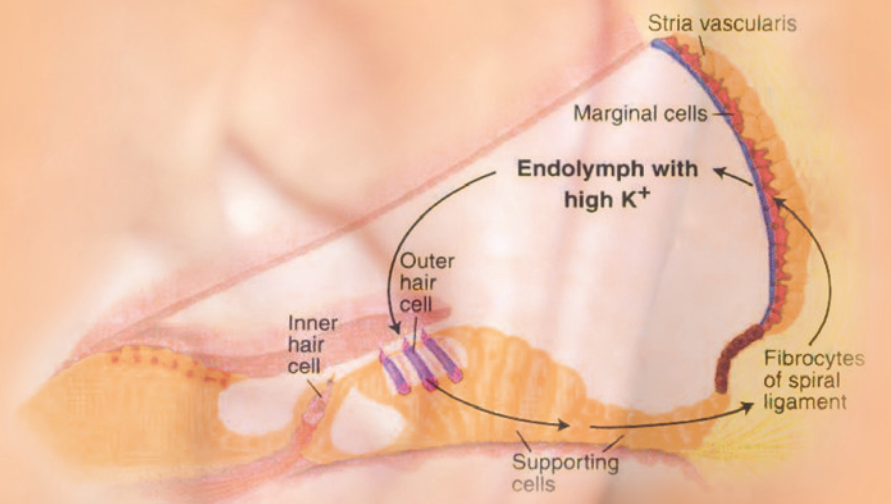
Acoustics Australia



SPECIAL ISSUE: MECHANISMS OF HEARING DAMAGE

- ***Spatial perception and masking***
- ***Plasticity in the adult auditory system***
- ***Efferent control of hearing***
- ***Genetics of hearing loss***
- ***Mitochondria, cell death and deafness***
- ***Cochlear mechanics and masking***
- ***Servo control in the cochlea***

Australian Acoustical Society ***Vol. 34 No. 1 April 2006***

The Dream Machine

SignalCalc ACE - QUATTRO

Everything that ACE-I has plus much more:-

Sound Power,
Demodulation,
Acoustic Intensity,
Rotordynamics,
Quality Control
IRIG-B Time Code,
Stepped Sine and with MIMO,
Multiple Input Multiple Output
Single to Multi-Plane Balancing
Shock Response Spectrum, TEDS,
and more ....!

All of the Old Stuff:
Record on all 4 channels up to a rate of 204.8 kS/sec for data acquisition in aircraft, in vehicles, on ship, in the field and in industrial environments. Perform Advanced Modal Testing, measure Histogram, Correlation, Real Time and synthetic 1/1 & 1/3 Octave, Auto Power Spectrum, Synchronous Average Sound Quality, Quality Control, Event capture, Human Vibration, Zoom and Waterfall Analysis, RPM and Order Track Analysis.

*** 2 to 4 Input Channels**
*** 0 to 2 Output Channels**
*** 1 Tachometer channel standard**
*** 24 bit similtaneous**
*** Max Sample Rate 204.8 kHz**
*** DC to 40 kHz or 93 kHz,**
*** > 120 dB Dynamic Range**
*** Coupling AC, DC, Diff, SE, ICP**
*** Anti Alias - 100dB protection**
*** Inputs Crosstalk < -100 dB**

*** Data by USB2**
*** mass is < 550 Grams**
*** 142 mm x 101 mm x 23 mm**
*** Operating Temp 0 to 55 deg C**
*** Powered by USB-2, bus powered ,**

and **INTRODUCING a new line of**
MEASUREMENT MICROPHONES.

Kingdom is now distributing BSWA Tech microphones & accessories in Australian & NZ. High quality, calibrated electret prepolarized microphones to class 1 standard. Accessories include ICP power sources, portable sound level calibrators, a USB powered 2 channel measurement soundcard peripheral, a 12 speaker dodecahedral sound source, compact light weight 2 channel power amplifiers. an impedance tube providing 125 Hz to 3200 Hz range and a self contained Tapping Machine sound source for foot fall measurements.

For more information phone: **02 9975 3272**
or visit: ***www.kingdom.com.au***

KINGDOM PTY LTD
Phone 02 9975 3272

AA 03/05

Acoustics Australia

Acoustics Australia
General Business
(subscriptions, extra copies, back issues, advertising, etc.)

Mrs Leigh Wallbank
P O Box 579
CRONULLA NSW 2230
Tel (02) 9528 4362
Fax (02) 9589 0547
wallbank@zipworld.com.au

Acoustics Australia
All Editorial Matters
(articles, reports, news, book reviews, new products, etc)

The editors, Acoustics Australia
School of Physics
University of New South Wales
Sydney 2052 Australia
61-2-93854954 (tel)
61-2-93856060 (fax)
aaeds@phys.unsw.edu.au
www.acoustics.asn.au
AcousticsAustralia@acoustics.asn.au
www.acoustics.asn.au

Australian Acoustical Society
Enquiries see page 60

Acoustics Australia is published by the Australian Acoustical Society (A.B.N. 28 000 712 658)

Printed by
Cliff Lewis Cronulla Printing Co
91-93 Parraweena Rd,
CARINGBAH NSW 2229
Tel (02) 9525 6588
Fax (02) 9524 8712
email: scott@clp.com.au
ISSN 0814-6039

Vol 34 No 1 April 2006

CONTENTS

PAPERS

- **Listening to the world around us.**
  Simon Carlile . . . . . **Page 5**
- **Plasticity In The Adult Central Auditory System**
  Dexter R. F. Irvine, James B. Fallon and Marc R. Kamke . . . . . **Page 13**
- **Efferent Control of Hearing**
  Wilhelmina H.A.M. Mulders . . . . . **Page 19**
- **Genetic Aspects Of Hearing Loss**
  Hans-Henrik Dahl, Shehnaaz Manji, Michelle de Silva, Marisel Peverelli and Michael Hildebrand. . . . . . **Page 25**
- **Mitochondria, cell death, and deafness: will it be possible to prevent presbyacusis?**
  James O. Pickles . . . . . **Page 31**
- **Functionality of Cochlear Micromechanics – As Elucidated By Upward Spread of Masking And Two Tone Suppression**
  D. Sen and J. B. Allen . . . . . **Page 37**
- **A Review Of Mechanical Evidence for a Servo-loop in the Mammalian Cochlea**
  Eric L. LePage . . . . . **Page 43**

FORUM

- **More About Automotive Exhaust Noise**
  A.D. Jones . . . . . **Page 52**

Future Meetings 53
News 54
FASTS 56
Standards Australia 56
Meeting Reports 57
New Products 58
Diary 59
Acoustics Australia Information 60
Australian Acoustical Society Information 60
Advertiser Index 60

Cover illustration: Xxxxx xxxx

From the President

It is with great sadness and shock that I write this President's Message due to the tragic death of Andrew Wearne at the end of last month. We have lost Australia's best – and probably one of the world's top five – railway noise and vibration acoustic engineers. I attended his memorial service along with approximately 800 others and there was overwhelming praise and recognition for Andrew's achievements from friends, colleagues and clients.

I was quite surprised how much this loss affected me personally, given that I only knew Andrew as a fellow professional and didn't know him socially. Although we had worked together on a number of projects over the last 13 or so years and others in our office had been working more closely with him recently, his name was always mentioned with the utmost respect.

I believe the real reason behind my feelings was the fact that Andrew was always so polite, easy to deal with and a true professional that you subconsciously knew what he would have been like as a husband, father, team mate and friend, hence you actually felt that you knew him well. I know that many other acousticians were similarly shocked and it was wonderful to see so many of his peers attend the memorial service which was a celebration of his life and achievements.

It is tragic circumstances like this that make you pause for a moment and take stock of your life. Do I enjoy my job? Do I have the right work / life balance? Am I contributing to society making the world a better place? The memorial service certainly indicated the great contribution Andrew has made through his skills as an engineer and also his dedication to friends in his local Berowra community. I trust that we can all reflect on the way we behave both professionally and socially to achieve the right outcomes. Hopefully this involves compromise and resolution rather than argument and conflict.

In our Articles of Association, the Acoustical Society is termed a "learned" society. Today we are a little less "learned". Andrew will be truly missed. The family has requested any donations be sent to African Enterprise www.africanenterprise.com.au

Looking to the future, it would appear from recent email correspondence that the first joint Australian and New Zealand Conference this November in Christchurch is shaping up to be one of the best ever in terms of likely attendance and number of papers. It really is the only opportunity each year to get together with your peers from around the region to share ideas and knowledge.

On a more local stage, the need to have regular get-togethers in your own State at technical meetings is also important so I would encourage you all to support these events by both offering to present and supporting your peers.

Neil Gross

From the Guest Editor

Since the last issue of Acoustics Australia directed at basic mechanisms in 1993, biological research has drawn over a billion of dollars of funding and is poised to make several huge advances. Hearing science has increasingly embraced other disciplines, such as genetics and molecular biology, which at first glance might seem to have little connection with acoustics. Accordingly, the Australian authors were challenged to condense into just a few pages those developments which may soon have application to acousticians and clinicians, i.e. the articles had to relate to sound parameters, signal processing, engineering concepts and auditory psychophysics.

Accordingly the articles are presented in a "top-down" order, from the psychophysics of sound localisation using Head Related Transfer Functions (Carlile). Next, Irvine and colleagues review the concept of plasticity of 'wiring' of the neural connections in the auditory cortex and how that has applicability to the fitting of cochlear implants. Further down the brainstem, Mulders reviews the extensive neural organisation with particular emphasis on the signals which descend to the cochlea to either control the mechanical processing of sound via the outer hair cells, or the excitability of primary neurons carrying the frequency analysis upward.

The next two articles are about the genetics of hearing loss (Dahl and colleagues) and the source of biological energy which drives cochlear processes (Pickles). These authors ask why deafness occurs; and what syndromes relate to malformations of molecular structures which allow ionic currents to flow. The charged ions must be pumped using energy provided by mitochondria. These two papers also contain the basis of mechanisms for characterising individual susceptibility to hearing loss. Basic hearing science now regards the effects of noise trauma as just another of the toxic influences which cause hair cells to die. Hair cell death occurs by two separate processes and, whereas we might once have had a simple mental connection between temporary threshold shift as an indicator for permanent loss, we now have a new branch of science.

Traditionally, reviews of cochlear mechanics discuss how the frequency analysis in terms of tuning curves for each frequency and the important nonlinear processes which occur due to outer hair cell activity. The sixth article (Sen) models two-tone interactions at the mechanical level and explains the upward spread of masking which started out being the basis of mpeg compression technology, but has deep associations with distortion product emissions, combination tones, and critical bands. Increasingly, analysis of cochlear mechanics suggests that the outer hair cells providing the frequency analysis are also involved with regulation. The last article (LePage) reviews direct mechanical evidence for an internal automatic volume control system which optimises cochlear performance during trauma and aging of the ear. The new insights into structure and function lead to some possible explanations of the relation between sound level and duration – Dixon Ward's equal energy relation, and suggest new approaches to hearing loss prevention based on actual mechanisms.

This special issue thus has particular significance because it draws attention to the exciting cross-fertilisation now taking place between the worlds of psychoacoustics and physiological acoustics. The next decade may well reveal precise explanations of well-known psychophysical phenomena and issues of individual susceptibility.

Eric LePage, guest editor

LISTENING TO THE WORLD AROUND US.

Simon Carlile,
School of Medical Sciences,
University of Sydney, NSW 2006

Our perception of auditory space depends on the integration of a number of acoustic cues to the locations of sound sources. The binaural cues to location arise as a consequence of the two ears being separated by an acoustically dense head which results in differences in the time of arrival and level of the sound at each ear. The outer ears also filter the sound in a directionally dependent manner providing the spectral cues to a sound's location. Real world listening involves separating out multiple concurrent sound sources and differences in their spatial locations provide a means by which auditory spatial attention can be focused on one sound of interest and other masking sounds are ignored. Recent work has demonstrated that spatial release from masking is more effective when the target and maskers are speech sounds and that this involves both bottom up perceptual processes and top-down cognitive processes. This work indicates that preservation of the spatial cues is essential for the effective use of hearing aids implicating both binaural and in-the-ear fitting strategies.

1. REAL WORLD LISTENING

Much of the time, listening in the real world is a very complex task. Rarely do sounds of interest occur on a background of silence. Rather, the world is a tumultuous mix of multiple sounds that overlap in frequency and time. Some sounds can represent threats or opportunities while others are simply distracters or maskers. In many listening situations reverberance and/or echoes further complicate the soundscape. All of these sounds arrive at the ear drum as a combined stream and jointly excite the inner ear. What is most remarkable is that the auditory system is able to sort out the many different streams of sound and provides the capacity to selectively focus our attention on one or another of these streams. The auditory system is quite unlike the senses of vision or touch in that the sensory epithelia codes frequency and not spatial location. Consequently, our perception of auditory space is based on a variety of acoustic cues that occur at each ear. This means that the acoustic cues to the different source locations also need to be deconvolved from the complex signal reaching the ears. Our capacity to focus attention on one sound of interest and to ignore distracting sounds is dependent, at least in part, on the differences in the locations of the different sound sources. This article reviews the acoustic cues that the auditory system uses to achieve this amazing feat of signal processing, how these cues lead to our perception of auditory space and how this contributes to the understanding of speech in complex acoustic environments.

The three principal dimensions of auditory spatial perception are direction, distance and spaciousness. In our qualitative descriptions of the location of objects in every day life we refer to horizontal direction, height above or below the audio-visual horizon and distance from the head. In addition to the perception of location, the extent or "spaciousness" of the space inhabited by the listener and the "width" or apparent size of the sound source are also important attributes. The sense of spaciousness also plays an important role in the generation of the sense of "presence" or "being there" enjoyed by the listener using a virtual auditory display (see [1]).

2. CUES FOR SPATIAL LISTENING

Our perception of auditory space is based on acoustic cues that arise at each ear. These cues result from an interaction of the sound with the auditory periphery which includes the two ears, the head and torso as well as with the reflecting surfaces in the immediate environment (for review [2]). As the two ears are separated by an acoustically dense head, the auditory system can simultaneously sample the sound field from two slightly different locations. This gives rise to the so-called binaural cues to the location of a sound source. For a source located off the midline, the path length difference from the source to each ear results in an interaural difference in the arrival times of the sound or a difference in the phases of the on-going component of the sound at each ear (Figure 1a). This is referred to as the interaural time difference (ITD) cue. As the auditory system only encodes the phase of a sound up to a few kilohertz, the interaural phase difference cue is limited to the lower frequency range of human hearing. However, the auditory system is also able to extract interaural time differences from the amplitude modulation envelopes of more complex sounds over the whole range of frequency sensitivity (e.g. [3] but see [4], recent review [5]). Psychophysical studies using headphone presented stimuli have demonstrated sensitivity to interaural time differences as small as 13 μs [6] for tones from 500 to 1000 Hz.

As the head is relatively large with respect to the wavelengths of mid to high frequency sounds to which the auditory system is sensitive, the ear furthest from the source will be acoustically shadowed giving rise to an interaural difference in the sound level at each ear. This is know as the interaural level (or intensity) difference (ILD) cue. Sensitivity to interaural level differences as small as 1 dB have been demonstrated for pure tone stimuli presented over headphone [7]. In summary, the ITD cues are believed to contribute principally at the low frequencies and the ILD cues at the mid to high frequencies – this is sometimes referred to as the duplex theory of localisation.

The binaural cues alone provide an ambiguous cue to the spatial location of a source because any particular interaural interval specifies the surface of a cone centred on the interaural axis - the so called "cone of confusion" (Figure 1b).

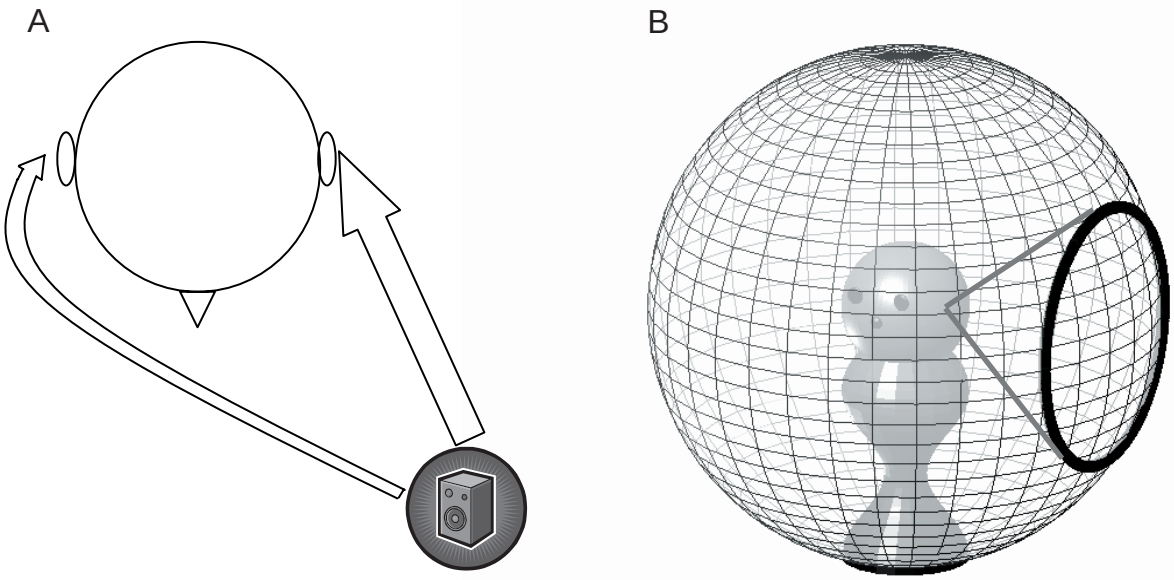


Figure 1: (A) When a sound source is located off the midline the separation of the two ear by the head results in differences in the path lengths between the sound source and each ear (length of arrows). This results in a difference in the time of arrival of the sound to each ear by up to 800 μs or more. The ear furthest from the sound source will be in the acoustic shadow cast by the head which leads to an interaural level difference (width of arrows). (B) The cone of confusion is shown for a particular interaural time and level difference corresponding to a location 60° from the midline.

The outer ear, the pinna and concha, is an asymmetrical and highly convoluted structure that filters sound in a manner that is dependent on the direction of the wave front (e.g. [8, 9]; Figure 2). This gives rise to the spectral (or monaural) cues to location. Reflections from the shoulder and torso may also contribute to the filtering in the lower frequency range where the wavelengths are long compared to the dimensions of the outer ear (see [2] for review). These location dependent filter functions can be measured by inserting small microphones into the ear canals and are referred to as the head related transfer functions (HRTF) [9, 10]. The spectral cues provide the basis for resolving the cone-of-confusion (Figure 1 and Figure 2) and, together with the head shadow [11], also explain the residual sound localisation capability observed in monaurally deaf individuals [12].

In summary, accurate determination of the direction of a sound source is dependent on the integration of the binaural and spectral cues to it's location (see [13];). The relative roles of the ITD and ILD are determined in part by the frequency content and the depth of amplitude modulation of the envelope of the sound [14]. The spectral cues from each ear are weighted according to the lateral angle of the source; the ipsilateral ear dominates for locations close to the interaural axis but there is an increase in the weighting of the contralateral cues as the sound location approaches the midline [15]. Interestingly, the interaural spectral difference per se is unable to support normal localisation at any lateral angle [16]. The sound level and duration of the stimuli also play an important role. At low (< 40 dB) and high (> 60 dB) sound levels, localisation accuracy on the cone of confusion decreases. In the latter case this has been attributed to saturation [17, 18] and/or compression [19] of the cochlear excitation patterns leading to distortion of the encoded spectra. The poor performance at low sound levels could result from level dependent non-linear amplification of the cochlea and subsequent distortion of the spectral profile or a poor signal to noise ratio leading to noisy analysis of the cue [19]. Localisation performance on the cone-of confusion has also been reported to deteriorate for stimuli less than 30 ms in duration suggesting that this may represent a minimum time window for spectral integration [18, 19]. A range of physiological studies have also demonstrated that neural representations of auditory space in the superior colliculus in mammalian midbrain are dependent on the integration of these binaural and monaural cues (reviewed in [20]).

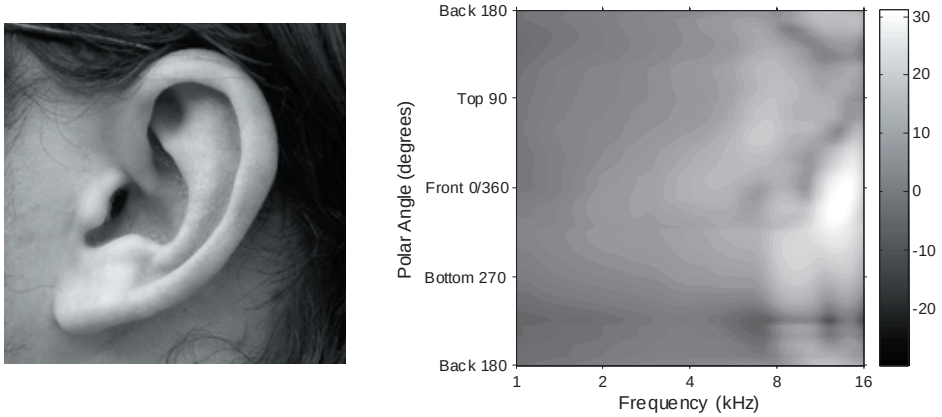


Figure 2: Left ear of a female subject and the head related transfer functions obtained for the mid-line cone of confusion. The scale bar indicates the variations in the level of the filter functions in dB.

While it is the interactions of the sound with the auditory periphery that provides the cues to source direction, it is the interactions between the sound and the listening environment that provide the four principal cues to source distance (for recent review see [21]). First, the intensity of a sound decreases with distance according to the inverse square law: this gives rise to a 6 dB decrease in level with a doubling of distance. Second, as a result of the transmission characteristics of the air the high frequencies (>4 kHz) are absorbed to a greater degree than low frequencies. This leads to a relative reduction of the high frequencies of around 1.6 dB per doubling of distance [22]. Notably for both of these cues there is a confounding of source characteristics (intensity and spectrum) with distance so they can only act as reliable cues for familiar sounds (speech is a particular case in point). The third cue is the ratio of the direct to reverberant energy [23]. The level of reverberation in a room is determined principally by the characteristics of the room and is basically constant throughout the room while the direct energy is subject to the inverse square law of distance. This is a particularly powerful distance cue but is dependent on the reverberant characteristics of the listening environment [24]. Recent work exploring distance perception for sound locations within arms reach (i.e. in the near field) has confirmed the very early observations of Hartley and Fry [25] that substantial changes in the interaural level differences can occur with variation in distance (see for instance [26]). The distance effect on interaural time difference appear to be less salient [27]. There are also distance related changes to the HRTFs in the near field because of the parallax change in the relative angle between the source and each ear with distance [28].

The perception of auditory spaciousness has been characterized by "apparent source width" which is related to the extent of early lateral reflections in a listening space and the relative sound level of the low frequencies (e.g: [29, 30]). A second aspect of spaciousness is "listener envelopment" which is related more to the overall reverberant sound field and is particularly salient with relatively high levels arriving later than 80 ms after the direct sound (see [31]).

An important but almost unstudied issue in auditory spatial perception is the extent to which a sound is heard externalized away from the head. When normally listening over headphones, the percept generated is of a sound source located within the head. By manipulating the ITD or ILD the phantom source can be lateralized towards one or the other side of the head but remains within the head. However, if the sound is first filtered with the head related transfer functions (HRTFs) for a particular location in space and then played back over headphones, the apparent source of the sound is heard externalized to the spatial location corresponding to the HRTFs used. On the one hand, this should not be surprising because if the headphone transfer functions are properly compensated for, then the pattern of sound waves at the ear drums should be identical to that produced by the sound actually out in space. On the other hand, this also demonstrates the important role the HRTFs play in enabling this sense of externalization. This manipulation of the sound is the basis of virtual auditory displays or so-called auditory virtual reality systems using headphone delivery. An important issue for virtual auditory displays is the match between the set of head related transfer functions (HRTFs) used to render the virtual auditory environment and the actual HRTFs of the listener. Even relatively small differences between the sets of HRTFs can degrade the accuracy with which sound sources can be rendered at specific locations in virtual space. There are also a range of other factors involved in generating or enhancing the percept of externalization. For instance, the reverberant characteristics of the sound and active head movement within the listening environment can both contribute to the sense of externalization and "presence" in the virtual auditory world [32].

3. LOCALISATION PERFORMANCE – DIRECTION AND DISTANCE

There are quite a number of studies of the accuracy and resolution of human auditory spatial perception (for reviews see [2, 33]). Absolute localisation accuracy has been assessed by allowing subjects to indicate the perceived direction of a sound source whose spatial location is randomly varied (e.g. [34-36]). Subject's perception of location has been measured using both continuous (e.g. [35, 36]) and quantized methods (e.g. [37, 38]) of indicating the perceived location. Knowledge about the potential locations of stimuli has also been shown to influence the subjects' responses in a non-sensory manner [39].

In general these experiments demonstrate two classes of localisation errors: (i) Large "front-back" or "cone of confusion" errors where the perceived location is in a quadrant different from the source but roughly on the same cone of confusion; (ii) Local errors where the location is perceived to be in the vicinity of the actual target. Average localisation errors are generally only a few degrees for targets directly in front of the subject (SD ± 6° - 7°). Absolute errors and the response variability around the mean, gradually increase for locations towards the posterior midline and for elevations away from the audio-visual horizon. For broadband noise stimuli the front-back error rates range from 3% to 6% of the of trials. However, localisation performance is also strongly related to the characteristics of the stimulus. Narrowband stimuli [13], particularly high or low sound levels (e.g. [19]) or reverberant listening conditions [40] can all significantly degrade performance.

A different approach to understanding auditory spatial performance is to examine the resolution or acuity of auditory perception. In these studies, subjects are required to detect a change in the location of a single source (e.g. [41]). This is referred to as a minimum audible angle (MAA). This approach provides insight into the just noticeable differences in the acoustic cues to spatial location. Consistent with the absolute accuracy studies, MAA studies have demonstrated that resolution is highly dependent on both the type of stimulus and the spatial location about which the change in location is measured (see [41, 42]). The smallest MAA (1-2°) is found for broadband sounds located around the anterior midline and the MAA increase significantly for locations away from the anterior median plane. The MMA is also much higher for narrow band stimuli. More recent work has also examined the ability of subjects to discriminate concurrent sounds as originating from different locations [43]. In this case, the ability to parse the locations of two concurrent stimuli with

identical spectral characteristics is dependent on interaural differences rather than the spectral cues.

The majority of localisation performance studies have been carried out in anechoic environments. Localisation in real world environments will of course include environments with some level of reverberation. Interestingly, localisation in rooms does not appear to be as robust as in anechoic space [40] but it does appear to be better than what might be expected based on how reverberation degrades the acoustic cues to location. For instance, reverberation will tend to de-correlate the waveforms at each ear because of the differences in the patterns of reverberation that combine with the direct wave front at each ear [44]. This will tend to disrupt the extraction of ongoing ITD although the auditory system may be able to obtain a reasonably reliable estimate of the ITD by integrating across a much longer time window. Likewise, the addition of delayed copies of the direct sound will lead to comb filtering of the sound that will tend to fill in the notches and flatten out the peaks in the monaural spectral cues and decrease the overall ILD cue. These changes will also be highly dependent on the relative locations of the sound sources, the reflecting sources and the listener (see review [45]).

4. THE COCKTAIL PARTY PROBLEM

In the course of most human communication, the speech we are attending to occurs against a background of other talkers and non-speech sounds. This is referred to as the cocktail party problem: that is, how the auditory system segregates and streams the talker of interest from multiple concurrent talkers and other sounds [46, 47]. In signal processing terms, the concurrent sounds are composed of different and relatively sparse spectral components that are changing dynamically over time. It is also likely that some spectral components will transiently overlap in different frequency regions. The first puzzle is how the auditory system groups together the spectro-temporal components and associates them with different sources (auditory objects). Secondly, how are these grouped elements connected over time into coherent and segregated streams of information? The overall process is referred to as auditory scene analysis [48] and two basic and complementary processes are conceived to be operating:

Primitive grouping: The notion of primitive grouping is based on the Gestalt principals of *proximity, similarity, common fate, set, continuity, symmetry and closure*. A number of processes have been identified psychophysically. One processes exploits harmonicity – that is, the energy in many natural sounds (including speech) is distributed harmonically across frequency and concurrent sounds will almost always have instantaneous differences in the fundamental frequency (F0). The associated spectral components can then be grouped on the basis of their respective harmonic relationships to the fundamental frequencies of the different sources. Spectral components are also grouped on the basis of common onset and/or offsets and common amplitude modulation (for review see [49]). These process are thought to be bottom-up and automatic. Once grouped together according to these rules the relevant spectro-temporal components are connected up over time into separate streams of information that are associated with different auditory objects (see [50] for review).

Schema based processes: With multiple concurrent sounds there will inevitably be intermittent spectro-temporal overlap and at various instances the louder sound will mask the presence or absence of energy from other sounds. This is an example of simple energetic masking which can interfere with the primitive grouping and compromise the integrity of the information in the streams. Therefore, the auditory system has to fill in the gaps in the streams and correct flawed groupings. In this classical view, when the sound of interest is a talker, schema based processes relying on the semantic and linguistic context can be used to help fill the gaps in the attended stream. This is generally conceived of as a knowledge based, cognitive and/or top-down process.

5. INFORMATIONAL AND ENERGETIC MASKING AND SPATIAL RELEASE FROM MASKING

The amount of energetic masking of a talker in the proximity of (or co-located with) other masking sounds can be reduced by spatially separating the target from the maskers. In the first instance, this spatial release from masking can be explained by an improvement in the signal to noise ratio in one or other of the ears (Figure 3). However, the work of Freyman [51, 52] and others (e.g. [53, 54]) has demonstrated that the spatial release from masking of speech produced by a concurrent talker (as opposed to a non-speech masker) is greater than that predicted by a simple energetic model of the interactions of the sounds at each ear. This additional masking is referred to as informational masking.

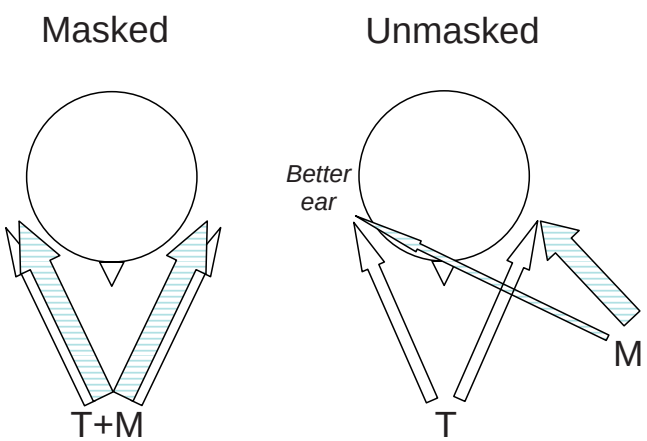


Figure 3: Spatial release from masking for non speech maskers can be understood in terms of the changes in signal to noise ratio at the "Better" or shadowed ear. T target talker of interest; M masker

Informational masking can be related to the similarity between the masker(s) and the target which leads to confusion about the assignment of different words to different streams [54]. The spectral components are correctly grouped and the information correctly identified but streaming fails because of confusion relating to higher level components in the information. An example is the confusion that can occur when two concurrent talkers have similar sounding voices.

Informational masking is also associated with stimulus uncertainty: i.e. when a stimulus is highly variable and the listener does not know what to expect (for discussion see [55]). Linguistic and semantic context are seen as important in helping to correct these sorts of errors as the information in the stream unfolds. The role of semantic analysis indicates the involvement of high level cognitive or schema based processes. Most interestingly, however, there is some data that suggests that the maskers do not have to be intelligible to produce informational masking. Freyman et. al. [52] demonstrated that almost the same amount of informational masking occurred when the masker talker was speaking in a language not understood by the listener compared to one that was understood by the listener. In addition, time reversed masker speech could also produce substantial informational masking. These two findings are problematic for an account of informational masking that relies on a top-down, semantic model as, although these stimuli are recognisable as human speech, they are clearly unintelligible.

In the context of spatial hearing, a most important finding is that perceived differences in the locations of target and masker talkers gives rise to a larger spatial release from masking than that observed with talkers masked by a purely energetic masker like speech shaped noise (see for review [56]). This indicates that when the target and maskers are co-localised there is interference in the schema based processes (informational masking) that is over and above the energetic masking. However, the differences in the locations are utilised by the auditory system to allow the listener to focus their spatial attention on the target talker and/or to disattend to the masker talkers [53] in a way that decreases the informational interference between the target and the masker. The differences in location appears to help to keep separate the informational streams associated with each talker. In the case of noise maskers, the spatial release from masking is governed by the reduction in the energetic masking when the masker is moved away from the target talker. With this type of masker there is no informational masking and nearly all of the spatial unmasking can be explained in terms of the signal to noise ratio at the better ear (Figure 3). The residual unmasking is probably related to binaural processing [53] and will be dependent on the nature of the sounds and the acoustic environment [57].

The ability to focus attention on a particular talker and indeed to switch attention between talkers plays a key role in solving the cocktail party problem. Although primitive grouping provides very effective means to separate concurrent talkers and other sounds, much human spoken communication is actually carried out under quite adverse listening conditions (the pub or the cocktail party are the case in point). Under such conditions, a talker will generally raise the level of his or her voice so that the signal to noise ratio is around 0 dB at the listener [58]. Under such conditions, where there is also the potential for substantial informational masking, the spatial separation of the target and maskers plays an important role in supporting good speech intelligibility under real world listening conditions.

6. HEARING IMPAIRMENT

Hearing impaired listeners are also able to capitalize on the differences in the locations of talkers to reduce the amount of masking. However, the spatial release from informational masking is reduced by 5 dB in listeners with even mild hearing impairment compared to normally hearing listeners under the same conditions [59]. Many studies have demonstrated that speech intelligibility falls off relatively quickly as a function of signal to noise ratio and a loss of 5 dB spatial unmasking results in a very significant reduction in the percentage of words understood in a noisy listening environment. These findings have an important implication. The hearing deficit will undoubtedly have degraded the quality of the cues to spatial location. It is important, therefore, to provide hearing aids that support the encoding of the acoustic cues to spatial location.

In the first instance this could be as simple as providing binaural aids that are properly calibrated to preserve the normal ITD and ILD cues. The more challenging question however, is how to preserve the information in the spectral cues. Certainly the development of relatively powerful digital hearing aids small enough to fit inside the auditory canal provides a means of preserving the normal spectral cues to location. However, the hearing impairment is also characterized by a significant reduction in sensitivity to the mid to high frequency range of hearing and it is over this range that the majority of location dependent spectral cues are generated (see [9, 60]. Recently, it has been suggested that transposing the spectral cues into a lower frequency range could provide the opportunity for the auditory system to relearn to use these new spectral cues ([61] see also [62])

REFERENCES

1. Durlach, N., “Auditory localization in teleoperator and virtual environment systems: Ideas, issues and problems”, Perception. 20, 543-554, (1991).
2. Carlile, S., “The physical and psychophysical basis of sound localization”, in Virtual auditory space: Generation and applications, S. Carlile, Editor. Landes: Austin. p. Ch 2, (1996).
3. Henning, G.B., “Detectability of interaural delay in high-frequency complex waveforms”, J Acoust Soc Am. 55, 84-90, (1974).
4. Eberle, G., et al., “Localization of amplitude-modulated high-frequency noise”, Journal of the Acoustical Society of America. 107 (6), 3568-3571, (2000).
5. Bernstein, L.R., “Auditory processing of interaural timing information: New insights”, Journal of Neuroscience Research. 66 (6), 1035-1046, (2001).
6. Zwislocki, J. and R.S. Feldman, “Just noticeable differences in dichotic phase”, J Acoust Soc Am. 28, 860-864, (1956).
7. Mills, A.W., “Lateralization of high-frequency tones”, J Acoust Soc Am. 32, 132-134, (1960).
8. Mehrgardt, S. and V. Mellert, “Transformation characteristics of the external human ear”, J Acoust Soc Am. 61 (6), 1567-1576, (1977).
9. Carlile, S. and D. Pralong, “The location-dependent nature of perceptually salient features of the human head-related transfer function”, J Acoust Soc Am. 95 (6), 3445-3459, (1994).
10. Pralong, D. and S. Carlile, “Measuring the human head-related transfer functions: A novel method for the construction and calibration of a miniature “in-ear” recording system”, J Acoust Soc Am. 95 (6), 3435-3444, (1994).

11. Van Wanrooij, M. and J. Van Opstal, "Contribution of head shadow and pinna cues to chronic monaural sound localization", J Neuroscience. 24, 4163-4171, (2004).
12. Slattery, W.H. and J.C. Middlebrooks, "Monaural sound localization: Acute verses chronic unilateral impairment", Hear Res. 75, 38-46, (1994).
13. Middlebrooks, J.C., "Narrow-band sound localization related to external ear acoustics", J Acoust Soc Am. 92 (5), 2607-2624, (1992).
14. Macpherson, E.A. and J.C. Middlebrooks, "Listener weighting of cues for lateral angle: The duplex theory of sound localization revisited", J Acoust Soc Am. 111 (5 Pt 1), 2219-2236, (2002).
15. Hofman, P.M. and A.J. Van Opstal, "Binaural weighting of pinna cues in human sound localization", Experimental Brain Research. 148 (4), 458-470, (2003).
16. Jin, C., et al., "Contrasting monaural and interaural spectral cues for human sound localisation", J Acoust Soc Am. 115 (6), 3124-3141, (2004).
17. Hartmann, W.M. and B. Rakerd, "Auditory spectral discrimination and the localization of clicks in the sagittal plane", J Acoust Soc Am. 94 (4), 2083-2092, (1993).
18. Macpherson, E.A. and J.C. Middlebrooks, "Localization of brief sounds: Effects of level and background noise", J Acoust Soc Am. 108 (4), 1834-1849, (2000).
19. Vliegen, J. and A.J. Van Opstal, "The influence of duration and level on human sound localization", J Acoust Soc Am. 115 (4), 1705-1713, (2004).
20. King, A.J. and S. Carlile, "Neural coding for auditory space", in The cognitive neurosciences, M.S. Gazzaniga, Editor. MIT Press: Boston. p. 279-293, (1994).
21. Zahorik, P., D.S. Brungart, and A.W. Bronkhorst, "Auditory distance perception in humans: A summary of past and present research", Acta Acustica United with Acustica. 91 (3), 409-420, (2005).
22. Zahorik, P., "Assessing auditory distance perception using virtual acoustics", J Acoust Soc Am. 111 (4), 1832-1846, (2002).
23. Mershon, D.H. and L.E. King, "Intensity and reverberation as factors in the auditory perception of egocentric distance", Percept Psychophys. 18 (6), 409-415, (1975).
24. Mershon, D.H., et al., "Effects of room reflectance and background noise on perceived auditory distance", Perception. 18, 403-416, (1989).
25. Hartley, R.V.L. and T.C. Fry, "The binaural location of pure tones", Physics Rev. 18 (6), 431-442, (1921).
26. Shinn-Cunningham, B.G. "Distance cues for virtual auditory space", in IEEE 2000 International Symposium on Multimedia Information Processing. Sydney, Australia, (2000).
27. Brungart, D.S. and W.M. Rabinowitz, "Auditory localisation of nearby sources. Head related transfer functions", J Acoust Soc Am. 106, 1465-1479, (1999).
28. Brungart, D.S. "Auditory parallax effects in the hrtf for nearby sources", in 1999 IEEE Workshop on Applications of Signal Processing to Audio and Acoustics,. New Paltz, New York, (1999).
29. Blauert, J. and W. Lindermann, "Auditory spaciousness: Some further psychoacoustic analyses", J Acoust Soc Am. 80 (2), 533-542, (1986).
30. Potter, J.M., J. Raatgever, and F.A. Bilsen, "Measures for spaciousness in room acoustics based on a binaural strategy", Acta Acustica. 3 (5), 429-443, (1995).
31. Okano, T., L.L. Beranek, and T. Hidaka, "Relations among interaural cross-correlation coefficient (iacc(e)), lateral fraction (lfe), and apparent source width (asw) in concert halls", Journal of the Acoustical Society of America. 104 (1), 255-265, (1998).
32. Durlach, N.I., et al., "On the externalization of auditory images", Presence. 1, 251-257, (1992).
33. Middlebrooks, J.C. and D.M. Green, "Sound localization by human listeners", Annu Rev Psychol. 42, 135-159, (1991).
34. Oldfield, S.R. and S.P.A. Parker, "Acuity of sound localization: A topography of auditory space i. Normal hearing conditions", Percept. 13, 581-600, (1984).
35. Makous, J. and J.C. Middlebrooks, "Two-dimensional sound localization by human listeners", J Acoust Soc Am. 87 (5), 2188-2200, (1990).
36. Carlile, S., P. Leong, and S. Hyams, "The nature and distribution of errors in the localization of sounds by humans." Hearing Res. 114, 179-196, (1997).
37. Butler, R.A., R.A. Humanski, and A.D. Musicant, "Binaural and monaural localization of sound in two- dimensional space." Percept. 19, 241-256, (1990).
38. Wightman, F.L. and D.J. Kistler, "Headphone simulation of free field listening. Ii: Psychophysical validation." J Acoust Soc Am. 85 (2), 868-878, (1989).
39. Perrett, S. and W. Noble, "Available response choices affect localization of sound", Perception and Psychophysics. 57 (2), 150-158, (1995).
40. Hartmann, W.M., "Localization of sound in rooms", J Acoust Soc Am. 74 (5), 1380-1391, (1983).
41. Mills, A.W., "On the minimum audible angle", J Acoust Soc Am. 30 (4), 237-246, (1958).
42. Grantham, D.W., "Spatial hearing and related phenomena", in Handbook of perception and cognition, B.C.J. Moore, Editor. Academic: San Diego, (1995).
43. Best, V., A.v. Schaik, and S. Carlile, "Separation of concurrent broadband sound sources by human listeners", J Acoust Soc Am. 115, 324-336, (2004).
44. Kopco, N. and B.G. Shinn-Cunningham. "Auditory localization in rooms: Acoustic analysis and behaviour", in 32 International Acoustical Conference. Slovakia, (2002).
45. Shinn-Cunningham, B.G. "Acoustics and perception of sound in everyday environments", in 3rd Int Workshop on Spatial Media. Aisu-Wakamatsu (Japan), (2003).
46. Cherry, E.C., "Some experiments on the recognition of speech with one and two ears", J Acoust Soc Am. 25, 975-979, (1953).
47. Bronkhorst, A.W., "The cocktail party phenomenon: A review of research on speech intelligibility in multiple-talker conditions", Acustica. 86, 117-128, (2000).
48. Bregman, A.S., "Auditory scene analysis : The perceptual organization of sound", Cambridge, Mass: MIT Press (1990).
49. Darwin, C.J. and R.P. Carlyon, "Auditory grouping", in Handbook of perception and cognition, volume 6: Hearing, B. Moore, Editor. Academic Press: Orlando, Florida. p. 387-424, (1995).
50. Moore, B.C.J. and H. Gockel, "Factors influencing sequential stream segregation", Acta Acustica United with Acustica. 88 (3), 320-333, (2002).
51. Freyman, R.L., et al., "The role of perceived spatial separation in the unmasking of speech", J Acoust Soc Am. 106 (6), 3578-3588, (1999).
52. Freyman, R.L., U. Balakrishnan, and K.S. Helfer, "Spatial release from informational masking in speech recognition", J Acoust Soc Am. 109 (5 Pt 1), 2112-2122, (2001).
53. Arbogast, T.L., C.R. Mason, and G. Kidd, "The effect of spatial separation on informational and energetic masking of speech", J Acoust Soc Am. 112, 2086-2098, (2002).
54. Brungart, D.S., et al., "Informational and energetic masking effects in the perception of multiple simultaneous talkers", J Acoust Soc Am. 110 (5 Pt 1), 2527-2538, (2001).

55. Durlach, N.I., et al., "Note on informational masking (l)", J Acoust Soc Am. 113 (6), 2984-2987, (2003).
56. Shinn-Cunningham, B.G. "Influences of spatial cues on grouping and understanding sound", in Proceedings of the Forum Acoustica, (2005).
57. Shinn-Cunningham, B.G., et al., "Spatial unmasking of nearby speech sources in a simulated anechoic environment", J Acoust Soc Am. 110 (2), 1118-1129, (2001).
58. Plomp, R., "Acoustical aspects of cocktail parties", Acustica. 38, 186-191, (1977).
59. Arbogast, T.L., C.R. Mason, and G. Kidd, "The effect of spatial separation on informational masking of speech in normal-hearing and hearing impaired listeners", J Acoust Soc Am. 117, 2169-2180, (2005).
60. Hofman, P.M. and A.J. Van Opstal, "Bayesian reconstruction of sound localization cues from responses to random spectra", Biological Cybernetics. 86 (4), 305-316, (2002).
61. Jin, C., et al. "Transposition of high frequency spectral information helps resolve the cocktail party problem in the mild to moderately hearing impaired listener", in Proceedings of the Australian Neuroscience Society. Sydney, (2006).
62. Hofman, P.M., J.G.A.V. Riswick, and A.J.V. Opstal, "Relearning sound localization with new ears", Nature Neurosci. 1 (5), 417 - 421, (1998).

ACOUSTICS ENGINEERS

NDYSound

- Challenging new opportunities
- Great career prospects with excellent advancement prospects in a firm which recognises the value Acoustics Engineers can contribute to the organisation
- Attractive remuneration packages and working environment
- Positions available in London, Sydney, Melbourne, Brisbane, Canberra, Perth and Auckland

Norman Disney & Young is Australia's largest Building Services Consultancy, with a major presence in New Zealand and the UK. Our strategic plan for ongoing expansion includes establishing a major presence in Acoustic Engineering. NDYSound is a group of experienced and collaborative Acoustic Engineers committed to sharing knowledge and ideas to enhance the service we offer to our clients as well as providing professional development within the company.

NDYSound is seeking Acoustic Engineers at a variety of levels in our established practices in Sydney and Auckland, and is looking for staff to assist in establishing and growing NDYSound within Norman Disney & Young's offices in London, Melbourne, Brisbane, Canberra and Perth.

The company has an enviable record of professionalism and innovation and has consistently been able to deliver a range of highly specialised services which have found strong acceptance by our clients. These abilities will result in NDYSound becoming a major presence as an Acoustics Consultant, and will provide significant opportunities for talented staff who are able to contribute to that success.

We are currently seeking the following staff:

- Managers: Acoustic consultants with proven abilities to market Acoustic Consulting Services, manage a team of acoustic engineers and provide competent advice to our clients.
- Senior Acoustic Consultants: Acoustic Consultants who have established track records and a minimum of five years experience.
- Acoustic Consultants: Acoustic Consultants who have established track records and a minimum of three years experience.

Successful applicants will need to demonstrate the following:

Educational Qualifications

A degree in Mechanical Engineering acceptable for CPEng status with the Institution of Engineers Australia, together with experience as an Acoustic Consultant and/or post graduate education in Acoustics.

Alternative qualifications will be considered.

Fields of Specialisation

Positions are available for specialists in the following fields:

- Architectural
- Mechanical
- Environmental
- Industrial

Excellent remuneration packages apply subject to negotiation.

Written applications can be submitted in the strictest of confidence, including a cover letter and resume detailing qualifications and experience to:

Dennis O'Brien – Director
Norman Disney & Young
Level 1 / 60 Miller Street
North Sydney NSW 2060
Tel (02) 9928 6822
Email: d.obrien@ndy.com

PLASTICITY IN THE ADULT CENTRAL AUDITORY SYSTEM

Dexter R. F. Irvine[1,2] , James B. Fallon[2] and Marc R. Kamke[3]

[1]School of Psychology, Psychiatry, and Psychological Medicine,
Faculty of Medicine, Nursing, and Health Sciences, Monash University, VIC 3800, Australia
[2]Bionic Ear Institute, 384-388 Albert Street, East Melbourne, VIC 3002, Australia
[3] School of Behavioural Science, University of Melbourne, VIC 3010, Australia

The central auditory system retains into adulthood a remarkable capacity for plastic changes in the response characteristics of single neurons and the functional organization of groups of neurons. The most dramatic examples of this plasticity are provided by changes in frequency selectivity and organization as a consequence of either partial hearing loss or procedures that alter the significance of particular frequencies for the organism. Changes in temporal resolution are also seen as a consequence of altered experience. These forms of plasticity are likely to contribute to the improvements exhibited by cochlear implant users in the post-implantation period.

1. INTRODUCTION

One of the most exciting discoveries of the last forty or so years in sensory neuroscience has been the extent to which the stimulus selectivity of neurons in, and the functional organization of, sensory cortical and subcortical structures are modifiable by experience (i.e., exhibit plasticity). The first reports of such plasticity were of changes that were maximal within restricted "critical periods" during early development [1], when neuronal pathways and connections were being formed. It was therefore believed for many years that such changes occurred only during development, and that sensory processing mechanisms were stable features of the adult brain. More recently, however, it has been demonstrated that these mechanisms can in fact be modified in adults as a consequence of altered patterns of input or of procedures that change the significance of particular sensory inputs. Kaas and Florence [2] provide a comprehensive review of such plasticity in a number of sensory systems.

It should be emphasised that not all changes in neural responsiveness and organization as a consequence of altered input are reflections of plasticity. Some changes are explicable as direct, or passive, consequences of the altered input. For example, in the auditory system, destruction of the outer hair cells results in immediate and marked changes in the frequency tuning of auditory nerve (AN) fibres [3], and of neurons throughout the auditory pathway. These changes are a direct consequence of the elimination of the cochlear amplifier [4], rather than of plastic processes. Although plasticity can be broadly characterized as involving some form of active or dynamic modification of neural properties that is triggered by the changed input, it is not always a simple matter to distinguish between plastic and non-plastic changes [5,6].

In the case of the auditory system, much of the evidence for adult plasticity has been obtained from neurophysiological studies of frequency selectivity and organization in animal models. There is additional evidence for adult plasticity from a number of studies of the temporal characteristics of responses to acoustic and intra-cochlear electrical stimulation. The animal data are also complemented by a growing body of evidence from functional imaging and psychophysical studies in adult humans. This evidence will be briefly reviewed in this paper.

2. PLASTICITY OF FREQUENCY PROCESSING MECHANISMS

2.1 Frequency tuning and tonotopicity

The majority of neurons at all levels of the auditory system are sharply tuned for frequency, commonly having V-shaped frequency tuning curves (plots of threshold as a function of frequency), with lowest threshold at the neuron's characteristic frequency (CF). At the level of the AN, the tuning curve of a single fibre reflects that of the inner hair cell (IHC) from which its input is derived, and thus the mechanical tuning of the point on the basilar membrane where that IHC is located. AN fibres innervating adjacent points on the basilar membrane project to adjacent points in auditory brainstem structures, with the consequence that these central projections are organized topographically with respect to the cochlea (i.e., are cochleotopically organized). Because adjacent points on the cochlea are tuned to different frequencies, this anatomical cochleotopy results in a functional organization with respect to frequency tuning (i.e., tonotopy). The tonotopic organization of primary auditory cortex (AI), as derived from determining the CFs of neurons across the surface of AI, is illustrated in Figure 1, A and B. So-called iso-frequency contours (more correctly, iso-CF contours) separate strips of cortex in which neurons with CFs within narrow frequency ranges are located.

Although the cochleotopic organization of anatomical projections is the basic substrate of central tonotopy, it should be emphasised that the frequency tuning of central neurons is not determined solely by these patterns of anatomical connectivity. Rather, there is a good deal of convergence of input derived from different regions of the cochlea (i.e., from different frequency channels) onto single neurons in central auditory structures, and the sharp tuning of central neurons is derived and maintained computationally by the integration of these convergent (excitatory and inhibitory) inputs. It is largely as a consequence of changes in the relative strengths of these convergent inputs and in the processes by which they are integrated that central plasticity of frequency selectivity is possible.

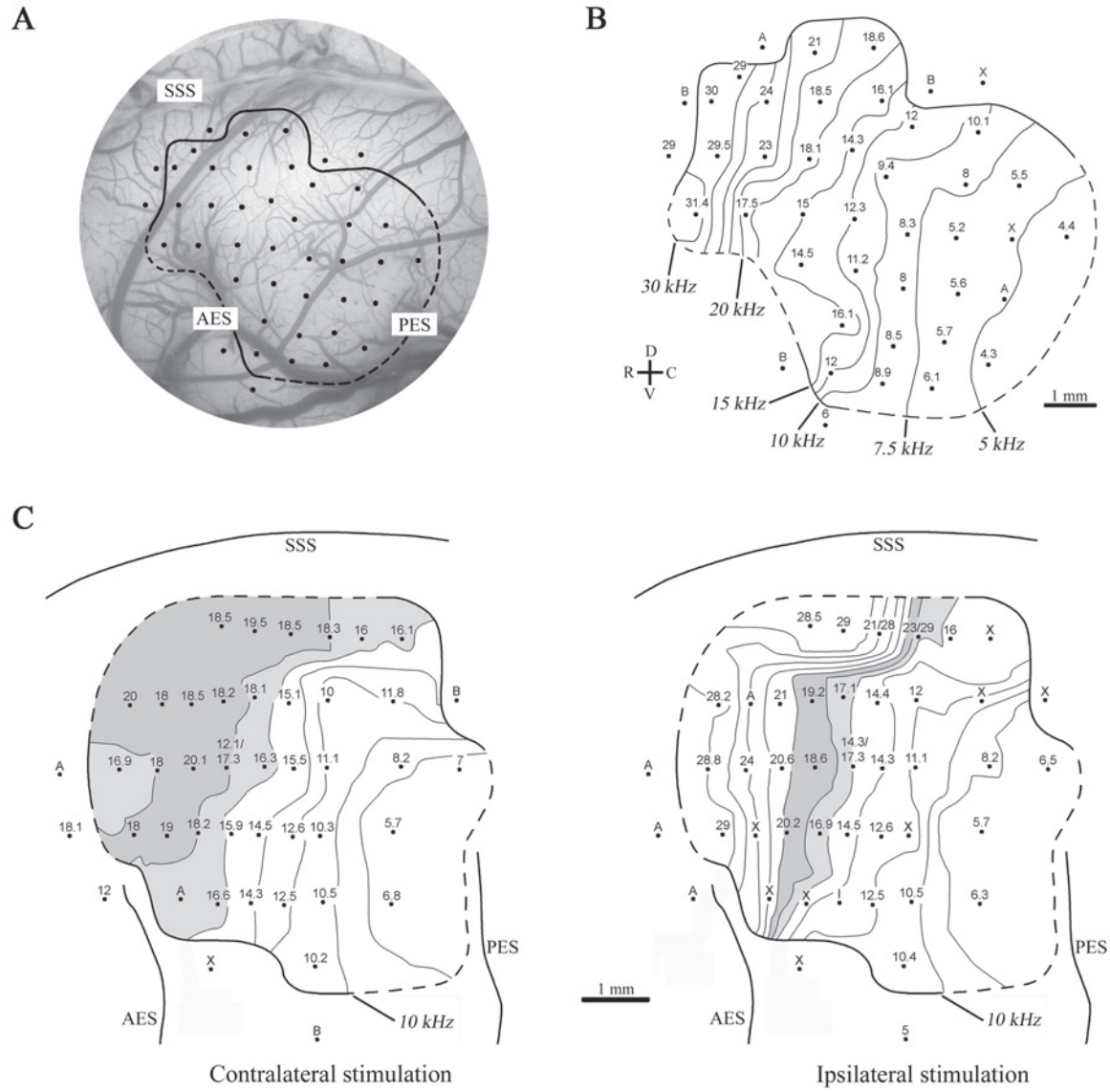


Figure 1. A Digital photograph of the exposed cortical surface of a cat with normal hearing. Dots indicate the sites at which microelectrode penetrations were made, and the solid black line indicates the physiological boundary of AI as defined from the data shown in B. Abbreviations: AES: anterior ectosylvian sulcus; PES: posterior ectosylvian sulcus; SSS: suprasylvian sulcus. **B**. Frequency map derived from matrix of penetrations shown in A. The CF of the neuron cluster recorded in each penetration is indicated above the dot; other penetrations are labelled 'X' (no response to acoustic stimulation), A (acoustically responsive, but CF could not be determined), B (broadly tuned) or I (inhibitory response). The line defining the physiological boundary of AI is broken where this boundary was not determined unequivocally. Thin lines indicate iso-CF contours (CF identified by figures at lower boundary of AI) fitted to the data at 2.5 kHz intervals using an inverse-distance smoothing function. R, C, D, and V indicate rostral, caudal, dorsal, and ventral directions, respectively. **C.** Frequency maps of AI in the hemisphere contralateral to a unilateral cochlear lesion for stimulation of the contralateral (lesioned) ear and the ipsilateral (normal) ear in a chronically lesioned cat. Conventions as in A and B. Light and dark shaded bands indicate the area of cortex containing neurons with CFs in the range 16–18 kHz and 18–20 kHz, respectively. Panels B and C reproduced from Reference [8], copyright 2005, with permission from Elsevier.

2.2 Lesion-induced plasticity of frequency processing mechanisms

Evidence for adult plasticity of frequency processing mechanisms has been derived from two major experimental paradigms. One has been to determine the effects of a restricted cochlear lesion, which eliminates output from the cochlea over a particular frequency range, on the frequency organization of central structures (i.e., lesion-induced plasticity). The second has been to determine the effects of behavioural conditioning procedures, in which a tone of particular frequency comes to have behavioural significance for the animal, on the frequency tuning of central auditory neurons (learning-related plasticity). Detailed accounts of this evidence have been given elsewhere [5], and it will be only briefly summarised here.

A mechanical lesion damaging the basal region of one cochlea eliminates output from that cochlea over a restricted range of high frequencies, producing deafness in that ear over the affected frequency range. If AI contralateral to the lesioned cochlea is examined some weeks after the lesion, the (high-

frequency) region of cortex deprived of its normal input by the cochlear lesion is not silent, but is occupied by an expansion of the area containing neurons with CF at frequencies represented at the edge of the cochlear lesion [7,8]. This pattern of results is illustrated in Figure 1C, which shows the frequency organization in AI in the left cerebral hemisphere of a chronically lesioned cat for stimulation of the lesioned right ear (i.e., contralateral stimulation) and of the normal left ear (i.e., ipsilateral stimulation). In normal animals, the frequency maps for stimulation of the two ears are in register, such that neurons at any given point have the same CF for stimulation of the contralateral and ipsilateral ears. The cochlear lesion in the cat for which data are presented in Figure 1C eliminated output from the right cochlea at frequencies above 17-19 kHz. Neurons with CF at these "lesion edge" frequencies occupy narrow strips of cortex in the frequency map derived from stimulation of the normal ipsilateral ear (see shading), and that map is indistinguishable from normal maps. In contrast, the area occupied by neurons with CF at lesion-edge frequencies in the map derived from stimulation of the lesioned contralateral ear is massively enlarged, and occupies the area of cortex in which the higher CFs would normally have been represented. Frequency map plasticity of this sort has been described in a range of species (including non-human primates), and as a consequence of cochlear lesions produced in different ways (e.g., noise trauma; ototoxic injections) [5]. Although changes in cortical frequency maps would be expected to occur as a passive consequence of cochlear lesions, the thresholds and other response characteristics of neurons in the enlarged areas of representation of lesion-edge frequencies indicate that they reflect plastic changes [7,8].

Plasticity indistinguishable from that seen in AI is observed in the major auditory thalamic nucleus (the ventral division of the medial geniculate body) after mechanical cochlear lesions [9]. However, such plasticity either does not occur, or occurs only to a limited extent, in the major auditory midbrain nucleus, the inferior colliculus (IC) after such lesions[10]. It therefore appears that the capacity for this form of plasticity is a characteristic of the thalamo-cortico-thalamic system, although the primary site of plastic change has not yet been established [5,9].

In most of these studies, the auditory cortex was mapped some weeks or months after the cochlear lesion, and the time course of the changes in cortical frequency organization is therefore not known. In the somatosensory system, in which analogous plasticity in cortical maps of the body surface is seen as a consequence of peripheral lesions (digit amputation or nerve section), some of the changes contributing to cortical reorganization occur immediately after the peripheral lesion, while others take place more gradually [6]. It is likely that lesion-induced auditory cortical plasticity involves similar short-term and longer-term changes.

2.3 Possible perceptual consequences of lesion-induced auditory cortical plasticity

Although it is tempting to think of plastic changes following damage to the cochlea in terms of a central nervous system compensation for the peripheral loss, it should be noted that the organism remains deaf in the frequency range affected by the lesion. It seems likely that this form of plasticity should be viewed as a manifestation of the brain's *capacity* for plastic change in response to altered patterns of input, rather than as a compensatory adaptation. However, the dramatic changes in the cortical patterns of activity evoked by lesion-edge frequencies would be expected to have perceptual consequences. This expectation is apparently confirmed by the finding that humans with hearing losses of the sort shown to produce cortical reorganization in animal studies show enhanced frequency discrimination ability at lesion-edge frequencies [11,12]. It seems likely that this enhanced discriminative capacity reflects plastic changes in the cortex, although this has not yet been directly established by demonstrating changed cortical frequency maps in the human participants in the psychophysical studies.

2.4 Learning-related plasticity of frequency processing mechanisms

The effects of learning on auditory frequency selectivity have been investigated using a number of paradigms [5]. The most common has been classical conditioning, using a tonal conditioned stimulus (CS) at a frequency within the frequency response area of a neuron (or multi-unit cluster) but differing from its best frequency (BF; the frequency evoking the largest response). Although there is some disagreement (see [5] for review), the most commonly reported result in such studies has been an increase in the strength of the response evoked by the CS frequency and a decrease in response at the pre-training BF and at other frequencies, such that the CS frequency becomes the post-training BF [13,14]. Similar changes in the spectro-temporal receptive fields of auditory cortical neurons have recently been described in ferrets trained to detect a target tone of a particular frequency embedded in a sequence of broad-band noise-like stimuli [15]. The changes in neuronal frequency selectivity observed in these studies can occur within a single training session, confirming the contribution of short-term changes in the nervous system (probably changes in "synaptic weights", i.e., the strength of particular excitatory and inhibitory inputs to the neurons) to auditory cortical plasticity. The short- and long-term mechanisms responsible for auditory cortical plasticity are discussed in more detail elsewhere [5].

3. PLASTICITY OF TEMPORAL PROCESSING MECHANISMS

3.1 Temporal resolution: Latency and frequency-following

Information encoded in the fine temporal structure of an acoustic signal cannot be encoded by the frequency processing mechanisms described above. Therefore, such information must be encoded in the temporal structure of the firing patterns of neurons within the auditory system. There are two main limits on the ability of the auditory system to encode temporal information. One is jitter in the response of each neuron, which includes variations in both the timing of the initiation of action potentials and the time for action potentials to propagate along axons. The second is the maximum firing rate of each neuron, which is related to the refractory period of the neuron (the

period within which the neuron is incapable of firing another action potential). At all levels of the auditory system, temporal resolution is poorest for near-threshold stimuli, and improves to a saturating limit as stimulus intensity is increased.

Langner [16] provides a comprehensive review of temporal processing in the auditory system, two aspects of which will be considered here. One is the latency with which neurons respond to the onset of a stimulus; the second is the precision with which neurons represent the temporal patterns of repetitive stimuli. The first-spike latencies of individual AN fibre responses are dependent on the mode of stimulation (e.g., acoustic vs electric), but minimum latencies to acoustic stimuli are in the order of 2 ms, with a jitter (standard deviation) of ± 0.2 ms. This precise timing in response to acoustic stimuli is maintained throughout the auditory system; individual units in AI respond with minimum latencies in the range of 10-20 ms (an increase reflecting the longer conduction distances and increased number of synapses in the multiple pathways over which input reaches AI), but without a marked increase in the jitter of the response [17]. Individual AN fibres are capable of phase locking to periodically modulated acoustic stimuli at modulation frequencies up to approximately 1 kHz. This level of temporal sensitivity is not maintained at higher levels; the ability of neurons in AI to follow complex periodic stimuli is an order of magnitude lower. The mechanisms responsible for this decrease in temporal processing are not clear, although inhibitory effects are thought to play a major role.

3.2 Deprivation- and activity-induced plasticity of temporal processing mechanisms

As with frequency processing mechanisms, deprivation of input to the auditory system, due to a sensorineural hearing loss, results in changes in some aspects of temporal processing. Interestingly, many of the changes in temporal response characteristics are only present in animals with a complete lack of auditory input (i.e. with bilateral profound deafness), as it appears that unilateral input is sufficient to maintain near normal temporal processing in the IC [18]. Studies of potential plastic changes in temporal processing mechanisms therefore commonly use intra-cochlear electrical stimulation, which by-passes the IHCs and directly excites the AN fibres, to activate the auditory system. Changes in temporal response characteristics as a result of the elimination of auditory input are then examined by comparison of responses to electrical stimulation in acutely and chronically deafened animals.

Long-term bilateral deafness does not significantly alter the temporal response characteristics of AN fibres when compared to acutely deafened controls [19]. However, at the level of the IC, long-term deafness sufficient to produce profound spiral ganglion cell (SGC) loss and demyelination of the remaining SGCs results in an increase in both the latency and jitter of responses of individual neurons to electrical stimulation, and a decrease in the maximum following rate [18]. It is unclear whether these changes in IC are simply passive consequences of the peripheral degenerative changes in SGCs produced by hair cell damage, or represent plasticity. Although the changes in IC would be expected to be reflected at higher levels, the temporal responsiveness of AI neurons does not appear to be significantly affected by long periods of deafness [20], suggesting the occurrence of plastic changes in cortex.

Subsequent to the changes consequent on hearing loss, reactivation of the auditory system via chronic electrical stimulation of the auditory nerve, similar to that delivered by a cochlear prosthesis, enhances its temporal processing capacity. Neurons in the IC of chronically stimulated animals respond with shorter latencies, and follow higher frequencies of electrical stimulation, than neurons in either chronically- or acutely-deafened animals [21,22].

3.3 Learning-related plasticity of temporal processing mechanisms

The temporal processing mechanisms of the auditory system are not only influenced by changes in activation at the periphery, but can also be altered by training. AI neurons in normal-hearing rats trained on a task in which the repetition rate of noise pulses increased with proximity to a target showed stronger phase locking and stronger responses to high-rate stimuli [23]. The mechanisms responsible for the increased temporal resolution are not clear, but are presumed to involve multiple neuromodulator systems.

4. IMAGING EVIDENCE FOR AUDITORY CORTICAL PLASTICITY IN HUMANS

Modern techniques for measuring brain activity in humans have provided evidence supportive of the animal evidence for plasticity of frequency processing mechanisms, although the bulk of this evidence relates to a different form of experience-related plasticity. In the only investigation of the organization of auditory cortex in humans with steeply-sloping hearing losses, Dietrich et al. [24] presented magnetoencephalographic (MEG) evidence for an expanded representation of lesion-edge frequencies of the type seen in animals with such losses. However, in the only study of the effects of classical conditioning in humans, Morris et al. [25] found that conditioning was associated with a decrease in response to the CS (as measured by positron emission topography). This result is at variance with the finding in the majority of animal studies, which implies an increase in the number of neurons responding most strongly to the CS frequency, although it is in agreement with a smaller number of animal studies (see [5] for discussion). The largest body of evidence for auditory cortical plasticity in humans is provided by a number of MEG studies that indicate larger responses to various pure and/or musical tones in musicians than in non-musicians. This correlation could reflect the fact that people with these characteristics are more likely to become musicians, rather than effects of musical training on neural processing mechanisms, but evidence from other studies indicates that at least in some cases the changes are training-specific [5, 26]

5. CONCLUSION

The predominantly neurophysiological evidence for central auditory system plasticity is complemented by a similar body of psychophysical evidence for plasticity in auditory perceptual processes [5]. There is no doubt that these forms of plasticity contribute to the plastic changes that underlie the remarkable

success of many humans with cochlear prostheses in achieving near-normal speech perception despite the abnormal (and in many ways impoverished) input provided by the prosthesis [27]. The evidence for central auditory plasticity is also matched by evidence for analogous plasticity in visual and somatosensory processing mechanisms [2]. This evidence has transformed our understanding of the nature of the processing of sensory information in the brain.

ACKNOWLEDGEMENTS

The authors' research is supported by the National Health and Medical Research Council of Australia and the National Institute of Deafness and Communication Disorders of the USA (N01-DC-3-1005). We are grateful to Rob Shepherd and two anonymous reviewers for their helpful comments on an earlier version of the manuscript.

REFERENCES

1. Hensch, T. K. (**2004**). "Critical period regulation," Annu. Rev. Neurosci. **27**, 549-579.
2. Kaas, J. H., and Florence, S. L. (2001), "Reorganization of sensory and motor systems in adult mammals after injury," in *The Mutable Brain*, edited by J. H. Kaas (Harwood Academic Publishers, Amsterdam), pp. 165-242.
3. Dallos, P., and Harris, D. (**1978**). "Properties of auditory nerve responses in absence of outer hair cells," J. Neurophysiol. **41**, 365-383.
4. Fettiplace, R., and Hackney, C. M. (**2006**). "The sensory and motor roles of auditory hair cells," Nature Rev. Neurosci. **7**, 19-29.
5. Irvine, D. R. F., and Wright, B. A. (2005), "Plasticity in spectral processing," in *Auditory Spectral Processing*, edited by M. Malmierca, and D. R. F. Irvine (Elsevier Academic, San Diego), pp. 435-472.
6. Calford, M. B. (**2002**). "Dynamic representational plasticity in sensory cortex," Neuroscience **111**, 709-738.
7. Rajan, R., Irvine, D. R. F., Wise, L. Z., and Heil, P. (**1993**). "Effect of unilateral partial cochlear lesions in adult cats on the representation of lesioned and unlesioned cochleas in primary auditory cortex," J. Comp. Neurol. **338**, 17-49.
8. Kamke, M. R., Brown, M., and Irvine, D. R. F. (**2005**). "Basal forebrain cholinergic input is not essential for lesion-induced plasticity in mature auditory cortex," Neuron **48**, 675-686.
9. Kamke, M. R., Brown, M., and Irvine, D. R. F. (**2003**). "Plasticity in the tonotopic organization of the medial geniculate body in adult cats following restricted unilateral cochlear lesions," J. Comp. Neurol. **459**, 355-367.
10. Irvine, D. R. F., Rajan, R., and Smith, S. (**2003**). "Effects of restricted cochlear lesions in adult cats on the frequency organization of the inferior colliculus," J. Comp. Neurol. **467**, 354-374.
11. McDermott, H. J., Lech, M., Kornblum, M. S., and Irvine, D. R. F. (**1998**). "Loudness perception and frequency discrimination in subjects with steeply sloping hearing loss: Possible correlates of neural plasticity," J. Acoust. Soc. Am. **104**, 2314-2325.
12. Thai-Van, H., Micheyl, C., Moore, B. C. J., and Collet, L. (**2003**). "Enhanced frequency discrimination near the hearing loss cut-off: A consequence of central auditory plasticity induced by cochlear damage?" Brain **126**, 2235-2245.
13. Weinberger, N. M. (**2004**). "Specific long-term memory traces in primary auditory cortex," Nature Rev. Neurosci. **5**, 279-290.
14. Ji, W. Q., Gao, E. Q., and Suga, N. B. (**2001**). "Effects of acetylcholine and atropine on plasticity of central auditory neurons caused by conditioning in bats," J. Neurophysiol. **86**, 211-225.
15. Fritz, J., Shamma, S., Elhilali, M., and Klein, D. (**2003**). "Rapid task-related plasticity of spectrotemporal receptive fields in primary auditory cortex," Nature Neurosci. **6**, 1216-1223.
16. Langner, G. (**1992**). "Periodicity coding in the auditory system," Hear. Res. **60**, 115-142.
17. Heil, P., and Irvine, D. R. F. (**1997**). "First-spike timing of auditory-nerve fibers and comparison with auditory cortex," J. Neurophysiol. **78**, 2438-2454.
18. Shepherd, R. K., Baxi, J. H., and Hardie, N. A. (**1999**). "Response of inferior colliculus neurons to electrical stimulation of the auditory nerve in neonatally deafened cats," J. Neurophysiol. **82**, 1363-1380.
19. Javel, E., and Shepherd, R. K. (**2000**). "Electrical stimulation of the auditory nerve: III. Response initiation sites and temporal fine structure," Hear. Res. **140**, 45-76.
20. Hartmann, R., Shepherd, R. K., Heid, S., and Klinke, R. (**1997**). "Response of the primary auditory cortex to electrical stimulation of the auditory nerve in the congenitally deaf white cat," Hear. Res. **112**, 115-133.
21. Vollmer, M., Snyder, R. L., Leake, P. A., Beitel, R. E., Moore, C. M., and Rebscher, S. J. (**1999**). "Temporal properties of chronic cochlear electrical stimulation determine temporal resolution of neurons in cat inferior colliculus," J Neurophysiol **82**, 2883-2902.
22. Snyder, R., Leake, P., Rebscher, S., and Beitel, R. (**1995**). "Temporal resolution of neurons in cat inferior colliculus to intracochlear electrical stimulation: Effects of neonatal deafening and chronic stimulation," J. Neurophysiol. **73**, 449-467.
23. Bao, S., Chang, E. F., Woods, J., and Merzenich, M. M. (**2004**). "Temporal plasticity in the primary auditory cortex induced by operant perceptual learning," Nature Neurosci. **7**, 974-981.
24. Dietrich, V., Nieschalk, M., Stoll, W., Rajan, R., and Pantev, C. (**2001**). "Cortical reorganization in patients with high frequency cochlear hearing loss," Hear. Res. **158**, 1-7.
25. Morris, J. S., Friston, K. J., and Dolan, R. J. (**1998**). "Experience-dependent modulation of tonotopic neural responses in human auditory cortex," Proc. Roy. Soc. Lond., Series B **265**, 649-657.
26. Pantev, C., Roberts, L. E., Schulz, M., Engelien, A., and Ross, B. (**2001**). "Timbre-specific enhancement of auditory cortical representations in musicians," NeuroReport **12**, 169-174.
27. McKay, C. M. (2005), "Spectral processing in cochlear implants," in *Auditory Spectral Processing*, edited by M. Malmierca, and D. R. F. Irvine (Elsevier Academic, San Diego), pp. 473-509.

EFFERENT CONTROL OF HEARING

Wilhelmina H.A.M. Mulders

**The Auditory Laboratory, Discipline of Physiology,
School of Biomedical, Biomolecular and Chemical Sciences,
The University of Western Australia, Crawley WA 6009, Australia.**

*Correspondence to: W. Mulders, The Auditory Laboratory, Discipline of Physiology, School of Biomedical, Biomolecular and Chemical Sciences M311, The University of Western Australia, 35 Stirling Highway, Crawley WA 6009, Australia. Phone +61 (8) 6488 7032 Facsimile +61 (8) 6488 1025 Email address hmulders@cyllene.uwa.edu.au

The auditory system comprises both ascending (afferent) and descending (efferent) pathways. The efferent pathways, which originate in a variety of higher brain centres, are capable of altering the activity in the afferent pathways. By modulating cochlear neural output and central auditory neural circuits, these efferent pathways could play an important role in key auditory processing such as optimising the detection of acoustic signals of interest in the presence of competing background noises. The present paper focuses on the final limb of the efferent pathways, the olivocochlear system, which projects directly to the cochlea. It will describe its proposed role in normal hearing and show how dysfunction of this efferent system could contribute to generation of tinnitus and to deterioration in the detection and processing of signals such as speech, especially in non-optimum listening environments.

INTRODUCTION

The mammalian auditory system comprises parallel afferent (ascending) and efferent (descending) neural pathways (see Figure 1). The afferent pathways start at the cochlea, in the organ of Corti where sound waves are transduced into neural information. From the cochlea the information travels through different brain centres undergoing further auditory processing to the auditory cortex, where sound is perceived by the listener. Efferent pathways can be found at every level of the afferent pathway and thus enable the brain to modify the processing of the ascending auditory information at various levels, regulating peripheral cochlear function and modulating signal processing at higher stages of the auditory pathway.

THE OLIVOCOCHLEAR SYSTEM

The final limb of the efferent pathways is formed by the olivocochlear (OC) system, which projects directly to the organ of Corti within the cochlea (Figure 1). The neurons of the olivocochlear system originate in the superior olivary complex in the brainstem and can be subdivided into two major subsystems, the medial and lateral OC system, on the basis of the location of their cell bodies in the brainstem and their targets in the cochlea. The medial OC system originates bilaterally in the periolivary regions and projects via myelinated axons to the outer hair cells. The lateral OC system originates ipsilaterally in and around the lateral superior olive and projects via unmyelinated axons to the afferent dendrites contacting the inner hair cells [36,61,62,74,75,80,82].

The lateral OC system, because it synapses directly onto primary afferent dendrites, seems to be in a prime position to affect both spontaneous and sound-driven neural firing as well as excitability of the auditory nerve fibres. Because of the location of the lateral OC neurons deep in the brainstem, and their unmyelinated axons, it has proven difficult to experimentally stimulate this system and information on the role of the lateral OC system is therefore limited. Nonetheless there are several studies reporting effects of the lateral OC system on cochlear output using a variety of methods. Studies investigating the effects of de-efferentation show a decrease of spontaneous rate of the auditory nerve fibres, suggesting an excitatory role for the lateral efferents [33,35,37,77,90]. However, evidence is mounting that the lateral system actually consists of multiple subsystems whose effects on the cochlea may depend on the neurotransmitter released. A variety of different neurotransmitters has been demonstrated to exist in the lateral efferents, such as acetylcholine, γ-aminobutyric acid (GABA), dopamine, enkephalin and calcitonin gene-related peptide (CGRP) [15,55]. Acetylcholine applied close to the inner hair cell synapse and thus close to the lateral OC synapse with the afferent fibres, results in increased spontaneous firing of the afferent fibres, supportive of an excitatory role for the lateral efferents [17]. However, intracochlear application of GABA or dopamine has been shown to result in a reduction of the driven firing rate of primary afferent fibres [17,49,64], revealing a capability of the lateral OC system to inhibit the firing rate of auditory afferent fibres. Interestingly, recent indirect stimulation of the OC system showed effects on cochlear output consistent with the notion that the lateral OC system exerts both excitatory and inhibitory effects in the cochlea [20,48], which is in line with anatomical evidence that there may be two different types of lateral OC fibres [79].

The actual biological role of the lateral OC system remains as yet to be elucidated, but several hypotheses have been put forward. Increases of spontaneous firing of the afferents, as can be evoked by the lateral efferents may also contribute to amplitude-modulated sound detection [12]. Ruel et al. [63] suggested that the tonic release of dopamine by the lateral efferents prevents sound-induced excitotoxicity of the afferent dendrites.

In contrast to the lateral OC system, the effects of activation of the medial OC system on cochlear output have been well described. Experimental activation of the medial OC system can be relatively easily achieved by electrical stimulation of their myelinated axons since these run close to the surface of the brainstem. Activation of the medial OC system is well known to suppress cochlear neural responses to low level

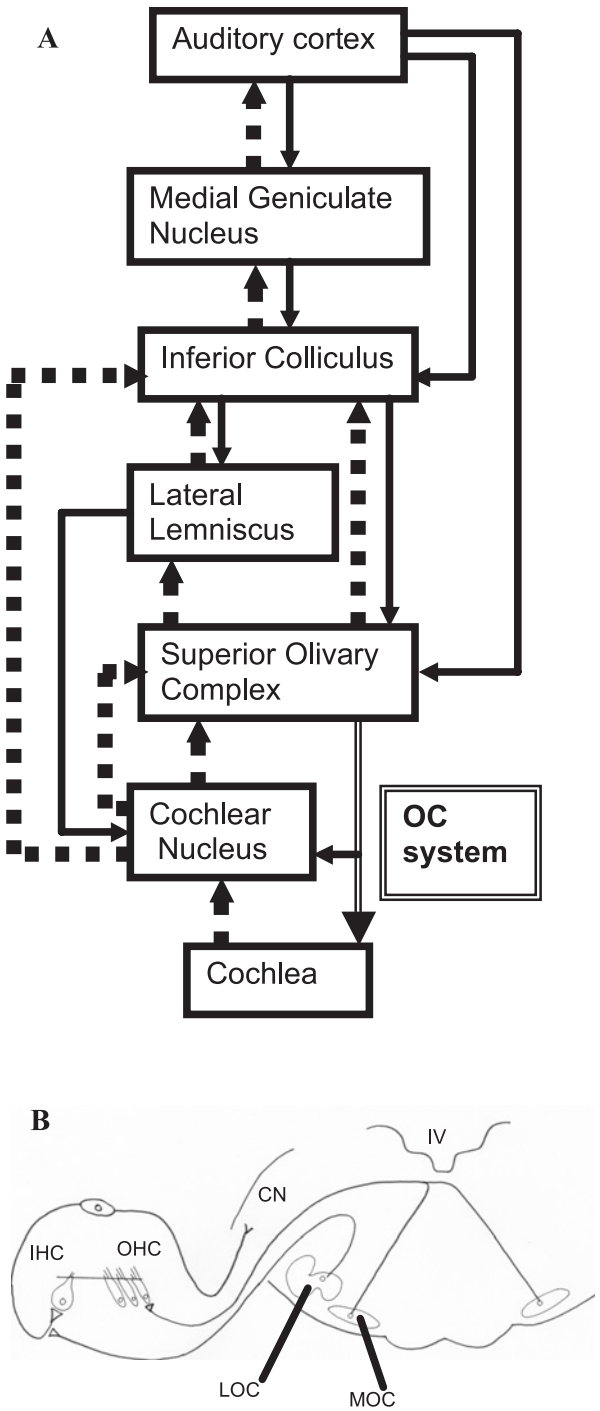


Figure 1: A: Schematic drawing of the ascending and descending pathways in the auditory system, excluding binaural pathways. Black lines are descending, dotted lines ascending projections. The olivocochlear system is indicated with a double line and illustrated in more detail in B. B: Schematic drawing of the olivocochlear system, showing the lateral OC system originating in the lateral superior olive and projecting ipsilaterally to the afferent dendrites contacting the inner hair cells and the medial OC system originating in the periolivary regions and projecting bilaterally to the outer hair cells. Abbreviations: CN: cochlear nucleus; IHC: inner hair cells; IV: IVth ventricle; LOC: lateral olivocochlear system; MOC medial olivocochlear system; OHC: outer hair cells.

acoustic stimuli [13,58,83]. Electrical stimulation of the medial OC axons results in a reduction of the compound action potential of the auditory nerve through the effects exerted on the outer hair cells [8,13,27,58,65,81,83]. The outer hair cells, which have electro-motile properties, are responsible for the cochlear gain by enhancing the vibration of the basilar membrane in response to sound. Release of acetylcholine from the medial OC synapse results in an increased conductance of the basolateral wall and subsequent hyperpolarization of the outer hair cells, thereby reducing the gain of the cochlear amplifier. Reduction of the cochlear gain leads to a decreased depolarisation and decreased neurotransmitter release from the inner hair cells, reducing auditory afferent firing, thus reducing the size of the compound action potential amplitude of the auditory nerve fibres [21].

Though the inhibitory effects of the medial OC system on cochlear output are well established, the biological role of this efferent system in hearing is still under debate. A first question to ask may be: "what activates the medial OC system in the awake, behaving organism?" Well, there is ample evidence that the medial OC neurons are excited by sound [6]. Anatomical studies have shown that the olivocochlear neurons in the brainstem receive ascending synaptic input from the cochlear nucleus [7,63,71]. Consistent with these anatomical observations, contralateral sound has been reported to result in inhibitory effects on the activity of auditory primary afferent fibres as well as the compound action potential of the auditory nerve in different mammalian species [9,34,57,81]. In addition, altered otoacoustic emissions following the application of contralateral sound have been reported in humans [41], cats [56] and guinea pigs [31,32,56]. All of the studies above indicate an excitatory action of the contralateral cochlea on medial olivocochlear neurons and suggest the olivocochlear system forms a feedback circuit at the level of the lower brainstem

One of the proposed roles for the medial OC system is consistent with it being part of a feedback loop at the level of the brainstem. It has been suggested that it serves to protect the cochlea from extensive receptor damage during intense noise exposure reducing hearing loss [52,58-60]. However, all experiments in which this protective mechanism was demonstrated used very loud sound intensities to damage the cochlea, much louder than naturally occurring sound levels. This makes it unlikely that the medial OC system evolved to serve this protective role as argued convincingly by Kirk and Smith [28], but rather that this protection that can be observed in the noisy environment of modern man is a fortuitous but convenient side-effect of the system that evolved for other reasons.

Another role put forward for the medial OC system is to provide homeostatic control of the endocochlear potential (EP). Very small fluctuations of the EP of only a few millivolt have been shown to be able to alter neurotransmitter release from the inner hair cells [51] and can alter neural firing. Increases of the EP, therefore, could lead to an increase of spontaneous activity, causing more excessive neural firing in the absence of sound, and could contribute to the generation of cochlear tinnitus. Since tinnitus, fortunately, is not a constant feature

of the auditory system, this means that a control mechanism must exist that keeps the EP constant, preventing this aberrant activity from occurring. Since medial OC activation can alter the EP [8,22], Patuzzi [50] suggests that the medial OC system may serve this controlling role.

A third role proposed for the medial OC system may be improving the signal to noise ratio and the dynamic range of the auditory system. Several studies have demonstrated an unmasking effect on the responses of auditory afferent fibres in noise following medial OC activation [26,83,85]. This unmasking effect at the primary afferent level may be responsible for improving the detection of signals in a noisy background and indeed behavioural studies support a role for the medial system in signal in noise detection. Lesions of the medial OC axons resulted in a reduced capacity to discriminate signals in noise in primates [14] and cats [39]. In humans, contralateral noise, known to stimulate the medial OC system, improved intensity discrimination in a noisy background [40]. Patients that have undergone a vestibular neurotomy, which disrupts the olivocochlear axons, show no improvement in discriminating speech in noise with application of contralateral noise whereas control subjects do [19].

In 1997 a paper appeared which suggested that the olivocochlear system could improve the detection of expected signals in noise by inhibiting the perception of frequencies adjacent to the signal [68]. The authors tested human patients, undergoing a vestibular neurotomy, severing the lateral and medial OC axons, before and after surgery. Patients were asked to recognise a signal in a noisy background, in some instances an expected signal (i.e. heard before) in other instances an unexpected signal, i.e. of a frequency close but not the same as the expected signal. Their results indicated that the olivocochlear system could provide a relative enhancement of the detection of expected target signals in noise, by inhibition of the adjacent unexpected frequencies. Before surgery the expected signals were detected better than the unexpected signals, whereas after surgery the expected and unexpected signals were detected equally well. Such a role of the OC system, improving selective attention in the auditory system, strongly implies that the OC neurons are not just part of a straightforward feedback system at the brainstem level but rather that the system operates in a more active "top-down" role driven by input from higher centres. In addition, it implies that the OC system must be able to act in a selective, spatially restricted way, within the cochlea.

TOP-DOWN CONTROL

Anatomical as well as physiological studies have shown evidence that the OC system is under the influence of higher brain centres. Anatomical studies have shown that the auditory brainstem receives direct descending input from higher centres, both from auditory structures such as the inferior colliculus and auditory cortex [16,43,44,72,76] as well as from non-auditory structures such as the locus coeruleus [46,47]. Here we will discuss two of these inputs in more detail, those arising from the inferior colliculus and from the locus coeruleus.

The IC seems to play a large role in efferent processing; it receives a large input from the auditory cortex [5,11,24,67,84] and it has been shown in multiple species that the cortex can modulate the responses of IC neurons to sound [18,38,54,70,89]. Axons arising from the inferior colliculus have been shown to make direct synaptic contact with the medial OC neurons [42]. Moreover, the projection from the inferior colliculus is tonotopically organized, a common feature of the auditory pathways. Dorsal, low frequency regions of the IC project to lateral regions of the peri-olivary regions, known to project to the low frequency regions of the cochlea, whereas ventral regions of the IC project to the medial regions of the peri-olivary regions, known to project to the high frequency regions of the cochlea. This suggest that the inferior colliculus may be capable of exerting frequency-specific effects on the medial OC neurons and thus on the cochlea. This would be in accordance with the results of Scharf et al. [67], which suggested that the OC system is capable of exerting frequency-selective effects in the cochlea to aid selective attention (see above).

Is the projection from the inferior colliculus to the OC neurons biologically relevant? Physiological studies using electrical stimulation of the inferior colliculus have shown that this results in inhibition of cochlear output, an effect qualitatively similar to stimulation of the medial OC system itself, though smaller than the maximum effect that can be achieved by electrical stimulation of the OC system itself [20,43,50,53]. This smaller size inhibition is not a surprising result since the inferior colliculus is a large structure and electrical stimulation may not activate all neurons projecting to the OC neurons. In addition, it is not known whether all medial OC neurons receive input from the inferior colliculus. One study also demonstrated evidence for frequency specific effects from the inferior colliculus to the medial OC neurons. This study showed larger inhibition of low frequency compound action potentials in the cochlea when dorsal regions of the inferior colliculus were stimulated and larger inhibition of cochlear responses to high frequency tones when more ventral regions of the inferior colliculus were stimulated [49].

Interestingly, some of the effects observed with stimulation of the inferior colliculus are more consistent with stimulation of the lateral OC system [20,43,48,50,53], which lead to the hypothesis that the inferior colliculus can also indirectly affect the lateral OC system. Further studies are underway to investigate this issue.

There are several lines of evidence to indicate that the OC system receives information from non-auditory structures. Within the auditory brainstem a variety of neurotransmitters have been shown to exist such as serotonin [73], substance P [88] and noradrenaline [45,87]. With respect to the latter, it has been demonstrated that noradrenaline-containing varicosities make direct synaptic contacts with both lateral and medial olivocochlear neurons [45,86]. Anatomical tracing studies have demonstrated that the noradrenergic input to the olivocochlear neurons arises from the locus coeruleus [46,47]. This nucleus also supplies noradrenergic input to other auditory brainstem nuclei, such as the cochlear nucleus and inferior colliculus [29,30].

In line with these anatomical data, electrophysiological *in vitro* studies in rat brain slices have demonstrated that noradrenaline exerts a generally excitatory action on medial olivocochlear neurons [78]. The effect of noradrenaline on

OC neurons has also been investigated in anaesthetized guinea pigs. These experiments revealed inhibitory effects on compound action potentials when noradrenaline was injected close to the medial OC neurons and excitatory effects when noradrenaline was injected close to the lateral OC neurons. These results are thus consistent with the notion that noradrenaline has an excitatory effects on both the medial and lateral OC neurons.

The question remains as to what function this projection from the locus coeruleus to the OC system has. The locus coeruleus is well known to play a role in attentive processes, showing high tonic activity during arousal, moderate, phasic activity during selective attention and low tonic activity during drowsiness and sleep [1,2]. Since the olivocochlear system has been hypothesized to play a role in selective auditory attention, attenuating unattended signals and in improving speech detection in noisy environments (see above), noradrenaline may be modulating this process.

CLINICAL IMPLICATIONS AND FUTURE STUDIES

Dysfunction of both the lateral and medial OC system has been associated with hearing associated pathologies. This is not surprising if one considers effects of both systems on cochlear neural output and their proposed roles in normal hearing. When the lateral OC neurons can affect spontaneous neural firing, abnormal activity can well lead to tinnitus, the phenomenon where noise is perceived in the absence of an external physical sound [3,66]. An interesting observation in this respect is that stress is known to exacerbate tinnitus [23,25]. This may well be an example of top-down control, since stress activates the locus coeruleus. This in its turn may increase the noradrenaline release to the lateral OC system, causing activation, enhancing the spontaneous neural firing of primary auditory afferent fibres. This may provide the perception of tinnitus, either directly, or by secondary alterations of activity in central pathways.

If the medial OC system serves a homeostatic role, keeping the endocochlear potential constant, then disruption of this control could also lead to increased spontaneous firing from auditory afferent fibres as explained above. In patients that suffer from tinnitus the medial OC system has been shown to be less effective, showing less suppression in otoacoustic emissions with contralateral noise [10]. However, it must be mentioned that studies of patients with ablated OC axons, i.e. patients that received a vestibular nerve section to alleviate Menière's disease, did not reveal a clear link between disruption of the OC systems and tinnitus. Baguley and co-workers using an extensive literature search found that in the majority of patients undergoing the procedure tinnitus symptoms were not worsened [4], but the effects were highly variable.

With regard to a proposed role for the OC systems in signal detection in noisy environments, a common complaint in patients with auditory processing disorders and sensory deafness is the difficulty in understanding speech in noisy environments. Interestingly, in some of these patients a low activity of the MOC system was demonstrated [42] by measuring oto-acoustic emissions. Malfunctioning medial OC pathways have also been demonstrated in auditory neuropathy patients, which showed an absence of the suppression of oto-acoustic emissions with contralateral noise [69]. In these patients of course it is unclear whether the OC system itself is dysfunctional or whether it is driven less by the reduced cochlear afferent input. All of these patients, with the exception of a very young child, reported speech comprehension as a major problem, which may be connected to the malfunction of the efferent pathway.

More research will be necessary to elucidate the biological role of the efferent pathways and to reveal whether and how malfunctioning of these pathways is involved in the generation of hearing associated pathologies. Moreover, when more information is gathered on how the system is activated biologically, it may well have future therapeutic benefits. It may then be possible by pharmacological or other intervention to alleviate symptoms associated with dysfunction or to modulate abnormal afferent activity associated with tinnitus.

REFERENCES

[1] Aston-Jones, G. and Bloom, F.E., (1981) Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle, J Neurosci, 1, 876-86.

[2] Aston-Jones, G., Rajkowski, J. and Cohen, J., (1999) Role of locus coeruleus in attention and behavioral flexibility, Biol Psychiatry, 46, 1309-20.

[3] Attias, J., Bresloff, I. and Furman, V., (1996) The influence of the efferent auditory system on otoacoustic emissions in noise induced tinnitus: clinical relevance, Acta Otolaryngol, 116, 534-9.

[4] Baguley, D.M., Axon, P., Winter, I.M. and Moffat, D.A., (2002) The effect of vestibular nerve section upon tinnitus, Clin Otolaryngol, 27, 219-26.

[5] Beyerl, B.D., (1978) Afferent projections to the central nucleus of the inferior colliculus in the rat, Brain Res, 145, 209-23.

[6] Brown, M.C., (1989) Morphology and response properties of single olivocochlear fibers in the guinea pig, Hear Res, 40, 93-109.

[7] Brown, M.C., de Venecia, R.K. and Guinan, J.J., Jr., (2003) Responses of medial olivocochlear neurons. Specifying the central pathways of the medial olivocochlear reflex, Exp Brain Res, 153, 491-8.

[8] Brown, M.C. and Nuttall, A.L., (1984) Efferent control of cochlear inner hair cell responses in the guinea-pig, J Physiol, 354, 625-46.

[9] Buno, W., Jr., (1978) Auditory nerve fiber activity influenced by contralateral ear sound stimulation, Exp Neurol, 59, 62-74.

[10] Chery-Croze, S., Collet, L. and Morgon, A., (1993) Medial olivo-cochlear system and tinnitus, Acta Otolaryngol, 113, 285-90.

[11] Coleman, J.R. and Clerici, W.J., (1987) Sources of projections to subdivisions of the inferior colliculus in the rat, J Comp Neurol, 262, 215-26.

[12] Cooper, N.P., Robertson, D. and Yates, G.K., (1993) Cochlear nerve fiber responses to amplitude-modulated stimuli: variations with spontaneous rate and other response characteristics, J Neurophysiol, 70, 370-86.

[13] Desmedt, J., (1962) Auditory-evoked potentials from cochlea to cortex as influenced by activation of the efferent olivocochlear bundle, J. Acoust. Soc. Am., 34, 1478-1496.

[14] Dewson, J.H., (1968) Efferent olivocochlear bundle: some relationships to stimulus discrimination in noise, J Neurophysiol, 31, 122-30.

[15] Eybalin, M., (1993) Neurotransmitters and neuromodulators of the mammalian cochlea, Physiol Rev, 73, 309-73.
[16] Feliciano, M., Saldana, E, Mugnaini, E, (1995) Direct projections from the rat primary auditory neocortex to nucleus sagulum, paralemniscal regions, superior olivary complex and cochlear nuclei., Aud. Neurosci., 1, 287-308.
[17] Felix, D. and Ehrenberger, K., (1992) The efferent modulation of mammalian inner hair cell afferents, Hear Res, 64, 1-5.
[18] Gao, E. and Suga, N., (1998) Experience-dependent corticofugal adjustment of midbrain frequency map in bat auditory system, Proc Natl Acad Sci U S A, 95, 12663-70.
[19] Giraud, A.L., Garnier, S., Micheyl, C., Lina, G., Chays, A. and Chery-Croze, S., (1997) Auditory efferents involved in speech-in-noise intelligibility, Neuroreport, 8, 1779-83.
[20] Groff, J.A. and Liberman, M.C., (2003) Modulation of cochlear afferent response by the lateral olivocochlear system: activation via electrical stimulation of the inferior colliculus, J Neurophysiol, 90, 3178-200.
[21] Guinan, J.J., Jr., (1996) Physiology of olivocochlear efferents. In P. Dallos, Popper, A.N., Fay, R.R. (Ed.), The cochlea, New York, pp. 435-502.
[22] Guinan, J.J., Jr. and Stankovic, K.M., (1996) Medial efferent inhibition produces the largest equivalent attenuations at moderate to high sound levels in cat auditory-nerve fibers, J Acoust Soc Am, 100, 1680-90.
[23] Hazell, J.W.P., (1995) Support for a neurophysiological model of tinnitus. In G.E. Reich, Vernon, J.A. (Ed.), Proceedings of the fifth international tinnitus seminar. American tinnitus association, Portland, OR, pp. 51-57.
[24] Herbert, H., Aschoff, A. and Ostwald, J., (1991) Topography of projections from the auditory cortex to the inferior colliculus in the rat, J Comp Neurol, 304, 103-22.
[25] Jastreboff, P.J., (1990) Phantom auditory perception (tinnitus): mechanisms of generation and perception, Neurosci Res, 8, 221-54.
[26] Kawase, T. and Liberman, M.C., (1993) Antimasking effects of the olivocochlear reflex. I. Enhancement of compound action potentials to masked tones, J Neurophysiol, 70, 2519-32.
[27] Kemp, D.T. and Souter, M., (1988) A new rapid component in the cochlear response to brief electrical efferent stimulation: CM and otoacoustic observations, Hear Res, 34, 49-62.
[28] Kirk, E.C. and Smith, D.W., (2003) Protection from acoustic trauma is not a primary function of the medial olivocochlear efferent system., JARO, 4, 445-465.
[29] Klepper, A. and Herbert, H., (1991) Distribution and origin of noradrenergic and serotonergic fibers in the cochlear nucleus and inferior colliculus of the rat, Brain Res, 557, 190-201.
[30] Kromer, L.F. and Moore, R.Y., (1980) Norepinephrine innervation of the cochlear nuclei by locus coeruleus neurons in the rat, Anat Embryol (Berl), 158, 227-44.
[31] Kujawa, S.G., Glattke, T.J., Fallon, M. and Bobbin, R.P., (1993) Contralateral sound suppresses distortion product otoacoustic emissions through cholinergic mechanisms, Hear Res, 68, 97-106.
[32] Kujawa, S.G. and Liberman, M.C., (2001) Effects of olivocochlear feedback on distortion product otoacoustic emissions in guinea pig, J Assoc Res Otolaryngol, 2, 268-78.
[33] Le Prell, C.G., Shore, S.E., Hughes, L.F. and Bledsoe, S.C., Jr., (2003) Disruption of lateral efferent pathways: functional changes in auditory evoked responses, J Assoc Res Otolaryngol, 4, 276-90.
[34] Liberman, M.C., (1989) Rapid assessment of sound-evoked olivocochlear feedback: suppression of compound action potentials by contralateral sound, Hear Res, 38, 47-56.
[35] Liberman, M.C., (1990) Effects of chronic cochlear de-efferentation on auditory-nerve response, Hear Res, 49, 209-23.
[36] Liberman, M.C. and Brown, M.C., (1986) Physiology and anatomy of single olivocochlear neurons in the cat, Hear Res, 24, 17-36.
[37] Liberman, M.C., Dodds, L.W. and Pierce, S., (1990) Afferent and efferent innervation of the cat cochlea: quantitative analysis with light and electron microscopy, J Comp Neurol, 301, 443-60.
[38] Ma, X. and Suga, N., (2001) Corticofugal modulation of duration-tuned neurons in the midbrain auditory nucleus in bats, Proc Natl Acad Sci U S A, 98, 14060-5.
[39] May, B.J. and McQuone, S.J., (1995) Effects of bilateral lesions on pure-tone intensity discrimination in cats, Aud. Neurosci., 1, 385-400.
[40] Micheyl, C., Khalfa, S., Perrot, X. and Collet, L., (1997) Difference in cochlear efferent activity between musicians and non-musicians, Neuroreport, 8, 1047-50.
[41] Mott, J.B., Norton, S.J., Neely, S.T. and Warr, W.B., (1989) Changes in spontaneous otoacoustic emissions produced by acoustic stimulation of the contralateral ear, Hear Res, 38, 229-42.
[42] Muchnik, C., Ari-Even Roth, D., Othman-Jebara, R., Putter-Katz, H., Shabtai, E.L. and Hildesheimer, M., (2004) Reduced medial olivocochlear bundle system function in children with auditory processing disorders, Audiol Neurootol, 9, 107-14.
[43] Mulders, W.H. and Robertson, D., (2000) Effects on cochlear responses of activation of descending pathways from the inferior colliculus, Hear Res, 149, 11-23.
[44] Mulders, W.H. and Robertson, D., (2000) Evidence for direct cortical innervation of medial olivocochlear neurones in rats, Hear Res, 144, 65-72.
[45] Mulders, W.H. and Robertson, D., (2000) Morphological relationships of peptidergic and noradrenergic nerve terminals to olivocochlear neurones in the rat, Hear Res, 144, 53-64.
[46] Mulders, W.H. and Robertson, D., (2001) Origin of the noradrenergic innervation of the superior olivary complex in the rat, J Chem Neuroanat, 21, 313-22.
[47] Mulders, W.H. and Robertson, D., (2005) Catecholaminergic innervation of guinea pig superior olivary complex, J Chem Neuroanat, 30, 230-42.
[48] Mulders, W.H. and Robertson, D., (2005) Diverse responses of single auditory afferent fibres to electrical stimulation of the inferior colliculus in guinea-pig, Exp Brain Res, 160, 235-44.
[49] Oestreicher, E., Arnold, W., Ehrenberger, K. and Felix, D., (1997) Dopamine regulates the glutamatergic inner hair cell activity in guinea pigs, Hear Res, 107, 46-52.
[50] Ota, Y., Oliver, D.L. and Dolan, D.F., (2004) Frequency-specific effects on cochlear responses during activation of the inferior colliculus in the Guinea pig, J Neurophysiol, 91, 2185-93.
[51] Patuzzi, R., (2002) Outer hair cells, EP regulation and tinnitus. In R. Patuzzi (Ed.), University of Western Australia, pp. 16-24.
[52] Patuzzi, R.B. and Thompson, M.L., (1991) Cochlear efferent neurones and protection against acoustic trauma: protection of outer hair cell receptor current and interanimal variability, Hear Res, 54, 45-58.
[53] Popelar, J., Mazelova, J. and Syka, J., (2002) Effects of electrical stimulation of the inferior colliculus on 2f1-f2 distortion product otoacoustic emissions in anesthetized guinea pigs, Hear Res, 170, 116-26.
[54] Popelar, J., Nwabueze-Ogbo, F.C. and Syka, J., (2003) Changes in neuronal activity of the inferior colliculus in rat after temporal inactivation of the auditory cortex, Physiol Res, 52, 615-28.

[55] Puel, J.L., (1995) Chemical synaptic transmission in the cochlea, Prog Neurobiol, 47, 449-76.
[56] Puel, J.L. and Rebillard, G., (1990) Effect of contralateral sound stimulation on the distortion product 2F1-F2: evidence that the medial efferent system is involved, J Acoust Soc Am, 87, 1630-5.
[57] Puria, S., Guinan, J.J., Jr. and Liberman, M.C., (1996) Olivocochlear reflex assays: effects of contralateral sound on compound action potentials versus ear-canal distortion products, J Acoust Soc Am, 99, 500-7.
[58] Rajan, R., (1988) Effect of electrical stimulation of the crossed olivocochlear bundle on temporary threshold shifts in auditory sensitivity. I. Dependence on electrical stimulation parameters, J Neurophysiol, 60, 549-68.
[59] Rajan, R., (2001) Noise priming and the effects of different cochlear centrifugal pathways on loud-sound-induced hearing loss, J Neurophysiol, 86, 1277-88.
[60] Reiter, E.R. and Liberman, M.C., (1995) Efferent-mediated protection from acoustic overexposure: relation to slow effects of olivocochlear stimulation, J Neurophysiol, 73, 506-14.
[61] Robertson, D., Cole, K.S. and Corbett, K., (1987) Quantitative estimate of bilaterally projecting medial olivocochlear neurones in the guinea pig brainstem, Hear Res, 27, 177-81.
[62] Robertson, D. and Gummer, M., (1985) Physiological and morphological characterization of efferent neurones in the guinea pig cochlea, Hear Res, 20, 63-77.
[63] Robertson, D. and Winter, I.M., (1988) Cochlear nucleus inputs to olivocochlear neurones revealed by combined anterograde and retrograde labelling in the guinea pig, Brain Res, 462, 47-55.
[64] Ruel, J., Nouvian, R., Gervais d'Aldin, C., Pujol, R., Eybalin, M. and Puel, J.L., (2001) Dopamine inhibition of auditory nerve activity in the adult mammalian cochlea, Eur J Neurosci, 14, 977-86.
[65] Ruggero, M.A. and Rich, N.C., (1991) Furosemide alters organ of corti mechanics: evidence for feedback of outer hair cells upon the basilar membrane, J Neurosci, 11, 1057-67.
[66] Sahley, T.L., Nodar, R.H. and Musiek, F.E., (1999) Endogenous dynorphins: possible role in peripheral tinnitus, Int Tinnitus J, 5, 76-91.
[67] Saldana, E., Feliciano, M. and Mugnaini, E., (1996) Distribution of descending projections from primary auditory neocortex to inferior colliculus mimics the topography of intracollicular projections, J Comp Neurol, 371, 15-40.
[68] Scharf, B., Magnan, J. and Chays, A., (1997) On the role of the olivocochlear bundle in hearing: 16 case studies, Hear Res, 103, 101-22.
[69] Starr, A., Picton, T.W., Sininger, Y., Hood, L.J. and Berlin, C.I., (1996) Auditory neuropathy, Brain, 119 (Pt 3), 741-53.
[70] Syka, J. and Popelar, J., (1984) Inferior colliculus in the rat: neuronal responses to stimulation of the auditory cortex, Neurosci Lett, 51, 235-40.
[71] Thompson, A.M. and Thompson, G.C., (1991) Posteroventral cochlear nucleus projections to olivocochlear neurons, J Comp Neurol, 303, 267-85.
[72] Thompson, A.M. and Thompson, G.C., (1993) Relationship of descending inferior colliculus projections to olivocochlear neurons, J Comp Neurol, 335, 402-12.
[73] Thompson, A.M. and Thompson, G.C., (1995) Light microscopic evidence of serotoninergic projections to olivocochlear neurons in the bush baby (Otolemur garnettii), Brain Res, 695, 263-6.
[74] Vetter, D.E., Adams, J.C. and Mugnaini, E., (1991) Chemically distinct rat olivocochlear neurons, Synapse, 7, 21-43.
[75] Vetter, D.E. and Mugnaini, E., (1992) Distribution and dendritic features of three groups of rat olivocochlear neurons. A study with two retrograde cholera toxin tracers, Anat Embryol (Berl), 185, 1-16.
[76] Vetter, D.E., Saldana, E. and Mugnaini, E., (1993) Input from the inferior colliculus to medial olivocochlear neurons in the rat: a double label study with PHA-L and cholera toxin, Hear Res, 70, 173-86.
[77] Walsh, E.J., McGee, J., McFadden, S.L. and Liberman, M.C., (1998) Long-term effects of sectioning the olivocochlear bundle in neonatal cats, J Neurosci, 18, 3859-69.
[78] Wang, X. and Robertson, D., (1997) Effects of bioamines and peptides on neurones in the ventral nucleus of trapezoid body and rostral periolivary regions of the rat superior olivary complex: an in vitro investigation, Hear Res, 106, 20-8.
[79] Warr, W.B., Boche, J.B. and Neely, S.T., (1997) Efferent innervation of the inner hair cell region: origins and terminations of two lateral olivocochlear systems, Hear Res, 108, 89-111.
[80] Warr, W.B. and Guinan, J.J., Jr., (1979) Efferent innervation of the organ of corti: two separate systems, Brain Res, 173, 152-5.
[81] Warren, E.H., 3rd and Liberman, M.C., (1989) Effects of contralateral sound on auditory-nerve responses. II. Dependence on stimulus variables, Hear Res, 37, 105-21.
[82] White, J.S. and Warr, W.B., (1983) The dual origins of the olivocochlear bundle in the albino rat, J Comp Neurol, 219, 203-14.
[83] Wiederhold, M.L. and Kiang, N.Y., (1970) Effects of electric stimulation of the crossed olivocochlear bundle on single auditory-nerve fibers in the cat, J Acoust Soc Am, 48, 950-65.
[84] Winer, J.A., Larue, D.T., Diehl, J.J. and Hefti, B.J., (1998) Auditory cortical projections to the cat inferior colliculus, J Comp Neurol, 400, 147-74.
[85] Winslow, R.L. and Sachs, M.B., (1987) Effect of electrical stimulation of the crossed olivocochlear bundle on auditory nerve response to tones in noise, J Neurophysiol, 57, 1002-21.
[86] Woods, C.I. and Azeredo, W.J., (1999) Noradrenergic and serotonergic projections to the superior olive: potential for modulation of olivocochlear neurons, Brain Res, 836, 9-18.
[87] Wynne, B. and Robertson, D., (1996) Localization of dopamine-beta-hydroxylase-like immunoreactivity in the superior olivary complex of the rat, Audiol Neurootol, 1, 54-64.
[88] Wynne, B. and Robertson, D., (1997) Somatostatin and substance P-like immunoreactivity in the auditory brainstem of the adult rat, J Chem Neuroanat, 12, 259-66.
[89] Yan, W. and Suga, N., (1998) Corticofugal modulation of the midbrain frequency map in the bat auditory system, Nat Neurosci, 1, 54-8.
[90] Zheng, X.Y., Henderson, D., McFadden, S.L., Ding, D.L. and Salvi, R.J., (1999) Auditory nerve fiber responses following chronic cochlear de-efferentation, J Comp Neurol, 406, 72-86.

GENETIC ASPECTS OF HEARING LOSS

Hans-Henrik Dahl, Shehnaaz Manji, Michelle de Silva, Marisel Peverelli, Michael Hildebrand.

Genetic Hearing Research,
Murdoch Childrens Research Institute, The Royal Children's Hospital
Parkville, Vic. 3052

Genes mediate the workings of cells, organs and organisms. Since normal hearing is dependent on highly specialised structures and cellular functions it is not surprising that many genes – as well as environmental factors – affect this complex process. A number of genes have been identified to date that have added to our knowledge of the molecular aspects of hearing. Mutations, or changes, in these genes cause deafness or hearing impairment demonstrating that these genes are essential for normal hearing function. Despite the advances we have made in the discovery of "deafness" genes, little is known about the genes that determine susceptibility to noise-induced deafness, ototoxic hearing loss or early onset presbyacusis. Increasing our knowledge of the genetic aspects of hearing loss will lead to improved genetic counselling and will help the development of novel cell-based, gene or drug therapies.

1. INTRODUCTION

Hearing loss is the most common sensory condition, affecting approximately 10% of Australians. Although 1 in 800 newborn children have a hearing problem, it is espcially an issue for adults and the elderly: by the age of 65 to 75 years, half the population experience hearing impairment. The financial, social and personal costs of deafness to affected people, their families and the society are significant [1].

Deafness is an etiologically heterogenous trait caused by genetic and environmental factors. It is known that mutations in a number of genes can cause inherited hearing loss as can environmental factors such as infections, noise exposure, premature birth and exposure to ototoxic drugs. Hearing loss is usually classified as conductive or sensorineural. Conductive hearing loss is caused when sound waves are not able to pass through the outer or middle ear. It is often reversible, and can be caused by otitis media, otosclerosis, and presence of a foreign body or a tumour. Sensorineural hearing loss is usually irreversible, and commonly involves damage to or loss of cells in the inner ear (incl. hair cells) or auditory nerves. In most instances, hearing loss of genetic origin is sensorineural. Although we state that 60% of cases of childhood deafness are genetic and 40% environmental, some cases are caused by a combination of both genetic and environmental factors, eg. aminoglycoside-induced hearing loss. It is also true that genetics and environmental factors interact in the most common types of adult-onset hearing loss: presbyacusis and noise-induced hearing loss. Many genes are needed for correct auditory function. Genetic changes (mutations) that result in malfunction of an important "auditory" protein can result in deafness. It is estimated that there are several hundred such "auditory" genes [2].

2. GENETICS OF HEARING LOSS

2.1 Classification of inherited deafness

A syndrome is a combination of clinical features seen repeatedly in different individuals. When a person presents with hearing loss as their only clinical feature their deafness is classified as non-syndromic. If the deafness is only one of the clinical features in a syndrome it is classified as syndromic deafness. Hearing loss is a major feature of over 400 syndromes [3], Table 1.

Table 1. The 10 most common syndromes in which deafness is a major feature (from [30]).

Syndrome
Hemifacial microsomia
Stickler syndrome
Congenital cytomegalo virus
Usher syndrome
Branchio-oto-renal syndrome
Pendred syndrome
CHARGE Association
Neurofibromatosis type II
Mitochondrial disorders
Waardenburg syndrome

Inherited conditions are said to be either simple or complex. Simple genetic conditions follow Mendel's laws by showing typical and characteristic inheritance patterns (recessive, dominant, X chromosome linked, maternal). Complex genetic conditions are the result of interaction between many genes and environmental factors and therefore do not follow Mendelian inheritance patterns. Most of the common conditions that affect us are complex genetic traits. With many genes and environmental factors causing deafness one would assume that deafness belongs in the 'complex condition' category. That is normally not the case, and certainly not when investigating genetic deafness in newborns or young people. In such cases the inheritance pattern within a given family usually follows simple Mendelian laws. When looking at non-syndromic hearing loss the inheritance pattern is autosomal recessive in ~80%, autosomal dominant in ~15%, X-chromosome linked in ~3% and maternal (mitochondrial) in ~2% of families [4], but will vary somewhat depending on ethnic background.

2.2 Genes that cause deafness

The fact that inherited deafness in many families follows Mendel's laws makes identification of genes associated with hearing loss easier. Geneticists can – if a family has

enough affected members and is of a suitable structure – take advantage of recent developments in tracking genes (so-called linkage analysis or gene mapping) and in knowledge obtained in the human genome project. The human genome project has produced the DNA sequence and chromosome "address" of known and predicted human genes. To find genes associated with deafness, geneticists will often use linkage analysis to determine which chromosome and in which region on that chromosome a mutated gene is located. They will then search human genome data for candidate genes in the chromosome region and determine if any of these genes have a mutation that might explain the deafness. This can be a laborious task and in many cases a "deafness" gene is mapped to a chromosome region, but the gene itself has not been identified. So far > 80 genes associated with syndromic or non-syndromic hearing loss have been identified (Table 2). Information on these genes and links to more information can be found on The Hereditary Hearing Loss Homepage [5].

Rapid progress has been made in identifying "deafness" genes. How has the identification of "deafness" genes, helped our understanding of the molecular basis of auditory function? It has become clear that "deafness" genes code for proteins with a large range of functions, including structural proteins, transcription factors, enzymes in metabolic pathways, ion channels and ion transporters (Table 2). It is not the purpose of this article to describe these genes in detail, but we will mention two of the more important genes, connexin 26 and pendrin.

Connexin 26

With so many different genes being able to cause deafness, it was somewhat of a surprise to discover that one gene, the connexin 26 gene, is the cause of hearing loss in approximately 40% of

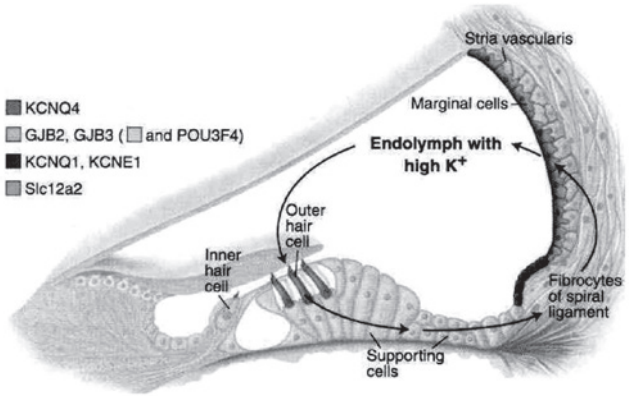


Figure 1 Potassium recycling in the cochlea. The route of potassium recycling from the outer hair cells through the supporting cells of the organ of Corti and fibrocytes of the spiral ligament. Na-K ATPase pumps, located in the marginal cells of the stria vascularis, pump the potassium ions back out into the endolymph. The anatomical localisation of the proteins encoded by common "deafness" genes in this pathway is depicted. From [8].

Australian children with prelingual, non-syndromic autosomal recessive hearing loss. We can calculate that approximately 1 in 50 Australians is an unaffected carrier of a connexin 26 mutation [6]. Connexin 26 mutations are some of the most common genetic mutations in our population [7]. Connexin 26 is a member of a family of transmembrane proteins that form intercellular gap junctions and whose function is to allow ions or small molecules to be transported between neighbouring cells. It is expressed in many tissues in the body, including the supporting cells, spiral ligament, fibrocytes and spiral limbus

Table 2. Examples of genes associated with hearing loss

Gene product	Type of deafness	Inheritance	Comments
Connexin 26	Non-syndromic	Recessive	The most common cause of prelingual inherited hearing loss. Connexin 26 caused deafness can in rare cases be syndromic or have dominant inheritance
Pendrin	Syndromic	Recessive	Pendrin mutations can also cause non-syndromic hearing loss
Mitochondrial 12S rRNA	Aminoglycoside induced	Maternal	
Myosin 7A	Non-syndromic or Syndromic	Dominant or Recessive	Myosin 7A mutations can cause Usher syndrome
Cadherin 23	Non-syndromic or Syndromic	Recessive	Cadherin 23 mutations can cause Usher syndrome
Harmonin	Non-syndromic or Syndromic	Recessive	Harmonin mutations can cause Usher syndrome
COCH	Non-syndromic	Dominant	Onset of deafness usually in teens
KCNQ4	Non-syndromic	Dominant	Voltage-gated potassium channel
PAX3	Syndromic	Dominant	PAX3 mutations can cause Waardenburg syndrome
SOX3	Syndromic	Dominant	SOX3 mutations can cause Waardenburg syndrome

of the cochlea [8]. It is thought that mutations in the connexin 26 gene disrupt the recycling of K+ back into the endolymph, thereby affecting endocochlear potential and/or cell viability.

Pendrin

Pendrin, or Solute carrier family 26 member 4 (SLC26A4), is another important gene associated with hearing loss. Studies suggest that pendrin mutations account for approximately 5% of all prelingual deafness [9]. Pendrin is an iodide-specific transporter. In the ear it is expressed throughout the endolymphatic duct and sac, as well as in nonsensory regions of the utricle, saccule and cochlea. These observations support the view that pendrin is involved in endolymphatic fluid resorption in the inner ear.

Mutations in the pendrin gene can cause a variety of clinical presentations. It was identified as the gene causing Pendred syndrome. However, mutations in the pendrin gene do not always cause goiter or cochlear malformations, such as Mondini dysplasia and enlarged vestibular aqueducts [10].

2.3 Why find genes for deafness?

The identification of "deafness" genes is a significant step forward in understanding the molecular basis of inner ear function. Although there are still large gaps in our knowledge, the study of genes coding for prestin, cadherins, harmonin, myosins, actins, TRP1 (the potential mechanoelectrical transduction channel) have – in combination with physiology and physics – given us unprecedented insight into cochlea function.

Identification of these genes also has clinical relevance [11]. Screening for connexin 26 mutations is now one of the most requested genetic tests. Identification of connexin 26 mutations in a family explains the cause of deafness, results in improved genetic counselling and has implications for prenatal and postnatal testing. In the future, new technology will make it practical and economically feasible to screen for mutations in many more "deafness" genes. One can also envisage that future treatments for hearing loss will target specific genes or functions.

2.4 Finding additional genes for hearing loss

Despite the recent successes, many more genes important in auditory function await identification and characterisation. Gene mapping and gene analysis of families affected by hearing loss have led to the identification of a number of "deafness" genes. For dominant conditions this requires large multigeneration families with many (usually >15) affected members. For recessive conditions large consanguineous families are often needed. Such families are not common in Australia, and the approach therefore not always an option. Most of the known genes associated with hearing loss are genes that cause early onset deafness. We know that there is a significant genetic contribution to the timing and severity of presbyacusis, but the genes and mechanisms involved are poorly understood, as are the genetic factors that influence the severity of a hearing loss.

How can we find these genes? Several approaches have been exploited by us and others in the hunt for the causative "deafness" genes. One such approach is to use microarray technology to gain insight into which genes are expressed at what level in specific structures of the inner ear or even in individual cells. Ideally one would compare gene expression between individuals with eg. early and late-onset presbyacusis, but because it is difficult to obtain human inner ear tissue, such comparisons are usually done on samples from animals, eg. mice [12; 13].

The analysis of mouse models for deafness is also a powerful approach to identifying human genes for hearing loss. The mouse inner ear is very similar to that of humans, and observations in mice are therefore usually relevant to humans. Large mouse families, consanguineous if necessary can readily be established so that genetic linkage studies can be done. Since the mouse genome project is nearly as advanced as the human genome project, identifying and investigating candidate genes is relatively straightforward. Obtaining relevant tissues and doing physiological or other studies is normally not a problem. A number of spontaneously occurring deaf mice exist, but more recently more systematic ENU mutagenesis and screening programs have led to the creation of novel deaf mouse strains. For example, we have in collaboration with the Australian Phenomics Facility in Canberra, currently identified more than 10 new mouse strains with congenital or later-onset recessive deafness. We have identified novel "deafness" genes in some of these strains (unpublished data).

3. DEVELOPMENT AND MATURATION OF HAIR CELLS

3.1 Genes involved in hair cell differentiation

Sensorineural hearing loss - the most common type of hearing impairment - is usually accompanied by inner ear hair cell degeneration. The severity of the hearing loss is correlated to the proportion of missing hair cells. In the mature mammalian organ of Corti the hair cells are not replaced, resulting in permanent hearing impairment. However, in the avian basilar papilla (the functional equivalent of the organ of Corti) hair cells regenerate in response to cellular damage resulting in restored hearing function. This phenomenon provides hope that by understanding the mechanisms that govern the genesis and regeneration of hair cells we will be able to develop cell-based strategies to delay, prevent, or even reverse the hearing loss in individuals with hearing impairment.

There is still a limited understanding of hair cell development in mammals. The hair cells are terminally differentiated cells and the vast majority arise before birth. In the mouse, hair cell and supporting cell proliferation culminates between embryonic days 13 and 15. We know that the process is highly complex in mammals and that the Notch signalling pathway plays a central role with *Notch1* and its ligands *Delta1, Jagged1* and *Jagged2* expressed in the developing inner ear. Transcription factor *Math1* is also expressed in the developing ear and its presence is essential for hair cell development after hair cell precursor selection has been specified during development of the organ of Corti [14]. Hair cells are absent in mice lacking *Math1* and in contrast, the overexpression of *Math1* causes the production

of extra hair cells [15; 16]. Once hair cells have been specified, their continued differentiation requires the class IV POU-domain gene, *Pou4f3*. Without the presence of this gene product, the hair cell precursor cells degenerate.

4. FUTURE CELL-BASED THERAPIES FOR HEARING LOSS

4.1 Replacing hair cells using gene, growth factor and/or cell-based therapies

Recently there has been much interest in the role of *Math1* in hair cell differentiation and its potential use in gene therapy treatment for deafness. [15; 17]. Transfer of adenoviral vectors expressing Math1 into the ears of guinea pigs resulted in the formation of "hair cell-like" cells [18]. This group went on to show the presence of immature hair cells in the organ of Corti five weeks post-*Math1* inoculation by scanning electron micrograph analysis. At two months, the surface of the auditory epithelium contained numerous cells with mature-looking stereocilia bundles. Cross sections of the organ of Corti revealed normal appearing inner hair cells, however, in the outer hair cell area, new hair cells were poorly differentiated [19]. Therefore, other factors must be required to specify outer hair cell regeneration and there are therefore more genes to be discovered that are necessary for hair cell development and regeneration.

It has been proposed that progenitor and/or differentiated hair cells generated *in vitro* from stem cells and delivered to the inner ear might restore auditory hair cell function in the deafened mammalian cochlea. Stem cells, by definition, have a capacity for self-renewal and are able to give rise to at least one differentiated cell type. In recent years, stem cells have been identified in a wide range of mature tissues including brain, skin, muscle and blood. These stem cells are considered to be multipotent, as they are able to give rise to a limited number of differentiated cell types. In contrast, embryonic stem (ES) cells, which are derived from the inner cell mass of blastocyst embryos, are pluripotent, and therefore capable of generating all embryonic tissues including the germline.

One of the first reports of stem cell delivery to the inner ear was a study by Ito *et al* [20] that demonstrated survival and migration of adult rat neural stem cells implanted into the rat cochlea. The cells migrated to the organ of Corti, and a limited number were shown to adopt hair cell-like morphology and to stain with phalloidin. Following on from this study, a report showed that transplanted neural stem cells migrated to the vestibular epithelium and approximately 5% expressed the hair cell marker myosin VIIa after 25 days. However, only a very small number of stem cells migrated to the cochlear sensory epithelium and none of them expressed the hair cell marker myosin VIIa [21].

Since then other groups have reported on the transplantation of ES cells into the inner ear. The study by Sakamoto *et al* [22] reported survival of ES cells predominantly in the vestibular region of the mouse inner ear and also some cells in the scala media of the cochlear duct after transplantation for four weeks. In comparison, the study by Hu *et al* [23] demonstrated the survival and migration of mouse ES cells along the auditory nerve after xenotransplantation into auditory nerve fibres of the rat cochlea. We directly transplanted cells into the scala media of deafened guinea pigs and showed that these cells survived in the scala media for a post-operative period of at least nine weeks [24]. Whilst these studies have demonstrated the survival of ES cells in the cochlea, hearing function has not been restored. This would not only require that the transplanted cells survive in the cochlea, but that they integrate at the right site and become part of the highly structured organ, develop into the correct cell types, and form the right connection to nerves and other cells. This is a huge ask, and in the end it is likely that it is a combination of approaches, namely the delivery of the correctly differentiated cell type to the correct compartment of the cochlea with the right growth and neurotrophic factors that will result in the successful reversal of hearing loss.

4.2 Pharmacological treatments

Administration of glucocorticoids has in some cases shown to have a positive therapeutic effect on sudden SNHL, Meniere's disease and noise-induced hearing loss [25]. This might not only be due to the anti-inflammatory and/or immunosuppressive actions of the drugs, but also to effect of glucocorticoids on regulation of genes associated with, for example, Na^+ transport in the inner ear [26]. Knowledge about the functions of genes that are associated with hearing loss offers new opportunities for the discovery of new drugs that might prove useful in the prevention or treatment of not only congenital, but also presbyacusis and noise-induced hearing loss. For example, the discovery that many of the "deafness" genes are involved in maintaining the inner ear homeostatic salt balance would suggest that drugs that stimulate K^+ transport could be useful pharmaceuticals for the treatment of certain types of hearing loss.

The inner ear is a highly energy demanding organ and it is therefore not surprising that near-optimal mitochondrial function is a requirement for normal hearing. Hearing loss is a feature in most syndromes involving mitochondrial dysfunction. Highly toxic reactive oxygen species (ROS) are generated in the mitochondria as a consequence of energy generation. ROS damage slowly impairs mitochondrial function by damaging biological molecules (including the mitochondrial DNA) and one consequence is likely to be a progressive hearing loss [27]. Antioxidants scavenge ROS before they cause damage and slow the self-amplifying cycle of damage and increasing ROS production. Antioxidant therapy can protect hearing and hair cells from noise-induced damage and ototoxicity [28; 29].

5. CONCLUSIONS

Identification of genes associated with hearing loss has led to a much better understanding of the molecular mechanisms of hearing. Despite rapid progress in this area there are still many "deafness" genes that await identification. Our understanding of the genes that modulate noise-induced deafness, ototoxic hearing loss and the timing and severity of presbyacusis is still poor. Knowledge of the genetic factors and their contribution to hearing loss has immediate consequences for counselling

affected families and will in the future enable us to identify people at high risk of developing a hearing loss. Hopefully, we will then also have available measures for preventing or attenuating the hearing loss.

ACKNOWLEDGMENTS

Our work is supported by The Garnett Passe and Rodney Williams Memorial Foundation, The Murdoch Childrens Research Institute, J. & J. Calvert-Jones and the NHMRC.

REFERENCES

1. Mohr, P.E., Feldman, J.J., Dunbar, J.L., McConkey-Robbins, A., Niparko, J.K., Rittenhouse, R.K., Skinner, M.W., "The societal costs of severe to profound hearing loss in the United States", *Int J Technol Assess Health Care* 16, 1120-1135 (2000)
2. Petit, C., "Genes responsible for human hereditary deafness: symphony of a thousand", *Nat Genet* 14, 385-391 (1996)
3. Gorlin, R.J., Toriello, H.V., Cohen, M.M., *Hereditary Hearing Loss and Its Syndromes*. Vol 28. Oxford University Press, New York (1995)
4. Morton, N.E., "Genetic epidemiology of hearing impairment", *Ann N Y Acad Sci* 630, 16-31 (1991)
5. Van Camp, G., Smith, R.J.H., Hereditary Hearing Loss Homepage, URL: http://dnalab-www.uia.ac.be/dnalab/hhh/
6. Dahl, H.H., Saunders, K., Kelly, T.M., Osborn, A.H., Wilcox, S., Cone-Wesson, B., Wunderlich, J.L., Du Sart, D., Kamarinos, M., Gardner, R.J., Dennehy, S., Williamson, R., Vallance, N., Mutton, P., "Prevalence and nature of connexin 26 mutations in children with non-syndromic deafness", *Med J Aust* 175, 191-194. (2001)
7. Denoyelle, F., Weil, D., Maw, M.A., Wilcox, S.A., Lench, N.J., Allen-Powell, D.R., Osborn, A.H., *et al*., "Prelingual deafness: high prevalence of a 30delG mutation in the connexin 26 gene", *Hum Mol Genet* 6, 2173-2177. (1997)
8. Steel, K.P., "Perspectives: biomedicine. The benefits of recycling [comment]", *Science* 285, 1363-1364 (1999)
9. Park, H.J., Shaukat, S., Liu, X.Z., Hahn, S.H., Naz, S., Ghosh, M., Kim, H.N., Moon, S.K., Abe, S., Tukamoto, K., Riazuddin, S., Kabra, M., Erdenetungalag, R., Radnaabazar, J., Khan, S., Pandya, A., Usami, S.I., Nance, W.E., Wilcox, E.R., Griffith, A.J., "Origins and frequencies of SLC26A4 (PDS) mutations in east and south Asians: global implications for the epidemiology of deafness", *J Med Genet* 40, 242-248. (2003)
10. Li, X.C., Everett, L.A., Lalwani, A.K., Desmukh, D., Friedman, T.B., Green, E.D., Wilcox, E.R., "A mutation in PDS causes non-syndromic recessive deafness [letter]", *Nat Genet* 18, 215-217 (1998)
11. Smith, R.J., Bale, J.F., Jr., White, K.R., "Sensorineural hearing loss in children", *Lancet* 365, 879-890 (2005)
12. Hildebrand, M.S., de Silva, M.G., Klockars, T., Rose, E., Price, M., Smith, R.J., McGuirt, W.T., Christopoulos, H., Petit, C., Dahl, H.H., "Characterisation of DRASIC in the mouse inner ear", *Hear Res* 190, 149-160 (2004)
13. Hildebrand, M.S., de Silva, M.G., Klockars, T., Solares, C.A., Hirose, K., Smith, J.D., Patel, S.C., Dahl, H.H., "Expression of the carrier protein apolipoprotein D in the mouse inner ear", *Hear Res* 200, 102-114 (2005)
14. Chen, P., Johnson, J.E., Zoghbi, H.Y., Segil, N., "The role of Math1 in inner ear development: Uncoupling the establishment of the sensory primordium from hair cell fate determination", *Development* 129, 2495-2505 (2002)
15. Bermingham, N.A., Hassan, B.A., Price, S.D., Vollrath, M.A., Ben-Arie, N., Eatock, R.A., Bellen, H.J., Lysakowski, A., Zoghbi, H.Y., "Math1: an essential gene for the generation of inner ear hair cells", *Science* 284, 1837-1841 (1999)
16. Zheng, J.L., Gao, W.Q., "Overexpression of Math1 induces robust production of extra hair cells in postnatal rat inner ears", *Nat Neurosci* 3, 580-586 (2000)
17. Woods, C., Montcouquiol, M., Kelley, M.W., "Math1 regulates development of the sensory epithelium in the mammalian cochlea", *Nat Neurosci* 7, 1310-1318 (2004)
18. Kawamoto, K., Ishimoto, S., Minoda, R., Brough, D.E., Raphael, Y., "Math1 gene transfer generates new cochlear hair cells in mature Guinea pigs in vivo", *J Neurosci* 23, 4395-4400 (2003)
19. Izumikawa, M., Minoda, R., Kawamoto, K., Abrashkin, K.A., Swiderski, D.L., Dolan, D.F., Brough, D.E., Raphael, Y., "Auditory hair cell replacement and hearing improvement by Atoh1 gene therapy in deaf mammals", *Nat Med* 11, 271-276 (2005)
20. Ito, J., Kojima, K., Kawaguchi, S., "Survival of neural stem cells in the cochlea", *Acta Otolaryngol* 121, 140-142. (2001)
21. Tateya, I., Nakagawa, T., Iguchi, F., Kim, T.S., Endo, T., Yamada, S., Kageyama, R., Naito, Y., Ito, J., "Fate of neural stem cells grafted into injured inner ears of mice", *Neuroreport* 14, 1677-1681 (2003)
22. Sakamoto, T., Nakagawa, T., Endo, T., Kim, T.S., Iguchi, F., Naito, Y., Sasai, Y., Ito, J., "Fates of mouse embryonic stem cells transplanted into the inner ears of adult mice and embryonic chickens", *Acta Otolaryngol Suppl* 55i, 48-52 (2004)
23. Hu, Z., Ulfendahl, M., Olivius, N.P., "Survival of neuronal tissue following xenograft implantation into the adult rat inner ear", *Exp Neurol* 185, 7-14 (2004)
24. Hildebrand, M.S., Dahl, H.H., Hardman, J., Coleman, B., Shepherd, R.K., de Silva, M.G., "Survival of Partially Differentiated Mouse Embryonic Stem Cells in the Scala Media of the Guinea Pig Cochlea", *J Assoc Res Otolaryngol*, 7, 1310-1318 (2005)
25. Lamm, K., Arnold, W., "Successful treatment of noise-induced cochlear ischemia, hypoxia, and hearing loss", *Ann N Y Acad Sci* 884, 233-248 (1999)
26. Pondugula, S.R., Raveendran, N.N., Ergonul, Z., Deng, Y., Chen, J., Sanneman, J.D., Palmer, L.G., Marcus, D.C., "Glucocorticoid regulation of genes in the amiloride-sensitive sodium transport pathway by semicircular canal duct epithelium of neonatal rat", *Physiol Genomics* 24, 114-123 (2006)
27. Pickles, J.O., "Mutation in mitochondrial DNA as a cause of presbyacusis", *Audiol Neurootol* 9, 23-33 (2004)
28. Kawamoto, K., Sha, S.H., Minoda, R., Izumikawa, M., Kuriyama, H., Schacht, J., Raphael, Y., "Antioxidant gene therapy can protect hearing and hair cells from ototoxicity", *Mol Ther* 9, 173-181 (2004)
29. Le Prell, C.G., Dolan, D.F., Schacht, J., Miller, J.M., Lomax, M.I., Altschuler, R.A., "Pathways for protection from noise induced hearing loss", *Noise Health* 5, 1-17 (2003)
30. Bradley Schaefer, G., Research Registry for Hereditary Hearing Loss, URL: http://www.boystownhospital.org/Hearing/info/genetics/syndromes/ten.asp

EXCELLENCE IN ACOUSTICS AWARD 2006

CSR Bradford Insulation

The Excellence in Acoustics award is sponsored by CSR Bradford Insulation The award aims to foster and reward excellence in acoustics and entries will be judged on demonstrated innovation from within any field of acoustics.

Any professional, student or layperson involved, or interested in, any area within the field of acoustics, with a body of work no older than 3 years, is eligible and encouraged to enter.

The winner will be presented with a trophy and a gift to the value of $2,500 and the runner up will receive a certificate and gift to the value of $500.

The award will be presented at the Annual Conference of the Australian Acoustical Society in November 2006.

Details for the submissions are available from www.acoustics.asn.au and are due by 30 July 2006.

MITOCHONDRIA, CELL DEATH, AND DEAFNESS: WILL IT BE POSSIBLE TO PREVENT PRESBYACUSIS?

James O. Pickles
Vision, Touch and Hearing Research Centre
School of Biomedical Sciences, University of Queensland
St. Lucia, 4072 Queensland, Australia.

Mitochondria are energy-producing structures within cells, using oxidation to produce the energy-rich compound ATP (adenosine triphosphate) which drives the cell's energy-consuming reactions. Mitochondria are also triggers of programmed cell death, called apoptosis. These two important aspects of cell function are linked: when energy production by the mitochondria fails, a set of biochemical reactions are initiated which lead to destruction of the cell. Some cells types are particularly vulnerable, including certain cells of the inner ear (e.g. outer hair cells and cells of the stria vascularis), leading to sensorineural deafness. It is argued here that this response may be an evolutionary maladaptation, that cell death may be sometimes be triggered unnecessarily, and therefore that some forms of sensorineural hearing loss such as that arising in old age might be preventable.

1. INTRODUCTION: MITOCHONDRIA, ENERGY AND CELL DEATH

Much of the hearing loss that occurs in old age, i.e. presbyacusis, is likely to be due to the long-term deterioration of the mitochondria in the cells of the cochlea.

Mitochondria are the main energy-producing structures of cells. In order to couple as much energy as possible for the production of ATP, high energy electrons, originally from the oxidation of glucose, are transferred to oxygen through a set of enzymes called the electron transport chain, where their energy level changes in many small steps so little energy is lost in heat, and where the energy made available at each step is coupled to pump protons into an intermembranous space within the mitochondria. In this way, the energy from each stage is summed. The resulting high concentration of protons gives rise to what is known as the mitochondrial potential, and is used to drive the production of ATP. The arrangement is thermodynamically very efficient. However because there are only small drops in energy level at each stage in the electron transport chain, electrons tend to be diverted out of the chain, where they can react with oxygen to make the highly reactive and damaging reactive oxygen species (ROS). Overproduction of ROS can among other actions damage the proteins and lipids of the mitochondria, interfering with the stages of the electron transport chain, and then induce further production of ROS, in a vicious cycle of damage.

Damaged mitochondria are a source of danger not only to themselves, but to the rest of the cell, because the highly reactive ROS are released generally into the cell body. There appears, however, to be a valuable evolutionary adaptation in that highly damaged mitochondria are degraded and removed from the cell. Once mitochondria are not functioning properly, the mitochondrial potential falls. As a result, a structure known as the permeability transition pore opens in the mitochondrial inner membrane. The pore is permeable to low molecular mass solutes which upset the osmotic balance of the inner and outer membranes of the mitochondrion, causing water to enter the mitochondrial matrix (central space). This then swells, which breaks the outer mitochondrial membrane, and leads to destruction of the mitochondrion. In this way, mitochondria that produce excessive ROS are removed from the cell (a process described as 'mitoptosis' by Skulachev [1]). This is undoubtedly a valuable adaptation in preserving the integrity of the cell. Given that there are a large number of mitochondria per cell (tens to thousands), other mitochondria will be available to replace those lost as a result of the mitoptosis, and there is evidence that if energy production becomes inadequate, the other mitochondria within the cell will be triggered to divide and increase in number.

The suicide of individual mitochondria, which preserves the integrity of the host cell, is also continued to the next level of organization. When mitochondria break open, they release apoptotic (cell-death) substances into the cell's cytoplasm (i.e. into the cell's interior). Destruction of only a few mitochondria will be insufficient to trigger the cell death pathway, but if larger numbers are destroyed the apoptotic substances accumulate to a sufficient level to trigger the programmed, systematic, destruction of the cell and its contents. In this way, if a cell has many sick mitochondria, the whole cell will be removed from the organism. Put in an alternative way, the whole cell now commits suicide and therefore the sick cell is unable to cause further damage to the organism [1].

2. MITOCHONDRIAL INTEGRITY

This process of self-sacrifice of the lowliest individuals in a colony (or organism) to preserve the life of the colony as a whole may work well at some levels of organization, but when applied to a whole human being has some negative consequences. If the damaged elements can be replaced without penalty, then these consequences may be avoided; however, at both the mitochondrial and cellular levels, replacement has problems. Mitochondria, like the bacteria from which they evolved, contain their own separate genetic system, and reproduce by dividing. The mitochondrial genome is copied

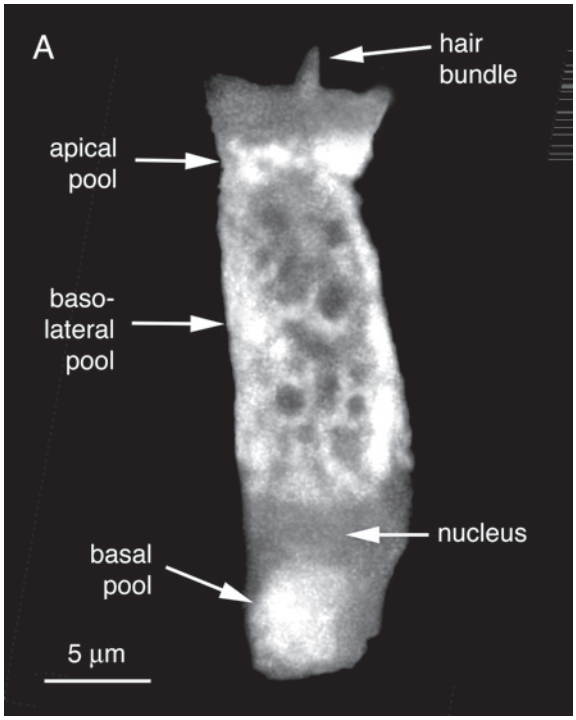


Figure 1. A. Functionally active mitochondria in a single outer hair cell of the guinea pig cochlea. The hair cell was stained with Mitotracker Red, a dye that is taken up by mitochondria with a normal mitochondrial potential. The active mitochondria are stained more intensely, against a less bright background stain, which allows the cell outline to be visible. Three pools of mitochondria are visible: (1) a pool just below the apical surface of the hair cell, (2) a pool around the basolateral walls of the hair cell, and (3) a pool just below the nucleus. The basolateral pool has a meshwork appearance. The image was reconstructed from multiple confocal images obtained at different depths in the specimen. For clarity, background signal unrelated to the cell was deleted in an image processing program.

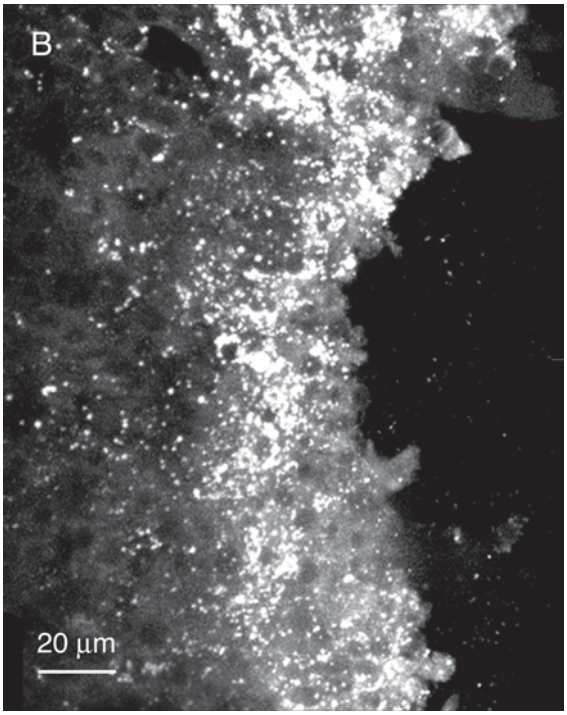


Figure 1. B. Active mitochondria in the stria vascularis of the mouse cochlea, shown by Mitotracker Red staining. The stria is the metabolically highly active secretory membrane that produces the endocochlear potential and secretes endolymph, which together provide energy for cochlear function. In this view, the stria is seen *en face*. Active mitochondria are brightly stained, against a lower level of background staining. The active mitochondria are scattered throughout the stria, but are found mainly in a thin layer in depth, corresponding to the basal ends of the marginal cells which contain many of the secretory enzymes. The mitochondria tend to be clustered around the cells' nuclei, which are non staining. Note difference in scale from Part A.

with each mitochondrial division. If a mitochondrion's DNA is mutated, then the daughter mitochondria will inherit the mutated DNA. If the DNA is only so slightly mutated that cell function is not normally compromised, then the mutated DNA can spread and populate many of the cell's mitochondria, to only reveal its effects when the cell is put under other, e.g. metabolic, stressors. Furthermore, if the trigger for reproduction in the cell is especially frequent because other, dysfunctional, mitochondria in the cell also contain mutated DNA, the mutated DNA will tend to be reproduced to a greater extent than in more normal cells. In other words, if the mutation is not so severe as to cause immediate mitoptosis of all damaged mitochondria, there is a danger that mutated DNA will come to dominate overall.

Preserving the integrity of mitochondrial DNA is a challenge for the organism. The approach inherited from bacteria, of jettisoning organelles with the damaged DNA, can have, as pointed out in the last paragraph, some negative consequences. Another approach inherited from bacteria is to have a safety factor by having many copies of the genome per mitochondrion, as against only two for eukaryotic cells (i.e. cells with nuclei). In addition, mitochondria have some DNA repair enzymes, although limited in function compared with the repair enzymes for the cells' main nuclear genomic DNA [2]. The enzyme that copies mitochondrial DNA, mitochondrial polymerase-A (pol-A) has some error-correction capability, although with a relatively high error rate compared with the corresponding enzyme for the cells' nuclear DNA [3]. While oxidative damage to mitochondrial DNA can be efficiently removed in vivo [2], other types of damage, such as the more complex of the nucleotide modifications, may be much less efficiently removed than with repair of nuclear DNA. The repair of mutated mitochondrial DNA is also dependent on the state of the cell: it is less efficient in cells with a low mitochondrial potential, but since these cells are also more likely to enter apoptosis, the result is that although their mitochondrial DNA is not error-corrected, it is also more likely to become excluded from the organism [4].

In spite of its disadvantages, preserving the integrity of mitochondrial DNA by killing cells that contain increased amounts of mutated mitochondrial DNA seems to work where the cells can be replaced afterwards. The removal of

mutated mitochondrial DNA from tissues that are renewed by mitosis (i.e. the production of new cells by cell division) may explain why inherited mutant loads have usually been found to *decrease* with age in renewable tissues such as epithelial cells and blood [5]. The removal of cells can therefore be advantageous if damaged cells are replaced by mitosis, and the mechanism is possibly an adaptation that has for this reason been favoured by evolution.

However, in some organs the cells cannot be renewed; in these cases the cells are entirely "postmitotic" – i.e. cannot undergo further rounds of cell division. Organs where the main cell types are postmitotic include neurones as in the brain, muscle cells, and many cells types of the inner ear. Here, the adaptation is definitely non-advantageous, and mitochondrially-induced apoptosis can eventually compromise the function of first the whole organ, and, in some cases, the entire organism. In terms of hearing, a consequence is the hearing loss of old age, or presbyacusis.

3. MITOCHONDRIA AND HEARING LOSS

What is the evidence that some at least of cochlear hearing loss is mitochondrially-induced? Evidence comes from two main sources:

1. Mitochondrial defects tend to affect cell types that are postmitotic, that have high energy requirements dependent on oxidative phosphorylation, and that are often heavily involved in ion pumping. Such cells in the ear are neurones of the spiral ganglion, the hair cells, and the cells of the stria vascularis. The latter cells provide the endocochlear potential, which is the battery that drives cochlear function. These are the cell types that degenerate first in many types of hearing loss.

2. Inherited mitochondrial diseases commonly first appear in the ear, brain, muscle, the eye, and kidney, and where there are known mitochondrial encephalomyopathies there is a high chance (42%) of associated hearing defects [6]. Inherited mitochondrial diseases usually occurs where mutated mitochondrial DNA is inherited from the mother (it is only from the mother, because all the mitochondria in the embryo come from the ovum; sperm contain no, or very few, mitochondria). The mutations may not be so severe so that the organism becomes non-viable and dies early in life; the mutated mitochondrial DNA comes to populates all or many cells in the organism, and shows its effects only later in life or when the organism is stressed. Many of these diseases show themselves in syndromes, where multiple organ types are affected: organs commonly involved are those with cells that are postmitotic, and have high energy requirements. Deafness is commonly a consequence [7 – 11], with degeneration particularly in the stria vascularis, spiral ganglion, and organ of Corti [9, 11].

Outer hair cells, which contain high levels of mitochondria, are among the first to degenerate in the inner ear. Why are these cells so vulnerable to energy disruption? It is not certain. A major function of outer hair cells is their active motile process, which generates the high sensitivity and sharp frequency tuning of the cochlea. However, the active process is thought to derive its energy from the ionic concentration and electrical potential of the endocochlear space (i.e. of the scala media) rather than from the outer hair cells themselves [12]. Outer hair cells are likely to have minimal neurotransmitter production and synaptic activation, since the type II afferent fibres which make synaptic connections with them have small, sparse synapses, and, as far as current information goes, do not generate a high rate of action potentials [13]. In contrast, in neurones, the energy requirements of synaptic activity are likely to be a major contributor to oxidative stress [14]. Mechanotransduction is another possible energy demand. However, the mechanotransducer current is mainly carried by K^+, which flows passively through the cell down its electrochemical gradient between scala media and scala tympani, and therefore should not make energetic demands on the cell [15]. Significant demand may be made by Ca^{2+}, which also enters through the mechanotransducer channels [48], and which is very far from its electrochemical equilibrium within the cell, and which therefore needs to be actively removed. The high concentration of mitochondria around the basolateral walls of the outer hair cells (Fig. 1A), through which the Ca^{2+} would have to be removed, suggests that this indeed is the major site of energy demand. However, there is no definitive evidence on this point.

The stria vascularis is a second important site for sensorineural hearing loss [50]. Cells such as the marginal cells and basal cells, which are heavily involved in ion pumping and which have a high concentration of mitochondria and a high energy consumption, become unable to generate the endocochlear potential. The latter forms the battery that drives the operation of the hair cells and the organ of Corti, and when the endocochlear potential falls, hearing loss is a consequence.

Reactive oxygen species (ROS) are responsible for some types of cochlear damage, with mitochondria and mitochondrial DNA among their possible targets. Knockout of an antioxidant enzyme called Gpx-1, which results in enhanced levels of ROS in tissues, elevates auditory thresholds and increases the susceptibility to acoustic trauma [16]. ROS induced by the application of paraquat to the inner ear causes hearing loss and loss of hair cells [49]. ROS is involved in some forms of ototoxicity: production of ROS in the cochlea is enhanced by both aminoglycoside antibiotics and by cisplatin, while anti-oxidants can provide some protection [e.g. 18 - 22]. The mitochondrial transition pore is involved in the apoptosis after aminoglycoside ototoxicity, since blocking the pore with cyclosporin A partially protects against the ototoxicity in culture [23]. Acoustic overstimulation causes oxidative damage to total cochlear DNA [17], while oxidative damage caused by knockout of the antoxidant enzyme SOD-1, produces deletions in mitochondrial DNA from whole cochleae [24]. Under the hypothesis presented here, the ROS-induced damage to the mitochondria causes a loss of efficiency of electron transport, so that still more ROS are produced, setting off the vicious cycle of degradation.

4. PROTECTION FROM HEARING LOSS INHIBITION OF THE CELL DEATH PATHWAYS

Loss of hair cells is a common result of ageing, acoustic trauma and ototoxicity, with apoptosis (otherwise known as programmed cell death) included as a mechanism [e.g. 25 - 27]. Proteins known as the caspases act as biochemical signals within cell death pathways; however, in the presence of caspase inhibitors, hair cells can survive doses of aminoglycosides or cisplatin that would otherwise be lethal [28 - 30]. Moreover, if members of another family of proteins called Bcl-2 are overexpressed, cell death is inhibited, and hair cells will survive an ototoxic insult that would otherwise be lethal to them [31]. This shows that in normal cells, i.e. those unprotected by the overexpressed Bcl-2, mitochondrially-triggered cell death occurs, although the cells otherwise might be capable of surviving the insult. The results suggest that apoptosis after insult may be an evolutionary adaptation which in the postmitotic cells of the cochlea, is not always necessary. It also suggests that were it possible to inhibit the cell death pathways, cells of the inner ear might survive and remain functional, where they otherwise might have degenerated.

One biochemical factor that may be involved in protecting hair cells, possibly by modulating the cell death pathways, is the heat shock protein Hsp70. This factor is induced in the cochlea by a wide variety of stresses including noise, hyperthermia and ototoxic drugs [34]. When Hsp70 is induced, there is protection from a subsequent noise that would normally cause a permanent hearing loss, and partial protection from ototoxic drugs [35, 36]. The same factors that induce Hsp70 also increase the level of a growth factor called glial cell line-derived neurotrophic factor (GDNF) in the cochlea. Moreover, GDNF, when applied to the cochlea, helps to protect the inner ear from acoustic trauma and ototoxicity, and in this it has similar effects to other diffusible growth factors such as neurotrophin-3 (NT-3) and the transforming growth factors TFG-α and TGF-β [37 – 39]. These growth factors may have direct effects on the cell death pathways and so promote cellular survival under stress [e.g. 40]. These latter results suggest that in the absence of such factors, the apoptosis that occurs after an insult may be an evolutionary adaptation which in the postmitotic cells of the cochlea, is not always necessary or indeed advantageous.

The arguments that apply to acoustic trauma or ototoxic damage also apply to ageing. One common change commonly found in ageing, and which is easy to detect, is what is known as the 'common ageing deletion'. It is a deletion of 4,977 base pairs from the mitochondrial genome that occurs as a result of anomalous annealing of the mitochondrial DNA during replication of the genome. Bai et al. [41] found that 14 out of 17 patients with presbyacusis had detectable levels of the 4,977-bp deletion in their cochlear tissues post mortem, but that the deletion was present in only 1 of 17 patients with normal audiograms. The 4,977-bp deletion was more common in the lymphocytes of patients with presbyacusis than in normal controls, and patients with higher degrees of hearing loss had a greater detection rate for the deletion [42]. This mutation is clearly associated with hearing loss, as shown in the unusual case of a family with inherited 4,977-bp mutations measurable in lymphocyte mtDNA. Even young members of this family could have profound hearing losses [43]. Sporadic mutations that arise randomly and are not inherited are also likely to contribute, being found at much higher rates - up to 14% in one case - in the spiral ganglion and membranous labyrinth of patients with presbyacusis than in normal controls [44].

Ageing may result in the production of increasing amounts of ROS as the mitochondria get progressively more damaged. Oxidative damage to the cochlea can be reduced by mitochondrial metabolites such as α-lipoic acid or acetyl-l-carnitine, both of which facilitate mitochondrial function. In a small-scale study, both compounds abolished further age-related hearing losses in aged Fisher rats, and reduced the amount of common-ageing deleted mitochondrial DNA extracted from stria vascularis and auditory nerve [45]. In a further small study, anti-oxidants were also found to reduce age-related hearing losses and mutations in mitochondrial DNA in rats, although dietary restriction had the most beneficial effect of all the treatments tried [46]. It is a common finding that basal hair cells are more vulnerable to ageing and to many insults than are apical hair cells, at least in part because they are more susceptible to ROS, associated with their lower levels of anti-oxidant protection [47].

5. CONCLUSION

Cells of the inner ear, like other cells, are vulnerable to disruption of their mitochondria. Some of the mechanisms that the body has evolved to protect itself against damaged mitochondria, many of which reflect the bacterial origin of mitochondria, have negative consequences. These include the programmed death of the vulnerable cells of the inner ear, leading to hearing loss. However, there is evidence that cells can otherwise survive the levels of damage at which the programmed cell death pathway normally kicks in. If this pathway can be inhibited in cells of the inner ear, there is the possibility that some of the most currently intractable forms of hearing loss, such as sensorineural hearing loss arising in old age, can be slowed or prevented.

ACKNOWLEDGEMENT

This work was supported by the Garnett Passe and Rodney Williams Memorial Foundation.

REFERENCES

1. Skulachev, V.P. "Mitochondria in the programmed death phenomena; A principle of biology: 'It is better to die than to be wrong'" *IUBMB Life* **49,** 365 - 373 (2000)
2. Shadel, G.S. and Clayton, D.A. "Mitochondrial DNA maintenance in vertebrates" Ann. Rev. Biochem. **66,** 409 - 435 (1997)
3. Kunkel, T.A. and Loeb, L.A. "Fidelity of mammalian DNA polymerases" *Science* **213,** 765 – 767 (1997).
4. Santos, J.H., Hunakova, L., Chen, Y., Bortner, C. and van Houten, B. "Cell sorting experiments link persistent mitochondrial DNA damage with loss of mitochondrial membrane potential and apoptotic cell death" J. Biol. Chem. **278,** 1728 - 1734. (2003)

5. Olsson, C., Johnsen, E., Nilsson, M., Wilander, E., Syvanen, A.C. and Lagerstrom-Fermer, M. "The level of the mitochondrial mutation A3243G decreases upon ageing in epithelial cells from individuals with diabetes and deafness" *Eur. J. Hum. Genet*. **9,** 917 – 921 (2003)
6. Zwirner, P. and Wilichowski, E. "Progressive sensorineural hearing loss in children with mitochondrial encephalomyopathies" *Laryngoscope* **111,** 515 - 521 (2001)
7. Prezant, T.R., Agapian, J.V., Bohlman, M.C., Bu, X., Oztas, S., Qiu, W.Q., Arnos, K.S., Cortopassi, G.A., Jaber, L., Rotter, J.I., et al. "Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness" *Nat. Genet*. **4,** 289 - 294 (1993)
8. Hutchin, T., Haworth, I., Higashi, K., Fischel-Ghodsian, N., Stoneking, M., Saha, N., Arnos, C. and Cortopassi, G., "A molecular basis for human hypersensitivity to aminoglycoside antibiotics" *Nucleic Acids Res.* **21,** 4174 - 4179 (1993).
9. Sue, C.M., Lipsett, L.J., Crimmins, D.S., Tsang, C.S., Boyages, S.C., Presgrave, C.M., Gibson, W.P., Byrne, E. and Morris, J.G., "Cochlear origin of hearing loss in MELAS syndrome" *Ann. Neurol.* **43,** 350 - 359 (1998)
10. Fischel-Ghodsian, N. "Mitochondrial RNA processing and translation: Link between mitochondrial mutations and hearing loss?" *Mol. Genet. Metab.* **65,** 97 - 104 (1998)
11. Nadol, J.B. Jr. and Merchant, S.N. "Histopathology and molecular genetics of hearing loss in the human" *Int. J. Pediatr. Otorhinolaryngol.* **61,** 1 - 15 (2001).
12. Ashmore, J. "Biophysics of the cochlea - Biomechanics and ion channelopathies" Brit. Med. Bull. **63,** 59 - 72 (2002)
13. Robertson, D. "Horseradish peroxidase injection of physiologically characterised afferent and efferent neurones in the guinea pig spiral ganglion" *Hear. Res*. **15,** 113 - 121 (1984)
14. Mattson, M.P. and Liu, D. "Energetics and oxidative stress in synaptic plasticity and neurodegenerative disorders" *Neuromolecular Med.* **2,** 215 - 231 (2002)
15. Pickles, J.O., *An Introduction to the Physiology of Hearing*, London, Academic Press, London (1988)
16. Ohlemiller, K.K., McFadden, S.L., Ding, D.L, Lear, P.M. and Ho, Y.S, "Targeted mutation of the gene for cellular glutathione peroxidase (Gpx1) increases noise-induced hearing loss in mice" *J. Assoc. Res. Otolaryngol.* **1,** 243 - 354 (2000).
17. Van Campen, L.E., Murphy, W.J., Franks, J.R., Mathias, P.I. and Toraason, M.A., "Oxidative DNA damage is associated with intense noise exposure in the rat" *Hear. Res.* **164,** 29 - 38 (2002)
18. Kopke, R.D., Liu, W., Gabaizadeh, R., Jacono, A., Feghali, J., Spray, D., Garcia, P., Steinman, H., Malgrange, B., Ruben, R.J., Rybak, L. and Van de Water, T.R., "Use of organotypic cultures of Corti's organ to study the protective effects of antioxidant molecules on cisplatin-induced damage of auditory hair cells" *Am. J. Otol.* **18,** 559 - 571 (1997)
19. Lopez-Gonzalez, M.A., Delgado, F. and Lucas, M., "Aminoglycosides activate oxygen metabolites production in the cochlea of mature and developing rats" *Hear. Res.* **136,** 165 - 168 (1999)
20. Lopez-Gonzalez, M.A., Guerrero, J.M., Torronteras, R,, Osuna, C. and Delgado, F., "Ototoxicity caused by aminoglycosides is ameliorated by melatonin without interfering with the antibiotic capacity of the drugs" *J. Pineal Res.* **28,** 26 - 33 (2000)
21. Sha, S.H. and Schacht, J., "Antioxidants attenuate gentamicin-induced free radical formation in vitro and ototoxicity in vivo: D-Methionine is a potential protectant" *Hear. Res.* **142,** 34 - 40 (1999)
22. Sha, S.H., Taylor, R., Forge, A. and Schacht, J., "Differential vulnerability of basal and apical hair cells is based on intrinsic susceptibility to free radicals" *Hear. Res.* **155,** 1 - 8 (2000)
23. Dehne, N., Rauen, U., de Groot, H. and Lautermann, J., "Involvement of the mitochondrial permeability transition in gentamicin ototoxicity" *Hear. Res.* **169,** 47 - 55 (2002)
24. Zhang, X., Han, D., Ding, D., Dai, P., Yang, W., Jiang, S. and Salvi, R.J., "Deletions are easily detectable in cochlear mitochondrial DNA of Cu/Zn superoxide dismutase gene knockout mice" *Chin. Med. J.* **115,** 258 - 263 (2002)
25. Zheng, Y., Ikeda, K., Nakamura, M. and Takasaka, T., "Endonuclease cleavage of DNA in the aged cochlea of Mongolian gerbil" *Hear. Res.* **126,** 11 - 18 (1998)
26. Hu, B.H., Henderson, D. and Nicotera, T.M., "Involvement of apoptosis in progression of cochlear lesion following exposure to intense noise" *Hear. Res.* **166,** 62 - 71 (2002)
27. Nakagawa, T., Kim, T.S., Murai, N., Endo, T., Iguchi, F., Tateya, I., Yamamoto, N., Naito, Y. and Ito, J., "A novel technique for inducing local inner ear damage" *Hear. Res.* **176,** 122 - 127 (2003)
28. Forge, A. and Li, L., "Apoptotic death of hair cells in mammalian vestibular sensory epithelia" *Hear. Res.* **139,** 97 - 115 (2000)
29. Matsui, J.I., Ogilvie, J.M. and Warchol, M.E., "Inhibition of caspases prevents ototoxic and ongoing hair cell death" *J. Neurosci.* **22,** 1218 - 1227 (2002)
30. Wang, J., Ladrech, S., Pujol, R., Brabet, P., Van De Water, T.R. and Puel, J.L., "Caspase inhibitors, but not c-Jun NH2-terminal kinase inhibitor treatment, prevent cisplatin-induced hearing loss" *Cancer Res.* **64,** 9217 - 9224 (2004)
31. Cunningham, L.L., Matsui, J.I., Warchol, M.E. and Rubel, E.W, "Overexpression of Bcl-2 prevents neomycin-induced hair cell death and caspase-9 activation in the adult mouse utricle in vitro" *J. Neurobiol*. **60,** 89 - 100 (2004)
34. Altschuler, R.A., Fairfield, D., Cho, Y., Leonova, E., Benjamin, I.J., Miller, J.M. and Lomax, M.I., "Stress pathways in the rat cochlea and potential for protection from acquired deafness" *Audiol. Neurootol.* **7,** 152 - 156 (2002)
35. Mikuriya, T., Sugahara, K., Takemoto, T., Tanaka, K., Takeno, K., Shimogori, H., Nakai, A. and Yamashita, H., "Geranylgeranylacetone, a heat shock protein inducer, prevents acoustic injury in the guinea pig" *Brain Res.* **1065,** 107 - 114 (2005)
36. Takumida, M. and Anniko, M., "Heat shock protein 70 delays gentamicin-induced vestibular hair cell death" *Acta Otolaryngol.* **125,** 23 - 28 (2005)
37. Kawamoto, K., Yagi, M., Stover, T., Kanzaki, S. and Raphael, Y., "Hearing and hair cells are protected by adenoviral gene therapy with TGF-beta1 and GDNF" *Mol. Ther.* **7,** 484 - 492 (2003)
38. Bowers, W.J., Chen, X., Guo, H., Frisina, D.R., Federoff, H.J. and Frisina R,D., "Neurotrophin-3 transduction attenuates cisplatin spiral ganglion neuron ototoxicity in the cochlea" *Mol. Ther.* **6,** 12 - 18 (2002)
39. Chen, X., Frisina, R.D., Bowers, W.J., Frisina, D.R. and Federoff, H.J., "HSV amplicon-mediated neurotrophin-3 expression protects murine spiral ganglion neurons from cisplatin-induced damage" *Mol. Ther.* **3,** 958 - 963 (2001)
40. Subramaniam, S., Shahani, N., Strelau, J., Laliberte, C., Brandt, R., Kaplan, D. and Unsicker, K., "Insulin-like growth factor 1 inhibits extracellular signal-regulated kinase to promote neuronal survival via the phosphatidylinositol 3-kinase/protein kinase A/c-Raf pathway" *J Neurosci.* **25,** 2838 - 2852 (2005)
41. Bai, U., Seidman, M.D., Hinojosa, R. and Quirk, W.S., "Mitochondrial DNA deletions associated with aging and possibly presbycusis: A human archival temporal bone study" *Am. J. Otol.* **18,** 449 - 453 (1997)
42. Ueda, N., Oshima, T., Ikeda, K., Abe, K., Aoki, M. and Takasaka,

T., "Mitochondrial DNA deletion is a predisposing cause for sensorineural hearing loss" *Laryngoscope* **108,** 580 - 584 (1998)
43. Bai, U. and Seidman, M.D., "A specific mitochondrial DNA deletion (mtDNA4977) is identified in a pedigree of a family with hearing loss" *Hear. Res.* **154,** 73 - 80 (2001)
44. Fischel-Ghodsian, N., Bykhovskaya, Y, Taylor, K., Kahen, T., Cantor, R., Ehrenman, K., Smith, R. and Keithley, E., "Temporal bone analysis of patients with presbycusis reveals high frequency of mitochondrial mutations" *Hear. Res.* **110,** 147 - 154 (1997)
45. Seidman, M.D., Khan, M.J., Bai, U., Shirwany, N. and Quirk, W.S., "Biologic activity of mitochondrial metabolites on aging and age-related hearing loss" *Am. J. Otol.* **21,** 161-167 (2000)
46. Seidman, M.D., "Effects of dietary restriction and antioxidants on presbyacusis" *Laryngoscope* **110,** 727 - 738 (2000)
47. Sha, S.H., Taylor, R., Forge, A. and Schacht, J., "Differential vulnerability of basal and apical hair cells is based on intrinsic susceptibility to free radicals" *Hear. Res.* **155,** 1 - 8 (2001)
48. Ricci, A.J., Crawford, A.C. and Fettiplace, R., "Tonotopic variation in the conductance of the hair cell mechanotransducer channel" *Neuron* **40,** 983–990 (2003)
49. Bielefeld, E.C., Hu, B.H., Harris, K.C. and Henderson, D., "Damage and threshold shift resulting from cochlear exposure to paraquat-generated superoxide" *Hear. Res.* **207,** 35-42 (2005)
50. Spicer, S.S. and Schulte, B.A., "Pathologic changes of presbycusis begin in secondary processes and spread to primary processes of strial marginal cells" *Hear. Res.* **205,** 225-240 (2005)

FUNCTIONALITY OF COCHLEAR MICROMECHANICS – AS ELUCIDATED BY UPWARD SPREAD OF MASKING AND TWO TONE SUPPRESSION

D. Sen
School of Electrical Engineering,
The University of New South Wales,
Sydney-UNSW, NSW 2052, Australia.

J. B. Allen
Electrical & Computer Engineering,
University of Illinois at Urbana Champaign,
Urbana, IL 61801, USA.

The effect of increasing the level of a low frequency masker on higher frequency probes can be observed in three paradigms: psychophysically (termed Upward Spread of Masking or USM), mechanically on the basilar membrane (Basilar Membrane Two Tone Suppression or BM-2TS) as well as neuro-physiologically at the auditory neurons (Neural Two Tone Suppression or Neural-2TS). This paper reviews various experimental USM, Neural-2TS and BM-2TS data with the aim of shedding light into the underlying physiological mechanisms in the cochlea.

INTRODUCTION

It is generally accepted that the sharp tuning observed at the characteristic frequency (CF) auditory nerve fibre can be attributed to the sharp mechanical response at the corresponding position of the basilar membrane (at the Best Place - BP). This observation has resulted in attention being focused on the basilar membrane and away from other micromechanical structures in the cochlea. However, at regions away from the BP, there is considerable evidence to suggest that the basilar membrane and auditory nerve response diverge. This is especially the case at regions basal to the BP (termed the "tail region" of the spatial response – see Fig 5b for an example of the "tail region") and introduces possibility of other physiological structures, in addition to the basilar membrane, contributing to the auditory nerve response. While most recent basilar membrane mechanical data show an excellent match to Neural responses at the CF [14], there is a clear and often marked difference in the two responses at the tail. This discrepancy seems especially pronounced in cats, where the slope of neural response in the tail region is about 1 to 4 dB/octave whereas the slope of the basilar membrane response is about 9 dB/octave [15].

This paper reviews various experimental data that suggest that the Upward Spread of Masking (USM) effect is simply a psychophysical observation of what is also observed at the auditory nerve as Neural-2TS. This is a satisfying result as it indicates that there is little difference between what is perceived and the auditory nerve response. Similarly, if the Basilar Membrane Two Tone Suppression (BM-2TS) data were to match Neural-2TS just as exactly, this would indicate that the basilar membrane response is identical to the auditory nerve response and, by the same token, to what is perceived (USM). However, our review shows that there is discrepancy in the BM-2TS and Neural-2TS data which suggests influence of structures such as the tectorial membrane (TM), inner hair cells (IHC) and outer hair cells (OHC), collectively called micromechanical structures, that act to modify the basilar membrane response to what is observed at the auditory nerve.

The stimuli used in USM, Neural-2TS and BM-2TS is composed of two simultaneous tones of differing frequencies. While in the psychoacoustic USM literature the two tones are called "probe" and "masker", in the 2TS literature, the same stimuli are termed "CF tone" and "suppressor". In this paper, we will concentrate only on the case where the probe/CF tone is at least an octave above the masker/suppressor, placing it at the tail region of the masker (see Fig 5b) and thereby facilitating the study of characteristics at that region.

This paper will review each of the three phenomena, emphasizing their similarities, dissimilarities and the relevance of the experimental data in terms of cochlear neuro-physiology. The conclusion resulting from this phenomenological review is that micromechanical structures play a significant role and are indeed essential in explaining transduction from mechanical to auditory nerve response. Finally, we describe a simple model of the micromechanical structures which is able to account for the discrepancy between the auditory nerve and basilar membrane response at the "tail region".

UPWARD SPREAD OF MASKING (USM)

The effect of simultaneous masking is depicted in Fig 1a, where a 400 Hz masker "tone" is presented at a certain level and the corresponding level of a second "probe" at its threshold of perception is recorded. The triangular masking functions (as a function of frequency) are used to hide quantization noise below the threshold of perceptibility in "MP3" compression systems. An important characteristic of simultaneous masking is that as the level of the masker is increased, the corresponding

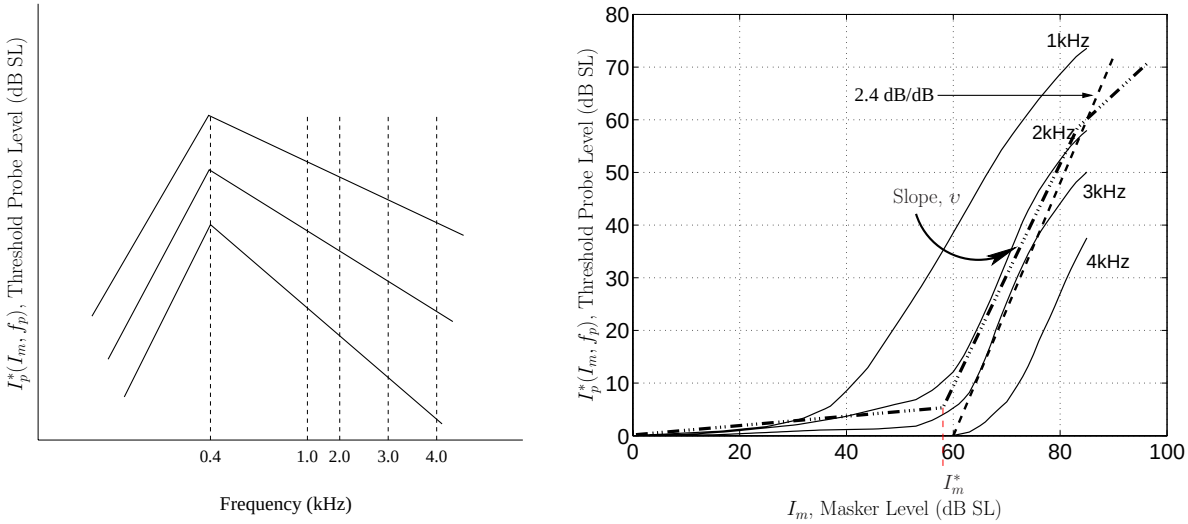


Figure 1. Upward Spread Masking. In (A), a cartoon depiction showing the effect of a 400 Hz tonal masker. For probe tones that have frequencies greater than the masker frequency (e.g. The 1, 2 and 3 kHz probes), the level increment required to keep the probe at its threshold of perception is greater than a proportional increase in the level of the masker. In (B) the same effect is quantified in experimental data [2] by plotting the threshold probe level versus masker level. The figure clearly shows that the probes need to be increased at a higher than proportional rate of the masker. The probes are at 1, 2, 3 and 4 kHz. The dashed line shows the maximum slope of 3 kHz probe to be about 2.4 dB/dB, meaning that every 1 dB increase in masker level will require the probe to be increased by 2.4 dB to keep it at the threshold of perception. For discussion purposes, we have modelled the effect using the dash-dot line. We will say the effect begins at masker level, I_m^*, and the strength of the effect is characterised by the slope, υ.

threshold level of a higher frequency probe tone needs to be increased more than the proportional increase in the masker level. This is clearly seen in Fig 1a for probes of 1, 2 and 3 kHz where the triangular masking curves seem to be spreading upwards – hence the term "upward spread of masking". The effect is also negligible when the probe is at a lower frequency than the masker. Fletcher [1] and Wegel & Lane [2] quantified the effect in the early 1920s. One such experimental result is shown in Fig 1b where the level of a 400 Hz masker is shown on the x-axis and the corresponding level of the probe at threshold is shown on the y-axis. The experimental results which have been verified in recent years [3] show that as the level of the masker is increased beyond 60-70 dB SPL, the higher frequency probes need to be increased by as much as 2.4 dB for every 1 dB increase in the masker (see Fig. 1B). Interestingly, this non-linear effect is difficult to make use of in typical music compression systems as the encoder typically has no indication of the volume set by the listener.

As indicated in Fig 1B, we will use two parameters to facilitate discussion of the USM effect: υ and I_m^*. The first parameter, υ, is the slope of the masking as a function of masker level, also known as the Growth of Masking (GOM). The parameter, υ, thus describes the "strength" of the masking. The * on the second parameter, I_m, indicates that the masker intensity is at the threshold level or the lowest level of the masker which causes masking of the probe. As such, I_m^* is a function of the masker frequency, f_m, and probe frequency, f_p. When the probe tone is thus at least an octave higher than the masker tone, (i.e $f_p > 2f_m$), slope υ is at its highest at about 2 to 3 dB/dB [3,4]. Similarly, I_m^*, can be estimated to be between 55-65 dB SPL in those same studies.

NEURAL TWO TONE SUPRESSION

Neural-2TS [5, 6] is the effect where the neural discharge rate of a CF auditory nerve fibre (hereafter termed probe neuron) is observed to reduce during the presence of a suppressing tone of different frequency (see Fig 2A). The CF tone is typically introduced at 6 to 10 dB above threshold. The ability of the suppressor tone to reduce the discharge rate of the probe neuron depends mainly on the suppressing tone's intensity and on its frequency relative to the CF. The curves in Fig 2A are clearly similar to the curves in Fig 1B once we account for the fact that, in USM, we need to increase the probe to account for its underlying suppression, while in Neural-2TS we are not attempting to raise the CF tone at all but just witnessing its suppression.

An interesting characteristic of Neural-2TS is shown in Fig 3A where the dotted line shows a normal threshold tuning curve. The three straight line curves represent the presence of a CF tone (at three different levels) and the corresponding level required by secondary tones (across the frequency range) to increase the discharge rate. The three open circles represent levels required by a suppressor tone to reduce the discharge rate back to threshold discharge rates when the CF tone is present at the three different levels. The three circles are clearly at or below the threshold levels required to excite the CF neuron – meaning that even though the three tones are individually unable to excite the CF-neuron, they are able to suppress the discharge rate of the CF/Probe tone. This means the suppressor is non-excitatory but suppressive at the CF neuron.

Suppression is most effective when the suppressor frequency is lower than CF, and we shall thus concentrate on

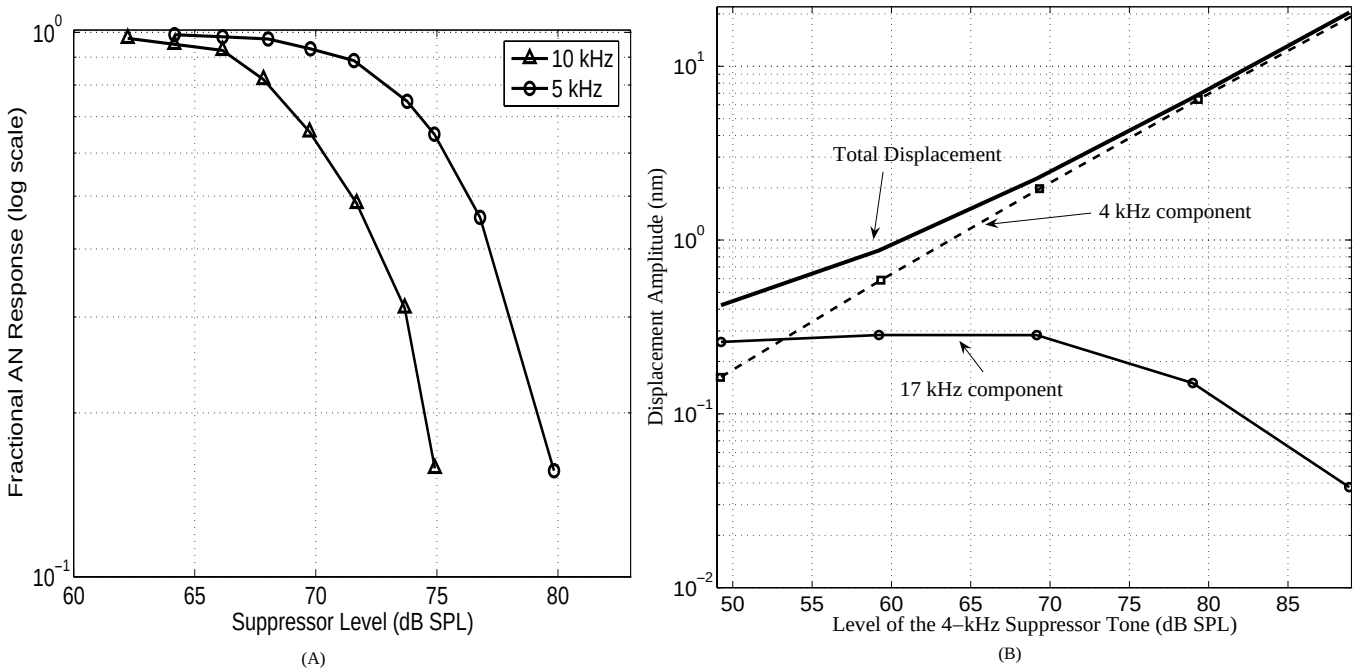


Figure 2: 2TS characteristics as a function of suppressor level. (A) Neural-2TS data from [5] showing average discharge rate from a single auditory nerve fibre with a characteristic frequency (CF) of 17.8 kHz as a function of suppressor level. The data is normalized by the discharge rate of the neuron when no suppressor is present. (B) BM-2TS data from Geisler [8]. Here the probe is at 17 kHz while the suppressor is at 4 kHz. The total response shown by the straight line actually increases with increasing suppressor level. However, when the 17 kHz component is extracted, it clearly reduces as a function of suppressor level.

the case when the suppressor frequency is at least an octave lower than the probe CF. This constraint is in essence identical to the constraint we placed on our USM of $f_p > 2f_m$, if we identify the CF tone frequency with f_p and the suppressor frequency with f_m.

Using the above analogy, we can compare I_m^* of the USM effect with suppressor threshold or the minimum level of the suppressor required to reduce the discharge rate of the CF neuron. This has been studied extensively by Fahey & Allen [7] and shown to be 65 dB SPL (± 5 dB) above 1 kHz. This is strikingly similar to the USM threshold, I_m^*, discussed in the previous section. Further, the Rate of Suppression (RoS), which is the slope of the auditory nerve discharge rate as a function of suppressor level, has been studied extensively [3,6] and found to be a maximum of 2.4 dB/dB. The RoS can be directly compared with USM's GOM or υ.

These similarities inevitably lead to the conclusion that USM and Neural-2TS are closely related and are possibly the same phenomena just observed psychophysically (in the case of USM) or in neural discharge rate measurements (in the case of Neural-2TS). This conclusion is given further credence when one also observes that, for both phenomena, the maximum effect occurs when the suppressor/masker frequency is below that of the probe/CF tone frequency.

BASILAR MEMBRANE TWO TONE SUPPRESSION (BM-2TS)

2TS is observed mechanically on the basilar membrane (BM-2TS). This is clearly seen in Fig 2B where the stimulus consists of a 17 kHz probe/CF tone along with a 4 kHz masker/suppressor tone. While the total RMS motion of the basilar membrane at the BP of the 17 kHz increases with increasing suppressor level, the 17 kHz component of the motion is seen to reduce. Quantitatively, this is dramatically different from Neural-2TS, where the total discharge rate is typically reduced when a suppressor tone is present simultaneously.

Most recent studies [8, 9] of BM-2TS have found the Rate of Suppression (RoS) to be about 1 dB/dB. In a study by Ruggero [10], the maximum RoS was found to be approximately 1.42 dB/dB (measured using iso-velocity analysis). There is thus a very large discrepancy in RoS between the BM-2TS and Neural-2TS (1 vs. 2.4 dB/dB). The difference between a 1 and 2.4 dB/dB suppression amounts to 10 dB and 24 dB of suppression for a 10 dB change in suppressor level (more than a factor of 4 deviation for every factor of 3 change in level).

The masker threshold, I_m^*, in USM plays a similar role to the suppressor threshold (lowest suppressor level that causes suppression at the CF or BP). While both USM and Neural-2TS is characterised by I_m^* of about 55-65 dB SPL, in BM-2TS, the suppressor must be more than 80 dB SPL before it suppresses the probe tone [8,9]. It is interesting to note that both the USM and the Neural-2TS effects are almost over when the masker/suppressor level is about 80 dB SPL (see Fig 1B).

Figure 2B shows the results from a BM-2TS study [9] where the frequency of the probe tone is 26 kHz and the suppressors (represented by open symbols) are at about 3.5, 7.5 and 20 kHz. Again, just as in the Neural-2TS study (Figure 2A), the probe tone is placed at 3 different levels (filled symbols) and the open circles represent the levels of the suppressors required to suppress the basilar membrane motion. We clearly see from this study that the suppressor levels are almost 18 dB on average above the threshold levels required

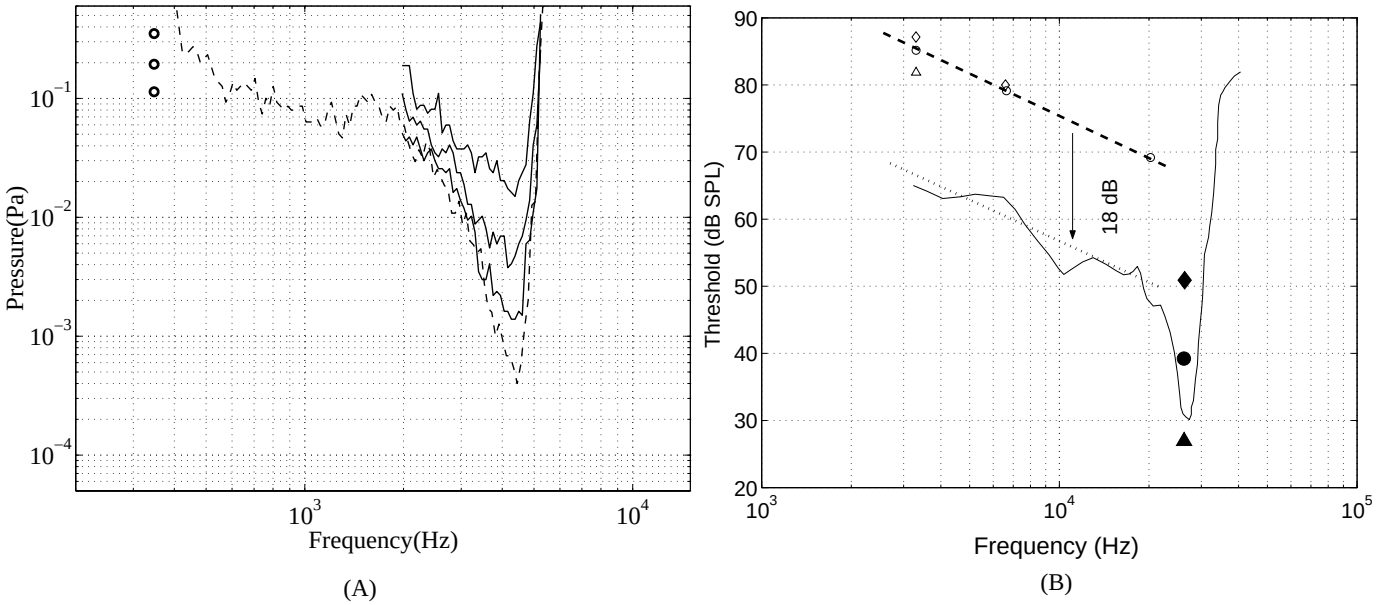


Figure 3. Two Tone Suppression characteristics as a function of frequency. (A) Neural 2TS data from [7]. The open circles show the level and frequency of the suppressor and the corresponding reduction in respond at the CF. The dotted line is for the case when there is no suppressor. Note that even though the suppressor tones excite the CF neurons (they are below the threshold tuning curve), they are able to suppress the CF tone. (B) Basilar membrane 2TS data from Cooper [9] (Figure 3D). The open symbols show the level and frequency of the suppressors required to suppress the tone near BF shown by filled symbols. The solid line show the levels of various tones required to evoke a constant amplitude (0.1 nm) vibration of the basilar membrane at the BP of the probe tone. Note that the low side suppressors are far above (approximately 18 dB) the levels required to produce threshold vibrations at the BP. The suppressor levels are also significantly higher than the minimum suppressor levels (around 65 dB SPL) required for Neural-2TS.

to produce the tuning curve given by the straight line. This is quite a sharp contrast from the suppressor levels in Neural-2TS which, as we discussed in the previous section, were actually below the tuning curve.

The discrepancies between BM-2TS and USM/Neural-2TS of (i) differences in suppressor threshold levels, (ii) differences in rate of suppression, and (iii) the fact that in neural-2TS unlike BM-2TS, the neural response is typically lower than the probe alone provides sufficient evidence to suggest that the two phenomena are quite different. Each of these pose a serious problem for theories which suggest that neural response is directly related to basilar membrane mechanics. The next section reviews existing models of 2TS as well as providing a plausible and elegant conceptual model that does not contradict modern views of cochlear mechanics and is yet able to resolve the discussed discrepancies.

MODELLING AND DISCUSSION

The prevailing explanation [8,13] for BM-2TS is that the nonlinear OHC response is saturated by the high level suppressor. Another explanation for BM-2TS is that it is an epiphenomenon of the half octave shift of the basilar membrane response (or "migration") towards the base as a function of intensity [11]. It can be imagined that, as the response moves towards the base with increasing level, the response at the BP decreases, giving the illusion of suppression. While both of these explanations model BM-2TS quite well, they are unable to explain the Neural-2TS and BM-2TS discrepancies discussed in the previous sections. However, if we accept that BM-2TS and Neural-2TS are inherently different, then either of the above explanations suffices and all that is required is: (i) an explanation for Neural-2TS and (ii) why an increasing basilar membrane response at the BP (when both the suppressor and CF tone is present – see Fig. 2B) is not reflected by an increasing discharge rate at the CF auditory neuron (which actually decreases).

Towards a solution to the second problem (ii) above, we suggest that the basilar membrane response is modified in its transduction path to the auditory nerve fibres [9]. The transduction path depicted in Fig 4, clearly shows that there is ample scope for the micromechanics (TM, Cilia, OHCs, IHCs) to modify the basilar membrane response. If the modification is of a high-pass nature, it will act to attenuate the basilar membrane response only in the area basal to the CF providing the required solution to the problem while not contradicting the prevailing view that basilar membrane and auditory nerve tuning at the CF are identical.

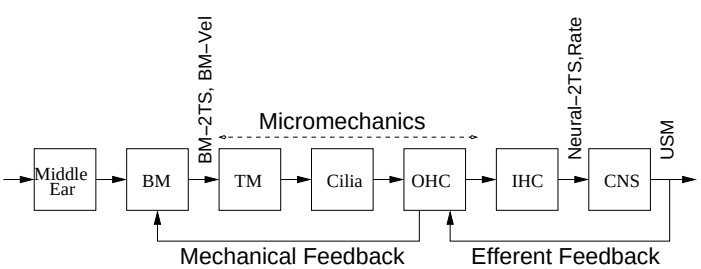


Figure 4. A block diagram depicting the transduction path in auditory physiology. This also is a block diagram for the computational model in the paper.

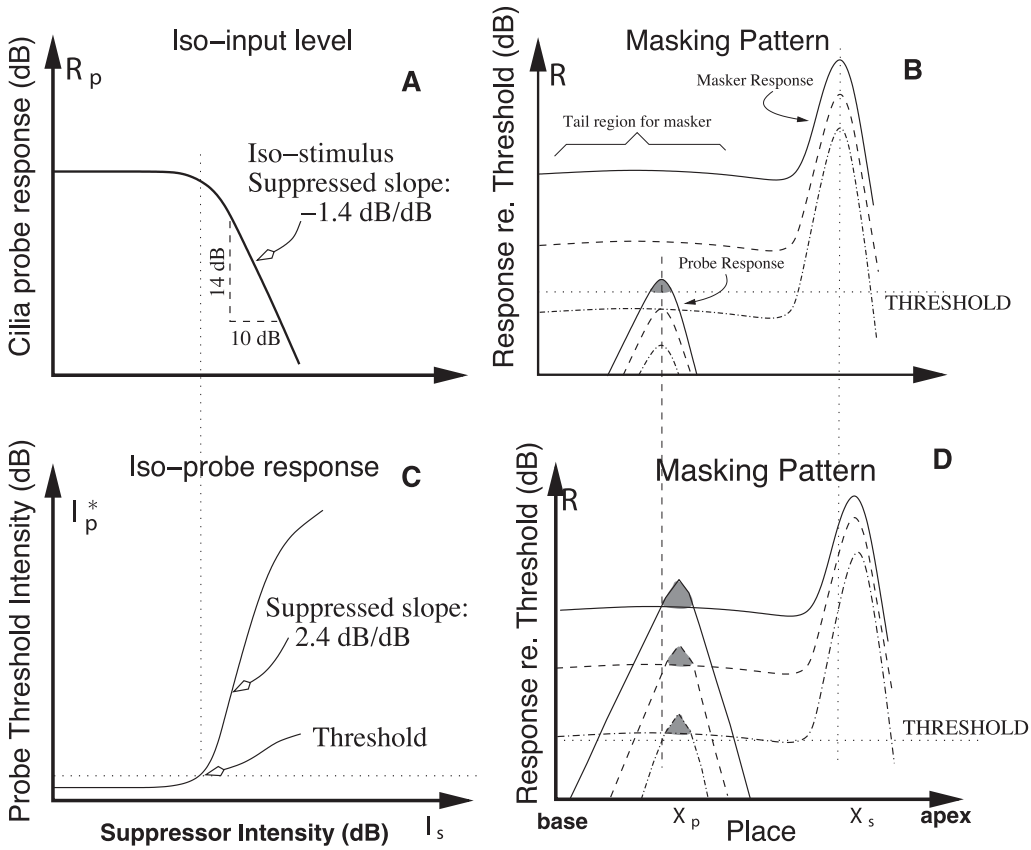


Figure 5. A cartoon explaining the physiological mechanism for USM and 2TS.

Another related observation in Neural-2TS, that requires explanation, is that low level suppressors while non-excitatory at the CF, are able to suppress the CF probe. This can be explained if we assume that OHCs are slightly more sensitive than IHCs. In this case, the OHCs will initiate the suppression even though the IHC neurons will not respond at the threshold of suppression, as observed.

Finally, we need an explanation of Neural-2TS (or USM). This is done phenomenologically in Fig 5. In Fig. 5A, we assume that the masker's tail response is able to suppress the probe at a rate of up to 1.4 dB/dB (Fig. 5A). The tail response is known to increase linearly with level, as shown in Figure 5B. In the USM experimental paradigm, the probe is required to overcome the effect of its suppression as well as the linear growth of the tail. This is shown in Fig 5D. In order for it to overcome both these effects, it has to be increased at a rate of (as much as) 1.4 + 1=2.4 dB/dB as shown. This will then agree with the experimental observation of a maximum 2.4 dB/dB GOM in USM. In USM, asking the subject to increase the probe tone such that it is just perceivable is the psychophysical equivalent of iso-discharge rate of the nerve fibres at the CF of the probe. Neural-2TS observations, which use iso-rate measurements to calculate the growth of suppression [6], also display this maximum rate of growth of about 2.4 dB/dB. The conclusion from this phenomenological model is that the underlying physiological suppression producing both Neural-2TS and USM must be at a rate of 1.4 dB/dB (or 1 dB/dB lower than the iso-response observation).

To test the above hypothesis, we have incorporated a simple micromechanical model into a hydromechanical macro-mechanical model of the cochlea. The TM is modelled

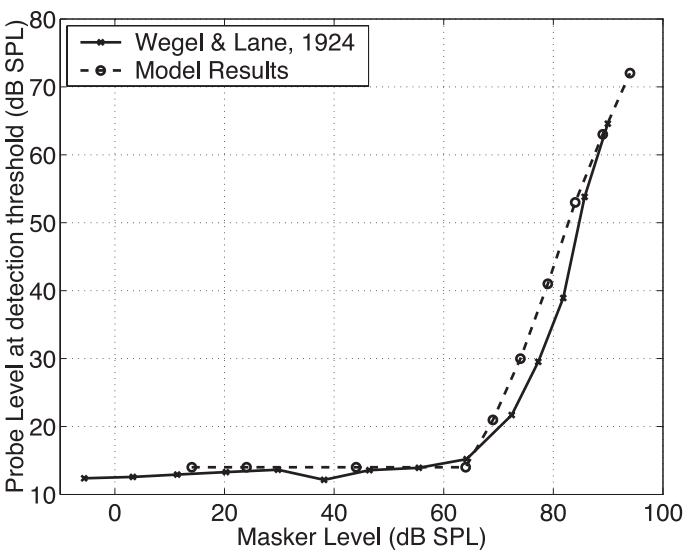


Figure 6. USM prediction from a computational model. The output from the model is compared to data from Wegel & Lane [2].

as a transmission line, terminated by the cilia (m_c, k_c, and r_c modeling the mass, stiffness and damping respectively). The micromechanical model acts to attenuate the response basal to the CP on the basilar membrane tail response. In the model, the flat tail of the low frequency masker (which grows linearly with masker level) changes the stiffness of the basilar membrane at the place of the probe/CF tone, which in turn suppresses the probe actuating the Neural-2TS/USM effect. The serial consecutive depiction of the model (see Fig. 4) is only broken by the feedback due to the OHC motility, which

is able to change the impedance of the cochlear partition and explains various non-linear phenomena (including Neural-2TS and others such as the half-octave shift of the basilar membrane and OAE effects). The high-pass micromechanical filter is also able to convert the 9dB/octave slope of the basilar membrane tail response to the almost place invariant (flat) neural tail, accounting for the discrepancy observed in [14]. Figure 6 shows results from the computational model as described here. The model is clearly able to predict the effect of USM (and therefore Neural-2TS) while not contradicting any existing theoretical and experimental observations.

REFERENCES

1. Fletcher, H., "Physical measurements of audition and their bearing on the theory of hearing", Journal of the Franklin Institute. 196 (3), 289–326, (1923).
2. Wegel, R and Lane, C., "The auditory masking of one pure tone by another and its probable relation to the dynamics of the inner ear", Physical Review 23, 266-285, (1924).
3. Bacon, S., Bodern, L., Lee, J. and Repovsch, J., "Growth of simultaneous masking for $f_m < f_s$: Effects of overall frequency and level", J. Acoust. Society Amer., 106 (1), 341–350, (1999).
4. Zwicker, E., and Fastl, H., "Psychoacoustics: Facts and Models", Springer, Berlin, 1990.
5. Abbas, P., Sachs, M., "Two–tone suppression in auditory–nerve Fibers: Extension of a stimulus–response relationship", J. Acoust. Soc. Amer. 59 (1), 112-122, (1976).
6. Delgutte, B., "Two-tone suppression in auditory-nerve Fibres: Dependence on suppressor frequency and level", Hearing Research 49, 225-246, (1990).
7. Fahey, P.F. and Allen, J. B., "Nonlinear phenomena as observed in the ear canal and at the auditory nerve", J. Acoust. Soc. Amer. 77 (2), 599–612, (1985).
8. Geisler, C. and Nuttall, A., "Two-tone suppression of basilar membrane vibrations in the base of the guinea pig cochlea using "low-side" suppressors", J. Acoust. Soc. Amer. 102 (1), 430–440, (1997).
9. Cooper, N., "Two-tone suppression in cochlear mechanics", J. Acoust. Soc. Amer. 99 (5), 3087–3098, (1996).
10. Ruggero, M., Robles, L. and Rich, N., "Two-tone suppression in the basilar memnbrane of the cochlea: Mechanical basis of auditory-nerve rate suppression", J. of Neurophys. 68 (4), 1087–1099, (1992).
11. McFadden, D., "The curious half–octave shift: Evidence of a basalward migration of the traveling–wave envelope with increasing intensity", in: R. Salvi, D. Henderson, R. Hamernik, V. Coletti (Eds.), Applied and Basic Aspects of Noise-Induced Hearing Loss, Plenum, (1986).
12. Geisler, C.D., Yates, G.K., Patuzzi, R.B. and Johnstone, B.M., "Saturation of outer hair cell receptor currents causes two tone suppression", Hearing Research 44, 241–256, (1990).
13. Patuzzi, R.B., Yates, G.K. and Johnstone, B.M., "Outer hair cell receptor current and sensorineural hearing loss", Hearing Research 42, 47–72, (1989).
14. Ruggero, M., Narayan, S., Temchin, A. and Recio, A., "Mechanical bases of frequency tuning and neural excitation at the base of the cochlea: Comparison of basilar-membrane vibrations and auditory- nerve-fiber responses in chinchilla", Proc. Nat. Acad. of Sciences 97 (2), 11744–11750, (2000).
15. Sen, D. and Dedhia, B., "Slope of the Human Auditory Nerve Response at the Tail", Midwinter Meeting of the Association for Research in Otolaryngology (ARO), (2003).
16. Allen, J.B and Sen, D., "An unified theory of two tone suppression and the upward spread of masking", in Proceedings of the 16th International Congress on Acoustics (ICA) and 135th meeting of the Acoustical Society of America, (1998)

A REVIEW OF MECHANICAL EVIDENCE FOR A SERVO-LOOP IN THE MAMMALIAN COCHLEA

Eric L. LePage

OAEricle Laboratory, Sydney, Australia
PO Box 6025 Narraweena, 2099
ericlepage@oaericle.com.au

The outer hair cells in the cochlea are recognised as the active mechanical elements in the normal operation of the cochlear amplifier. Yet the functions of their two motor mechanisms are still not clear. Increasingly, the outer hair cells are also being implicated the control elements in homeostasis – normal regulation of cochlear activity by the descending neural pathway. This review targets articles with mechanical data and suggests new clues as to structure and function in terms of a mechanical-feedback loop for dc-stabilisation. The literature relevant to such an idea is reviewed and directly leads to clues underlying the notion of a time-intensity trade-off for noise exposure, the cause of Ménière's disease and the upward spread of masking.

INTRODUCTION

The cochlear amplifier

In presenting a modern review of cochlear mechanics it is essential to mention the work of Gold [1] who showed that the cochlea must have an active mechanism to achieve its sharp tuning and high sensitivity. Yet a general recognition that this was the case took 30 years. It came with Kemp's unambiguous evidence [2] of evoked emissions plus the demonstration that low hearing thresholds were necessary to see nonlinear behaviour in the basilar membrane (BM) resonance [3]. Soon after, it was shown that the BM was as sharply tuned as the neural tuning curves [4] and the notion of "cochlear amplifier" was introduced by Hallowell Davis in 1983 [5]. It was an idea with strong intuitive appeal because of widespread take up of hearing aids when the internal amplifier failed with age. Indeed at threshold, the vibrations of the basilar membrane are fractions of a nanometre [4]. Since that time increasingly sensitive sophisticated measurement techniques have been used widely, such as laser interferometry coupled with confocal scanning microscopy to view the motion of the whole organ in three dimensions [6-11].

The weakness of invasive mechanical measurements has been the possibility of adversely damaging these delicate preparations. All the earliest experiments damaged the organ so that it did not show sharp tuning, and from that time [6] no mechanical measurement has been acceptable if there was not simultaneous sharp tuning to prove 'normal physiological operation' [6,12-13]. Yet as we see below, this insistence may have dramatically impeded progress in relating structure to function.

There are, of course, now thousands of publications on otoacoustic emissions, and most of these display correlates of the behaviour discussed and are reviewed elsewhere [14-16].

Special properties of the outer hair cells

The outer hair cells (OHC) are central to providing the gain of the cochlear amplifier. They are now recognised as perhaps the most specialised motor cells in the body for several reasons, not least because they possess not one, but two motor mechanisms (summary Kros [17]). The roles for these motor mechanisms are still the subject of intense debate, but the hair-bundle motor at the apex of the cell is thought responsible for amplification of the audio signals [18], and Hopf bifurcation is proposed to account for the process poised on the verge of instability [19] and how that state is regulated. On the other hand, the somatic motility is due to a cylindrical 'girdle' [20] located just inside the OHC cell membrane binding thousands of motor molecules christened *prestin* [21] to exert efficiently an axial force. The name stems from its own high-frequency electromotility described in piezoelectric terms, but increasingly associated with slow motility [17]. Indeed the latter is well accepted to account for relatively huge length changes [22], which, by virtue of their mechanical coupling in the organ of Corti, are linked back to modify OHC transduction at their stereocilia [23]. While most of the literature is concerned to use this feedback to overcome the effects of damping it is becoming clear that OHC slow motility also regulates the operating point (OP) of stereocilia transduction. What is not being answered specifically is why this stabilisation is needed.

Another remarkable specialisation of the OHC is that they effectively have not just one membrane potential, but two. Viewing both potentials from within the cell, these batteries would seem to be driving current in opposite directions. One steady potential (the endocochlear potential, EP ~+80mV) exists across the cuticular plates at their apex. The "regular" cell resting membrane potential for the lower cell membrane supported below the cuticular plate is of -70 mV relative to the 0 mV of the surrounding perilymph. Having a whole chamber such as the scala media (SM) at a voltage different from the surround is unique in mammalian physiology. Yet its function in holistic terms is unexplained. It clearly has not evolved just to provide a gain of 6 dB. This falls far short of explaining the 50 dB gain of the cochlear amplifier. It is tempting to speculate that the potential across the cuticular plates exists so as to power current flow, or OHC tonic force generation

in both axial directions for the very same reason that an electronic amplifier has positive and negative supply rails. Numerous studies of OHC in isolation show that they can contract or elongate according to the current pulses delivered to them, e.g. [24].

Homeostasis in the cochlea

There has been another line of interest in the mechanics of the labyrinth and this realm is most populated by otologists. In their regular practices they are confronted with patients who, in addition to having hearing problems, also present with a variable set of vestibular symptoms, including positional vertigo and debilitating violent giddy attacks. The literature devoted to these symptoms is as extensive as any other branch of hearing science. It reveals extensive knowledge on fluid dynamics within the cochlea and vestibular apparatus [25,26]. There are two basic fluid compartments – a high-sodium, low-potassium fluid (perilymph), and the reverse (endolymph). Perilymph is derived from the cerebrospinal fluid (CSF, via the cochlear duct) which fills the two outer chambers of the cochlea, *scala vestibuli* (SV), and *scala tympani* (ST), which are connected at the apex via a small hole termed the helicotrema. There are substantial pressure variations in the CSF due to exercise or change in posture. These are transmitted through to the cochlea [27,28], and while they could potentially affect the acoustic signal-processing they are generally discounted because 1) cochlear fluids are primarily water and therefore incompressible, and 2) being low frequency, pressure fluctuations are believed to equalise rapidly across the two chambers and to constitute no pressure differential to stimulate the hair cells.

The reason for inserting homeostasis into a review of cochlear mechanics lies with static pressures in the centre compartment, *scala media* (SM). It is widely recognised that SM can swell large enough to cause serious hearing and vestibular problems, i.e. to affect the OHC transduction operating point. This centre chamber is bordered 'above' by Reissner's membrane, 'below' by the Reticular membrane and the Stria Vascularis lining the outer bony wall. The whole chamber normally only contains a tiny amount of endolymph (~ 1-2 µl) yet this volume may vary by hundreds of percent. When the SM swells to a pathological extent, hearing loss may occur because the pressure displaces the whole sensory apparatus in the direction of ST and constitutes a bias disabling OHC forward transduction [29]. This condition is termed *hydrops*. The morphological evidence appears to be that it does not develop suddenly – it appears as if the pressure drifts upward slowly over many years. The basis for this creep in "pressure set-point" has been described in principle [30,31] without specifically invoking OHC as the control elements (see Fig. 1.C).

It was thought for many years that any excess build-up of endolymph normally drains away via the endocochlear duct, which connects with the vestibular apparatus. It was long supposed that if, for some reason, the flow resistance of endolymphatic sac rises then this would account for the abnormal rise in endolymph pressure. In an important series of articles by Salt and colleagues [25] it has been shown this

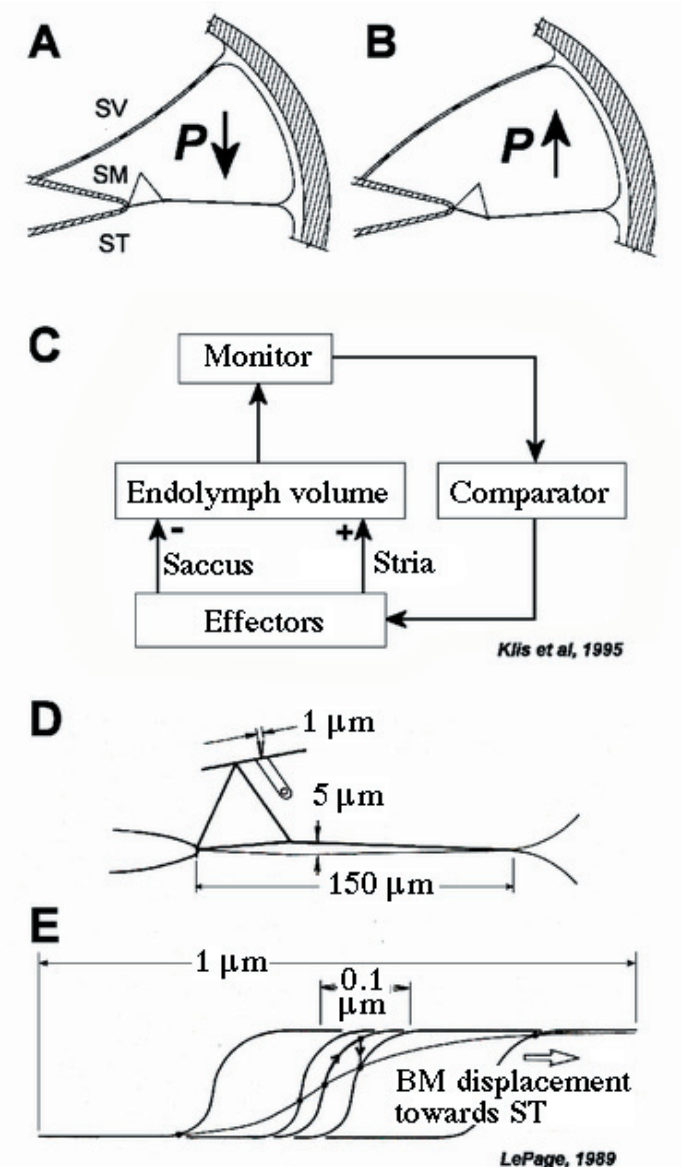


Figure 1. Panels A and B show that the basilar membrane is subjected to transverse movement by change in static pressure in scala media – pressure down will produce excitatory shear of the OHC stereocilia, pressure up will cause suppression. Panel C shows the schematic control system envisaged by Klis (1995) to effect control of endolymph volume. Panels D and E indicate the need for a mechanism to regulate operating point (see text).

theory has no basis. Using tracers, there is no regular flow. Since removal or partial removal of the fluid resistance at the sac has been the basis of surgical procedures to provide relief from patient distress [32], this new finding has resulted in intense interest in looking for alternate causes. The result is considerable interest in the processes of cochlear homeostasis. This has become a very important branch of hearing science and is well summarised in this edition with reviews by Dahl et al [33] and Pickles [34].

At the 5th international conference on Ménière's Disease and Inner ear Homeostasis Disorders in Los Angeles last year, some 187 scientific papers were presented where the overwhelming emphasis was on 1) the genetic and molecular-

biological factors regulating the volume of endolymph under normal circumstances, and 2) how to manage this abnormal condition. The bulk of presentations, and indeed the keynote address [35] dealt with biochemical aspects of transport of potassium ions (K^+) into SM from the stria vascularis. At this time the new candidate explanation is that hydrops is caused by *potassium intoxication* of the endolymph [36] which stemmed from pioneering work of Johnstone and colleagues [37]. The central idea is that K^+ accumulates in SM because, although the ions are recycled in a loop, this current loop is not like a passive electric circuit. These ions need to be actively transported against potential gradients and it would appear that the rate of transport of K^+ out of SM is not perfectly matched to the rate at which the ions are delivered into endolymph [38]. Loud noise exposure results in a rise in K^+ concentration. A couple of presentations only were directed at mechanical correlates. Quadratic distortion products (QDP) are now being added [39] to the battery of tests available to diagnose hydrops. The QDP are the lowest frequency components of the distortion product family and therefore most likely to best represent baseline changes.

Previously mechanical measurements by Flock [40] have observed, in guinea pigs exposed to loud sound, substantial "dc-shifts" in the motion of the Hensen cells (where "dc" is conventional terminology denoting the instantaneous value of the baseline). Flock interpreted these shifts as signifying the presence of hydrops. Since then it has been shown using a two tone suppression algorithm that that baseline pressure changes can be measured directly in the ear canal with an otoacoustic emission probe [41,42].

IMPLICATIONS 1

A fact which seems poorly appreciated is that variations in hydrostatic pressure in this centre compartment are presented *unattenuated* to the OHC. Investigators interested in frequency analysis have largely dismissed this influence 1) because of being outside the frequency range of interest, and 2) because such pressure changes are considered pathological and therefore beyond consideration of mechanisms of cochlear amplification. Pressure variations within SM seem rarely considered as being important or comparable. Yet it is becoming recognised they must be considered because 1) they are graded, i.e. they exist before the condition causes disability, 2) the hearing of sufferers might be compromised, but the mechanisms must cope with pressure variations, 3) the OHC are sensitive to displacement, and 4) the same ion species fundamental to OHC transduction is also responsible for the pressure rise in scala media. These displacements caused by such pressure fluctuations are superimposed on the sound vibrations to cause shear of the OHC stereocilia (see Fig. 1 A, B and D). The implication is that "pathological" issues cannot be ignored while trying to understand the cochlear amplifier. To do so might allow missing important clues.

In order for potassium intoxication to occur there must be a mismatch between the rate at which potassium enters SM and the rate at which it leaves. Flock's work implies that sound evokes a spike of K^+ entering the chamber, which depends on the characteristics of the sound. On the other hand, much recent work suggests that K^+ is being removed from SM at a rate which is determined not by sound but by energy-dependent processes [34]. One might surmise a simple analogy is that of a bilge pump in a boat. While ocean waves splash over the bow of a boat at highly variable rates, the water collecting in the hull is removed at a constant rate. There seems to be general interest in the explanation that the osmolality of SM varies according to the ratio of ions accumulating in endolymph. Although the mechanism by which this happens is far from clear, there is great interest in aquaporins – water flow through pores into the SM and raising the pressure [26,43]. It is postulated that water enters the SM under an osmotic gradient [29]. This means that there is substantial capacity for pressure rise in the SM, which cannot be neglected from the point of view of operation of the OHC and, if it occurs to any extent, cannot be ignored in respect of signal processing.

Evidence for control processes involving the OHC

We learn from the accompanying articles in this special edition, that the auditory system possesses a plethora of control systems (Mulders, [44]) which can modify cochlear sensitivity, the internal protective response. The brainstem can be regarded as a control centre with a host of motor programs to control not only OHC motility, but also the excitability of the primary afferent neurons. The medial olivo-cochlear (MOC) fibres may achieve this by varying the local stiffness of the basilar membrane and the damping of the structure. Efferent effects are produced by changes in OHC membrane potential and changes in slow motility. Because the OHC are so exquisitely sensitive to displacement, modifying the standing K^+ current and responding with force — the MOC must also be involved in cochlear homeostasis.

Mechanical correlates of homeostatic processes: a new look at old data

There are now many reports of cochlear mechanics displaying history-dependent effects. The classic description is that of high sound level exposure producing a temporary perturbation of the mechanical activity, and associated with temporary threshold shift (TTS) [45].

Another frequently studied phenomenon (and one easy to demonstrate psychophysically) is the mechanical bias experiment, which results in an instantaneous loss of hearing sensitivity if the basilar membrane is displaced towards ST [46]. In order to conduct the experiment using acoustic stimuli one needs typically a 25 Hz and >100 dB SPL tone. Such a bias tone will modulate most cochlear measures at acoustic frequencies [47-50].

The history of direct mechanical measurements describing the BM displacement in guinea pigs includes three separate series increasingly focussed on detecting mechanical correlates of homeostasis. These were early studies and at the time published they did not fit in completely with the prevailing travelling wave theory.

This author's experiments began in 1974, when, instead of using the prevailing approach of the time (the Doppler-shift, velocity-sensitive Mössbauer technique), he began using a capacitive probe [51] to measure basilar membrane motion in guinea pig ears by inserting a probe through a hole in

the wall of ST in the basal turn, the tip being brought close to the surface of the BM. Being displacement sensitive, it immediately revealed slow components of the motion never been previously reported. By comparison with the accepted approach, and also well-behaved neural data, the capacitive probe produced displacement data displaying a high degree of variability [50]. These "artifacts" were put down either to 1) the required temporary draining of ST (shown to result in poor neural sensitivity [52,53]), or 2) suspicion that they were due to poor surgical technique. The probe signal was viewed on an oscilloscope in real time, and the immediacy of the baseline variations was impossible to ignore. The output signal of the sensor probe was recorded digitally and averaged synchronously with the stimulus pulses to extract the submicroscopic vibrations. Earliest visual observations formed an indelible impression. In response to sound, even the stimulus clicks used to obtain the impulse response, the basilar membrane moved slowly towards the tip of the probe which was initially located 3 μm distant from the surface. The drifts amounted to micrometres of dc-drift in comparison with nanometres of ac-vibration. Such behaviour was totally inconsistent with the history of studies of cochlear mechanics and models. Nonetheless, the technique and results were accepted insofar as the approach did confirm the story that the basilar membrane motion was nonlinear and first revealed the connection with hearing sensitivity [3,50].

The second set of capacitive probe experiments took place after Brownell had shown OHC length changes *in vitro* amounting to 10 μm [22]. These experiments [54] tested specifically for baseline shifts in basilar membrane motion consistent with OHC length changes which might have been missed with velocity-sensing techniques. The capacitive probe data resulted from low- to medium-threshold preparations in which measurements were made near the round window, from where the summating potential (SP) was recorded on a second channel. To date, only one other report of doing so simultaneously has appeared [11]. They showed not only that there were small baseline shifts in the motion of the BM at the time of the tone burst, but that their polarity reversed systematically, consistent with the polarity changes in the SP. Perhaps more importantly in hindsight, the data were processed to differentiate short-term shifts (during tone bursts) from longer-term baseline shifts. Both measures showed the same polarity for regions away from the characteristic frequency (CF) of the place of measurement. By contrast, at the CF, short term shifts towards SV during the tone bursts were superimposed upon drift towards ST in the longer-term ([54], Fig. 9). The short term excitatory displacements produced a long-term response taking the movement in the direction of lower overall sensitivity – behaviour not dissimilar from what one might expect from a servo-control (automatic gain control) mechanism [54-56].

The third series used a fibre optic technique which did not require draining in the region of the measurement [57]. A small mirror was placed on the basilar membrane to yield an input noise level of the displacement sensor of *ca.* 1 nm. These data did show what appeared to be large tone-produced movements of the basilar membrane – the displacements were of the same order as moving the probe tip 1 μm relative to the BM. The displacement responses also displayed two opposing components of the motion each with different time courses – and occurring at the expected characteristic frequency of the place measured (see Fig 1D). One of the components was physiologically vulnerable to the extent that it disappeared with loss of activity, and could be manipulated by substances known to mimic efferent activity (perfusion of acetylcholine) or interfere with it (strychnine and atropine). The opposing component had a very different time course; after loud tone stimulation it wandered to full scale and stayed there or showed strong hysteresis [58].

Since the publication of those controversial data, two reports have appeared which claim to have adequately repeated these three series of measurements and using a highly displacement-sensitive laser interferometer. No evidence was found for any of the described behaviour at the base of the guinea pig cochlea [13]. However, at the apex, baseline shifts attributable to OHC activity were seen [59]. The preparations were deemed to have high hearing sensitivity, the data free of artifacts. However, it may be significant that the author waited until the preparation "settled down" before obtaining the published data.

SUMMARY 1

A servo-loop is being considered to explain not tuning, but homeostasis. Since the OHC are both detectors and actuators, a new idea surfaces. It is that OHC motor responses may not be triggered invariably by raw sound signals causing vibrations of the basilar membrane, so much as *error-signals* whenever the OHC operating point is displaced. This kind of motor response may not be continuously present but may depend upon "how challenged" are the OHC. This new realisation puts the direct basilar membrane measurements in a totally new light. The outcome of any experiment would then vitally depend upon the expectation that the dc-shifts are an inevitable consequence of acoustic stimulation. Insisting upon low thresholds and sharp tuning may mean that the error-signal is small so no dc-shifts will be seen. If on the other hand the OHC are strongly biased by e.g. draining, their dc-responses may be large which would explain the remarkably large deflections of the basilar membrane [57], particularly if the error signal could not be nulled, these direct measurements support the growing notion of an AGC loop in the mammalian ear, shutting down sensitivity for louder sounds and vice versa.

Why the need for a servo-loop?

It is necessary to consider the exquisite sensitivity of the OHC in comparison to the relatively large displacements they can produce when excited. A 50 to 100 nm stereocilia deflection will produce a full scale electric response (See Fig. 1E). Compared with the micrometre displacements which might result from pressure fluctuations in SM, this deflection is 40 dB smaller. Without any dc-compensation, the OHC transduction will be either off, or saturated most of the time. A servo-loop is necessary to maintain the OHC operating under small signal conditions. The OHC slow motility has the means to hold the operating point close to its most sensitive position (highest

gradient on the transducer curve). An externally applied bias moving the operating point will result in a motor response tending to stabilise the operating point, but resulting in a dc-shift at the same time (Fig. 1E). Any sustained contraction of the OHC will tend to pull the tectorial membrane down upon the inner hair cell stereocilia and excite them generating a receptor potential with both ac and dc components [60]. A full set of speculations about likely changes in hair cell stimulation were invited in a chapter on mechanical triggers of tinnitus [61].

In terms of signal analysis, it seems inescapable that the cochlea must deal with any fluctuations in pressure, but still attempt to deliver a signal to the auditory nerve fibres in which all such fluctuations have been removed leaving only essential details indicating the presence of any frequency component. This means that *at every point along the basilar membrane* these acutely displacement-sensitive hair cells must act so as to 'buck out' the pressure signal. Before the days of highly stable dc amplifiers, such an amplifier was termed a "bootstrap amplifier" – a dc-amplifier which compensated for drift in the input stage. It would make considerable sense of the whole structure if the slow motility of the OHC, acting via the leverage of the arch, can follow whatever is the slow pressure-bias in the system. This further supports the notion of a servo-control system in which the error signal is proportional to the difference between the current transduction operating point, and the absolute position of the bias displacement.

A role for efferent control of OHC motility

There is a 1000:1 variation in stiffness of the basilar membrane along its length. This will produce a large gradation in bias due to any value of hydrostatic pressure which is equally distributed throughout the vessel and is expected to cause larger biases where the basilar membrane is less stiff (Hooke's Law). While the OHC set-points could be "hard-configured" along the length of the cochlea to account for this bias curve versus distance, such an arrangement will not cope with ongoing decline in the numbers of OHC due to noise damage and ageing. The MOC system can thus be conceived to be also providing minor adjustments to the operating point (OP), not just in the short-term, but indeed over life. It follows that there must be a frequency range over which the OHC cannot distinguish between a deflection due to sound or due to a bias.

Control element for a biological servo-control mechanism

What therefore sets the transduction OP for any stimulus condition? A hypothesis [50,54,57] is that, since the OHC generate tonic force as well as amplify at audio-frequencies, there must be two mechanisms working in opposition and the OP is set at which their opposing effects balance. Quite apart from electrical balance, the stability of the operating point for any mechanoreceptor *must* depend upon the collective response of two opposing forces. One force might be passive (or osmotic in origin), the other active. There is growing agreement that multiple processes are interacting [62,63].

Flock's observations are important for a holistic overview of cochlear function. Hydrops may not be such a pathological condition so much as a "runaway stage" of the standard cochlear response to sound. In these terms OHC participation in homeostasis cannot be isolated from OHC participation in tuning. Disruption of any part of the potassium circulation, such as rendering connexons non-functional [33] or downgrading the energy available to these pumps [34] may mean that restoration may take much longer, and maybe even never complete, resulting in a permanent shift in operating point of the hair cells to the point of cell death. As the OHC response weakens there is permanently raised pressure in SM. *In these terms normal hearing is redefined as the capacity of OHC motility (both contraction and elongation) to track displacements caused by potassium intoxication.*

A recent set of studies set out to test the idea in humans using otoacoustic emissions [41,42]. It has been shown that signal-averaging of otoacoustic emission destroys evidence of homeostatic regulation which appears to be contained within the otoacoustic emission signal. This is revealed when the distortion product magnitudes are directly related to measures of static bias. In the two-tone probe/masker experiment the resulting distortion products are related to baseline pressures in the ear canal at the time the second tone is turned on. The result is widespread high correlations between the size of the distortion product and estimates of the current baseline-pressure signal. Moreover, the correlations are pronounced for frequencies which are meaningful in terms of distortion product generation, particularly the behaviour of the QDP [39].

It follows that, after acoustic trauma, it may take many hours of quiet to reset pressure in SM to pre-exposure values. Expressed in other words this describes the recovery function from temporary threshold shift. However, if raised pressure in SM is a normal accumulation which resets away from noise we arrive at the notion of 'Daily Dose' by another approach. If so, there should be existing data which might support the notion of pressure rise being normal. Moreover, if it is normal process, then it should be observable with sub-traumatic exposure; it may even be observable as a diurnal variation in other measures of cochlear mechanics.

Diurnal variation in cochlear mechanics

While otoacoustic emissions are not part of this review, there is one key result which has no explanation from conventional cochlear mechanics. Figure 2 suggests that such a diurnal variation exists in unambiguously cochlear mechanical data. The data shown are for over 300 babies and infants up to 12 months of age. ILO88 apparatus was used to obtain standard click-evoked otoacoustic emissions [16,64] and the waveform reproducibility is plotted versus the time of day. This variable is taken here as representing the incremental work being done by the OHC over the period of 1 click (20 ms). This suggests that the incremental OHC tonus rises slowly as the SM pressure rises. Since only daytime recordings were ever made, the observed trend is unidirectional, but there is a clear increase in the waveform reproducibility of 2.5% / hr from 9am through 6pm. The upward trend is significant ($p<0.01$) for both ears. If this seems a strange result, it nevertheless belongs to a broader class of influences on the mechanics [65].

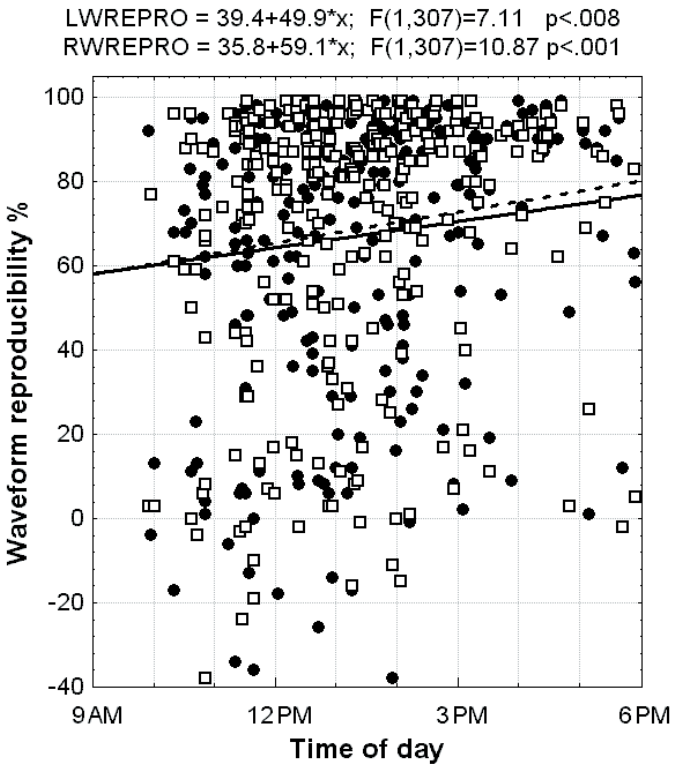


Figure 2. The scatterplot shows the Waveform Reproducibility (%) of standard click-evoked otoacoustic emissions versus the time of day of the measurement for left and right ears (circles and squares respectively) of over 300 neonates and infants up to 12 months of age. The trends which are significant ($p<0.01$) shows that this measure of the activity of the OHC rises over the course of a 9 hour period.

IMPLICATIONS 2

In the past cochlear mechanical studies have almost exclusively focussed upon the origin of the sharp tuning in the cochlea. Increasingly, the issue of cochlear stability is widening the debate, yet there has been a residual selectivity for data which conforms to preconceived notions of tuning so that other prerequisites of energy expenditure have been neglected. The issue of large slow motions of cochlear structures has certainly gained credibility. Nevertheless, the effort has gone towards examining the fine details of the vibration to support the current theories, rather than seriously considering the many systems of the body in which chamber turgor pressure is vital to its normal physiological function. Stability of operating points of the hair cells needs regulation of two opposing forces; one of which is OHC slow motility. It is by no means inconsistent that the other force should be pressure in SM. If it is normally regulated, then it is to be expected that this regulation should occasionally fail.

Ménière's disease

There are many corollaries for this theory, but we have gone some way to explaining the complex set of distressing symptoms of Ménière's disease. Unlike the slow homeostatic drifts, the violent vestibular attacks are certainly sudden, and – with variations on a theme – are generally attributed to rupture of the centre vessel when hydrops becomes too advanced, leaking endolymph into the perilymph spaces with severely toxic effects [66]. In the context here, if a static pressure influences OHC transduction at all, it is of decided interest [67] particularly in respect of acoustic signal processing, because it can be reasonably expected that the ear has evolved so that it loses hearing as a very last resort.

Conceptual problems arising from considering OHC as the only source of force

A second major corollary of the theory is that the long-term baseline shifts in the motion of the basilar membrane may have a time course which is not strongly coupled to timing of the sound stimuli. Any mechanical experiment averaging many responses to improve the signal-to-noise ratio will likely fail to register any longer-term effect. Indeed, the signal may be perceived to be highly noisy; the response deemed to be small, and many repetitions needed to extract the tiny response from the "noise". More importantly, the large basilar membrane shifts observed [57] are likely the result of a large pressure bias due to draining, to which the OHC have responded with a large compensatory push in the reverse direction. Cochlear preparations with low challenges to OHC stabilisation do not capture this effect [6,13]. Unless one designs an experiment to look for much broader-ranging behaviour one will be tempted to interpret the data as noise.

Loss of hearing sensitivity

The third corollary of the theory is that cochlear hearing sensitivity remains normal while the local tonic force capability of the OHC (related to its turgor pressure and somatic motility) can match any basilar membrane displacement-bias due to a slow accumulation of pressure in SM. As the numbers of OHC decline with age and with toxic influences (including accumulated noise exposure), or the individual cells deteriorate [68], the sensory transducer operating point deviates from the point of highest sensitivity and the gain of the cochlear amplifier (proportional to the local slope of the transducer characteristic at the operating point) is reduced.

Audiometric variability

The fourth corollary is an explanation for the huge variability in the outcomes of any experiment. The variability is not only attributable to recent trauma. Audiometric thresholds themselves, under test-retest conditions, vary by ±5 dB for most frequencies, and up to ±27 dB at 6 kHz [69] a variation which clinically is managed rather than ever seriously questioned. Nothing about the process of obtaining a pure tone audiogram or its classic interpretation takes the number of known internal control mechanisms into account. Indeed, *the variability in all ear and hearing experiments (biophysical and psychophysical alike) is invariably so great* that the researcher typically must either 1) select, describe and interpret a representative set of individual responses to any particular experiment, or 2) conduct an analysis of variance, and in so doing effectively (and often implicitly) bypass any consideration of underlying mechanisms.

Basis of the *Equal Energy Rule*

A fifth corollary is that the servo-theory provides a ready basis for explaining the *Equal Energy Rule* [70-72]. *The basis for the explanation provided here is that the absorbed acoustic energy is stored essentially as potential energy in the stiffness of the basilar membrane*, now seen as a spring being stretched by the SM pressure. The higher level the sound, the longer it is present, the more that SM is distended and the higher the stretch applied. The slower process of recovery from temporary threshold shift (TTS) is identified as the removal of potassium, which will occur continuously at a constant rate (explaining the exponential recovery of TTS in terms of a first order differential equation). This model potentially explains 1) the recovery process which occurs away from noise, 2) the basis of the trade-off, 3) the diurnal variation which is implicit in the notion of "daily-noise dose" and 4) dissipation of hydropic pressure before the next industrial work shift.

Cochlear response to noise trauma

A sixth corollary is an explanation of why high-level sound causes discomfort and feelings of "fullness" often mistaken for effusion of the middle ear and accompanied by tinnitus. When sound is externally amplified to make up for loss of internal amplification, a newly appreciated effect will be a bias due to swelling of SM which will invoke a compensation response while any viable outer hair cells remain. Attempts to adjust the spectrum of speech sounds to match hearing losses will not achieve the desired localised effect because the rise in pressure will be distributed and affect adjacent areas. Such a distribution probably underlies the upward spread of masking and the tails of tuning curves as outlined in the article by Sen [73] herein.

What is normal operation of the cochlea?

The key evidence, here re-presented for consideration, is the notion that the 'artifacts' BM displacement recordings were indeed mechanical correlates of homeostatic processes in operation, as previously highlighted in principle by Klis and Smoorenburg [29,31]. Any insights presented here lead to our new definition: *"Normal hearing" is not just the existence of low thresholds, but, more generally, the existence of viable homeostasis mechanisms.* The single factor contributing to homeostasis may well be as Pickles describes in this volume: the availability of energy to drive both the servo-loop and potassium recycling.

SUMMARY 2

Diverse contributions to the recent literature are drawn together to yield a new level of understanding structure and function of the mammalian cochlea. It is that the scala media is a pressure vessel in which acoustic stimulation normally releases potassium ions causing an osmotic pressure rise deflecting the basilar membrane towards the scala tympani creating shear of the OHC stereocilia. The pressure rises because of a mismatch in potassium inflow and removal from scala media by ion pumps. The OHC respond by using their slow motility to track this mechanical bias using the leverage of the arch to stabilise their transduction operating point. Any error-signal at the OHC stereocilia due to changing pressure is thus normally zeroed out. The result is a very efficient mechanism for expanding the dynamic range of the mammalian ear beyond that of the hair cells alone. While the OHC have the capacity to track the pressure bias, hearing will be normal. If the pressure grows too large, or if the OHC are depleted in numbers or de-energised, hearing loss is the result. It follows there should be a diurnal cycle of pressure fluctuation which forms the basis of the so-called Equal Energy Rule describing the level/duration trade-off for loud sound exposure. Preliminary OAE evidence is provided for such a diurnal fluctuation.

ACKNOWLEDGEMENTS

I thank Dr. N.M. Murray particularly and numerous other clinicians for obtaining the neonatal OAE data presented here. I thank all my collaborators and particularly the early formative stimulating interactions with Drs. B.M. Johnstone and Hallowell Davis. I thank the reviewers for their valuable comments.

REFERENCES

1. Gold, T. (1948). Hearing II. The physical basis of the action of the cochlea. Proc. Royal Soc. Lond. B: 135, 492-498.
2. Kemp, D. T. (1978). Stimulated acoustic emissions from within the human auditory system. J Acoust Soc Am 64(5), 1386-91.
3. Le Page, E. L., & Johnstone, B. M. (1980). Nonlinear mechanical behaviour of the basilar membrane in the basal turn of the guinea pig cochlea. Hear Res 2(3-4), 183-9.
4. Sellick, P. M., Patuzzi, R., & Johnstone, B. M. (1982). Measurement of basilar membrane motion in the guinea pig using the Mossbauer technique. J Acoust Soc Am 72(1), 131-41.
5. Davis, H. (1983). An active process in cochlear mechanics. Hear Res 9(1), 79-90.
6. Recio, A., Rich, N. C., Narayan, S. S., & Ruggero, M. A. (1998). Basilar-membrane responses to clicks at the base of the chinchilla cochlea. J Acoust Soc Am 103(4), 1972-89.
7. Nuttall, A. L., Dolan, D. F., & Avinash, G. (1990). Measurements of basilar membrane tuning and distortion with laser Doppler velocimetry. In: Lecture Notes in Biomathematics: Vol. 87. The Mechanics and Biophysics of Hearing (pp. 288-295). New York: Springer-Verlag..
8. Cooper, N. P. (1999). An improved heterodyne laser interferometer for use in studies of cochlear mechanics. J Neurosci Methods 88(1), 93-102.
9. Ren, T., & Nuttall, A. L. (2001). Recording depth of the heterodyne laser interferometer for cochlear vibration measurement. J Acoust Soc Am 109(2), 826-9.
10. Gummer, A. W., Hemmert, W., & Zenner, H.-P. (1993). Resonant tectorial membrane motion in the inner ear: its crucial role in frequency tuning. Proc.Natl.Acad.Sc.USA, 8727-8732.
11. Fridberger, A., de Monvel, J. B., Zheng, J., Hu, N., Zou, Y., Ren, T., & Nuttall, A. (2004). Organ of Corti potentials and the motion of the basilar membrane. J Neurosci 24(45), 10057-63.
12. Robles, L., Ruggero, M. A., & Rich, N. C. (1986). Basilar membrane mechanics at the base of the chinchilla cochlea. I. Input-output functions, tuning curves, and response phases. J Acoust Soc Am 80(5), 1364-74.
13. Cooper, N. P., & Rhode, W. S. (1993). Nonlinear mechanics at the base and apex of the mammalian cochlea: in-vivo observations using a displacement-sensitive laser interferometer. In 5th International symposium on the mechanics of hearing:

Biophysics of Hair Cell Sensory Systems (pp. 249-257). Singapore, New Jersey: World Scientific Publishing.
14. Shera, C. A. (2004). Mechanisms of mammalian otoacoustic emission and their implications for the clinical utility of otoacoustic emissions. Ear Hear 25(2), 86-97.
15. Lonsbury-Martin, B. L., & Martin, G. K. (2003). Otoacoustic emissions. Curr Opin Otolaryngol Head Neck Surg 11(5), 361-6.
16. Kemp, D. T. (2002). Otoacoustic emissions, their origin in cochlear function, and use. Br Med Bull 63, 223-41.
17. Kros, C. (2005). Hearing: aid from hair force. Nature 433(7028), 810-1.
18. Kennedy, H. J., Crawford, A. C., & Fettiplace, R. (2005). Force generation by mammalian hair bundles supports a role in cochlear amplification. Nature 433(7028), 880-3.
19. Nadrowski, B., Martin, P., & Julicher, F. (2004). Active hair-bundle motility harnesses noise to operate near an optimum of mechanosensitivity. Proc Natl Acad Sci U S A 101(33), 12195-200.
20. Brownell, W. E., Spector, A. A., Raphael, R. M., & Popel, A. S. (2001). Micro- and nanomechanics of the cochlear outer hair cell. Annu Rev Biomed Eng 3, 169-94.
21. Zheng, J., Shen, W., He, D. Z., Long, K. B., Madison, L. D., & Dallos, P. (2000). Prestin is the motor protein of cochlear outer hair cells. Nature 405(6783), 149-55.
22. Brownell, W. E., Bader, C. R., Bertrand, D., & de Ribaupierre, Y. (1985). Evoked mechanical responses of isolated cochlear outer hair cells. Science 227(4683), 194-6.
23. Evans, B. N., & Dallos, P. (1993). Stereocilia displacement induced somatic motility of cochlear outer hair cells. Proc Natl Acad Sci U S A 90(18), 8347-51.
24. Santos-Sacchi, J., Kakehata, S., & Takahashi, S. (1998). Effects of membrane potential on the voltage dependence of motility-related charge in outer hair cells of the guinea-pig. J Physiol 510 (Pt 1), 225-35.
25. Salt, A. N. (2001). Regulation of endolymphatic fluid volume. Ann N Y Acad Sci 942, 306-12.
26. Andrews, J. C. (2004). Intralabyrinthine fluid dynamics: Meniere disease. Curr Opin Otolaryngol Head Neck Surg 12(5), 408-12.
27. Buki, B., de Kleine, E., Wit, H. P., & Avan, P. (2002). Detection of intracochlear and intracranial pressure changes with otoacoustic emissions: a gerbil model. Hear Res 167(1-2), 180-91.
28. Marchbanks, R. J., & Reid, A. (1990). Cochlear and cerebrospinal fluid pressure: their inter-relationship and control mechanisms. Br J Audiol 24(3), 179-87.
29. Klis, S. F., & Smoorenburg, G. F. (1994). Osmotically induced pressure difference in the cochlea and its effect on cochlear potentials. Hear Res 75(1-2), 114-20.
30. Salt, A. N. (2006). Low frequency pressure changes may participate in endolymph volume regulation. Proceedings of the 5th International Symposium: Meniere's Disease and Inner Ear Homeostasis Disorders (pp. 27-29). 2100 West Third Street, Los Angeles, CA 90057: House Ear Institute.
31. Klis, S. F. L., & Smoorenburg, G. F. (1995). A comparison of several experimental animal models for Meniere's disease. Meniere's disease: 16th Danavox Symposium (pp. 123-139).
32. Portmann, D. (2006). Why Sac surgery is still our first choice. Proceedings of the 5th International Symposium: Meniere's Disease and Inner Ear Homeostasis Disorders (p. 100). 2100 West Third Street, Los Angeles, CA 90057: House Ear Institute.
33. Dahl, H.-H., Manji, S., de Silva, M., Peverelli, M., & Hildebrand, M. (2006). Genetic aspects of hearing loss. Acoust. Aust., **(**), **-**.
34. Pickles, J. O. (2006). Mitochondria, cell death, and deafness: will it be possible to prevent presbyacusis? Acoust. Aust., **(**), **-**.
35. Petit, C. (2006). Inner ear K^+ homeostasis disorders: what have we learned from the deafness genes? Proceedings of the 5th International Symposium: Meniere's Disease and Inner Ear Homeostasis Disorders (pp. 9-11). 2100 West Third Street, Los Angeles, CA 90057: House Ear Institute.
36. Gibson, W. P. R. (2006). The cause of attacks of vertigo in Meniere's disease: Potassium intoxication theories versus the drainage theory -- electrophysiological investigations. Proceedings of the 5th International Symposium: Meniere's Disease and Inner Ear Homeostasis Disorders (pp. 323-324). 2100 West Third Street, Los Angeles, CA 90057: House Ear Institute.
37. Johnstone, B. M., Patuzzi, R., Syka, J., & Sykova, E. (1989). Stimulus-related potassium changes in the organ of Corti of guinea-pig. J Physiol 408, 77-92.
38. Schulte, B. (2006). Inner ear K^+ recycling pathways. Proceedings of the 5th International Symposium: Meniere's Disease and Inner Ear Homeostasis Disorders (pp. 68-72). 2100 West Third Street, Los Angeles, CA 90057: House Ear Institute.
39. Sirjani, D. B., Salt, A. N., Gill, R. M., & Hale, S. A. (2004). The influence of transducer operating point on distortion generation in the cochlea. J Acoust Soc Am 115(3), 1219-29.
40. Flock, A., & Flock, B. (2000). Hydrops in the cochlea can be induced by sound as well as by static pressure. Hear Res 150(1-2), 175-88.
41. LePage, E. L., Murray, N. M., & Seymour, J. D. (2006). Baseline shifts measured in the human ear canal pressure related to distortion product generation and two tone suppression. Presented at the Mid-winter meeting of the Association for Research in Otolaryngology (pp. Session D4: Inner Ear: Mechanics I, Poster #75).
42. LePage, E. L., Murray, N. M., & Seymour, J. D. (2006). Otoacoustic emission correlates of intracochlear pressure variations in humans: Summating behaviour. Proceedings of the 5th International Symposium: Meniere's Disease and Inner Ear Homeostasis Disorders (pp. 110-111). 2100 West Third Street, Los Angeles, CA 90057: House Ear Institute.
43. Löwenheim, H., Hirt, B., & Zenner, H.-P. (2006). Endolymph regulation and mechanism of hydrops - aquaporins in the inner ear. Proceedings of the 5th International Symposium: Meniere's Disease and Inner Ear Homeostasis Disorders (pp. 42-44). 2100 West Third Street, Los Angeles, CA 90057: House Ear Institute.
44. Mulders, W. H. A. M. (2006). Efferent control of hearing. Acoustics Aust., **(**), **-**.
45. Patuzzi, R. (1998). Exponential onset and recovery of temporary threshold shift after loud sound: evidence for long-term inactivation of mechano-electrical transduction channels. Hear Res 125(1-2), 17-38.
46. Patuzzi, R., Sellick, P. M., & Johnstone, B. M. (1984). The modulation of the sensitivity of the mammalian cochlea by low frequency tones. III. Basilar membrane motion. Hear Res 13(1), 19-27.
47. Bian, L. (2004). Cochlear compression: effects of low-frequency biasing on quadratic distortion product otoacoustic emission. J Acoust Soc Am 116(6), 3559-71.
48. Patuzzi, R., & Moleirinho, A. (1998). Automatic monitoring of mechano-electrical transduction in the guinea pig cochlea. Hear Res 125(1-2), 1-16.
49. Lukashkin, A. N., & Russell, I. J. (2005). Dependence of the DPOAE amplitude pattern on acoustical biasing of the cochlear partition. Hear Res 203(1-2), 45-53.
50. LePage, E. L. (1981). The role of nonlinear mechanical processes in mammalian hearing. Unpublished doctoral dissertation, The University of Western Australia, available at www.oaericle.com.au.

51. LePage, E. L. (1987). The application of a capacitive probe technique for direct observation of electromechanical processes in the guinea pig cochlea. J Acoust Soc Am 82(1), 126-38.
52. Robertson, D. (1974). Cochlear neurons: frequency selectivity altered by perilymph removal. Science 186(4159), 153-5.
53. Patuzzi, R., Sellick, P. M., & Johnstone, B. M. (1982). Cochlear drainage and basilar membrane tuning. J Acoust Soc Am 72(3), 1064-5.
54. LePage, E. L. (1987). Frequency-dependent self-induced bias of the basilar membrane and its potential for controlling sensitivity and tuning in the mammalian cochlea. J Acoust Soc Am 82(1), 139-54.
55. Lyon, R. F. (1990). Automatic gain control in cochlear mechanics. In: Lecture notes in Biomathematics, v. 87. The Mechanics and Biophysics of Hearing (pp. 395-402). New York, Springer-Verlag 1990.
56. van der Heijden, M. (2005). Cochlear gain control. J Acoust Soc Am 117(3 Pt 1), 1223-33.
57. LePage, E. L. (1989). Functional role of the olivo-cochlear bundle: a motor unit control system in the mammalian cochlea. Hear Res 38(3), 177-98.
58. LePage, E. L. (1992). Hysteresis in cochlear mechanics and a model for variability in noise-induced hearing loss. In Noise-Induced Hearing Loss, edited by A. Dancer, D. Henderson, R.J. Salvi , & R.P. Hamernik. Chapter 10 (pp. 106-115). St.Louis : Mosby-Year Book.
59. Cooper, N. P., & Rhode, W. S. (1995). Nonlinear mechanics at the apex of the guinea-pig cochlea. Hear Res 82(2), 225-43.
60. Russell, I. J., & Sellick, P. M. (1978). Intracellular studies of hair cells in the mammalian cochlea. J Physiol 284, 261-90.
61. LePage, E. L. (1995). A model for cochlear origin of subjective tinnitus: excitatory drift in the operating point of inner hair cells. In Jack A. Vernon and Aage R. Moller Mechanisms of Tinnitus (Vol. Chapter 11pp. 115-148). Boston: Allyn and Bacon.
62. Guinan, J. J. Jr, Lin, T., & Cheng, H. (2005). Medial-olivocochlear-efferent inhibition of the first peak of auditory-nerve responses: evidence for a new motion within the cochlea. J Acoust Soc Am 118(4), 2421-33.
63. Cooper, N. P., & Guinan, J. J. Jr. (2003). Separate mechanical processes underlie fast and slow effects of medial olivocochlear efferent activity. J Physiol 548(Pt 1), 307-12.
64. LePage, E. L. and Murray, N. M. Click-evoked otoacoustic emissions: comparing emission strengths with pure tone audiometric thresholds. Aust.J.Audiol. 1993; 15 :9-22.
65. Bell, A. (1992). Circadian and menstrual rhythms in frequency variations of spontaneous otoacoustic emissions from human ears. Hear Res 58(1), 91-100.
66. Zenner, H. P., Reuter, G., Zimmermann, U., Gitter, A. H., Fermin, C., & LePage, E. L. (1994). Transitory endolymph leakage induced hearing loss and tinnitus: depolarization, biphasic shortening and loss of electromotility of outer hair cells. Eur Arch Otorhinolaryngol 251(3), 143-53.
67. Zenner, H. P. (1993). Possible roles of outer hair cell d.c. movements in the cochlea. Br J Audiol 27(2), 73-7.
68. LePage, E. L., Reuter, G., & Zenner, H. P. (1995). A threshold decrease for electrically stimulated motor responses of isolated aging outer hair cells from the pigmented guinea pig. Eur Arch Otorhinolaryngol, 252, 215-221.
69. Macrae, J. H. (1979). An investigation of repeated testing as a means of improving the accuracy of audiometry. NAL Informal Report #64, National Acoustic Laboratories, Sydney.
70. Ward, W. D., Santi, P. A., Duvall, A. J. 3rd, & Turner, C. W. (1981). Total energy and critical intensity concepts in noise damage. Ann Otol Rhinol Laryngol 90(6 Pt 1), 584-90.
71. Clark, W. W., Bohne, B. A., & Boettcher, F. A. (1987). Effect of periodic rest on hearing loss and cochlear damage following exposure to noise. J Acoust Soc Am 82(4), 1253-64.
72. Ahroon, W. A., Hamernik, R. P., & Davis, R. I. (1993). Complex noise exposures: an energy analysis. J Acoust Soc Am 93(2), 997-1006.
73. Sen, D. & Allen, J.B. (2006). Functionality in cochlear micromechanics – As elucidated by upward spread of masking and two-tone suppression. Acoustics Aust., **,**-**.

MORE ABOUT AUTOMOTIVE EXHAUST NOISE

A.D. Jones,
Belair, South Australia

Your article in Acoustics Forum [1] caught my attention. I have had a considerable involvement with exhaust noise acoustics and simulation from doctoral research, nine years in the exhaust manufacturing industry and several more in consulting [2, 3, 4]. However, I don't have to run a simulation to know that the exhaust system pictured in the article will make a car very noisy. I anticipate a broad noise peak at around 200 Hz with about 20 dB more noise than from an original vehicle, and about 10 dB more noise at other low frequencies to 500 Hz.

Legally, all new vehicles must adhere to a number of Australian Design Rules (ADRs). ADR 28 exists to "define limits on external noise generated by motor vehicles in order to limit the contribution of motor traffic to community noise". In my experience, no vehicle could pass the mandated drive-by test unless is were quiet: conversely, no vehicle perceived as even slightly noisy would pass the test. In practice, a sample vehicle is tested before vehicles are sold. Second-hand vehicles are free of the need for compliance with ADR 28, and to my knowledge, are subject to regulations imposed by the states. These regulations generally involve a different in-service test, and are far more generous in noise level permitted than ADR 28, by about 10 to 15 dB or so. I believe that some old Harley Davidson motorcycles have been imported into the country without ADR scrutiny. Many I see are unmuffled – these would certainly fail in-service tests.

Yes, some exhaust systems are fitted just to make noise. The excuse of wanting low back pressure is untenable. Original exhaust systems are designed for backpressure of no more than about 0.5 atmospheres at maximum engine speed and load. However, I have taken measurements of backpressure of exhaust systems on vehicles in on-road use many times and was able to observe that backpressure in most practical circumstances was near zero. Maximum engine speed and load is a long way from the envelope of normal driving circumstances!

It is unfortunate that there is very little checking and enforcement of vehicles in service. An in-service test will still be needed for our imported second hand vehicles. However, a more effective way to put an end to noisy cars would be for legislation to put the onus on the fitter of the replacement part not to cause the vehicle to breach the ADR. Enforcement at muffler fitting shops, with financial penalties would put an end to noisy exhausts. It is possible that the Society could assist a third party's lobbying for a change like this, however we do need to find the third party, with clout, who wants this change.

1. N.H. Fletcher, "What are we doing about exhaust noise" Acoust. Aust. 33, 106 (2005).
2. A.D. Jones, "Techniques for Studying Muffler Performance", Proc. Aust. Acoustical Soc. Conference on Motor Vehicle and Traffic Noise, Leura Gardens, New South Wales, pp 93-99 (1985).
3. A.D. Jones, "Exhaust Noise Modelling for Muffler Design", SAE-Australasia Paper No. 871198, Fourth Intl. Pacific Conference on Automotive Engineering, Melbourne, (1987)
4. A.D. Jones, W.K. Van Moorhem and R.T. Voland "Is a Full Nonlinear Method Necessary for the Prediction of Radiated Engine Exhaust Noise", Noise Control Engineering J., 26, 74-80 (1986)

Editors note: For example, the Maserati GranSport boasts an electronically controlled pneumatic valve system that enables a driver to increase exhaust noise by opening multiple ports in the exhaust system when the 'Sport' button is pressed on the central console.

Future Meetings

Acoustics 2006

1st Joint NZAS and AAS Conference

20-22 November, Christchurch

The 2006 Australian and New Zealand Acoustical Society Conference with the theme "Noise of Progress" will be held at the Clearwater Resort, Christchurch, New Zealand November 20-22 2006. Clearwater offers exceptional conference and accommodation facilities. Home to the Bob Charles designed NZPGA championship golf course, the resort also has a range of other recreational opportunities including archery, fishing and walking. A range of hotel suites, rooms and apartments has been block booked at the Outrigger at Clearwater. These will be available to book either through the online registration process or registration form from July 2006

An exciting program is being developed with over 80 abstracts received so far. The deadline for Abstracts for contributed papers is 28 April but late abstracts may be accepted if submitted by email directly to the conference chair – see web page for details. Full papers must be submitted by 31 July and all papers will be subject to a peer review. Early Bird registration rates will be available till 1 September.

The Keynote Speakers will include Professor Michael Vorlander, University of Aachen who will talk on "Building acoustics: From prediction models to auralisation" and Professor Chris Tindle, University of Auckland on "Sounds interesting: Wavefronts, caustics, whales and reefs". A varied social program is being developed including a Conference Dinner at the Christchurch Town Hall. The dinner speakers will be Sir Miles Warren who has been at the forefront of New Zealand's architectural profession and Professor Harold Marshall who established Marshall Day Acoustics.

Information about the conference from www.conference.co.nz/acoustics06

ACTIVE 06

18-20 September, Adelaide

ACTIVE 06, The 2006 International Symposium on Active Control of Sound and Vibration, is being organised by the South Australian Division of the Australian Acoustical Society. The Symposium will be held on 18-20 September 2006 at the University of Adelaide, which is located in the centre of the city of Adelaide. The Symposium is a continuation of the series of biannually-organised meetings on Recent Advances in Active Control of Sound and Vibration which have been held for the past 15 years.

The keynote speakers include: Professor Sen Kuo, (USA) on Digital Signal Processing algorithms and implementations on active noise control systems, Dr. Paolo Gardonio (UK) on the choice of sensors and actuators for smart panels implementing Active Structural Acoustic Control, Professor Scott Sommerfeldt (USA) Global Energy-Based Active Noise Control and the use of Energy Density sensing methods, Professor Jie Pan (Australia) active vibration and motion control of ocean vehicles, Dr. Marty Johnson (USA) on How big is you head? A discussion of system complexity, inverse problems and acoustic arrays, which cover numerous topics such as system-complexity, active control, radiation modes, inverse methods, HRTFs and acoustic arrays.

The list of over 100 abstracts for contributed papers is available from the web page. The full papers are rolling in for what should be an outstanding meeting covering all aspects of active control. And the social program has not been overlooked – there will be a reception at the Art Gallery, a conference Banquet, trip to the zoo and concluding BBQ. Early bird registration rates are available till 23 June.

Information from http://www.active2006.com

WESPAC IX 2006

26-28 June, Seoul

The 9th Western Pacific Acoustics Conference with the theme 'Better Life Through Acoustics' will be held June 26-28, 2006 in Seoul, Korea, the Land of Morning Calm. Those who attended the excellent Wespac conference in Melbourne will know the benefits that can be gained from attending Wespac conferences.

Wespac has a reputation for excellent invited speakers and the line up for 2006 includes plenary speakers: Ronald A. Roy, Better Life through Bubbles in Biomedical Ultrasound, Sang-chul Lee, IT as a New Social Infrastructure, Hideki Kawahara, A Precursor to Ecologically Relevant Speech Science and keynote speakers: Xifen Gong, Physical and Nonlinear Acoustics, Jeff Simmen, Underwater Acoustics, Kirk Shung, Biomedical Acoustics, Victor Akulichev, Underwater Acoustics, Angelo Farina, Architectural Acoustics, Christopher Tam, Aeroacoustics, Jung-Kwon Ih, Computational Acoustics

Over 580 abstracts have been received from 37 countries and these will be accommodated in 7 parallel sessions. The social program includes a welcome reception, banquet and a farewell reception

Information from http://www.wespac9.org

ICSV 13

2-6 July, Vienna

The 13th International conference on Sound and Vibration will be held 2 to 6July, in Vienna, Austria. This conference will comprise an extensive scientific program with plenary lectures by Jorge ARENAS (Chile) on Noise Attenuation of Barriers, Voichita BUCUR (France) on Acoustics of Wood, Hugo FASTL (Germany) on Sound Quality and Evaluation, Daniel INMAN (USA): on Passive and Active Damping of Structures, Hiroshi WADA (Japan) on Human Auditory System, Semyung WANG (Korea) on Compressor Noise Control and Franz ZIEGLER (Austria): Vibration Damping of CE Structures. Over 1,000 papers have been accepted and the abstracts can be accessed from the web page. In addition to the regular sessions for contributed papers there will be 40 Structured Sessions on particular subjects and the program is now available.

Details of the conference can be found from http://icsv13.tuwien.ac.at/

Note that the next conference, ICSV 14, will be held Cairns Australia in July 2007

Internoise 2006

3-6 December, Hawaii

Internoise 06 with the theme "Engineering a Quieter World" will be held at Sheraton Waikiki in Honolulu, Hawaii, USA 3–6 December, 2006. This conference will have all the features that one expects at an Internoise Conference as well as being in the relaxing environment of Honolulu - the congress banquet will be a traditional luau.

Details of the special and structured sessions are available from the webpage. Abstracts are due 15 May with completed papers 18 August. Early bird registration rates are available till 18 August.

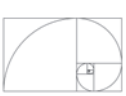
Information from www.internoise2006.org

ASA ASJ Joint Meeting

28 Nov-2 Dec, Hawaii

This 4th joint meeting of the Acoustical Society of America and the Acoustical Society of Japan will be held in Hawaii just preceding Internoise. Abstracts are due by 30 June and Early bird registration rates are available till 24 October.

Information from http://asa.aip.org



News

CitySounds2 - Acoustic Design Resource

The City of Melbourne and RMIT University's Spatial Information Architecture Laboratory have developed the CitySounds2 Acoustic Design Resource to provide information to assist architects, builders, developers and residents to minimise noise when designing, renovating or solving noise problems in city apartments. Using web design and audio software to create a virtual CBD living space, the program lets users hear real sounds of Melbourne and learn ways to reduce noise levels entering homes. A series of fact sheets have also been developed to provide comprehensive and accessible information on acoustic design considerations.

The City of Melbourne Noise Management website also contains the results of an innovative community based sound survey, acoustic terminology, information about sound insulation and the Victorian Acts and Regulations controlling noise. CitySounds2 and the City of Melbourne Noise Management website can be found at www.melbourne.vic.gov.au/noise

Assessing Vibration – a Technical Guideline

To help protect the health and wellbeing of the community, particularly those living and working inside buildings, the NSW Department of Environment and Conservation (DEC) has produced an interim vibration technical guideline entitled "Assessing Vibration – a Technical Guideline".

The interim vibration guideline is largely based on British Standard BS 6472:1992 *Guide to Evaluation of Human Exposure to Vibration in Buildings (1Hz to 80Hz).* DEC's practice over a number of years has been to recommend the use of British Standard 6472:1992 for instances not covered by the Noise Control Guideline on "Vibration in Buildings", for example, intermittent operations of freight and light rail. However, it is understood that BS 6472:1992 is to be revised. The vibration guideline is published as an interim guideline until such revision has been made to BS 6472.

The interim guideline is designed to be applied when evaluating and assessing human responses to vibration from industry, transportation and machinery. It presents recommended, preferred and maximum vibration acceleration levels to protect human sensitivity for vibration. The criteria are non-mandatory. Instead they are goals that should be sought to be achieved through the application of feasible and reasonable mitigation measures.

The interim guideline provides guidance on the characteristics of vibration and associated effects, which can disturb the community, particularly those living or working inside buildings, criteria defining values of vibration to protect amenity, procedures for the measurement and evaluation of vibration values and other associated emissions. It covers sources of vibration in the community such as construction, demolition and excavation equipment, railways and heavy road traffic and industrial machinery. For blasting, the DEC applies the ANZECC guideline 'Technical Basis for Guidelines to Minimise Annoyance Due to Blasting Overpressure and Ground Vibration' (September 1990).

This guideline is essentially the same as the previous guideline, except for the following main differences:

- presentation of the criteria for continuous and impulsive vibration has been simplified from the format in the previous guideline.
- the guideline addresses vibration along the *x*- and *y*-axes as well as along the *z*-axis. The previous guideline dealt with vibration only along the *z*-axis.
- the guideline includes an approach for the assessment of intermittent vibration involving a 'vibration dose' concept. This approach can be used for evaluating and assessing vibration from a range of intermittent sources. These are potential sources of widespread disturbance in the community, and it is therefore important that appropriate techniques be provided for their assessment.
- more guidance is given on measurement techniques for vibration assessment.

More information or a copy of the interim technical guideline can be obtained from www.environment.nsw.gov.au/noise or tel 131 555.

NSW Industrial Noise Policy: Application Notes

The NSW Industrial Noise Policy (INP) was published by the NSW Department of Environment and Conservation (DEC) in 2000. The INP provides a framework and process to assess noise impacts from industrial developments and to derive noise limit conditions for consents and licences. The processes and criteria in the policy are to be followed by industry and acoustic practitioners for developments that EPA regulates, as scheduled in the *Protection of the Environment Operations Act 1997*. The INP also includes guidance on determining feasible and reasonable mitigation measures and applicable licence conditions. Some flexibility is provided in this process through the ability of the proponent to negotiate with the regulatory authority or affected residences and to balance any residual noise impacts (after all feasible and reasonable mitigation measures are applied) against local circumstances.

All impact assessments for noise that are submitted for EPA approval must apply the appropriate noise criteria and identify the relevant project-specific noise levels from the processes set down in the INP. DEC has developed a set of *Policy Application Notes* to clarify important and commonly queried topics covered in the INP. Furthermore, DEC has become aware of alternative interpretations of particular topics in the INP, while reviewing Noise Impact Assessments lodged by industry and acoustic practitioners for developments regulated by the Environment Protection Authority (EPA).

The Policy Application Notes cover a number of topics, such as:

- Applying the urban/industrial interface amenity category
- Amenity criteria in high traffic noise areas
- Identifying which of the amenity or intrusive criteria apply
- How to account for operations that only occur for part of the day, evening or night period

For example, one issue that has been raised is how calm is defined when using the INP in an assessment of meteorological effects on noise. The following guidance is provided in the Application Notes.

> In the assessment of wind effects, the INP requires the assessment of wind speeds of up to 3 metres per second where these speeds are a feature of the area (they occur for 30 percent of the time or more) but does not specify the minimum wind speed that needs to be assessed. The calm condition is typically represented by wind speeds less than or equal to 0.5 metres per second as this is likely to be the lower limit of measurement.

This is an example of just one of the application notes currently in the document. DEC will update or add to the Application Notes on a regular basis as future issues arise. The Policy Application Notes can be obtained from www.environment.nsw.gov.au/noise or tel 02 9995 5786.

Awful Sounds Survey

Fingernails scraping down a blackboard…the scream of a baby…your neighbour's dog

barking: what's the worst sound in the world? BadVibes is a new science project from Salford University that aims to find out just that. People can log on to the BadVibes website at www.sound101.org where they listen and vote on a collection of awful sounds, use the horrible sound mixer and even download horrible sound effects as ring tones.

But as Professor Trevor Cox from Salford University's Acoustics Research Centre explained, there's a serious side to the research as well. "The idea behind the project is to get people thinking about the complex way we listen to and interpret sounds. For instance, you can find out why we find the sound of retching horrible. By examining people's voting patterns we will learn more about people's perception of horrible sounds. We hope to learn about what is the worst sound in the world, and maybe why it is the worst sound."

The project also includes an exhibit which is at the Museum of Science and Industry in Manchester. The work is funded by EPSRC. EPSRC is the main UK government agency funding research and training in engineering and the physical sciences, investing around £500 million a year in a broad range of subjects – from mathematics to materials science, and from information technology to acoustic engineering.

More information from http://www.sound101.org

Violin Society 17th International Competition

The Violin Society of America announces its 17th International Competition for new violins, violas, cellos, basses and their bows from 6 to 12 November, 2006 in Baltimore, Maryland. Now recognized as one of the major events of its kind in the world, the VSA competition is held biennially and offers the opportunity for makers from all countries to compete. The purpose of the competition is to inspire the creation of outstanding quality instruments and bows. Workmanship and tone judges select those instruments and bows having the greatest artistic merit, technical execution and tone quality. The application deadline is October 1, 2006 and information from www.vsa.to/

FASTS

The Federation of Australian Scientific and Technological Societies (FASTS) is the peak representative body for 60,000 Australian scientists and technologists.

Productivity Commission Study To Provoke Rethink Of Innovation

FASTS welcomes the announcement that the Productivity Commission will examine the economic, social and environmental returns on public investment in science and innovation in Australia. The President of FASTS, Professor Tom Spurling said the Productivity Commission study was a welcome opportunity for rigorous examination of the R&D and innovation policy framework. "There is a growing recognition the science and innovation policy framework needs careful re-thinking and this Productivity Commission report will be highly relevant to doing just that. Science and innovation appears to be dropping down the Government's priorities. A sophisticated examination of the innovation system, as a system, rather than *ad hoc* reviews of specific programs, may be the catalyst required for renewed focus on innovation policy and funding issues."

"The review will be an important challenge for both the Commission and the science and innovation sectors as quantifying returns on investment in innovation are notoriously difficult because of the complexity of valuing spillover benefits and the long time frames involved. A credible review requires robust evidence but the Commission must also avoid the trap of allowing the limitations of economic modelling to explain away or ignore benefits that are not commercially quantifiable over short time periods. FASTS are also pleased the terms of reference will also address are the value and effectiveness of benchmarks used to examine returns on investment of public investment in innovation", concluded Professor Spurling.

Research and Development Expenditure

Amid a spate of announcements from Australian manufacturers that they are heading offshore, a KPMG survey suggests that an increase in Research and Development (R&D) expenditure rather than a search for low-cost labour and manufacturing facilities may be the key to survival in a global market. The report released from the Economist Intelligence Unit (EIU), commissioned by KPMG International, highlights the fact that many Western countries are investing too little in R&D to compete on the basis of innovation and technology and to protect themselves from intense price pressures.

Australia lags behind the rest of the world with business expenditure on R&D as a percentage of Gross Domestic Product (GDP) resting at 0.89 percent in 2003-04 compared to 2.36 percent in Japan, 1.79 percent in the US and 1.24 percent in the UK. According to KPMG's Industrial Markets Partner, Ian Dinnison, this low level of investment in R&D may leave Australian industries vulnerable to commoditisation and hence competition from low-cost centres.

"Continuous innovation will be a primary defence against increasing competition from China, India and other emerging market players. The EIU's research indicates that most manufacturers will have to take a long-term perspective on investment decisions and carve out areas of expertise where they can command high-end prices. Companies must also focus on ensuring that product innovation is tightly connected to customer demands. New products must be brought to market with greater speed and efficiency." said Mr Dinnison. The survey highlights that the Australian experience is not unique, manufacturers across the world are trying to work out how to respond to the challenges from low-cost countries. "Australian businesses must now consider how they will combat this challenge, they cannot rely solely on government or unions to act, they must take the initiative themselves. Some will become global design centres, distributing product manufactured overseas, concentrating on product development and supply chain expertise. This seems to be the model for the textile, clothing and footwear (TCF) and electrical consumer product industries. Some will focus on import competitive products, other will need to be businesses that are truly competitive on a global basis."

Standards Australia

The Australian Government has asked the Productivity Commission to undertake a **research study** into the Australian Government's relationship with Standards Australia Limited and the National Association of Testing Authorities. The Commission invites interested people and organisations to make a **submission** on any matter they see as relevant to the **terms of reference** and **forward** it to the study team. The key details on the review is given at The issues paper and more information and is available at: http://www.pc.gov.au/study/standards/index.html with KEY DATES Due date for submissions was 21 April 2006 , Release of draft report - end June 2006, Draft report roundtables - August/September 2006, Final Report - 2 November 2006

In the executive summary of their submission to the Productivity Commission's Review of Standards and Conformance, Standards Australia states that it "recognises that just as the standards themselves must change in line with new demands and new realities so too must the system for their development. The traditional premise that there is

surplus industry and government expertise available to provide an unending supply of time and expertise to Standards Australia for voluntary standards development is becoming increasingly unsustainable. That is not to say that there is a lack of demand or resources for standards development. It is just that to tap into this need there has to be a change of attitude and philosophy on the part of Standards Australia, its stakeholders, contributors and end-users. The reliance upon Standards Australia and its limited resources to meet the bulk of Australia's voluntary and consensus standards needs is nearing an end. We see the future for the development of standards in Australia as evolving to a system based more on a direct partnership between Standards Australia and those industries or agencies seeking standards development. This new model offers a broader product range, developed in a more flexible, timely and professional manner and better matched to market needs. The details of our new model are described at a conceptual level on our website: www.standards.org.au"

New Documents

AS ISO 140.4-2006 Acoustics - Measurement of sound insulation in buildings and of building elements - Field measurements of airborne sound insulation between rooms (ISO 140-4:1998, MOD)

AS ISO 140.6-2006 Acoustics - Measurement of sound insulation in buildings and of building elements - Laboratory measurements of impact sound insulation of floors

AS/NZS ISO 140.7:2006 Acoustics - Measurement of sound insulation in buildings and of building elements - Field measurements of impact sound insulation of floors (ISO 140-7:1998, MOD)

AS ISO 140.8-2006 Acoustics - Measurement of sound insulation in buildings and of building elements - Laboratory measurements of the reduction of transmitted impact noise by floor coverings on a heavyweight standard floor

AS ISO 354-2006 Acoustics - Measurement of sound absorption in a reverberation room

Meeting Reports

WTN2005 Berlin

The first international conference on wind turbine noise, "WTN2005 – Wind Turbine Noise: Perspectives for Control", was held in Berlin on 17 and 18 October 2005. INCE/Europe was the sponsor of the conference, which was convened and organised by Geoff Leventhal. Of the 130 delegates from 22 countries, four were from Australia.

The keynote address, "A review of wind turbine noise" was given by Helmet Klug, chairman of the IEC technical committee overseeing the progressive development of IEC standard 61400-11 Wind Turbines – Part 11: Acoustic noise measurement techniques". He noted that there has been a lot of work over the past 10 to 15 years on reducing machinery noise and understanding tip noise, such that now machinery noise is not really a major contributor to noise emission. Tip noise can be reduced by 3 dB by making them straight rather than curved. Current work is looking at trailing edge noise and its interaction with the turbulent boundary layer – a relationship of sound level to rpm has been found, and a 10% reduction in rpm reduces PWL by 10 dB. Modifications to the IEC measurement method now require sound levels to be compared to wind speed measurements at rotor hub-height, not 10m elevation as previously. This allows comparison of PWL at various hub-heights. New work on the next amendment to the standard is to consider uncertainty – measuring reproducible PWLs at high wind speeds.

28 other papers were presented, including:

- a Swedish survey of human response to wind farms - community concerns on noise in a small population sample found a dose-response rate higher than for exposure to industry noise, so more work is recommended for this area;
- managing public opinion opposed to a wind farm development in New Zealand;
- problem solving of gear noise on a NZ designed two-bladed 500kW wtg;
- the effects of wind gradient on noise emissions, especially the higher wind speeds at elevation at night causing higher noise emissions;
- CFD visualisation of noise emission from a savonious rotor generator,
- new software models and comparison of predicted noise from wind generators using different software models – a round robin of validation of predictions was considered something for consideration in the next amendment to the Standard;
- consideration of underwater noise from off-shore generators and their potential effects on marine wildlife;
- low-frequency seismic vibration and infrasound from generators potentially affecting the comprehensive test ban treaty monitoring site in Scotland, and thereby affecting Scotland's plan to generate 40% of its electricity from renewable resources by 2020; and,
- two projects providing visualisation of noise emission from rotors. The Sirocco project was of particular interest and its visualisation studies are being used to develop the next generation of quiet rotors. These studies are showing the highest noise emission is directed forwards from the trailing edge of the rotor.

Of the subjects discussed, the three areas which stood out for me in terms of relevance to future projects in Australia were the need to do more community noise dose response studies post construction, the need to consider higher wind speeds at higher elevations and their effect on PWL, and validation of model results – there are many models but few have been validated against results from more than one or two wind farms.

The location of the conference was at the Stuttgarter Hof hotel in Anhalter Strasse, just a few wind generator tower-lengths from Checkpoint Charlie and Potsdam Platz. So it was relatively central and convenient for sightseeing before and after the conference. The next conference is likely to be in 2 years time in Spain. Congratulations to INCE and Geoff Leventhal and his team for a well organised, friendly and very interesting conference. Papers are available from INCE Europe, www.inceurope.org

Bionic Ear - Vic Division

The final Victoria Division technical meeting for 2005 was a dinner meeting held at the Malvern Valley Golf and Reception Centre on Dec 6, with Prof Graeme Clark as the invited speaker. 37 members and friends were present.

Prof Clark outlined his work of developing the Bionic Ear to bring hearing to the profoundly deaf for whom conventional hearing aids are of no help, and how this wonderful development arose from a driving ambition and much hard work. The Bionic Ear or multi-electrode cochlear implant helps deaf people hear through electrical stimulation of the hearing nerve.

His years of graduate and post-graduate education in the 1950s and 60s gave him training as an ear, nose and throat doctor, and provided him with the necessary qualifications and research experience in physiology, pathology of the ear, surgical anatomy, electronics and psycho-acoustics to enable him to meet the challenges ahead. These challenges presented themselves in questions such as *Could the hearing nerve be stimulated? Could sensory brain function be restored?* in spite of the apparent impossibility, and *Could wires in the inner ear reproduce what the brain detects?*

Graeme Clark's research into understanding how we hear began in 1967. Preparatory reading revealed that we recognize the

pitch of a sound by the pattern of electrical responses in the brain cells through both a time and a place code. Subsequent research, including surgery on animals, showed that stimulating hearing nerves via the place coding of frequency, and inserting multiple electrodes in the inner ear were required.

His appointment in late 1969 as Foundation Professor in Otolaryngology at the University of Melbourne meant that he could now direct research into electrical stimulation of the hearing nerve as a cure for deafness, and made his future less uncertain. Subsequent work and development resulted in an implant package and its associated bundle of electrodes being ready for the first human implant operation on 1978. The implant package was assembled using assistance with silicon chips from Silicon Valley, silkscreen-printed circuit wafers from Telecom [now Telstra] Research Labs, and circuitry help from Hybrid Electronics.

This operation at the Royal Victorian Eye and Ear Hospital [RVEEH] proved successful, with the multiple-electrode implant justifying its greater expense. Its first press announcement was in September 1978. With much further developmental work, the implant was brought to the stage that those fitted with them could recognize the sounds they heard as intelligible speech and other sounds.

The inaugural speech processor developed commercially by Nucleus Ltd [later Cochlear Ltd] was approved by the US Food and Drug Administration [FDA] in late 1985. A design modified by Nucleus Ltd allowed increased amounts of speech information to be transmitted, and was clinically trialled and approved by the US FDA in 1986. The Bionic Ear Institute was inaugurated in August 1984. Research continues not only in hearing but in spinal cord repair, infection control for implantable devices, and early treatment of epileptic seizures.

The Bionic Ear Institute is an Australian not-for-profit biomedical research organization, established to undertake research to assist in the ongoing development of devices to allow deaf people to communicate. Its researchers are world leaders in innovative biomedical research whose work to date has contributed to improved hearing for more than 70,000 severely and profoundly deaf children and adults world wide.

Louis Fouvy

Orchestral Pit – NSW Div

On 6 December the NSW Division Technical presentation on Orchestral pits was from two aspects: 'A Design Philosophy for Orchestral Pits' by Donald Woolford and 'The Orchestral Pit – A Musician's View' by Euan Huggett

Donald Woolford is an experienced orchestral leader, of amateur status, in symphonic, oratorio and light opera presentations. Formerly an engineer with the Australian Broadcasting Corporation, he now consults in acoustics. His slide presentation included specially acquired photos of an historical theatre in Ferrara, Italy and the Wang Centre in Boston, plus a representation of the Wagner pit in Festival Theatre at Bayreuth, Germany. Don briefly traced the opera theatre from Northern Italy in the 17th century and the transition to the 20th century science and engineering with the Chicago Auditorium Theatre in 1889 and the Boston Symphony Hall in 1900. Present day theatres are usually multipurpose, with application ranging from grand opera, operettas to musicals and ballet.

Don said that opera house pit configurations vary from the fully covered and sunken Wagner pit, to sunken fully and partially open pits, and open shallow pits such as the Wang Centre. He echoed Leo Beranek's ideal requirements for successful orchestral pits. Discussed also were elements necessary to achieve the best design compromise for the range of functions, to include acoustic tuning of the pit and acoustic coupling to theatre and stage, playing environment considerations, auditory perception, the preservation of tradition, and present day use of electronic assistance. Modern day matters of pit ergonomics and hearing conservation were introduced.

Euan Huggett has been a wind player in the Australian Opera & Ballet Orchestra for nearly thirty years, and is a former President of that orchestra. He studied music in New Zealand and the Royal College of Music, London. The orchestra was originally run by the Elizabethan Theatre Trust and was formed in order to accompany the national opera and ballet companies, although now it is a fully integrated part of Opera Australia and works almost exclusively in the Opera House. The orchestra currently performs over 250 times a year – that is more than any other similar orchestra in the world.

The orchestra is part of the overall spectacle and therefore emphasis on good pit design is essential. An orchestra needs useable space in which to play. A nice bowed front to the pit may look pretty on paper but it causes great angst amongst the back desks of the strings where things start to get a bit tight. Good sight lines to the conductor are also important. Whereas a typical orchestra set-up on stage will have the orchestra raised at the rear, it is usual for a pit floor to be stepped down which means a player must look down at the music on their stand and up to the conductor who is often standing in a direct line with the follow spots. Finally, of course, there are the acoustics of the space – not only within the pit but also how it balances the sound with the stage which together feed into the auditorium. The pit acoustic actually forms an important part of the orchestral sound – it not only colours our sound but the way in which it is played.

All orchestral instruments are designed to be played in a fairly warm acoustic environment. Although they have developed over the years, this has been a fairly slow process. It is possible to play in an unsympathetic acoustic. However, an orchestra in which the players are struggling to produce the sound they hear in their heads and fighting to project a solo may not always produce an ideal performance.

The Opera Theatre pit, as you may be aware, is not ideal. Of course, it was never designed to be used in the current way – that we manage it at all is a minor miracle in itself. The major problem is that in order to provide a space large enough to accommodate an orchestra suitable for accompanying most opera and ballet repertoire, almost two thirds of the pit is buried under the stage with little more than a 2.3 metre ceiling height.

There have been a number of acoustic reports over the years into the problems of the pit and how it could be improved. However, the same conclusions have been reached: the only way is to uncover the orchestra, either by moving the pit forward or the stage back. There is nowhere to go backwards but moving the pit forward is also a major job because it means cutting through the tie-wires forming part of the major theatre structure. Arup, who were the original structural engineers, proposed to move the wires which met with general approval. They also estimated that it would take up to two years to complete the work.

Another option was proposed that if the theatre was going to be dark for two years, they could use the time to realign the stage area. Over the years, various improvements and alterations have been made in order to facilitate handling modern sets and productions, but this always had to be accomplished within the annual four weeks' down-time.

An ideal plan evolved in that by gutting the whole theatre and taking everything down one level, the seating could be increased and the acoustics improved in the auditorium. This would enable a full- sized pit suitable for the different needs of opera and ballet, increase the size of the stage and improve its acoustics. Furthermore, by digging a tunnel in from the fountain that ended in a space two levels below the current basement, they could provide a proper loading dock and scenery handling space similar to that originally proposed. This plan actually makes complete sense of the building. It would provide us with a more usable, more economically viable opera theatre and more than fulfil Utzon's original concept. …..That's the dream.

Rodney Stevens

New Products

Bradford Insulation Webpage

Bradford Insulation's website has recently been updated, providing an inspiring and useful forum through which to access information about Bradford's product range and applications. The new look site has been designed to provide specific information for builders, architects, specifiers and contractors, as well as consumers. Encapsulating the new branding, 'Bradford for smarter environments', the web provides information in an easy to use format across the following areas: • Product information; Homeowners; Commercial; Industrial; Building regulations; and Brochure and technical support. Informative and user-friendly, the new Bradford Insulation site not only provides up to date information regarding insulation, but is also an ideal forum through which to access important information on building regulations and energy efficiency issues relevant to the industry. www.bradfordinsulation.com.au

Kingdom

Signalcalc-BALANCE on Quattro

Kingdom Pty Ltd has released a version of the powerful and precise Dynamic Signal Processor (DSP) hardware called QUATTRO which provides stand alone rotating machinery shaft balancing. "The Signalcalc-BALANCE on Quattro" (SBQ) is a highly portable and rugged instrument using a powerful 24 bit DSP engine and is provided with its own balancing software running under Windows operating system. It requires no FFT analysis software to support it thus providing a very cost effective single plane balancing solution." says Dick Lovegrove, MD of Kingdom Pty Ltd.

The QUATTRO hardware weighs only 475 grams and measures 160 mm long including the BNC connectors, 100 mm wide and 25 mm thick yet it also provides real time analysis of sound and vibration with a dynamic range in excess of 120 - 130 dB QUATTRO uses a USB2 interface connection to the host computer, notebook or desktop. USB2 provides file transfers 40 times faster than USB 1 or 1.1. It comes complete with an elegant and intuitive Graphical User Interface for instrumentation setup, rotor geometry definition and a complete measurement wizard for the balancing measurements and correction mass calculations.

Information Kingdom Pty Ltd 02 9975 3272 or www.kingdom.com.au

Impulse Hammer

When an engineer makes measurements of a structure it is not only to determine its physical dimensions but also to establish its mechanical characteristics. The mechanical characteristics which particularly interest the engineer are those features which determine how a structure moves or flexes when it is shaken, bumped, hit or pounded, in other words excited. Any physical system will vibrate if excited. The frequency at which vibration naturally occurs is called resonance or natural frequency. The shapes which the resonating (vibrating) system assumes are physical properties of the structure and can be measured experimentally by a vibration analyser and displayed by using Modal Analysis. Impulse hammers are used by many engineers to "excite" a structure in order to measure the distribution and dissipation of energy (transfer function) across the structure. The size of the hammer used must be sufficient to create a sufficient impulse, that is it must induce sufficient energy into the structure to cause it to vibrate.

One such hammer kit supplied by Kingdom Pty Ltd from Dytran Instruments is the 5803A, a 12 lb sledge hammer. The Dytran 5803A incorporates a force sensor in the head of the hammer and is teamed with an accelerometer placed on the rail to measure the vibration response resulting from an impact. Dytran also supplies a full range of accelerometers, pressure, force, and impact sensors and electronics.

Information from Kingdom Pty Ltd on 02 9975 3272 or visit www.kingdom.com.au

Davidson Measurement 831 Sound Level Meter/Real Time Analyser

The Larson Davis Model 831 brings the latest in digital technology to some of the most important applications in the field of engineering acoustics! The Model 831 includes firmware optimized for environmental noise measurement and long or short term noise monitoring. Automatically measure and store the following parameters: basic time history, advanced time history, interval history and exceedance history. The features include: Real-time 1/1, 1/3 Octave Frequency Analysis; Audio Recording; Voice annotation; USB 2.0; GPRS. Information from Davidson Measurement tel 1-300-SENSOR, www.davidson.com.au

Soundblock Barrierboard

Barrierboard is an Australian-made patented plasterboard composite product that can reduce noise levels by as much as 75 per cent. Barrierboard consists of two sheets of differing thickness separated by an insulating layer. The panels are available in a number of standard sizes. Unlike standard plasterboard panels, the composite Barrierboard product is rigid, ensuring that no sagging or bowing occurs when it is fixed in place. The relatively thin panels (32mm) can be fixed directly to common walls with minimal changes to doorway construction and architraves. The end result is maximum performance from minimum thickness - an Rw improvement of 10dB in CSIRO testing.

Barrierboard is ideal for apartments, dual occupancies, townhouses and general housing. It can also be used to effectively reduce noise in commercial situations such as inter-office walls, conference rooms and general office partitions. On industrial sites it can be used to divide walls between offices and factory workplaces or to reduce noise emanating from plant rooms.

Information Soundblock® Solutions tel: (02)93277410, www.soundblock.com.au

Wavecom Entertainment Venue Logger and Control Aid

Wavecom Instruments are pleased to announce the development of an entertainment venue logger. The EVLCA has been developed in Adelaide to meet the requirement where monitoring for exceedances is needed. Common examples are in live music venues. The system is built around an industrial panel PC touch control screen in an aluminium housing for wall mounting. The microphone can be direct mounted to the housing or remotely located using a microphone extension cable. In-coming sound is analysed in selected bands which are all logged. When the SPL in any band exceeds a preset level for the time interval selected, the bar for that band changes colour on the screen and an alarm status light is turned on. A flag is indicated in the recorded data to show exceedence and frequency band. Reaching alarm status can simply turn on the indicator light. However it can also be used to activate various control measures.

To operate the EVLCA, the authorised operator (or acoustic consultant) has a password to enable configuration changes. All logged data are date and time stamped and may be viewed in spread sheet format for printing purposes. All data are stored in 24 hour files allowing easy access to download and recall data.

Information from Wavecom Instruments tel 08 8243 3500 or www.wavecom.com.au.

Book Reviews

Reviews of books by Peter C. Wille, Tim South, Geoff Taylor et al, and the Violin Society of America will appear in the next Acoustics Australia.

Diary

2006

30 May - 1 June, Tampere
Euronoise2006
http://www.euronoise2006.org

5 - 7 June, Morgantown
1st American Conference on Human Vibration
RKD6@cdc.gov

12 - 15 June, Carvoeira
8th European Conference on Underwater Acoustics.
http://www.ecua2006.org

13-15 June, Cavtat
7th WSEAS Intl Conference Acoustics & Music: Theory & Applications
http://www.worldses.org/conferences/2006/croatia/amta/index.html

18-23 June Amalfi
Engineered Adaptive Structures
http://www.cira.it/

19-23 June Anconia
Vibration Measurements by Laser Techniques
http://www.aivela.org

26-28 June, Seoul
WESPAC9
www.wespac9.org

26 -29 June, St. Petersburg, Russia.
11th International Conference on Speech and Computer.
http://www.specom.nw.ru

03 - 07 July, Vienna
13th International Congress on Sound and Vibration (ICSV13)
http://icsv13.tuwien.ac.at

7-10 July, Athens
2nd Int Conference From Scientific Computing to Computational Engineering
http://ic-scce2006.upatras.gr/

17 -19 July, Southampton.
9th Int Conf on Recent Advances in Structural Dynamics
www.isvr.soton.ac.uk/sd2006/index.htm

17-19 July Melbourne
Vehicle Noise and Vibration Intensive Short Course
lorraine.curtis@adm.monash.edu.au

22 - 26 August, Bologna
9th International Conference on Music Perception and Cognition.
http://www.icmpc2006.org

18-20 September, Leuven
ISMA2006, Noise and Vibration Engineering Conference
http://www.isma-isaac.be

18 - 20 September, Adelaide
ACTIVE 2006
http://www.active2006.com

18 - 20 September, Bristol.
12th Int Conference on Low Frequency Noise & Vib and Control.
http://www.lowfrequency2006.org

18 - 21 September, Pittsburgh
INTERSPEECH 2006 - ICSLP.
www.interspeech2006.org

27-29 September, Sydney
8th National Injury Prevention Conference
secretariat@aipn.com.au

3 - 6 October, Vancouver
IEEE International Ultrasonics Symposium.
http://www.ieee-ultrasonics2006.org

19-20 October, Cincinnati
Noise induced hearing loss in children at work and play
http://www.hearingconservation.org/conf_childrenconf.html

20 – 22 November Christchurch
1st Joint Australian/New Zealand Acoustical Societies Conference
"Noise of Progress"
http://www.conference.co.nz/index.cfm/acoustics06

28 November - 02 December, Honolulu
Acoustical Soc of America & Acoustical Soc of Japan Joint Meeting.
http://asa.aip.org

3-6 December, Honolulu
Inter-Noise 2006
Engineering a Quieter World
www.internoise2006.org

3-8 December, Brisbane
AIP Conference
www.aipc2006.com

2007

10 - 12 April, Loughboro
4th Int Conf on Bio-Acoustics.
http://www.ioa.org.uk

16 - 20 May, Honolulu,
IEEE Int Conf on Acoustics, Speech & Signal Processing (IEEE ICASSP 2007)
http://www.icassp2007.org

9-12 July, Cairns
ICSV14
n.kessissoglou@unsw.edu.au

26-29 August, Istanbul.
Inter-noise 2007.
http://www.internoise2007.org.tr

27-31 August, Antwerp
INTERSPEECH 2007.
conf@isca-speech.org

2-7 September, Madrid
ICA2007
www.ica2007madrid.org

9-12 September, Barcelona.
Symposium on Musical Acoustics (ISMA2007)
www.ica2007madrid.org

9 - 12 September, Sevilla
Symposium on Room Acoustics
www.ica2007madrid.org

17-19 September, Lyon
Fan noise 2007
www.fannoise2007.org

2010

23-27 August, Sydney
ICA2010
http://www.ica2010sydney.org/

Meeting dates can change so please ensure you check the www pages. Meeting Calendars are available on http://www.icacommission.org

New Members

Member

Alistair Bavage (Vic)
Thomas Boxoen (NSW)
Emma Carlisle (Qld)
Gordon Downey (NSW)
Mark Enersen (NSW)
Alexander Gavrilov (WA)
Sylvia Jones (Vic)
Michael Kidner (SA)
Rachel Labruyere (NSW)
Paul McMullen (Vic)
Alex Marchuk (SA)
Andrew Mitchell (Vic)
Matthew Ottley (NSW)
Fadia Sami (NZ)
Roger Treagus (NSW)
George Watts (WA)
Jingfeng Xu (NSW)

Graduate

Vladimir Pavasovic (Vic)

Subscriber

Michael Rosmolen (Thailand)

Student

Justin Cartwright (Vic)
Jack Lawrence (UK)

AUSTRALIAN ACOUSTICAL SOCIETY ENQUIRIES

NATIONAL MATTERS

* Notification of change of address
* Payment of annual subscription
* Proceedings of annual conferences

General Secretary
AAS– Professional Centre of Australia
Private Bag 1, Darlinghurst 2010
Tel/Fax (03) 5470 6381
email: GeneralSecretary@acoustics.asn.au
www.acoustics.asn.au

SOCIETY SUBSCRIPTION RATES

For 2004/2005 Financial Year:

Fellow and Member	$110.00
Graduate, Associate and Subscriber	$85.00
Retired	$35.00
Student	$25.00

Including GST

DIVISIONAL MATTERS

Enquiries regarding membership and sustaining membership should be directed to the appropriate State Division Secretary

AAS - NSW Division
Noise and Sound Services
Spectrum House
1 Elegans Avenue
ST IVES NSW 2075
Sec: Ken Scannell
Tel: (02) 9449 6499
Fax: (02) 9402 5849
noiseandsound@optusnet.com.au

AAS - Queensland Division
PO Box 760
Spring Hill Qld 4004
Sec: Richard Devereux
Tel: (07) 3217 0055
Fax: (07) 3217 0066
rdevereux@acran.com.au

AAS - SA Division
Department of Mech Eng
University of Adelaide
SOUTH AUSTRALIA 5005
Sec: Anthony Zander
Tel: (08) 8303 5461
Fax: (08) 8303 4367
azander@mecheng.adelaide.edu.au

AAS - Victoria Division
PO Box 417
Collins St. West
PO MELBOURNE 8007
Sec: Jim Antonopoulos
Tel (03) 9695 9100
Fax (03) 9695 9111
jim.antonopoulos@heggies.com.au

AAS–WA Division
Unit 3
2 Hardy Street,
SOUTH PERTH 6151
Sec: Norbert Gabriels
Tel (08) 9316 3881
Fax (08) 9364 6665
gabriels@iinet.net.au

ACOUSTICS AUSTRALIA INFORMATION

GENERAL BUSINESS

Advertising Subscriptions

Mrs Leigh Wallbank
PO Box 579, CRONULLA 2230
Tel (02) 9528 4362
Fax (02) 9589 0547
wallbank@zipworld.com.au

ARTICLES & REPORTS NEWS, BOOK REVIEWS NEW PRODUCTS

The Editor
Acoustics Australia
Acoustics & Vibration Unit, ADFA
CANBERRA ACT 2600
Tel (02) 6268 8241
Fax (02) 6268 8276
AcousticsAustralia@acoustics.asn.au

PRINTING, ARTWORK

Scott Williams
Cliff Lewis Cronulla Printing Co.
91-93 Parraweena Road
CARINGBAH NSW 222
Tel (02) 9525 6588 Fax (02) 9524 8712
email: scott@clp.com.au

SUBSCRIPTION RATES

	Aust	Overseas
1 year	A$63.80	A$73.00
2 year	A$110.00	A$130.00
3 year	A$156.20	A$187.00

Australian rates include GST.
Overseas subscriptions go by airmail
Discounted for new subscriptions
20% Discount for extra copies
Agents rates are discounted.

ADVERTISING RATES

B&W	Non-members	Sus Mem
1/1 Page	$660.00	$588.50
1/2 Page	$429.00	$385.00
1/3 Page	$330.00	$297.00
1/4 Page	$275.00	$247.50

Spot colour: $121.00 per colour
Prepared insert: $357.50 Conditions apply
Column rate: $22.00 per cm (1/3 p 5.5cm width)
All rates include GST

Discounted rates for 3 consecutive ads in advance

Special rates available for 4-colour printing

All enquiries to: Mrs Leigh Wallbank
Tel (02) 9528 4362 Fax (02) 9589 0547
wallbank@zipworld.com.au

ACOUSTICS AUSTRALIA ADVERTISER INDEX - VOL 34 No 1

Accord 18
ARL 18
ACU-VIB Electronics 30
Bruel & Kjaer . . . . . 2, back cover
CLP Cronulla Printing Co. 11
Davidson 4
Elsevier . . . . . Insert
Enviro-Acoustics 96
ERM . . . . . Insert
ETMC . . . . . Inside back cover
Kingdom . . . . . Inside front cover
Matrix . . . . . 2, Insert
Monash University 18
Noise Control Australia 2
Norman Disney & Young 12
Peace 36
Peace & Quiet . . . . . Insert
RTA Technology 11
Soundguard 17

NORSONIC
Sound Level Meters

Nor130 series of Sound Level Meters

- Single Measurement Range
- Parallel LAeq and LCpeak
- Real-time octave
- Large internal memory
- Clock synchronized measurements
- Statistical analysis
- Transfer software included

Nor131

The Nor130 Series of Sound Level Meters are designed and manufactured to the latest sound level meter standards and comprises two products. The Nor131 is a Class 1 (precision) instrument whilst the Nor132 is designed in accordance with the less accurate Class 2 requirements. Both meters offer the same features with exception of the detachable preamplifier which is only available on the Nor131 version.

Applications

- Noise hazards in the workplace
- Prescription of hearing protection
- Environmental noise investigations
- Product noise testing

ETMC Technologies

619 Darling Street ROZELLE NSW 2039

Tel: (02) 9555 1225 Fax: (02) 9810 4022 Web: www.etmc.com.au

Modular *Platform*

Type 2250's combination of software modules and innovative hardware makes the analyzer a dedicated solution for high-precision measurement tasks, in environmental, occupational and industrial noise application areas.

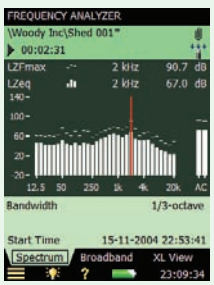
New software modules can easily be added, thus giving you the option of adding more functionality as your measurement requirements change. This way the platform ensures that your investment is securely protected now and in the future.

Currently available applications include:

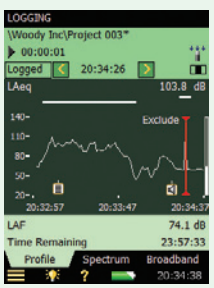
- **Frequency Analysis Software** – for real-time analysis of 1/1- and 1/3-octave bands
- **Logging Software** – log broadband data and spectra at intervals from 1 s to 24 h
- **Enhanced Logging Software** – for continuous monitoring and logging of periodic reports
- **Sound Recording Option** – record measurements signals to identify and document sound sources

Type 2250 has been designed in co-operation with users to be easy, safe and clever.

For more information please contact your local sales representative or go to ***www.type2250.com***



Frequency Analysis Software



Logging Software

Enhanced Logging Software

Sound Recording Option

BA 0848 – 11

Hand-held Analyzer *Type 2250*

HEADQUARTERS; DK-2850 NÆRUM • DENMARK • TELEPHONE: +4545800500
FAX: +454801405 . HTTP://WWW.BKSV.COM . E-MAIL: INFO@BKSV.COM

Brüel & Kjær Australia
Suite 2, 6-10 Talavera Road, P.O. Box 349, North Ryde NSW, 2113 Sydney
Tel: +61 2 9889 8888 Fax: +61 2 9889 8866 • www.bksv.com.au • bk@spectris.com.au

MELBOURNE: Suite 2, 2 Compark Circuit, Mulgrave, Victoria, 3170 Melbourne
Tel: +61 3 9560 7555 Fax: +61 3 9561 6700 • www.bksv.com au • bk@spectris.com au

Brüel & Kjær