Modeling and clinical diagnosis of dead regions in the cochlea

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Chapter 1

GENERAL INTRODUCTION
1.1 Sensory systems

We, humans, use sensory information to interact with our surroundings, to formulate thoughts, to store memories and to interact as social beings. We are able to participate in a society by sharing our knowledge and resolve (or inflict) conflicts through speech and written language. The effectiveness of spoken language depends on our ability to produce complex speech and using an extensive vocabulary and rules of grammar, but also depends on our ability to hear, to analyze, and to comprehend spoken messages.

The auditory system is, in terms of the physical range of detection, superior to any other sensory system. We are able of detecting differences in air pressure, e.g. sound waves, over a range of more than 6 orders of magnitude between absolute threshold and the uncomfortable loudness level (UCL), which is equal to a million-fold change. Over this entire range, pressure changes of less than 1 decibel (dB) are heard. In the frequency domain, the auditory range extends between 20 Hz and 20 kHz. The frequency sensitivity of the auditory system is such that sounds with a difference of only 0.2 % can be discerned. This enormous range of the auditory sensitivity scales well with the spectral range of human speech as is shown in Fig. 1.1.

Panel A of Fig. 1.1 shows the auditory space in physical units. Sound intensities are conventionally expressed logarithmically in terms of a level in relation to a reference. The sound pressure level (SPL) is a reference that corresponds to the atmospheric pressure of $20 \mu Pa$. Another commonly used reference is the hearing level (HL), which corresponds to the human threshold of hearing. This absolute threshold indicates the lowest level at which sounds can be detected by the average normal-hearing listener. The auditory system is most sensitive to sounds between 0.5 and 4 kHz. The sensitivity reduces towards lower and higher frequencies. Sounds are audible at levels between the absolute threshold and the UCL. Above the UCL sounds may be heard up to the threshold of pain at about 140 dB SPL. However, perception at these high-levels is, as the names imply, far from pleasant and can cause physical damage. Above the threshold of pain, the structures of the auditory system are assumed to be acutely and permanently damaged by the exposure to excessive sound levels. The auditory space that covers the frequencies and intensities that are needed to understand speech is known as the speech banana due to its shape on a level to frequency graph. The speech banana is represented in Fig. 1.1 by the yellow area.

1.2 Hearing impairment

Verbal communication consists of the production of speech, the transmission of sound, and the perception and understanding of messages. Ideal communicative conditions involve the pronunciation and the transmission of messages where every sentence, every word and every vocalized speech characteristic\(^a\) reach the

\(^a\)Speech is in terms of level and frequency very much like noise. Speech information is mostly contained in phonological and linguistic properties. For example, different intonation
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Figure 1.1. The auditory range of humans in relation to the physical sound pressure level (SPL) reference. Zero dB SPL corresponds to 20 Pa. (A) The lowest level sounds that can be perceived are at the absolute threshold level. The auditory system is most sensitive to the frequencies that are used in speech, which is approximately represented by the yellow speech banana. The letters inside the speech banana roughly correspond to the average level and frequency of human utterance of corresponding letters. The uncomfortable loudness level (UCL) indicates the loudness ceiling above which sounds become very uncomfortable to listen to. (B) The total dynamic range of perception (and speech) is reduced by a high-frequency dead region with an edge frequency ($F_e$) at about 2 kHz. The effects of the dead region on the high-frequency parts of the speech banana are severe.

Recipient. This requires clear speech, absence of disturbing sound sources, low reverberation, and proximity of speaker and listener. In realistic conditions, parts of speech information are lost by poor pronunciation, background signals and poor acoustical conditions. Fortunately, a normal-hearing listener skilled in the spoken language can understand even a partially perceived message. Missing parts can be filled in by knowledge of the structure of the language and the context of the message (Bosman, 1989; Bronkhorst et al., 1993). In adverse auditory conditions, such as in a crowd, the amount of guesswork may increase to a level where communicative mistakes are made.

Subjects with auditory disabilities, i.e., hearing-impaired (HI) listeners, usually have difficulties perceiving speech. To some degree, the perception of hearing-impaired perception can be compared to the perception of normal-hearing listeners experiencing adverse auditory conditions (Moore, 2007), even when the environmental conditions are ideal (for example, when conditioned in a soundproof booth). Damage to the auditory system can reduce the auditory sensitivity and the precision of speech perception. Therefore, hearing-impaired

and the length of a silence in between vocations can alter the meaning of an utterance.
listeners may perceive speech, but are unable to comprehend the message. The loss of hearing can impair communication and can even (partially) exclude a HI listener from normal social participation (Punch et al., 2006).

A type of severe auditory impairment that significantly hampers the auditory capabilities of a listener is a dead region\(^b\). A dead region eliminates the auditory functionality within a range of frequencies. Low-, and high-frequency dead regions are defined as a dead region with a frequency range that extends from an edge frequency \(F_e\) to lower-, and higher frequencies, respectively (Moore et al., 2000; Warnaar & Dreschler, 2012). Panel B of Fig. 1.1 shows the effects of a typical high-frequency dead region on the hearing range of a HI listener. Information that falls in the frequency range of a dead region is lost. Information in the speech banana that coincides with the dead region, represented by a dark area in the figure, is lost for communications.

### 1.3 Rehabilitation in modern society

Modern medicine and rehabilitation programs offer numerous possibilities that can help HI listeners. These include, among others, surgery, hearing aids, cochlear implants, and guide dogs (and other trained animals). Surgical operations are mainly aimed at improving the auditory capabilities by implantation of artificial devices into the auditory system. Techniques to repair and reconstruct body tissues are limited, because most structures of the auditory system are very small and delicate. The amount of hearing aids on the market is staggering. There are many international companies that supply the market with a wide variety of hearing aids. Hearing aids provide linear and/or non-linear amplification of sound. Many hearing aids offer sound processing strategies to enhance the informational content of speech or to improve the listening comfort of the listener. An advanced hearing aid that needs surgery is the cochlear implant. Cochlear implants provide an elementary form of substitute for the sensory cells of the auditory system. Guide dogs are trained to notify their owner to functional sounds that are inaudible to the owner, such as the doorbell or the horn of an approaching car.

Ironically speaking, one of the most effective aids for many HI listeners today is still the classical ‘old-fashioned’ iron horn (Dreschler, 2009). The small opening of this tube is placed at the ear and the large opening is directed to the sound source. The horn provides directional amplification and, more importantly, increases the awareness of speakers about the auditory disabilities of the HI listener.

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\(^b\)There is not much known about the prevalence of dead regions. The study with the largest population that focussed on dead region diagnosis was performed by Hornsby & Dundas (2009). This study investigated 117 ears with a single test method (TEN test). They found that dead regions are more common at frequencies with hearing losses exceeding 60 dB HL.
1.4 **Clinical Diagnosis**

Although the best solution for the communicative disabilities that HI listeners face may still be to increase general awareness, many HI listeners benefit greatly from hearing aids and other rehabilitation programs. The benefits of aids depend on a correct diagnosis of residual auditory capabilities of the HI listener. A diagnosis includes the selection of test methods and the interpretation of the test results. As an example, a pure-tone audiogram aims to determine the absolute threshold of a listener by measuring the detection threshold of single-frequency (pure) tones in a sound attenuating booth. The test results are used to estimate the degree of hearing loss at a number of frequencies. The estimations can be used to recommend patient-specific hearing aid settings, such as the amount of frequency-specific amplification (Cornelisse et al., 1995; Byrne et al., 2001). However, amplification does not always benefit HI listeners. One obvious reason for this disappointing effect can be that representative pure-tone audiograms measured in listeners with a dead region suggest strong amplification inside the frequency range of the dead region. Contrary to the intentions to improve the auditory capabilities by amplification, amplification inside a dead region may actually have an adverse effect on the speech intelligibility of the listener (Vickers et al., 2001; Baer et al., 2002). In these studies, the effects of high-frequency amplification on perception of vowel-consonant-vowel nonsense syllables were examined in listeners with severe high-frequency losses. The syllables were filtered with a lowpass filter. In some listeners the perception worsened as the cutoff frequency of the lowpass filter was increased.

Several studies (Johnson-Davies & Patterson, 1979; O’Loughlin & Moore, 1981) have shown that sounds can be heard in neighboring frequency regions of the auditory system through off-frequency listening\(^\text{c}\). This ability may lead to the detection of pure-tones that are administered at frequencies corresponding to a dead region. Pure-tone audiograms are, therefore, ill-suited for diagnosis of dead regions because the method cannot discriminate between dead regions and other frequency regions with moderate to severe hearing loss. Tests that are better equipped for diagnosis of dead regions are the psychophysical tuning curves (PTC) test and the threshold equalizing noise (TEN) test (Moore et al. 2000; 2004). The PTC test and the TEN test estimate the contribution of off-frequency listening by measurements of masking thresholds of pure tones (probes) in spectrally shaped noise (maskers).

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\(^\text{c}\)Off-frequency listening is used by the healthy ear to optimize signal-to-noise ratios, but can also be used to detect sound ‘residuals’ that would otherwise not be heard. Off-frequency plays an important role in the detection of sounds presented inside a dead region, the diagnosis of dead regions, and may even affect perception of sound inside a dead region.

1.5 **Psychophysical Measurement**

Experimental and clinical investigations of the auditory system depend on psychophysical measurements. A psychophysical test presents a listener with a
physical stimulus and measures the behavioral response through a psychological task. The results provide insights into the functional relationship between physical properties of the stimulus and the psychological perception of the stimulus. For example, in the PTC test and the TEN test, the masking threshold of a pure-tone is measured in noise as a function of the pure-tone frequency. Masking thresholds cannot be determined at fixed levels. Instead, a masking threshold corresponds to a probability of detection. The probability is a psychometric function of the difficulty of the task. A masking threshold corresponds to a point on the psychometric function with a detection probability determined by the convergence rules of the test procedure\textsuperscript{d}. Figure 1.2 shows a typical psychometric function for a detection task of a tone in noise. The signal-to-noise (S/N) ratio is defined as the level of the tone divided by the level of the noise. At very low signal-to-noise ratios the probability of detection is at chance level, i.e. the chance is equal to guessing. At higher signal-to-noise ratios the probability of detection increases above chance to almost 100 %. The test procedure sets rules for a convergence of the masking threshold at an equilibrium at some point of the psychometric function. Rules that converge to a point on the steep slope of the psychometric function result in the smallest measurement errors.

A well designed psychophysical test produces results that depend on a single physical property of the stimulus, while controlling for all others. In some psychophysical hearing experiments, however, properties are strongly connected. Typical PTC-, and TEN test measurements compare tones and noises that are presented at different levels and at different frequencies. Throughout this thesis, it will be shown that the interpretation of the results of dead region tests is far from straightforward, because the frequency and the intensity are highly interdependent variables within the auditory system.

1.5.1 Auditory filter

Fletcher (1940) showed that the auditory system has a finite frequency selectivity that can be described by a filterbank of critical bands. Critical bands were precursors of the auditory filter (Moore & Glasberg, 1996). The frequency response of an auditory filter is shown in panel A of Fig. 1.3. The response is maximal at the characteristic frequency (CF) of the filter, and is asymmetrically attenuated towards lower and higher frequencies. In the field of audiology, it is often practical to express the bandwidth of an auditory filter by a single value, such as the equivalent rectangular bandwidth (ERB). The response of an ERB is centered at CF, and produces the same level response as an auditory filter to a white noise input stimulus. Psychophysical experiments have estimated the ERB to be roughly 10 % of CF (Glasberg & Moore, 1990):

\[
ERB = 24.7(4.37 \cdot 10^{-3} \, CF + 1) \, \text{Hz}
\]  

\textsuperscript{d}A typical set of rules make the psychophysical task harder when correct answers are given, and reduce the difficulty of the task when incorrect answers are given (see for an analysis of up-down procedures: Levitt, 1971).
Figure 1.2. Auditory information is perceived and comprehended depending on the quality of sound reaching the hearing system, the quality of the hearing system, and the mental effort that is focused on understanding the information. In psychophysical measurements, the environmental conditions are controlled and the auditory task can, for example, be simplified to a detection task. (A) The listener response can be described by a psychometric function, shown by the black curve. When the task is made very difficult, the chance for a correct response is equal to guessing. When the task is made very easy, the response approaches a nearly 100% correct score. The S/N ratio, and thereby the slope of the curve, are determined by the test conditions and the auditory system. The slope of the curve determines the precision of the experiment. (B) An adaptive psychophysical measurement typically presents a listener with a number of presentations. In each subsequent presentation the difficulty of the task is increased or decreased according to the correctness of the listener’s response. The green dots and red dots indicate correct and false responses of the listener, respectively. In the example, a set of test rules is used that require two consecutive correct answers at the same level of the stimulus before the task is made more difficult, i.e. a 1-up 2-down procedure. This procedure converges to a 71% chance on the psychometric function (Levitt, 1971).

The auditory system applies a variety of strategies to increase the frequency, and level resolution. One of these strategies can be described in terms of a non-linear response of auditory filters to the input level of the filter. Panel B of Fig. 1.3 shows the relative passband of an auditory filter for input levels ranging between 20 and 70 dB SPL/ERB. The auditory filter at very low levels is sharply tuned and has a very steep skirt towards lower frequencies. At high levels, the auditory filters are less tuned and include a wider range of frequencies. The formula for the size of an ERB, as given in Eq. (1.1), is representative for input levels of 51 dB/ERB (Glasberg & Moore, 1990), but can be adapted for other input levels.
Figure 1.3. Auditory filter shapes for normal-hearing listeners are presented by solid black lines. (A) The bandwidth of an auditory filter is often, for practical reasons, expressed by a single scalar value, e.g. by the equivalent rectangular bandwidth (ERB). The size of an ERB is roughly the size of the bandwidth of the auditory filter at -3 dB below the filter output level at CF. (B) The shape of the auditory filter depends on the input level of the filter. The numbers indicate levels in dB SPL/ERB at the input of the filters. At high level the shape is asymmetric around CF with a steep skirt towards higher frequencies. At lower levels, the shape is more symmetric and more sharply tuned, i.e. have a lower ERB value (orange arrows).

Panel A of Fig. 1.4 shows a filterbank of overlapping auditory filters with filter density of one filter per ERB along the frequency axis. A stimulus can be represented in several auditory filters as shown in the figure. The audibility of the tone, i.e. detection threshold, depends on the combined representation of the tone in multiple filters of the auditory filterbank. A more complex stimulus, such as speech in noise, can contain a range of frequencies. The frequency and level information that can be extracted is determined by the combined information of all auditory filters, as shown in panel B of Fig. 1.4.

*Note that the auditory system uses not only frequency and level information to interpret speech. Timing information, such as phase, are essential for understanding speech.*
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1.5.2 Off-frequency listening

Patterson and Nimmo-Smith (1980) have shown that normal-hearing PTC data are influenced by off-frequency listening. Off-frequency listening is the ability of the auditory system to use auditory filters with any characteristic frequency to improve signal-to-noise ratios at the output of the auditory filters. The effects of off-frequency listening on the detection of a pure-tone in noise are illustrated in Fig. 1.5. In panel A of Fig. 1.5 the detection of a pure-tone in broadband noise, such as threshold equalizing noise (TEN), is shown. One of the auditory filters is positioned such that its characteristic frequency aligns with the frequency of the tone to optimize the detection of the tone. However, auditory filters that optimize the signal-to-noise ratio are not necessarily positioned at the frequency of the tone. Panel B in Fig. 1.5 shows a typical masking condition used in measurements used to measure PTCs. A narrowband noise is presented at a frequency higher than the frequency of the pure-tone. The auditory filter that is positioned at a frequency slightly below the pure-tone frequency can provide a better signal-to-noise ratio than an auditory filter at the characteristic frequency of the tone. The shift of the auditory filter improves the overall signal-to-noise ratio by reducing the representation of the narrowband noise in the filter, while only slightly reducing the representation of the tone in the filter.

Figure 1.4. The frequency selectivity of the auditory system can be described in terms of a filterbank of auditory filters. Each filter contributes to the frequency resolving power by providing a frequency-to-output response. (A) A pure-tone in quiet is detected by a number of neighboring filters, each providing information about the level of the tone. (B) A complex stimulus, such as speech, is represented in a large number of auditory filters. Each filter is centered at a specific frequency, but is also sensitive to neighboring frequencies.
1.5.3 Psychophysical measurement of hearing impairment

The effects of hearing impairment on psychophysical results are diverse and specific for each individual HI listener. Typical psychophysical changes are increased absolute thresholds, loudness recruitment, and poor frequency selectivity (Pick et al., 1977; Glasberg & Moore, 1986; Tyler, 1986; Moore, 1998).

Reduced sensitivity to sounds increases the absolute threshold of detection, and can vary considerably between (adjacent) frequencies. Listeners with loudness recruitment have an abnormal loudness perception that grows non-linearly with stimulus level. They typically have a reduced dynamic range of hearing and can experience hypersensitivity to loud sounds (hyperacusis). Listeners with poor frequency selectivity are typically unable to distinguish closely spaced frequencies and have more trouble discriminating temporal and spectral information in sound signals. The loss of frequency selectivity can create a sound image that is blurred in comparison to normal-hearing perception. In terms of an auditory filterbank, poor frequency selectivity can be represented in terms of auditory filters as a broadening of the filters.

The effects of dead regions on sound perception varies considerably between HI listeners. Some listeners with dead regions suffer a complete loss of sound perception inside a dead region. However, frequency information that falls inside a dead region can be represented in auditory filters that are off-frequency,
outside the dead region, and thus, may be audible through off-frequency listening. Other effects that have been associated with dead regions are the loss of spectral information (Moore & Glasberg, 1997; Moore et al., 2000; Moore, 2001; Moore & Alcántara, 2001), the insensitivity of perceiving sounds at low levels (Markessis et al., 2009), and the distorted perception of sounds, such as a noise-like perception of pure-tones (Huss & Moore, 2005).

1.5.4 **Dead region diagnosis using off-frequency listening**

Moore (2001) and Moore and colleagues (2004) suggested that off-frequency listening is a representative measure for the diagnosis of dead regions. They argued that a stimulus, such as a pure-tone, that is presented at a high-level inside a dead region can be detected listening outside the dead region, using off-frequency listening. Because the detection level of the tone at the off-frequency site is lowered, a relatively low level masker presented off-frequency is sufficient to mask the tone.

The concept of a relatively low level masking by an off-frequency masker is used in PTC measurements and the TEN test to diagnose dead regions. In a PTC measurement the listener is presented a pure-tone (probe) that is fixed in frequency and level, and a narrowband masker that is presented at different frequencies. Masking thresholds are measured by changing the level of the masker. The PTC is obtained by fitting a curve through the measured masking threshold as a function of the masker frequency. The frequency that corresponds to the lowest masking threshold in the curve is referred to as the PTC tip. The tip is assumed to indicate the optimal detection frequency for the probe. In normal-hearing listeners, the PTC tip corresponds to the frequency of the probe (Turner et al., 1983). In case of a dead region, the PTC tip is believed to shift to the edge frequency of a dead region, i.e. $F_e$ (Thornton & Abbas, 1980; Florentine & Houtsma, 1983; Turner et al., 1983; Moore & Alcántara, 2001).

Moore and colleagues (2000; 2004) designed the TEN test for clinical diagnosis of dead regions. The TEN is a broadband noise shaped spectrally to produce an equal masking level in normal-hearing listeners over a wide range of frequencies. In listeners with dead regions, the broadband TEN provides efficient masking. Typically, a high-level probes that is presented inside a dead region is perceived outside the dead region at a much lower level. A relatively low-level TEN is, therefore, sufficient to mask the probe. Provided that the probe is presented at sufficient level above the absolute threshold, a difference between the probe level and the level of TEN indicates that the probe is detected through off-frequency listening. A large level difference between probe and masker implies the presence of a dead region at the frequency of the probe.
1.6 Physical structures of the auditory system

The auditory system consists of structures that mechanically react to sound waves, transform mechanical (kinetic) energy to electric action potentials, and central nervous complexes that interpret bilateral sensorineural information. The chain of organs that are involved in hearing are drawn in Fig. 1.6. An anatomic ordering of organs separates the auditory system into an outer-, middle-, and inner ear which are respectively represented in Fig. 1.6 by red, green and blue color palettes.

![Diagram of the auditory system](image)

**Figure 1.6.** The outer, middle, and inner ear of the auditory system. The outer ear consists of the pinna and the ear channel, and provides directional collection of pressure variations from the environment. The middle ear consists of the tympanic membrane and the ossicles. The middle ear structures transform the air pressure on the tympanic membrane to a vibrating movement on the cochlea. The cochlea, or inner ear, contains the sensory cells of the auditory system. These hair cells transduce mechanical vibrations into electrical action potentials that are transported by the auditory nerve to the retro-cochlear structures, such as the brainstem and central nervous system.
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1.6.1 Outer ear and middle ear

The pinna collects sound waves from the surrounding environment. The rolling surface of the pinna shatters the sound waves into wave patterns that contain directional information of the sound source. The waves enter the ear channel. The ear channel has a diameter and length that are optimized for the transmission of frequencies of the speech banana (see Pralong & Carlile (1996) and panel A in Fig. 1.1).

Sound waves that reach the end of the ear channel create a tympanic movement by exercising pressure differences on the tympanic membrane. The movement of the tympanic membrane is transmitted by the ossicles to the oval window of the cochlea.

The ossicles consist of three small bones. The bones are the malleus with a connection to the tympanic membrane, the incus, and the stapes with a footplate embedded in the oval window of the cochlea. The shape and alignment of the ossicles create a lever function that amplifies tympanic movement to an oval window movement (Gyo et al., 1987). It is believed that the amplification that is provided by the ossicles is mostly linear, but can be reduced at very low frequencies and at high levels. The middle ear muscles can reduce the transmission of energy through the ossicular chain with a delay of 10 to 150 ms in response to loud sounds (Rossi & Solero, 1983).

1.6.2 Cochlea

The cochlea, drawn in panel A of Fig. 1.7, is contained in the otic capsule, a cartilaginous structure that becomes bony after about half a year after birth. The cochlea is embedded in the mastoid of the temporal bone, and resembles a tube that is spiraled nearly three times around the modiolus.

When cut perpendicular to the spiral, as illustrated in panel B of Fig. 1.7, the cochlea consists of three compartments, or scalae, that are filled with fluid. The scala vestibuli, scala media, and the scala tympani are separated by, respectively, the Reissner’s membrane and the basilar membrane (BM). The scala media is filled with endolymph, a solution with high concentrations of potassium. The stria vascularis resupplies the scala media with potassium (Kuijpers et al., 1967). The scala vestibuli and scala tympani are filled with a high-sodium solution.

Figure 1.7. (Next two pages) The organ of Corti houses the sensory cells of the auditory system, the hair cells. Hair cells are activated by a relative motion with respect to the tectorial membrane. One row of inner hair cells is positioned towards the modiolus. Inner hair cells, when activated, evoke actions potentials in the nerve fibers. The outer hair cells are positioned in, typically, three rows towards the periphery of the cochlea. The purpose of the outer hair cells is to provide enhancement of the basilar membrane, by actively changing the length of their cell bodies. Because outer hair cells require special freedom to change size, they are only partly connected to supporting cells.
Panel C in Fig. 1.7 shows the cochlea structure after unfolding the cochlea along a straight line. At the apical end of the cochlea, the scala vestibuli and scala tympani share a connection through an opening called the helicotrema. The cochlea interacts with the footplate of the stapes at a membrane-covered oval window in the scala vestibuli. Another membrane-covered opening in the otic capsule, the round window, is located at the basal end of the scala tympani. The BM is connected at the base of the cochlea to the otic capsule and extends towards the cochlear apex where it is joined with the Reissner’s membrane at the helicotrema.

Dynamics of the cochlea to sound are drawn in panel D of Fig. 1.7. Sound waves create oscillating pressure differences on the oval window. A pressure increases the fluid pressure in the scala vestibule, which is transmitted by the Reissner’s membrane to the scala media. An increased pressure in the scala media forces a downward movement of the BM and a compression of the scala tympani. The oscillating pressure of sound waves creates vibrating excitation of the BM (Békésy, 1942). The excessive pressure in the scala tympani is released through an outward movement of the round window and by a flow through the helicotrema. The helicotrema can also neutralize pressure gradients in a cochlea in rest.

1.6.3 Organ of Corti

The organ of Corti, drawn in Fig. 1.8, provides mechanical amplification of BM movement and mechanoelectrical transformations of BM movement into action potentials in the auditory nerve. The organ is rigid and flexible at the same time, which makes it able to react to slow-, and fast pressure differences in the cochlea. In order to achieve this mix of properties, the cells in the organ of Corti are not only highly specialized in size, shape and functionality, but they are also connected through various cell bindings (Zetes et al., 2012).

1.6.4 Sensorineural hair cells

The organ of Corti contains two types of hair cells. One row of inner hair cells (IHCs) and typically three rows of outer hair cells (OHCs) run along the spiral length of the cochlea. The prefix ‘inner’ and ‘outer’ of hair cells are given by their medial position within the cochlea. The IHCs are connected to auditory nerve fibers that exit the organ of Corti in the modiolus. The OHCs are positioned in the organ of Corti as free columns, with only connection to supporting cells at the apical side. The IHCs and OHCs have different functions and different anatomic properties, but they also share some similarities.

The name ‘hair’ comes from bundles of cellular extensions, which are called stereocilia, protruding the cells. The stereocilia of individual hair cells are ordered in three rows that are shaped in a flat ‘U’ pattern on IHCs, and ‘V’ or ‘W’ patterns on OHCs. Stereocilia in a single row have similar length, but are longer in rows that are positioned towards the exterior of the cochlea. Stereocilia between rows are connected with filament connections, i.e. tip links. The
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The organ of Corti houses the sensory cell of the auditory system, the hair cells. Hair cells are activated by a relative motion with respect to the tectorial membrane. One row of inner hair cells is positioned towards the modiolus. Inner hair cells, when activated, evoke actions potentials in the nerve fibers. The outer hair cells are positioned in, typically, three rows towards the periphery of the cochlea. The purpose of the outer hair cells is to provide enhancement of the basilar membrane, by actively changing the length of their cell bodies. Because outer hair cells require special freedom to change size, they are only partly connected to supporting cells.

Figure 1.8. The organ of Corti houses the sensory cell of the auditory system, the hair cells. Hair cells are activated by a relative motion with respect to the tectorial membrane. One row of inner hair cells is positioned towards the modiolus. Inner hair cells, when activated, evoke actions potentials in the nerve fibers. The outer hair cells are positioned in, typically, three rows towards the periphery of the cochlea. The purpose of the outer hair cells is to provide enhancement of the basilar membrane, by actively changing the length of their cell bodies. Because outer hair cells require special freedom to change size, they are only partly connected to supporting cells.

The stereocilia of a hair cell are believed to be detached or weakly attached to the tectorial membrane that resides on top of the organ of Corti.

As a result of BM movement, the stereocilia are displaced by very small distances of a few nm, relative to the tectorial membrane and endolymph fluid of the scala media (Furness et al., 1997). A deflection of the stereocilia bundle towards the longer stereocilia, as is drawn in panel A of Fig. 1.9, increases the tension on the cell membranes of the stereocilia by a stretching of the tip links. The tension opens stress-induced ion channels in the short stereocilia, by which potassium flows into the hair cell and induces an excitatory hair cell response. A deflection of the stereocilia bundle towards the shortest stereocilia releases the tension, thereby, creating an inhibitory hair cell response (Hackney & Furness, 2013), as is drawn in panel B of Fig. 1.9.

The potassium ions that enter a hair cell through the stereocilia increase the polarization of the cell, thereby, activating the sensory response of the hair cell. After a sensory response, the equilibrium state is recovered by depositing excessive potassium ions to the BM. Eventually the potassium is recycled by the stria vascularis to replenish the ion concentration in the scala media.
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Figure 1.9. (Previous page) The inner-, and outer hair cells are the sensory cells of the auditory system. The ‘hairs’ of the cells, i.e. stereocilia, are protruding extensions of the cells that touch the tectorial membrane. (A) A deflection of the stereocilia towards the longest stereocilium opens stress-induced ion-channels through which potassium ions can enter the hair cell. (B) Deflection towards the smallest stereocilium closes the ion-channels. (C) An increase of potassium concentration stimulates the production of neurotransmitters in the inner hair cell. (D) These transmitters are released in the synaptic cleft between the hair cell and an auditory fiber. (E) An increase of potassium concentration in outer hair cells activates a high-energy consuming contraction of the cell. (F) The size of the outer hair cells is believed to be reduced by folding the cell membrane by shearing cisterns that are located along the cell membrane. (G) Finally, the motion of the basilar membrane is coded by electric action potentials that are transmitted to retrocochlear structures.

1.6.5 Inner hair cells

The IHCs are the auditory sensory cells that are responsible for the mechanoelectrical transformation of BM movement to electrically evoked potentials. The body of an IHC has the shape of a laboratory flask, as is drawn in panel C of Fig. 1.9, with the stereocilia protruding at the neck. Activation of the IHC by potassium uptake consists of producing neurotransmitters and the release of neurotransmitters in the nerve cleft at the wider part of the IHC, as is drawn in panel D of Fig. 1.9.

1.6.6 Outer hair cells

While the activation mechanism of OHCs through potassium uptake in the stereocilia is similar to that of IHCs, the shape, position, as are drawn in panel E of Fig. 1.9, and the function of OHCs are different. The sensory response of OHCs is a mechanical contraction of the cell (Evans & Dallos, 1993). The OHCs can reduce their length by using a subsurface system of cisterns (Prieto et al., 1986), as is drawn in panel F of Fig. 1.9.

Contractions of OHCs are directly transmitted to the BM movement, thereby, providing a local amplification of BM excitation. The feedback has a twofold effect on the BM excitation that are directly related to the properties of the auditory system (Russell et al., 1986). Firstly, displacements of the BM are amplified at very low-levels, effectively increasing auditory sensitivity. Secondly, the feedback enhances tuning of the BM, thereby, increasing the frequency selectivity of the system. Because the OHC change in size along the BM (Bohne & Carr, 1985), and are activated by a narrow frequency band of sounds, it is possible that the OHCs have their own internal eigenfrequency. However, experimental evidence that supports or invalidates this hypothesis is not yet available.
1.6.7 RETROCOCHLEAR STRUCTURES

Each IHC is innervated by approximately 20 afferent fibers (Spoendlin, 1978). These fibers collect neurotransmitters in the IHC-to-auditory nerve cleft, and generate a pulse train of action potentials, as is drawn in panel G of Fig. 1.9. The electric activity is transmitted to the superior olivary nucleus in the brainstem and finally to higher level nuclei in the central nervous system, as is drawn in Fig. 1.10. The pathways of the ipsi-, and contralateral auditory systems (left and right ear), are combined in the brainstem and at higher levels.

Figure 1.10. The electric action potentials in the auditory nerve fibers are processed in retrocochlear structures. The auditory nerve enters the brainstem via the cochlear nucleus. The signal is then carried to the superior olivary nuclei on the ipsilateral- and contralateral sides of the brainstem. The olivary nucleus is the first stage in the auditory chain where auditory information of the two cochleae converges. A description of higher level structures is outside the scope of this work.

Approximately 5 to 15 % of the afferent fibers innervate multiple OHCs.
1.8 General introduction

(Spoendlin, 1978). In addition, IHCs and OHCs are innervated by efferent fibers coming from the ipsi-, and contralateral nuclei of the central nervous system. In particular the efferent fibers to OHCs form a web of synaptic connections, with each efferent innervating multiple OHCs. However, the function of afferent fibers in OHCs and efferent fibers are not fully explained and are subject to future research studies.

1.7 Physical impairment

Hearing loss can be caused in different parts of the hearing system. If we concentrate at hearing loss due to cochlear dysfunction, hearing loss can be caused by undeveloped growth or through physical damage of structures. Structures can be damaged by, among others, loud noise, illness, drugs, medicine, surgery and old age. The duration of exposure also affects the risk and type of hearing loss. For example, excessive loud sounds can physically tear the stereocilia from hair cells and prolonged exposure to less loud sounds can degrade hair cells by producing waste products, such as intoxicating oxidants, over time. Illness, drugs and medicine can cause damage by intoxicating cochlear structures or disrupting the chemical consistency of the fluids in the scalae.

Old age and noise-induced hearing loss are often associated with the loss of hearing at high frequencies. The relative sensitivity of high frequencies suggests that the basal hair cells that are associated with the high frequencies are more prone to damage than the apical low frequency hair cells.

1.7.1 Dead regions

Originally, a dead region has been defined as a physical or functional loss of IHCs and/or the afferent fibers of the auditory nerve (Moore & Glasberg, 1997; Moore et al., 2000; Moore, 2001; Moore & Alcántara, 2001). The BM movement in an area of the cochlea that is associated with a dead region is, therefore, not transmitted to the brainstem and is functionally lost for auditory tasks. However, dead regions are also frequently associated with the diagnostic outcome of PTCs and the TEN test. In this thesis, a dead region that is defined as a physical impairment is referred to as a physical dead region. A frequency region that was identified as a dead region by psychophysical diagnostic testing is referred to as a psychophysical dead region.

1.8 Indirect evaluation of the auditory function

A practical problem that is highlighted in this work is that the structural mechanisms of the auditory system cannot be measured directly in human listeners. Existing methods that can directly measure the physical status of the cochlea are not suited for clinical use because they can cause damage to the delicate
structures of the auditory system. Methods that can estimate the electrical response of IHCs and the auditory nerve to sounds, such as brain evoked response audiometry, are not very cost effective and may not provide sufficient information to differentiate between IHC loss, OHC loss and the loss of auditory nerve fibers.

Instead, a functional model description of the auditory system is used to circumvent the problems associated with direct measurement of structures in the cochlea. Many functions of the outer-, middle-, and inner ear can be (partially) isolated and simulated in models. The model simulations can be calibrated using data from animal studies and validated by comparing predictions of the psychophysical behavior with measured listener data. A schematically overview of the approach is shown in Fig. 1.11.

1.9 Thesis overview

This thesis attempts to establish, using a model framework, a relationship between the psychophysical measurement of off-frequency listening and the functional auditory loss caused by dead regions in the cochlear. The results are used to evaluate the clinical value of dead region diagnosis with PTCs and the TEN test.

Chapter 2 describes the current problems with PTCs and the TEN test. The results show that in roughly one quarter of the listeners the diagnostic results for dead regions were not in agreement between PTCs and the TEN test. It is also shown that PTCs were influenced considerably by the frequency and level of probes in some listeners, and that, consistent with a study of Markessis et al. (2009), TEN test results depend on the level of TEN.

Chapter 3 validates and optimizes a functional model of the auditory system for simulations of PTCs and TEN test results. Simulated PTCs and TEN test results are compared to measured results of normal-hearing listeners. The model optimizations were used in chapters 4 and 5 to simulate, respectively, PTC-, and TEN test results in listeners with dead regions.

Chapter 4 shows that, in a model framework, off-frequency listening in PTCs is affected by different types of hearing impairment. The dependency of PTC results on probe settings can be explained by (partially) active OHCs near the edge of a dead region.

Chapter 5 uses the model parameters to simulate PTCs in HI listeners to predict TEN test results for the same listeners. The findings of chapters 4 and 5 suggest that the loss of IHCs results in off-frequency listening, but off-frequency listening does not necessarily imply the presence of a dead regions.

Chapter 6 concludes this thesis by several discussions related to dead regions; the clinical relevance of the results presented in chapters 4 and 5, the inequality of physical impairment of IHCs and psychophysical measurement of dead regions, a classification of dead regions, and research areas that may be exploited in future research projects.
1.9 General introduction

Figure 1.11. The relationship between physical structures of the auditory system (upper left) and the psychophysical measurement of the auditory function (upper right) is not straightforward. For example, the presence of a dead region cannot be measured by pure-tone audiometry, because of off-frequency listening. More sophisticated methods are needed, such as PTCs and the TEN test, to test for dead regions. Unfortunately, these methods produce results that cannot be easily explained (see Chapter 2). In this study, an indirect approach is used to evaluate the effects of impaired hearing structures on psychophysically measured results. A functional model (bottom left) is modified for different types of hearing losses associated with dead regions, and is used to simulate psychophysical responses to PTC and TEN test stimuli (see Chapters 4 and 5). The model simulations are compared with normal-hearing listener data to evaluate the model predictions, and with hearing-impaired listener data to describe PTC, and TEN test results. Studies on animals (bottom right) provide basic parameters for the functional model.