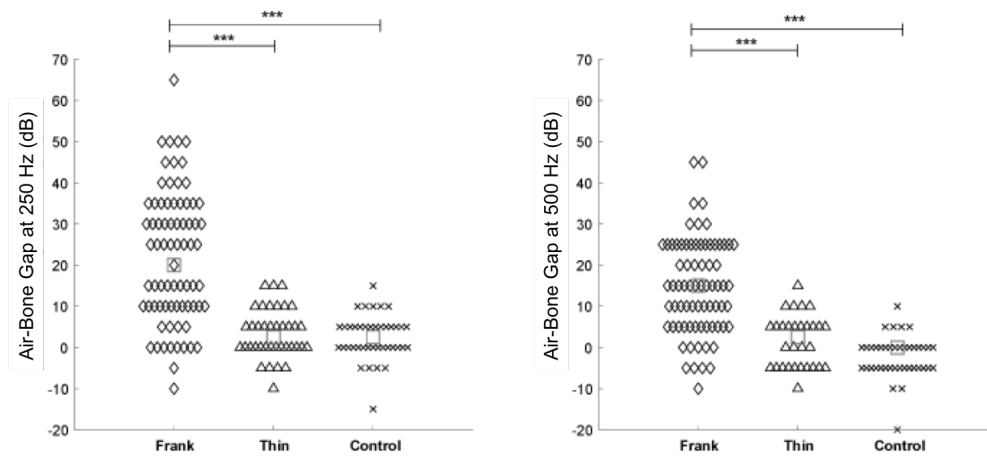


Figure 7.8: ABG at 250 Hz (panel A) and 500 Hz (panel B) shown for every ear in each group. *** indicates a statistical significance of $p < 0.000167$ between the groups indicated.

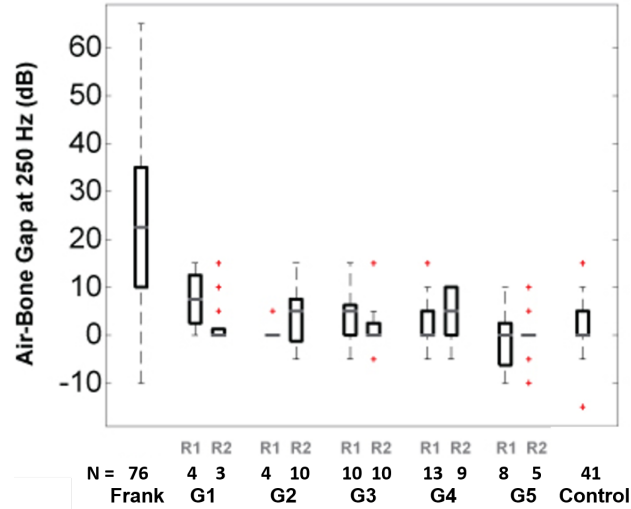


Figure 7.9: Boxplot of ABG at 250 Hz for the different grades of Thin-Bone ears, the Frank-Dehiscence group, and the control group. Thin Bone ears, regardless of grade, have similar ABG thresholds as the control ears. Statistical differences were not found across Thin-Bone groups and Control ($p > 0.05$). The number of ears (N) are indicated below the x-axis.

3.5 Power Reflectance in Frank-Dehiscence, Thin-Bone and control groups

Previously we demonstrated that ears with SCD were found to have PR with a narrow-band decrease, a “notch”, at the notch frequency range of 600-1800 Hz as compared to normal ears (Merchant et al. 2015).. Here, we use the features, *notch size* and *notch depth* (calculated as in Merchant et al. 2015 and described above in Methods section), to compare between the Frank-Dehiscence group, Thin-Bone group and control group. The control groups for PR features were the combinations of Rosowski-Normal and Contra-Normal.

As shown in Chapter 5, high frequency PR content also appeared to aid in differentiating SCD from normal ears. Thus, we also extracted the PR magnitude at approximately 5 kHz for each ear (by averaging a 1/3 octave band centered at 5074 Hz), then compared between the groups.

A significant difference in PR *notch size* across the 3 groups (Frank-Dehiscence, Thin-Bone, and control) was found (KW $\chi^2 = 7.26$, $p = 0.026$), and the *notch size* for each group are

plotted in Fig. 7.10A. Post-hoc MW-U tests with Bonferroni correction for the 3 comparisons required a p-value of <0.0167 for significance. The Frank-Dehiscence group (median = 0.20) had a significantly larger *notch size* than the control group (median = 0.147) with $U = 1240$ and $p = 0.015$. No significant differences in *notch size* was found between Frank-Dehiscence group (median = 0.20) and Thin-Bone group (median = 0.151) with $U = 1200$ and $p = 0.062$. No significant difference was found between the Thin-Bone group and the control group (median = 0.147) with $U = 696$, $p = 0.81$.

A significant difference was found in PR *notch depth* across the groups (KW $\chi^2 = 19.02$, $p = 7.42E-05$), and the *notch depth* for each group are plotted in Fig. 10B. Post-hoc MW-U tests needed $p < 0.0167$ for significance. It revealed that the Frank-Dehiscence group (median = 0.17) had a significantly larger *notch depth* than the Thin-Bone group (median = 0.11), with $U = 1486$ and $p = 5.62e-04$. The Frank-Dehiscence group (median = 0.17) also had a significantly larger *notch depth* than the control group (median = 0.093), with $U = 1475$ and $p = 4.27e-04$. No significant difference in notch depth was found between the Thin-Bone and control group ($U = 464$, $p = 0.82$).

A significant difference was found in the high-frequency (5 kHz) PR magnitudes across the groups (KW $\chi^2 = 10.825$, $p = 0.0045$). The post-hoc MW-U tests required $p < 0.0167$ for significance, and the comparisons are plotted in Fig. 7.10C. The Frank-dehiscence group (median = 0.67) had a significantly larger high-frequency PR magnitude than the control group (median = 0.53), with $U = 1434$ and $p = 0.0018$. No significant difference was found in the high-frequency PR between the Frank-Dehiscence group (median 0.67) and Thin-Bone group (median = 0.59), with $U = 1557$ and $p = 0.1045$. The Frank-Dehiscence group (median = 0.67) and the control group (median = 0.53) also did not show significant difference ($U = 672$, $p = 0.093$).

We then compared the PR *notch depth* between the different grades of the Thin-Bone ears, the Frank-Dehiscence group, and the control group. The *notch depth* was statistically similar across the different groups of Thin-Bone grades (Fig. 7.11). All Thin-Bone grades were statistically similar to the control group. Further analysis with more samples in each grade is necessary to test for significance. We combined Grades 3 and 4 to statistically compare to Frank-Dehiscence and control groups. Statistical differences using MW-U tests were found between Frank-Dehiscence (median = 0.17) and Thin-Bone (Grades 3 and 4; median = 0.084, $p < 0.0066$) and Frank-Dehiscence and control groups ($p = 4.27e-04$). Details on the analysis can be found in the Appendix in section A7.3.

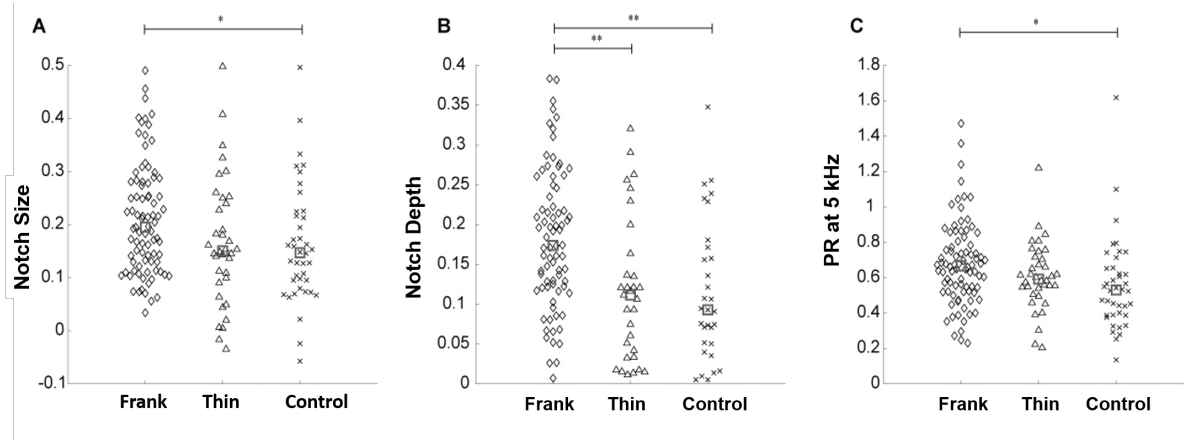


Figure 7.10: Comparison of PR features: A) Notch Size, B) Notch Depth, C) PR magnitude at 5 kHz
 * indicates a significance level of $p < 0.0167$, ** indicates a significance level of $p < 0.00167$

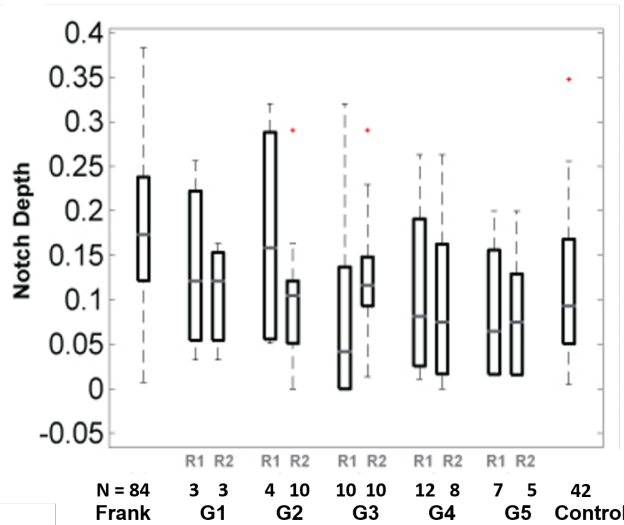


Figure 7.11: Boxplot comparing Notch Depth of the different grades of Thin-Bone to both the Frank-Dehiscence group and the control group.

3.6 Umbo Velocity in Frank-Dehiscence, Thin-Bone, and control groups

UV referenced to sound stimulus tended to be higher in magnitude in ears with SCD than in normal ears below 2 kHz, with a corresponding phase change near the frequency where the magnitude increased (Rosowski et al. 2004). This suggested the influence of a decrease in cochlear impedance. Here we determine if the *peak magnitude* of UV at low frequencies below 2 kHz, as well as the *slope of the phase* centered at the frequency of the peak-magnitude differs in the Frank-Dehiscence group as compared to the Thin-Bone group and control group.

UV magnitudes for each group is plotted in Figure 7.12A. The median *peak magnitude* in the Frank-Dehiscence group (median = 0.33 mm/sPa) was higher than the median *peak magnitude* found in the Thin-Bone group (median = 0.26 mm/sPa) as well as the control group (median = 0.25 mm/sPa). A KW-test revealed barely significant differences across groups in peak value (KW chi-square = 6.07, $p = 0.048$). However, multiple post-hoc MW-U tests (requiring $p < 0.0167$ for significance) did not reveal any significant differences between the 3

groups. A trending difference in UV peak value was found between Frank-Dehiscence (median = 0.33 mm/sPa) and Thin-Bone (median = 0.26 mm/sPa), with $U = 1124$ and $p = 0.023$.

For the slope of the UV phase at the frequency of the peak magnitude, the KW-test revealed a significant difference between groups (KW chi-square = 18.98, $p = 7.6E-05$). The UV phase slope for the three groups are plotted in Fig. 7.12B. The MW-U tests (requiring $p < 0.0167$ for significance) revealed that the Frank-Dehiscence group (median = 250 μsec) had a steeper negative phase slope than the Thin-Bone group (median = 187 μsec) with $U = 1458$ and $p = 7.3E-4$. The Frank-Dehiscence group (median = 250 μsec) also had a steeper slope than the control group (median = 197 μsec) with $U = 958.5$ and $p = 2.9E-04$. This corresponded to a longer UV group delay for ears with Frank-Dehiscence. No significant difference was found between the Thin-Bone (median = 187 μsec) and control (median = 197 μsec) groups ($U = 1039$, $p = 0.85$).

The UV phase slopes for the different Thin-Bone grades were compared to the Frank-Dehiscence group and control group. Figure 7.13 shows that the negative phase slopes were similar across the different Thin-Bone grades, and all Thin-Bone grades were similar to the control group. Further analysis with more samples in each grade is necessary to test for significance. We combined Grades 3 and 4 to statistically compare to Frank-Dehiscence and control groups. Statistical differences using MW-U tests were found between Frank-Dehiscence (median = 250 μsec) and Thin-Bone (Grades 3 and 4; median = 174 μsec , $p < 0.0018$) and Frank-Dehiscence and control groups ($p = 2.9E-04$). Details on the analysis can be found in the Appendix in section A7.4.

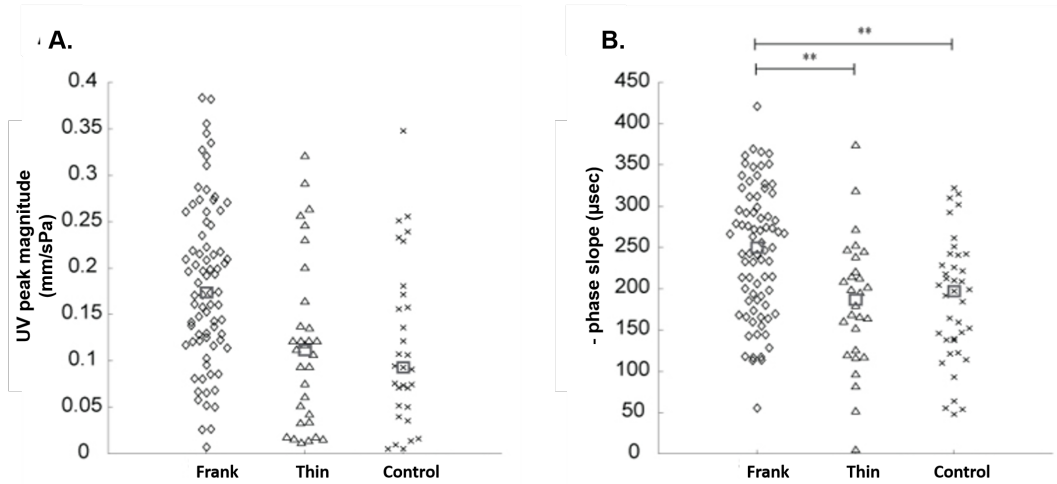


Figure 7.12: Comparison of UV features: A) UV peak magnitude, and B) Negative of the UV phase slope. ** indicates a significance difference of $p < 0.00167$.

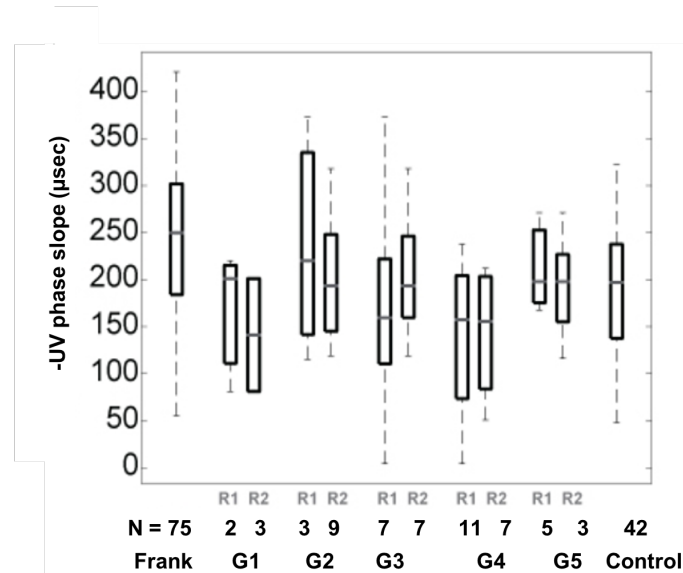


Figure 7.13: Boxplot comparing Negative of the UV phase slope of the different grades of Thin Bone to both the Frank-Dehiscence group and control group. Numbers of ears are at the bottom of the x-axis for each group.

4. Discussion

In this study we investigated symptomatic cases of patients with thin bone over the SSC (*i.e.* near dehiscence). Because patients with thin SSC bone sometimes present with symptoms similar to SCD symptoms, diagnosis and treatment is challenging. In some cases, SCD

symptoms for patients with thin SSC bone, that appears intact with direct visualization during surgery, have been alleviated by intentionally making a dehiscence then repairing this dehiscence (Ward et al. 2013). Yet it is unknown whether thin SSC bone is indeed similar to SCD. The current literature related to thin bone over the SSC is limited. The most important work so far has been the investigation of audiometric (Ward et al., 2013; Noij et al., 2017), oVEMP (Ward et al., 2013) and cVEMP (Noij et al., 2017) measurements. The Noij et al. study was unable to distinguish differences in audiometric and cVEMP measurements between ears with thin SSC bone and normal ears, although ears with SCD differed from thin SSC and normal ears. In the Ward et al. (2013) study, 4 out of 11 thin-bone ears showed elevated ABG (> 15 dB), and 5 out of 11 ears had elevated oVEMP amplitude (>18 μ V), similar to SCD ears. In the present study, we investigated symptoms, audiometric measures (AC, BC, ABG), cVEMP thresholds, as well as mechanical measures (PR from WAI, and UV) to determine if SSC with thin bone is similar to SCD. The present study generally had reasonably large numbers of ears in each group allowing for statistical strength.

4.1 Symptoms between Frank-Dehiscence and Thin-Bone

Ward et al. (2013) found that out of 157 symptomatic patients diagnosed with SCD, 10 patients (11 ears) were found to have thin SSC bone by surgical inspection. Retrospectively, they found from pre-operative information that patients with thin SSC bone had a mix of symptoms, similar to patients with SCD. Likewise, in the present study, we found that the incidence of various auditory and vestibular symptoms was similar across patients in the Thin-Bone and Frank-Dehiscence groups. Interestingly, Ward et al. (2013) reported that surgical repair of the thin SSC bone relieved at least one primary symptom in all patients.

SCD is usually diagnosed by CT imaging. Currently, no established definition of thin bone over the SSC exists, and varying methods among radiologists to determine thin SSC bone result in inconsistent diagnostic reports. In the present study, two experienced neuro-radiologists independently graded the images while blinded to all information except the images of the Thin-Bone group. The Thin-Bone group consisted of ears that had previous diagnostic reports by varying radiologists describing thin bone over the SSC. In our study, the two blinded neuro-radiologists graded the images of the Thin-Bone group similarly, especially with respect to the order of grades from 1 to 5 across images. The two neuro-radiologists determined that some of the images in the Thin-Bone group actually had a noticeable small SCD (Grade 1), while others had a normal covering of bone (Grade 5). Yet as mentioned above, we found that symptoms were similar between the Frank-Dehiscence group and all the Thin-Bone grades. However, the reliability of statistical analyses of each grade of Thin-Bone was reduced due to the low number of ears in each grade.

Our cohort in the Thin-Bone group were all symptomatic (we did not include incidental CT findings of thin SSC bone). Though diagnosed as thin with CT, it is possible that the Thin-Bone group included ears with micro-dehiscences not visible under CT or under surgery. Pisano et al. (2012) hypothesized the possibility that multiple micro-dehiscences in thin SSC bone could add together to affect the ear similarly to a small pinpoint (~0.5 mm) dehiscence. In fresh human temporal bone, such small pinpoint dehiscence was shown to not only decrease intracochlear pressure at low frequencies (similar to larger dehiscences), but sometimes also to decrease intracochlear pressure at mid frequencies. This mid-frequency decrease normalized with increase in dehiscence size while the low-frequency decrease decreased further. The mid-frequency pressure change observed in pinpoint dehiscent SSC may be due to an increase in resistance at

the small dehiscence, which would not be affecting large dehiscence and no dehiscence. It is possible that SCD-type symptoms are the result of micro-dehiscences. As will be discussed below, although symptoms were similar between Frank-Dehiscence and Thin-Bone groups, audiometric, as well as cVEMP and most features of mechanical measures were not similar between Frank-Dehiscence and Thin-Bone groups. For all measures, the Thin-Bone group was similar to the control group.

4.2 Audiometric and cVEMP measurements between Frank-Dehiscence and Thin-Bone

Audiometric measures (AC, BC, ABG), and cVEMP thresholds generally differed between the Frank-Dehiscence groups and the Thin-Bone groups. Furthermore, the Thin-Bone groups were similar to the control groups for these measurements. For the different grades of Thin-Bone, we had expected Grade 1 (small SCD) to be similar to Frank-Dehiscence; however, all grades were generally similar to the control group.

Because the Thin-Bone group included what appeared to be small SCD (Grade 1) and normal bone over SSC (Grade 5), analyses were performed on a combined group of grades 3 and 4. We found that the combination of grades 3 and 4 (n=23) were indistinguishable from the control group. Also, the Frank-Dehiscence group differed from the combination of grades 3 and 4. These analyses are detailed in the Appendix.

Past studies have shown that audiometric measurements can differ between SCD and normal ears. Noij et al. (2017) found that both ABGs at 250 Hz and cVEMP thresholds at 500 Hz can differ between the SCD group and the thin SSC bone group, but neither measurements differed between the thin SSC bone group and normal control group. Our results in the present study were consistent with their findings; the Frank-Dehiscence group exhibited lower cVEMP

thresholds and larger ABGs than the Thin-Bone and the control group. The Thin-Bone and control groups were similar. We also analyzed AC and BC thresholds and found that the increase in AC thresholds in the Frank-Dehiscence group was the major contributing factor to the larger ABGs seen in the Frank-Dehiscence group at low frequencies (250 and 500 Hz). For BC thresholds, the Frank-Dehiscence group had lower than normal thresholds at low frequencies (< 1 kHz), but statistically significant difference was only found at 250 Hz.

4.3 Mechanical measures between Frank-Dehiscence and Thin-Bone

The mechanics of the ear measured at the ear canal with PR (extracted from WAI) and UV were compared between the symptomatic Thin-Bone group, the symptomatic Frank-Dehiscence group and the control group with normal bone cover over the SSC. For PR, a notch-detecting algorithm (Merchant et al. 2015) extracted two features—the *notch size* and the *notch depth*. For *notch size*, the median of the Thin-Bone group was between the median of the Frank-Dehiscence group and median of the control group. However, the only significant difference in *notch size* between groups was found between the Frank-Dehiscence group and the control group. The Frank-Dehiscence group and the Thin-Bone group did not have a significant difference. Also, the Thin-Bone group and the control group had no significant difference. With *notch depth*, the Frank-Dehiscence group statistically differed from the Thin-Bone, and the Frank-Dehiscence group differed from the control group. The Thin-Bone and control groups did not have a significant difference. As in Merchant et al. (2015), the present study suggests that the PR notch-detection algorithm has potential diagnostic utility to determine SCD (Frank-Dehiscence) from normal ears (control). However, the Thin-Bone group was not mechanically similar to Frank-Dehiscence, but more similar to normal ears.

Another feature, the PR magnitude at 5 kHz, was analyzed to compare between groups. The Thin-Bone group had a median magnitude that was in-between the medians of the Frank-Dehiscence group and the control group. However, the only statistically significant difference between groups was between the Frank-Dehiscence group and the control group. No significant difference was found between Frank-Dehiscence and Thin-Bone groups, nor between Thin-Bone and control groups.

Another mechanical measure analyzed was the UV. Similar to previous studies (Rosowski et al., 2008), Frank-Dehiscence group resulted in higher UV magnitudes below 2 kHz than the control group. In our study, two UV features were analyzed: the *peak magnitude* of a resonance below 2 kHz, and the corresponding phase change (negative slope of the phase versus frequency) at that resonance frequency. The phase slope of the Frank-Dehiscence group had a statistically significant steeper slope compared to both the Thin-Bone and control groups. No statistical difference in phase slope was found between the Thin-Bone and control groups. The UV *peak magnitude* did not show statistically significant difference between groups. This was likely due to the large variation in UV *peak magnitude* for each group. Also, the frequency resolution for UV measurements was low, preventing accurate *peak magnitude* measurements for a resonant frequency because the true *peak magnitude* may have occurred between measured frequency points.

4.4 Limitations of audiometric, cVEMP and mechanical measures

Although some measures showed statistical difference between some groups, using any of the studied measures have limitations for diagnostic purposes. For example, cVEMP and ABG results from individual ears have overlapping values between the Frank-Dehiscence group and the control group. Hunter et al. (2017) previously showed that cVEMP thresholds less than or

equal to 70 dB normalized hearing level (nHL, which is equivalent to 103 dB peSPL) can differentiate SCD ears from normal hearing ears with 73% sensitivity and 94% specificity. As shown in Figure 7.4 for cVEMP thresholds, only 2 Thin-Bone ears and 4 control ears were equal to or less than 70 dB nHL or 103 dB peSPL. Although the cVEMP thresholds in the Frank-Dehiscence group is significantly different from both the Thin-Bone group and the control group, 20 Frank-Dehiscence ears fell in the range of the control group. Similarly, ABG from individual ears can overlap between the Frank-Dehiscence group and both the Thin-Bone and control groups. ABG considered normal (i.e. below 20 dB) are observed in all groups (Figure 7.5); for example, approximately 36% of Frank-Dehiscence ears have normal ABG. Previously, it was observed that the effect of SCD on AC threshold increases with decreasing frequency. Although this trend is similar across ears, the absolute effect in dB of SCD can vary across ears (Cheng et al. 2019). Less overlap and better differentiation between Frank-Dehiscence and control may be possible if we could obtain AC thresholds at lower frequencies than 250 Hz in the future.

Overlap of mechanical measurements – features of PR and UV – among individual ears across groups were also observed. Therefore, a single metric is unable to classify SCD from normal ears and from Thin-Bone ears with accuracy. In the future, we plan to utilize machine learning techniques to incorporate multiple features to improve classification of SCD and Normal (as in Chapter 5).

5. Conclusion

Patients presenting with symptoms similar to SCD symptoms are sometimes found to have thin bone over the SSC. We determined whether symptoms observed in the Thin-Bone group are similar to symptoms in the Frank-Dehiscence group. Because of the difficulty and variability in judging Thin-Bone among various radiologists, two experienced neuro-radiologists graded the

Thin-Bone group (initially grouped as Thin-Bone from information in the CT reports written by various radiologist). Typical SCD symptoms – autophony, hyperacusis, aural fullness, audible bodily sounds, vestibular symptoms (i.e. Tulio’s phenomenon, Hennebert sign as well as imbalance) – were found to be similar between the Thin-Bone and Frank-Dehiscence groups.

Audiometry and cVEMP were not similar between Thin-Bone and Frank-Dehiscence groups. AC, BC and cVEMP thresholds, and ABG, all were generally similar between the Thin-Bone and control groups. However, the Frank-Dehiscence group differed from Thin-Bone and control groups. Furthermore, all grades of Thin-Bone were similar to control ears, and all grades of Thin-Bone differed from the Frank-Dehiscence group.

The possibility of mechanical differences between Thin-Bone and control groups was investigated to explain the SCD-like symptoms in the Thin-Bone group. However, we found that the ear-canal measurements such as WAI and UV in the Thin-Bone group did not show features that were different from the control groups. Two features – *notch size* and PR magnitude at 5 kHz – did not differ between Frank-Dehiscence and Thin-Bone, nor between Thin-Bone and control. However, these two features did show significant differences between Frank-Dehiscence and control. It is possible that more data is necessary to show statistical difference between Thin-Bone and control. In conclusion, our study was unable to determine audiometric, cVEMP or mechanical measurements at the ear canal that showed similarity between Thin-Bone and Frank-Dehiscence, despite their similarity in symptoms. Furthermore, the Thin-Bone group with SCD-type symptoms appeared similar to the normal control in all metric. It is possible that the Thin-Bone group with SCD-type symptoms have a different etiology than that of SCD, especially because some of these symptoms are considerably common among other otologic pathologies. It is also possible that the symptoms experienced by the Thin-Bone group is due to micro-

dehiscence of the SSC, but audiometric, cVEMP, PR and UV are not sensitive to the mechanical changes imparted by such a small dehiscence.

**CHAPTER 8. Fracture of the incus caused by digital manipulation of the ear canal and its
diagnosis using wideband acoustic immittance**

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ABSTRACT

Objective: To describe the first reported case of a fracture of the long process of the *incus* due to digital manipulation of the ear canal and to discuss diagnostic markers for ossicular fractures.

Patient: 46-year old woman with incessant clicking and crunching in her left ear, and hearing loss after digital manipulation of the wet ear canal.

Intervention: Diagnostic evaluation and therapeutic ossiculoplasty

Main Outcome Measure(s): Audiometric and wideband acoustic immittance (WAI) measurements were made prior to surgery to investigate the cause of conductive hearing loss (CHL).

Results: The clinical suspicion of an ossicular fracture was confirmed by a large narrow-band decrease in power reflectance (calculated from WAI) at frequencies between 600-700 Hz, and a mid- to high-frequency air-bone gap. Exploratory tympanotomy revealed an ossicular fracture of the distal aspect of the long process of the *incus*. Ossiculoplasty with bone cement resolved bothersome clicking sounds.

Conclusion: A finger inserted into the ear canal can produce an air seal, and subsequent quick removal of the finger can result in the fracture of an ossicle. The public and medical community should be cognizant of this form of trauma because insertion of a finger, ear plug, and earphone into the ear canal are common. Ossicular fractures can result in high-frequency CHL, and can be misdiagnosed as sensorineural loss because bone conduction thresholds are not measured above 4-kHz. As in this case, an ossicular fracture may be misdiagnosed and result in inappropriate treatment. Here, WAI, a non-invasive measure of ear mechanics, accurately diagnosed an ossicular fracture.

1. Introduction

We report an *incus* fracture due to digital ear-canal manipulation for the first time. Malleus fracture by this form of trauma has been reported (Blanchard, Abergel, Ve, Williams, & Ayache, 2011; W Chien et al., 2008a; Iurato & Quaranta, 1999; Niklasson & Tano, 2010; Orabi, Baumgartner, Gstoettner, & Hamzavi, 2006; Pedersen, 1989; Punke & Pau, 2006; Tan, Ullman, Pearl, & Carey, 2016). When a finger in the ear canal produces a seal (especially with moisture such as after exercise, swimming or a shower), a quick outward movement of the finger can create a sudden negative pressure, producing enough force to fracture an ossicle (Niklasson & Tano, 2010). Diagnosing an ossicular fracture can be difficult. Conductive hearing loss (CHL) in an ear with a normal tympanic membrane and an aerated middle ear cavity can be due to various macro-mechanical pathologies: ossicular discontinuity (e.g. fracture), ossicular fixation (e.g. otosclerosis) or inner-ear lesion (e.g. superior canal dehiscence). For a loose ossicular chain, only a high-frequency hearing loss above 4 kHz may be evident, leading to assumption of only a sensorineural hearing loss. Even during middle-ear surgery, determining an ossicular fracture can be challenging depending on the location of the fracture. Here, we discuss the diagnostic markers for ossicular fractures to prevent misdiagnosis and inappropriate treatments. In addition to audiometric measures, we use wideband acoustic immittance (WAI), a promising measurement for the differential diagnosis of CHL (H. H. Nakajima et al. 2012a). This non-invasive ear-canal measurement examines the acoustic power response of the middle ear across a wide frequency range (200 – 6000 Hz) under ambient pressure. Power reflectance (PR), derived from WAI, is the ratio of acoustic power reflected from the middle ear to the incident power. Thus, a PR of 1 indicates that all power is reflected by the tympanic membrane (representing a stiff middle-ear

system), and 0 indicates that all power is absorbed. Here, we show that PR, a measure of middle-ear mechanics, can accurately diagnose a loose ossicular chain.

2. CASE REPORT

A 46-year-old woman with history of osteoporosis developed sudden symptoms of clicking sound, as well as aural fullness and mild hearing loss in her left ear after digitally manipulating the wet ear canal. She is otherwise healthy. She previously underwent prophylactic oophorectomy, hysterectomy and bilateral mastectomies for having a BRCA1 mutation in the setting of a strong family history of breast and ovarian cancer. The only prescription medication she takes is estradiol. After the incident in her left ear, she was particularly bothered by “incessant” loud clicking and crunching sounds that changed in response to certain tones and pressure changes. She also experienced intermittent autophony in the left ear and intermittent hearing loss that changed with head position. She was treated for presumptive diagnosis of sensorineural hearing loss by an outside otolaryngologist with four intratympanic steroid injections for 4-6 weeks, but experienced no improvement. She was evaluated by another otolaryngologist and received an additional series of intratympanic steroid injections. After a year of no improvement in symptoms, she presented to our institution for a third opinion.

Physical exam showed normal tympanic membranes and aerated middle ears bilaterally. Tuning fork tests were normal at 512 Hz. The audiogram showed a 20 dB CHL at and above 1 kHz in the left ear (Fig. 8.1). A standard 226-Hz tympanogram showed high middle-ear compliance on the left. Acoustic reflexes to broadband stimulation were present bilaterally—such reflexes are typically absent in ossicular pathology and present in “third window” pathologies of the inner ear, such as superior canal dehiscence (SCD). To aid in establishing the diagnosis, the patient underwent WAI measurements to assess middle-ear mechanics. As shown in Figure 2A, the PR in the affected left ear showed a large narrow-band decrease (indicated by

an arrow) between 600-700 Hz, while the right ear showed PR within the normal limits. This WAI diagnostic measurement, in addition to the high-frequency CHL, was consistent with partial ossicular discontinuity—likely an ossicular fracture (Farahmand et al. 2016; Nakajima et al. 2012a). The unaffected right ear was audiometrically normal. Unremarkable computed tomography (CT) of the left temporal bone provided no evidence of ossicular fracture or SCD.

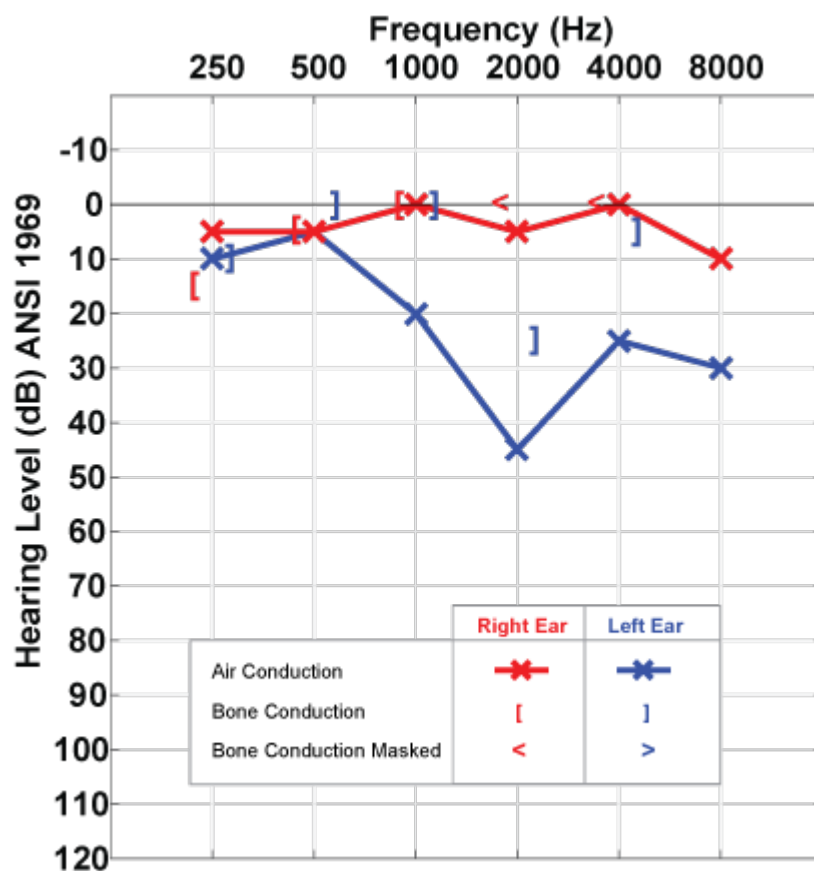


Figure 8.1: Audiogram for the right (red) and left (blue) ear. The left ear shows conductive hearing loss at mid and high frequencies with a Carhart notch at 2000 Hz.

The hearing loss was not severe: only a high-frequency 20 dB air-bone gap; thus, her hearing loss was not the reason for surgical intervention. However, she elected surgery because she was severely distraught by the extremely bothersome loud clicking sounds in her left ear sustained after finger manipulation, and both audiogram and WAI was consistent with ossicular

looseness. Exploratory tympanotomy revealed a displaced fracture of the distal aspect of the long process of the incus. The intraoperative image in Figure 3 shows a subtle step-off (black arrow), where the subtleness of the fracture is due to the fibrous tissue surrounding the incus. Upon gentle palpation, the opposing ends of the incus fracture moved freely and independently of each other. Removal of the fibrous tissue prior to gluing revealed a complete fracture with displacement (not photographed). Otherwise the middle ear appeared normal, and ossicles were mobile. Ossiculoplasty with OtoMimix bone cement was performed to repair the incudal fracture. Immediately after surgery, she was delighted with the resolution of the clicking and reported subjective improvement in hearing. The post-operative audiogram and PR did not significantly change relative to the pre-operative ones.

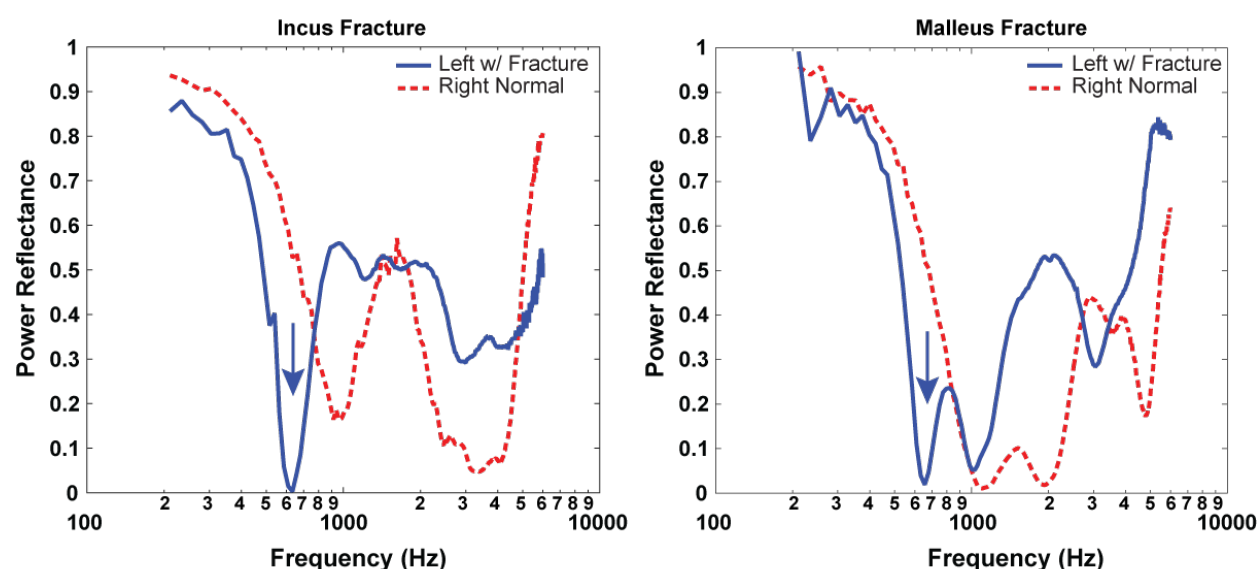


Figure 8.2: A) Power reflectance measurements for this study's patient with a fracture at the long process of the incus on left ear. B) A different patient with a fracture of the malleus in the left ear. A and B, Arrow for the affected left ear (blue solid line) indicates a narrow frequency notch around 600 to 700 Hz. The unaffected right ear (red dashed line) has a normal frequency response.

3. DISCUSSION

This is the first report of a fracture of the incus due to digital manipulation of the external auditory canal to the best of our knowledge. In previous case studies, patients presenting with a history of digitally manipulating the ear canal were diagnosed with isolated fractures of the malleus (W Chien, McKenna, Rosowski, & Merchant, 2008b; Niklasson & Tano, 2010). Both incus and malleus fractures produce a similar PR notch around 600-700 Hz, as shown in the examples of Figure 8.2. Both patients in Figure 8.2 had sudden hearing loss after digital manipulation of the ear canal, resulting in a fracture of the long process of the incus (this study; Fig. 8.2A) and of the manubrium of the malleus (Fig. 8.2B) confirmed during surgery. Furthermore, the patient in the current case study had a history of osteoporosis, a condition that has been clinically linked to increased risk of ossicular fracture (Babich M, Hoffmeister D, Doughty A, 2009; Radaei & Gharibzadeh, 2013).

Diagnosis of an ossicular fracture can be difficult with conventional diagnostic methods, even during surgery if the fracture line is not easily visible. CT generally cannot diagnose ossicular fractures (with no or minimal displacement) due to limited resolution (Hato, Okada, Hakuba, Hyodo, & Gyo, 2007). Also, standard 226 Hz tympanometry is poor at detecting fractures because the prominent effect is near 600-700 Hz. In a previous study, tympanometry was shown to be normal in all six surgically confirmed cases of ossicular discontinuity (Nakajima et al. 2012a). Stapedial reflex can sometimes differentiate CHL pathologies because it is often absent in ossicular pathologies and present in inner-ear lesions (such as SCD). However, the presence of stapedial reflex in this case underscores that stapedial reflex is an unreliable measure of an ossicular fracture, where the low-frequency sound transmission is normal.

Often, as in this case, misdiagnosis results in inappropriate treatment and significant delay of correct diagnosis. When air-bone gaps at high frequencies are significantly larger than at low frequencies, clinicians should suspect loose ossicular chain, where normal contact of an ossicular joint or continuous bony segment is replaced by soft tissue or simply by contact of opposing bones, as demonstrated in a study with clinical and experimental evidence (Farahmand et al., 2016). However, as in this patient, ossicular fractures may be misdiagnosed as a sensorineural hearing loss, especially if hearing loss is only above 4 kHz where CHL is not tested. Furthermore, though high-frequency CHL can be useful diagnostically, some fractures and partial discontinuity can also result in low-frequency CHL, thus similar to other conductive pathologies such as ossicular fixation, SCD and complete ossicular discontinuity.

We found that WAI, a simple non-invasive measurement, can help diagnose a loose ossicular chain. PR in these cases reveals a significant decrease at a narrow band of frequency at around 600 Hz (Fig. 8.2). Previously, we showed that differentiating ossicular discontinuity from other pathologies with CHL and normal otologic exam using WAI and audiometric measurements had a high sensitivity of 83% and a specificity of 96% (Nakajima et al. 2012a, 2013c). In this case study, the patient had a prominent notch in PR near 600 Hz and mid- to high-frequency CHL, which confirmed the clinical suspicion of ossicular fracture prior to exploratory tympanotomy. Surgical exploration of the middle ear confirmed the diagnosis and revealed a displaced fracture of the long process of the incus near the stapes (Figure 8.3). Her most concerning symptom and indication for surgery was the bothersome clicking; this completely resolved after repair of the displaced fracture of the incus with bone cement. The stable post-operative PR and audiogram possibly reflects residual looseness of the ossicular chain. This

could be due to loosening of ossicular joints or fracture of the malleus or stapes (consistent with Farahmand et al. 2016).

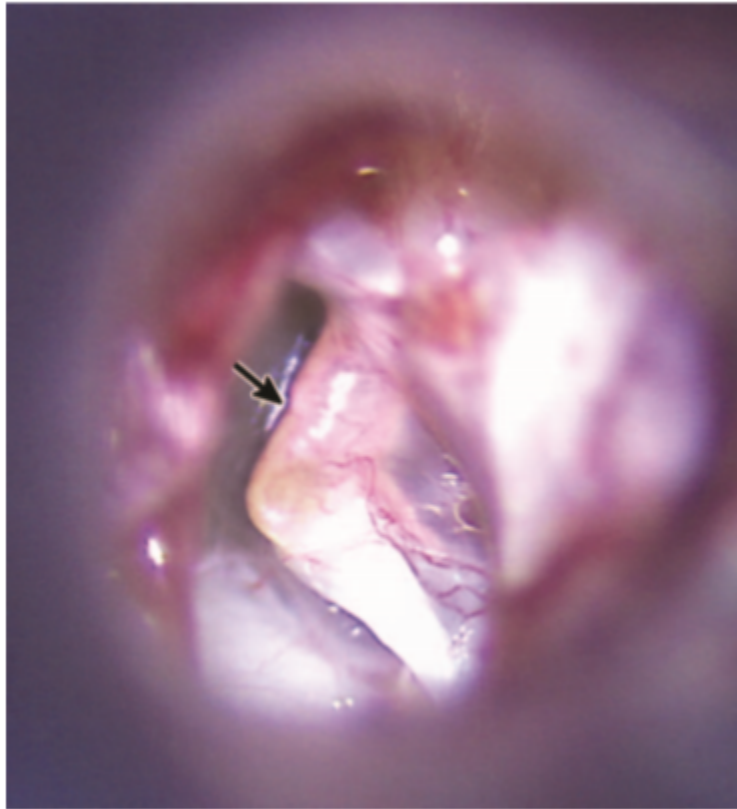


Figure 8.3: Intraoperative view of the distal end of the incus with a subtle fracture, as indicated by arrow pointing to step-off. Upon palpation, the opposing ends of the incus fracture moved freely and independently of each other.

4. CONCLUSION

Clinicians should suspect ossicular fracture: 1) if there is a history of manipulating the auditory canal with a finger resulting in sudden hearing loss, 2) if conductive hearing loss is more significant at high than low frequencies, and 3) if power reflectance shows a large sharp notch at around 600-700 Hz. Ossiculoplasty can provide immediate symptoms such as clicking sound due to an ossicular fracture. We urge the public to avoid inserting a finger in the ear canal, and to be aware of the possible harm of rapidly extracting earplugs or earphones from the ear canal.

CHAPTER 9. Conclusions

This dissertation explores the use of non-invasive, ear-canal measures to diagnose conductive hearing loss (CHL). When a patient with CHL presents with a normal tympanic membrane and an aerated middle ear, it is difficult to pinpoint the location of the mechanical lesion. It can be a middle ear abnormality such as a loose ossicular chain or fixation of one or more of the middle ear bones, or it can be an inner ear lesion such as a dehiscence overlying the bony superior semicircular canal. In these CHL pathologies, the symptoms vary across ears and thus make it difficult to determine the pathology solely by symptomology. Clinicians currently use audiograms, tympanograms, acoustic reflex, and sometimes vestibular evoked myogenic potentials (VEMPs) to determine whether the CHL occurs due to a middle ear or an inner ear lesion. One single diagnostic cannot accurately differentiate these mechanical lesions of the ear, and at times a combination of these conventional methods still fail to detect the lesion. To confirm diagnosis of a CHL pathology with a normal tympanic membrane and an aerated middle ear, otologists perform exploratory middle ear surgery or order and review a high-resolution temporal bone CT scan—both diagnostics that are not typically standard of care for CHL patients. This leads to delay in diagnosis or unnecessary treatment. Here, we proposed that wideband acoustic immittance (WAI), a non-invasive, inexpensive diagnostic method can be used to measure mechanics to differentiate between various pathologies to prevent misdiagnosis and avoid wrong and unnecessary treatment.

One of the main goals of this dissertation was to build diagnostic classifiers to differentiate CHL pathologies using wideband acoustic immittance (WAI) measures. From chapters 2-5, we propose multiple methods to classify pathological and non-pathological ears. In chapters 2-4, we took a structure-based model approach to simulate WAI patterns of otosclerosis, ossicular discontinuity and superior canal dehiscence. In Chapter 2, we performed a thorough

analysis of 3 previously published middle ear models to determine which model best simulates WAI measures and umbo velocity in 1) healthy, normal ears, 2) ears with stapes fixation and 3) ears with ossicular disarticulation. The Rosowski and Merchant (1995) model, modified from Kringlebotn's (1988) model, produced the best estimates of WAI measures. Thus, in Chapter 3, we built a new structure-based model that incorporated the Rosowski and Merchant (1995) middle ear model. The ear canal was modeled as a lossy 1D transmission line and the inner ear included the impedances of the round window, cochlea and superior semicircular canal. Chapter 3 explored the use of this new structure-based model to differentiate pathological ears from normal ears simply by fitting the model to individual ears and comparing model parameter values across ears. In this particular study, we collected WAI data measured in SCD patients before and after surgical repair of the dehiscence. WAI measures after surgical repair was similar to WAI measures in normal, healthy ears, and thus post-surgical data was used to compare against pathological, SCD ears. The resistance and mass parameters (R_{SCD} and L_{SCD}) of the superior canal impedance branch were vastly different across these two groups. When the model was fit to individual post-surgical data, the values of R_{SCD} and L_{SCD} were extremely large, where the branch acted as an open circuit, and thus the model was similar to a normal, baseline model (without dehiscence). By simply using these two model parameters we were able to classify SCD and post-surgical repair ears with a generalized error rate of only 4%.

Chapter 4 aimed to differentiate SCD and two middle ear lesions: stapes fixation and ossicular discontinuity, and provided an automated method to distinguish between these CHL pathologies that are often misdiagnosed in the clinic. We modify the same structure-based model developed in Chapter 3 to simulate stapes fixation (decrease the compliance of the annular ligament 10-folds) and ossicular discontinuity (decrease the impedance of the incudo-stapedial

joint so the branch acts as a short circuit). A decision tree that combined both ABG and WAI data classified each ear as stapes fixation (SF), SCD, and ossicular discontinuity (OD). The first level of the decision tree used air-bone gap information to separate ears into 4 categories in order to decide between a maximum of 2 pathologies. The second level of the decision tree used a structure-based model approach to determine which pathological (SF, OD, or SCD) model produced the least error (difference between model and actual data). By using these classification methods, the overall accuracy of detecting the correct diagnosis was 91%. The average sensitivity and specificity of the decision tree classifier was 91.3% and 96.7%, respectively.

Chapter 5 explores the use of machine learning techniques to automate diagnosis for future larger sample sizes. We were able to detect important features in WAI measures that differentiated healthy, normal ears and SCD. Out of the three CHL pathologies we studied, SCD is the most difficult to diagnose using WAI. The characteristic 1 kHz decrease (notch) in power reflectance (or increase in absorbance) is observed in many SCD ears but can also be seen in normal, healthy ears. Thus, we aimed to find other important features across a larger frequency span and determine whether there were differences in the notch shape between normal and SCD ears. We built a RF classifier that incorporated 6 important features: power reflectance at 790 Hz, 1000 Hz and 5070 Hz, ABG at 250 Hz, notch size and notch depth. Model performance was evaluated based on sensitivity and specificity values. With a RF classifier with this particular feature set, we were able to achieve high sensitivity (91%) and specificity (87%). In the future with larger sample sizes, a multi-class classification method can be used to differentiate SCD from other mechanical lesions. Additionally, parameter values of the structure-based model (fit to individual ears) can be used as features to improve classification.

In Chapter 6, SCD effects on WAI were carefully studied in human cadaveric temporal bones. In five temporal bones, we measured power reflectance across a wide frequency span (20-10kHz) to assess mechanical changes before and after SCD. Similar to clinical WAI patterns in SCD ears, a notch occurs at frequencies between 0.48 and 0.76 kHz. However, in several experiments, we observed decreased power reflectance (i.e. notch) around the same frequency range in the normal state before SCD due to the specimen's open middle ear cavity (MEC). Due to the effects of both SCD and open MEC between low to mid frequencies, some of the SCD effect can be masked by the effect of the MEC in temporal bone specimens. This study showed the limitations of carefully studying SCD with WAI in an open MEC specimen. However, with careful manipulation of the temporal bone to simulate SCD, we found that an ear-canal measure like WAI can pick up on mechanical changes due to an inner lesion like SCD.

In Chapter 7, we meticulously studied objective and subjective measures to differentiate thin bone and frank dehiscence of the bone overlying the superior semicircular canal (SSC). The reported subjective symptoms of groups of patients with SCD or thin SCC bone were very similar, however objective measures such as audiological thresholds, cVEMP thresholds, WAI, and umbo velocity were significantly different between the two groups. The results of the objective tests in thin bone patients were similar to those in normal, healthy ears. We also showed the difficulty in visualizing and differentiating thin intact bone from a dehiscent SSC using a high-resolution temporal bone CT scan. Currently, the only method to diagnose SCD is via CT scan, but due to limitations of CT, it is sometimes difficult to pinpoint a dehiscence. In these cases, we suggest using objective measures such as WAI or umbo velocity (via laser Doppler vibrometry) to determine if there are any mechanical changes due to a dehiscence of the SSC.

Chapter 8 was a case report that clearly illustrated the problems in current clinical diagnostics that led to delayed diagnosis and unnecessary treatment for a patient who experienced bothersome clicking sounds due to a subtle fracture of the incus. With WAI, we were able to detect a notch in PR that occurred at 700 Hz, a pattern commonly found in patients with loose ossicular chain. In this paper, we advised clinicians to suspect ossicular fracture if conductive hearing loss is more significant at high than low frequencies, and if power reflectance shows a sharp notch in power reflectance at around 600 to 700 Hz. When it is difficult to pinpoint a middle or inner ear lesion using currently available diagnostics, we advise the use of WAI, a non-invasive, ear-canal measure that shows distinct patterns for ossicular fixation, ossicular discontinuity and superior canal dehiscence.

Appendix A2

1) The lossy transmission-line models of tube segments used to model an air-filled ear canal is as follows

$$Y = j\omega \left[1 + \frac{2(\gamma-1)}{k_p a} \frac{J_1(k_p a)}{J_0(k_p a)} \right] \text{ where } k_p = \sqrt{\frac{j\omega}{h^2}}, h^2 = \frac{\kappa}{\rho c_p}$$

$$Z = j\omega \frac{\rho}{\pi a^2} \left[1 + \frac{2}{k_s a} \frac{J_1(k_s a)}{J_0(k_s a)} \right]^{-1} \text{ where } k_p = \sqrt{\frac{-j\omega\rho}{\mu}}$$

$$G = l_{EC} \sqrt{Y \times Z}$$

$$Z_0 = \sqrt{\frac{Z}{Y}}$$

$$A = \cosh(G)$$

$$D = A,$$

$$B = Z_0 \times \sinh(G),$$

$$C = \frac{\sinh(G)}{Z_0},$$

$$Z_{in} = \frac{AZ_{TM} + B}{CZ_{TM} + D}$$

$J_1()$ and $J_0()$ are Bessel functions of the 1st and 0th order. Z_{in} is the estimated input impedance of the ear canal and Z_{TM} is the terminating impedance. Other constants relate to properties of air:

$\gamma = 1.41$ ratio of specific heats of the medium

$c = 345$ m/s speed of sound in air

$\rho = 1.18$ kg/m³ density of air

$\kappa = 0.025856658$ W/(m – K) thermal conductivity of air

$\mu = 1.8215568 \times 10^{-5}$ kg/(m-s) absolute viscosity

$c_p = 1005.4152$ J/(kg μ K) specific heat of air

Table A2.1: Parameter values for each of the middle ear models tested in this chapter

Rosowski and Merchant (1995) parameters for middle and inner ear mechanics			
Symbol	Value	Units	Meaning
A_{tm}	6×10^{-5}	m ²	Area of the eardrum

A_{fp}	3.2×10^{-6}	m^2	Area of the stapes footplate
N_{LR}	1.3	Unitless	Lever ratio of malleus-incus complex
C_A	3.9×10^{-11}	m^5/N	Acoustic compliance of the aditus
C_{TC}	4.0×10^{-12}	m^5/N	Acoustic compliance of the tympanic air space
R_A	6×10^6	$Pa \cdot s/m^3$	Acoustic resistance of the aditus
L_A	100	Kg/m^4	Acoustic mass of the aditus
C_T	3.0×10^{-12}	m^5/N	Acoustic compliance parameter of TM model
C_{T2}	1.3×10^{-11}	m^5/N	Acoustic compliance parameter of TM model
R_T	2×10^6	$Pa \cdot s/m^3$	Acoustic resistance parameter of TM model
R_{T2}	1.2×10^7	$Pa \cdot s/m^3$	Acoustic resistance parameter of TM model
L_{T1}	750	Kg/m^4	Acoustic mass parameter of TM model
L_T	6.6×10^3	Kg/m^4	Acoustic mass parameter of TM model
C_{TS}	0.0011	m^5/N	Mechanical compliance of eardrum suspension
R_{TS}	4.3×10^{-2}	$N \cdot s/m$	Mechanical resistance of eardrum suspension
C_{MI}	0		Mechanical stiffness of malleus and incus
R_{MI}	7.2×10^{-3}	$N \cdot s/m$	Mechanical stiffness of malleus and incus
L_{MI}	7.9×10^{-6}	kg	Mechanical mass of malleus and incus
L_S	3.0×10^{-6}	kg	Mechanical mass of stapes
R_J	3.6	$N \cdot s/m$	Resistance of ossicular joints
C_J	4.9×10^{-4}	m^5/N	Compliance of ossicular joints
C_{AL}	9.1×10^{-15}	m^5/N	Acoustic compliance of the annular ligament
R_{AL}	0	$Pa \cdot s/m^3$	Acoustic resistance of the annular ligament
R_C	2×10^{10}	$Pa \cdot s/m^3$	Acoustic resistance of cochlea

L_C	2.4×10^6	Kg/m^4	Acoustic mass of cochlea
Liu and Neely (2010) Hybrid parameters for middle-ear mechanics			
A_{TM}	5×10^{-5}	m^2	Area of eardrum
L_M	8.5×10^{-6}	kg	mass of malleus-incus-eardrum
R_M	0.02	kg/s	resistance of malleus-incus-eardrum
K_M	150	kg/s^2	stiffness of malleus-incus-eardrum
N_{LR}	1.43	Unitless	Malleus-incus lever ratio
R_I	0.4	kg/s	Resistance of incudostapedial joint
C_I	2×10^{-4}	s^2 / kg	Compliance of incudostapedial joint
A_{FP}	6.25×10^{-6}	m^2	Area of stapes footplate
L_S	5×10^{-6}	kg	mass of stapes
R_S	0.08	kg/s	resistance of stapes
K_S	500	kg/s^2	stiffness of stapes
R_C	1.4×10^{10}	kg/s	Acoustic Resistance of cochlea
L_C	$1.6e \times 10^6$	kg/m^4	Acoustic mass of cochlea
K_{RW}	1.1×10^{13}	$\text{kg}/(\text{s}^2 \text{m}^4)$	Acoustic stiffness of round window
R_{RW}	1.29×10^9	kg/s	Acoustic resistance of round window
L_{RW}	5.42×10^5	kg/m^4	Acoustic mass of round window
O'Connor and Puria (2008) model parameters for middle and inner ear mechanics			
T_{tm}	4.61×10^{-5}	s	Eardrum Transmission Line Parameter: wave propagation delay
Z_{0tm}	10.5×10^7	kg/s-m^4	Eardrum Transmission Line Parameter: characteristic impedance
A_{TM}	6×10^{-5}	m^2	Area of the eardrum
M_M	3.24×10^{-6}	kg	mass of malleus
C_M	0.002	s^2 / kg	stiffness of malleus
R_M	0.14	kg/s	resistance of malleus
N_{LR}	1.3	Unitless	lever ratio of malleus-incus complex

C_{IMJ}	6.85×10^{-4}	s^2 / kg	Compliance of incudo-malleal joint
R_{IMJ}	4.56×10^{-2}	kg/s	Resistance of incudo-malleal joint
M_I	7.3×10^{-2}	kg	mass of incus
C_{ISJ}	1×10^{-4}	s^2 / kg	Compliance of incudostapedial joint
R_{ISJ}	3.04×10^{-2}	kg/s	Resistance of incudostapedial joint
A_{FP}	3.14×10^{-6}	m^2	Area of the stapes footplate
L_S	3.55×10^5	Kg/m^4	mass of stapes
C_{SC}	9.01×10^{-15}	$kg/(s^2 m^4)$	Compliance of annular ligament and round window
R_{SC}	2.99×10^{10}	$kg/(s m^4)$	resistance of annular ligament and cochlea

Table A2.2: Voss et al., (2000) middle ear cavity parameter values

Symbol	Value	Units
R_{ad}	$0.05 \times 10^6 \sqrt{f}$	N-s/m
M_{ad}	890	Kg/m^4
C_a	6.3×10^{-12}	m^5/N
C_t	6.3×10^{-12}	m^5/N

2) Error function to determine best model

Outlined below is the error function used to quantify the fit to the actual median WAI data. The total error was the sum of the root mean square error (RMSE) of 1) the log magnitude ($20 \times \log_{10}$) of the impedance (Z_{in}) magnitude between model and actual data and 2) the absorbance level (A) between model and actual data.

$$RMSE (\log |Z_{in}|) = \sqrt{\frac{1}{N} \sum_{i=1}^N |\log(|Z_{in,model}^i|) - \log(|Z_{in,patient}^i|)|^2}$$

$$RMSE (A) = \sqrt{\frac{1}{N} \sum_{i=1}^N (A_{model}^i - A_{patient}^i)^2}$$

where N is the total number of frequency points compared between the model and the patient data. The total error which is shown in Table 1 of Chapter 2 was calculated as:

$$\text{Total Error} = RMSE (\log Z_{in}) + RMSE (A)$$

Appendix A3

Outlined below is the cost function used to fit the model to the data. We would like to match the model's 1) log magnitude and phase of the impedance, 2) magnitude and phase of the reflectance and the 3) power reflectance (or absorbance) to real patient data. To accomplish this, we minimize the root mean square error (difference between model and data) of the following measures: log magnitude of Z_{in} , reflectance magnitude and phase ($|R|$ and $\angle R$), and power reflectance (PR). The total error is the sum of all the RMSE of these measures. The error of the impedance magnitude is weighted more heavily than the other measures to improve fits to the data. For example, the root mean square error (RMSE) of the log impedance magnitude, $|R|$ and $\angle R$, and PR were calculated from the following equations:

$$RMSE (\log |Z_{in}|) = \sqrt{\frac{1}{N} \sum_{i=1}^N |\log(|Z_{in,model}^i|) - \log(|Z_{in,patient}^i|)|^2}$$

$$RMSE (|R|) = \sqrt{\frac{1}{N} \sum_{i=1}^N (R_{mag,model}^i - R_{mag,patient}^i)^2}$$

$$RMSE (\angle R) = \sqrt{\frac{1}{N} \sum_{i=1}^N (R_{phase,model}^i - R_{phase,patient}^i)^2}$$

$$RMSE (PR) = \sqrt{\frac{1}{N} \sum_{i=1}^N (PR_{model}^i - PR_{patient}^i)^2}$$

where N is the total number of frequency points compared between the model and the patient data. The total error was calculated as:

$$Total\ Error = 5 * RMSE (\log |Z_{in}|) + RMSE (|R|) + RMSE (\angle R) + RMSE (PR)$$

Table A3.1: Baseline model values for middle and inner ear mechanics

Baseline parameter values for middle and inner ear mechanics			
Symbol	Value	Units	Meaning
$l:A_{tm}$	$1/(6 \times 10^{-5})$	m^2	Turns ratio of TM volume velocity to malleus velocity transformer
$A_{fp}:l$	3.2×10^{-6}	m^2	Turns ratio of the ossicular velocity to volume velocity transformer
$l_i:l_M$	1.3	Unitless	Lever ratio of malleus-incus complex
V_{total}	6.35×10^{-6}	m^3	Total volume of the middle ear cavity
V_{TC}	$0.0625 \cdot V_{total}$	m^3	Volume of the tympanic cavity
V_{MC}	$V_{total} - V_{TC}$	m^3	Volume of the antrum and air cells
C_A	4.13×10^{-11}	N/m^5	Acoustic stiffness of the mastoid air space
C_{TC}	2.75×10^{-12}	N/m^5	Acoustic stiffness of the tympanic air space
R_A	6×10^6	$Pa \cdot s/m^3$	Acoustic resistance of the aditus
L_A	100	Kg/m^4	Acoustic mass of the aditus
C_T	3×10^{-12}	N/m^5	Acoustic stiffness parameter of TM model
C_{T2}	1.97×10^{-10}	N/m^5	Acoustic stiffness parameter of TM model
R_T	2×10^6	$Pa \cdot s/m^3$	Acoustic resistance parameter of TM model
R_{T2}	1.2×10^7	$Pa \cdot s/m^3$	Acoustic resistance parameter of TM model
L_{T1}	750	Kg/m^4	Acoustic mass parameter of TM model
L_T	6.6×10^3	Kg/m^4	Acoustic mass parameter of TM model
C_{TS}	1.1×10^{-3}	N/m^5	Mechanical stiffness of eardrum suspension
R_{TS}	4.3×10^{-2}	$N \cdot s/m$	Mechanical resistance of eardrum suspension
C_{MI}	0	N/m^5	Mechanical stiffness of malleus and incus
R_{MI}	7.2×10^{-3}	$N \cdot s/m$	Mechanical stiffness of malleus and incus
L_{MI}	7.9×10^{-6}	kg	Mechanical mass of malleus and incus
L_S	3.0×10^{-6}	kg	Mechanical mass of stapes
R_J	3.6	$N \cdot s/m$	Resistance of ossicular joints
K_J	2.04×10^3	N/m^5	Stiffness of ossicular joints
K_{AL}	1.21×10^{14}	N/m^5	Acoustic stiffness of the annular ligament
R_{AL}	0	$Pa \cdot s/m^3$	Acoustic resistance of the annular ligament
R_C	1.4×10^{10}	$Pa \cdot s/m^3$	Acoustic resistance of cochlea
L_C	1.57×10^6	Kg/m^4	Acoustic mass of cochlea
L_{RW}	6.03×10^5	Kg/m^4	Acoustic mass of round window
C_{RW}	4.9×10^{-8}	N/m^5	Stiffness of the round window
R_{RW}	1.29×10^9	$Pa \cdot s/m^3$	Acoustic resistance of round window

L_{SCD}	1×10^7	Kg/m^4	Acoustic mass of superior canal dehiscence
R_{SCD}	2.5×10^{10}	$Pa-s/m^3$	Acoustic resistance of superior canal dehiscence

Appendix A4

Table A4.1: Parameter values of baseline normal model

Baseline parameter values for middle and inner ear mechanics			
Symbol	Value	Units	Meaning
A_{tm}	6×10^{-5}	m^2	Area of the eardrum
A_{fp}	3.2×10^{-6}	m^2	Area of the stapes footplate
N_{LR}	1.3	Unitless	Lever ratio of malleus-incus complex
V_{total}	6.35×10^{-6}	m^3	Total volume of the middle ear cavity
V_{TC}	$0.0625 \cdot V_{total}$	m^3	Volume of the tympanic cavity
V_{MC}	$V_{total} - V_{TC}$	m^3	Volume of the antrum and air cells
C_{MC}	4.13×10^{-11}	N/m^5	Acoustic stiffness of the mastoid air space
C_{TC}	2.75×10^{-12}	N/m^5	Acoustic stiffness of the tympanic air space
R_A	6×10^6	$Pa \cdot s/m^3$	Acoustic resistance of the aditus
L_A	100	Kg/m^4	Acoustic mass of the aditus
C_T	3×10^{-12}	N/m^5	Acoustic stiffness parameter of TM model
C_{T2}	1.97×10^{-10}	N/m^5	Acoustic stiffness parameter of TM model
R_T	2×10^6	$Pa \cdot s/m^3$	Acoustic resistance parameter of TM model
R_{T2}	1.2×10^7	$Pa \cdot s/m^3$	Acoustic resistance parameter of TM model
L_{T1}	750	Kg/m^4	Acoustic mass parameter of TM model
L_T	6.6×10^3	Kg/m^4	Acoustic mass parameter of TM model
C_{TS}	1.1×10^{-3}	N/m^5	Mechanical stiffness of eardrum suspension
R_{TS}	4.3×10^{-2}	$N \cdot s/m$	Mechanical resistance of eardrum suspension
C_{MI}	0	N/m^5	Mechanical stiffness of malleus and incus
R_{MI}	7.2×10^{-3}	$N \cdot s/m$	Mechanical resistance of malleus and incus
L_{MI}	7.9×10^{-6}	kg	Mechanical mass of malleus and incus
L_S	3.0×10^{-6}	kg	Mechanical mass of stapes
R_J	3.6	$N \cdot s/m$	Resistance of ossicular joints
K_J	2.04×10^3	N/m^5	Stiffness of ossicular joints
K_{AL}	1.21×10^{14}	N/m^5	Acoustic stiffness of the annular ligament
R_{AL}	0	$Pa \cdot s/m^3$	Acoustic resistance of the annular ligament
R_C	1.4×10^{10}	$Pa \cdot s/m^3$	Acoustic resistance of cochlea
L_C	1.57×10^6	Kg/m^4	Acoustic mass of cochlea
L_{RW}	6.03×10^5	Kg/m^4	Acoustic mass of round window
C_{RW}	4.9×10^{-8}	N/m^5	Stiffness of the round window
R_{RW}	1.29×10^9	$Pa \cdot s/m^3$	Acoustic resistance of round window
L_{SCD}	4.83×10^{19}	Kg/m^4	Acoustic mass of superior canal dehiscence
R_{SCD}	1.22×10^{19}	$Pa \cdot s/m^3$	Acoustic resistance of superior canal dehiscence

Table A4.2: Initial, upper and lower bound value for each parameter free to vary

Pathological Model	Parameter free to vary	Units	Initial Value (IV)	Lower Bound	Upper Bound
Ossicular Discontinuity Model	R_J^M	N-s/m	0	0	0
	C_J^M	m^5/N	0.0049	$0.5*IV$	$2*IV$
Stapes Fixation Model	C_{AL}	m^5/N	8.28×10^{-16}	$0.0625*IV$	$2*IV$
Superior Canal Dehiscence Model	L_{SCD}	Kg/m^4	1×10^6	$100*IV$	$0.0625*IV$
	R_{SCD}	$Pa-s/m^3$	1×10^{10}	$100*IV$	$0.0625*IV$

Appendix A7

Table A7.1: Patient demographics within the thin bone group, when graded by two neuro-radiologists. Age in years.

		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Reader 1	Number of ears (# subjects)	4 (4)	4 (4)	10 (10)	13 (13)	8 (7)
	Mean Age (SD)	54.8 (3.3)	39.5 (15.2)	48.1 (8.2)	49.3 (11.6)	44.3 (9.5)
	Age range	49-57	17-57	37-63	24-65	31-59
	Female sex, %	100	25	80	76.9	57.1
Reader 2	Number of ears (#subjects)	4 (3)	10 (10)	10 (10)	9 (9)	5 (4)
	Mean Age (SD)	54.3 (4.6)	45.2 (13.2)	51.8 (9.9)	47.4 (8.2)	42 (12.2)
	Age range	49-57	17-63	35-65	35-65	31
	Female sex, %	66.7	80	70	77.7	59

Figure A7.1 cVEMP Threshold at 500 Hz

A KW test was performed to test for significant differences across groups for cVEMP thresholds at 500 Hz. Findings revealed a highly significant difference across groups ($p < 4.7E-11$). MW-U tests further revealed lower thresholds for the Frank-Dehiscence group (median = 98 dB peSPL) compared to the group consisting of grade 3 and 4 (median = 113 dB peSPL, $p < 2.9E-6$). No other significant differences were found across groups, except for those already stated in the previous results section (i.e. the Frank-Dehiscence group was found to have lower cVEMP thresholds than the normal control).

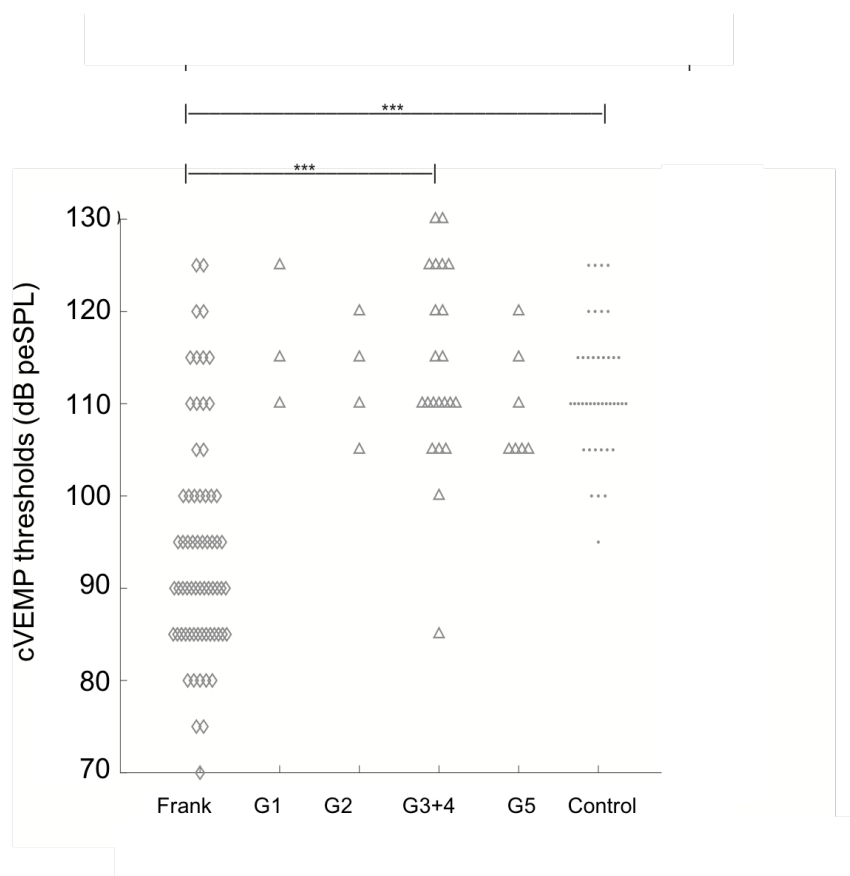


Figure A7.1: cVEMP thresholds at 500Hz for every subject in each group are displayed.
*** indicates a significance level of $p < 0.000125$.

A7.2 Audiometric data

For AC thresholds a KW-test revealed a significant difference between groups at 250 ($p < 1.6E-10$) and 500 Hz ($p < 5.9E-10$). MW-U tests revealed that the Frank-Dehiscence group had higher thresholds at both 250 Hz (median = 20 dB) and 500 Hz (median = 20 dB) than the group consisting of grade 3 and 4 (250Hz with median = 10, $p < 1.8E-8$; 500Hz with median = 10, $p < 8.6E-5$). No other significant differences across groups were found, at neither 250 or 500Hz, except those previously stated.

For BC thresholds at 250 and 500 Hz, no significant difference was found between groups, except those earlier stated.

For ABG a KW-test revealed a significant difference at both 250 ($p < 5.3E-10$) and 500 Hz ($p < 2.3E-13$). MW-U tests further revealed that the Frank-Dehiscence group had larger ABGs (250 Hz with median = 25; 500 Hz with median = 15) than the group consisting of grade 3 and 4 (250 Hz with median = 5, $p < 6.8E-7$; 500Hz with median = -2.5, $p < 3.2E-6$). No other significant differences were found between groups, except those previously stated.

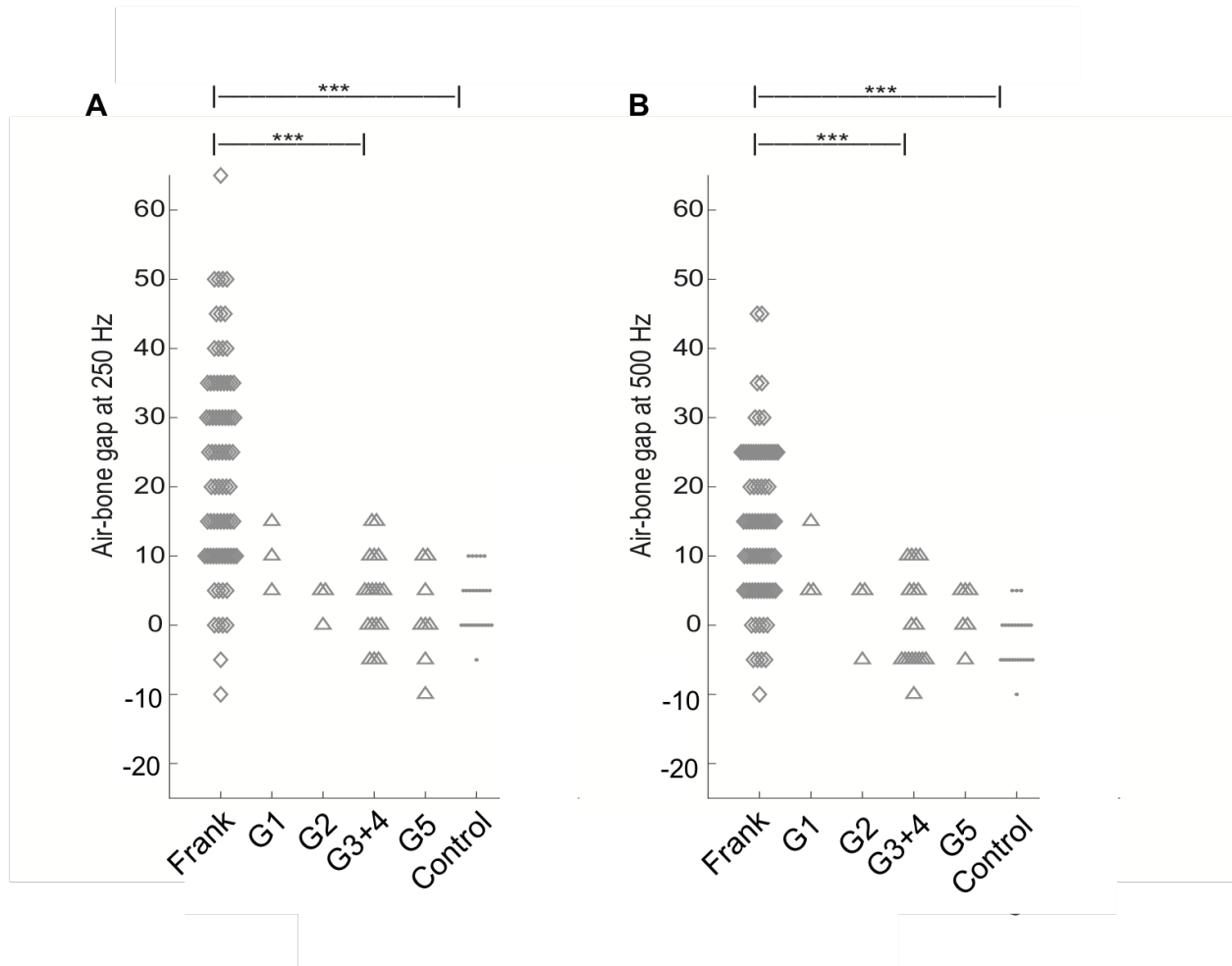


Figure A7.2: Air-bone gaps at 250 and 500 Hz shown for every individual in each group. *** indicates a significance level of $p < 0.000125$.

A7.3 WAI information

A7.3.1 Notch Detector

The notch detector algorithm was applied to the Frank-Dehiscence group, control group, as well as the group of Grades 3 and 4. No significant difference was found across groups for *notch size*. For *notch depth*, a KW-test revealed a significant difference ($p < 0.0016$). MW-U tests further revealed that the Frank-Dehiscence group (median = 0.17) had a larger *notch depth* than the group of grade 3 and 4 (median = 0.084, $p < 0.0066$). No other significant difference was found across groups except those previously stated.

A7.3.2 High frequencies

High-frequency PR magnitude was extracted for the subjects graded with Grade 3 and 4. A KW-test revealed a significant difference between groups ($p < 0.016$). MW-U tests revealed no further significant differences except those previously stated. The group consisting of grade 3 and 4 are indistinguishable from all the three other groups-

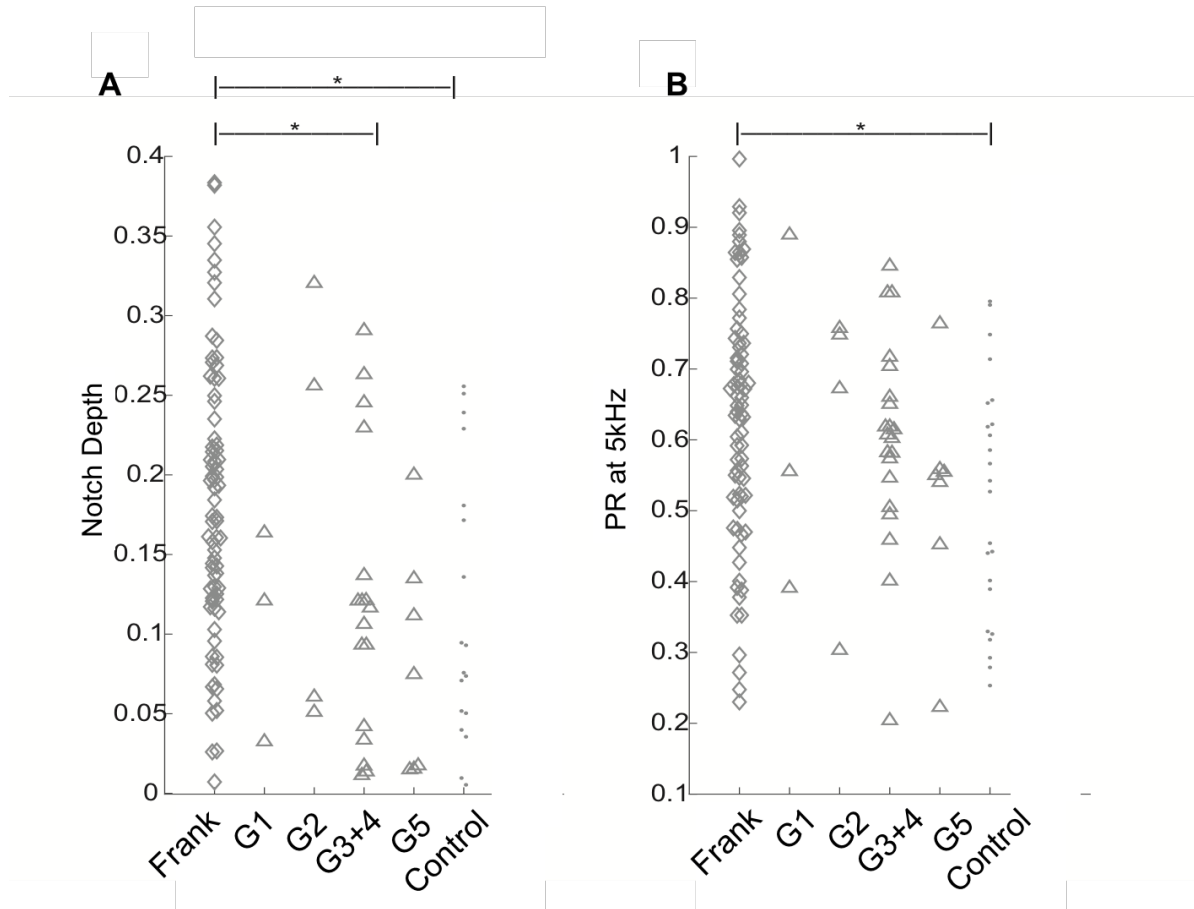


Figure A7.3: PR features for every ear in each group. A) shows *notch depth*, B) shows PR at a frequency interval of $\pm 1/3$ octave around 5 kHz.

* indicates a significance level of $p < 0.0125$.

A7.4 Umbo velocity

Magnitude peak value and peak width were extracted and analyzed. No significant differences across groups could be found. Also extracted was the phase slope for all subjects. For negative phase slope, a KW-test revealed a significant difference between groups ($p < 5.0E-5$). Besides the previously found differences between the Frank-Dehiscence and the control group, MW-U tests further revealed that the SCD group (median = $2.5E-4$ sec) had a steeper slope than the group consisting of grade 3 and 4 (median = $1.7E-4$ sec, $p < 0.0018$).

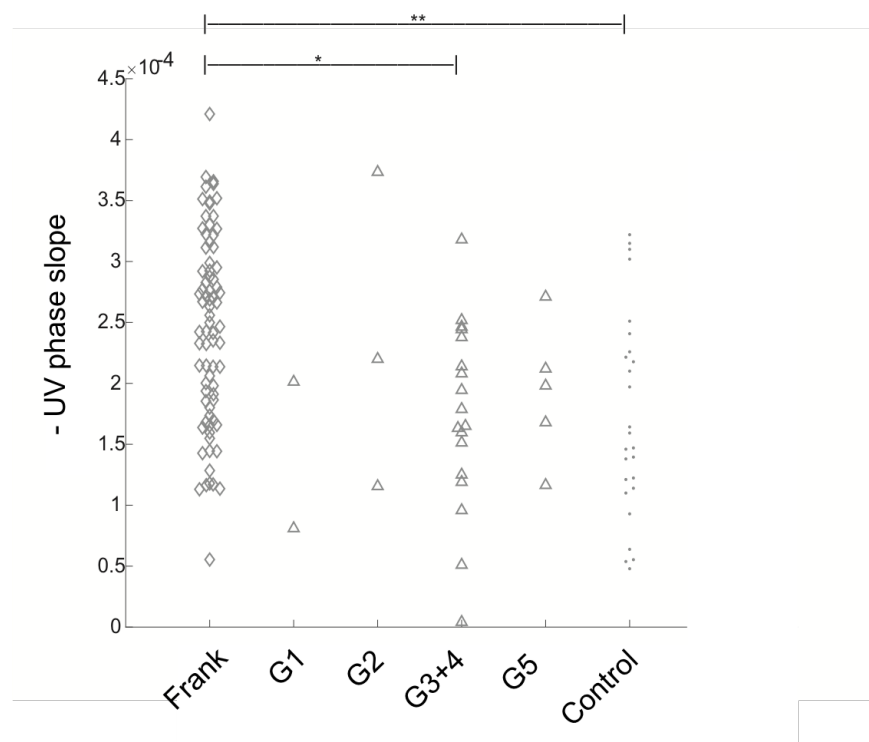


Figure A7.4: The phase slope between 700 and 1500 Hz for every individual in each group are displayed.
 * indicates a significance level of $p < 0.0125$, ** of $p < 0.00125$.

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