UNIVERSITY OF SOUTHAMPTON

IMPROVING ACQUISITION OF AUDITORY EVOKED POTENTIALS FOR CLINICAL DIAGNOSIS AND MONITORING

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PhD THESIS

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ABSTRACT

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Doctor of Philosophy

IMPROVING ACQUISITION OF AUDITORY EVOKED POTENTIALS FOR CLINICAL DIAGNOSIS AND MONITORING

by Steven Lewis Bell

Auditory evoked potentials (AEPs) represent the response of the brain to an auditory stimulus and they are recorded using electrodes placed on the scalp. They have a number of clinical applications including estimating hearing threshold, detection of pathology in the auditory pathway and possibly indicating depth of anaesthesia during surgical procedures. The aim of this study was investigate new methods to improve the acquisition of AEPs for clinical monitoring purposes.

The approach adopted has been primarily to optimise the stimulation used to elicit AEPs, rather than focusing on signal processing to improve extraction of the signal from background noise. New stimulation methods to acquire AEPs have been investigated using normative experiments. Two such experiments investigated three possible methods to improve acquisition of the AEP known as the Middle Latency Response (MLR). These methods were a) varying conventional stimulation rate b) using high maximum length sequence (MLS) stimulation rates (a form of pseudorandom binary sequence) and c) using chirp stimuli (rising frequency sweeps) designed to compensate for frequency dispersion on the basilar membrane. The use of chirp stimuli presented at high MLS stimulation rates appears to reduce the acquisition time of the MLR significantly compared to conventional stimulation methods.

The use of band-limited chirp (rising frequency sweeps across a limited frequency range) stimuli to obtain the Auditory Brainstem Response (ABR) was also investigated. The use of such stimuli appear to produce better objective estimates of low frequency thresholds than have been reported for other transient stimuli such as tone bursts. This is consistent with the chirp stimuli improving the neural synchrony of low frequency responses, although it may be a consequence of the spread of excitation to high frequencies. As the stimuli have significant spectral spread, their clinical application to assess frequency specific thresholds may be limited.

Finally a clinical feasibility study investigated the MLR evoked with MLS-chirps as a potential indicator of depth of anaesthesia, on patients awaiting heart surgery. The MLR was recorded from patients as they were anaesthetised prior to surgery. They were allowed to emerge from the anaesthetic, then re-anaesthetised and corresponding changes in the MLR were tracked. Recordings did not appear to show a shift in MLR latency with anaesthesia, which has been reported previously. Rather there was a categorical change in the amplitude of the MLR with conscious awareness. The MLS-chirp evoked MLR probably has potential as an indicator of conscious awareness, but does not shown the graded change required to indicate depth of anaesthesia. A larger study with good recording conditions is needed to confirm this finding.

The approach of improving the stimulation used to generate AEPs appears to produce significant benefits in the acquisition of the signals. These benefits may lead to improvements in clinical diagnosis or monitoring. However, further research is needed to assess their clinical significance.

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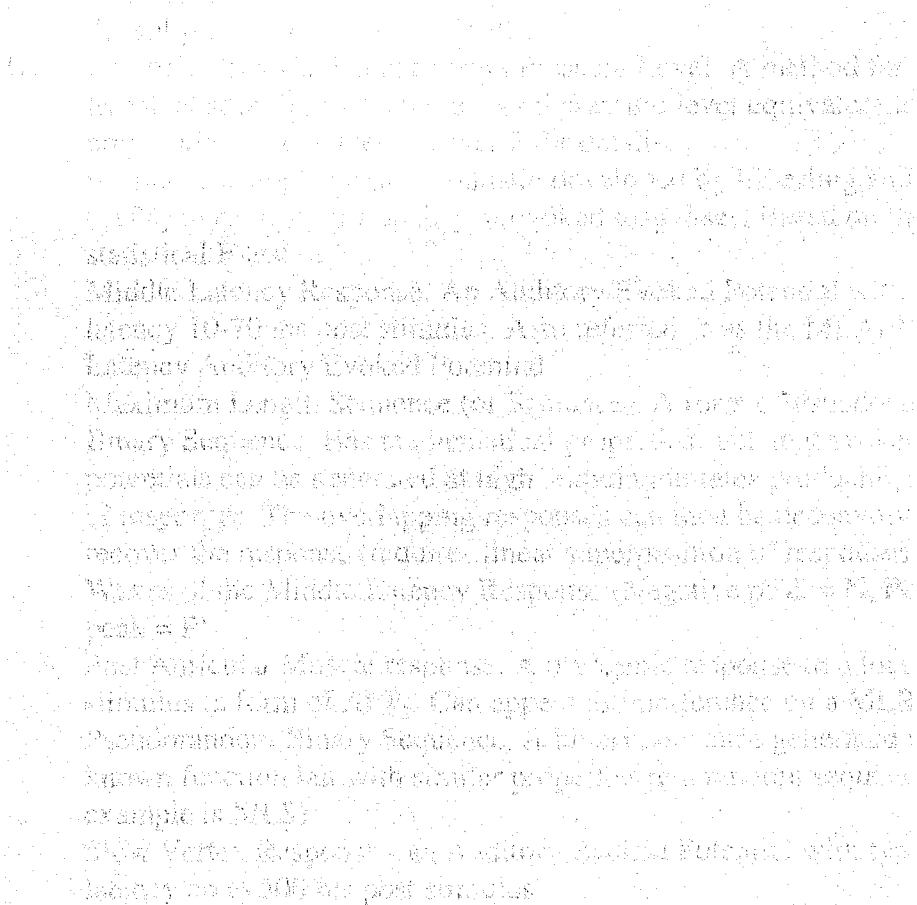


LIST OF ABBREVIATIONS

ABR	Auditory Brainstem Response - an Auditory Evoked Potential with typical latency less than 10 ms post stimulus
AEP	Auditory Evoked Potential - a neural potential evoked by an auditory stimulus such as a click. Can be recorded using surface electrodes on the scalp or depth electrodes
ARMA filter	Autoregressive Moving Average filter. A general form of parametric digital filter
ARX modelling	Autoregressive modelling with Exogenous input. An estimate of a signal in noise produced by parametric filtering of a known reference signal to produce the least squares match with the noisy signal
BIS	Bispectral Index. A parameter derived from the EEG as a possible indicator of depth of anaesthesia.
CED	Cambridge Electronic Design
ECG	Electrocardiogram. The electrical activity generated by the heart. It is usually monitored during anaesthesia.
EEG	Electroencephalogram. The electrical activity generated by the brain. A source of noise when recording AEPs.
dB nHL	Decibels Normal Hearing Level. The level of the stimulus above the average threshold of a group of subjects (to the stimulus) in dB.
dB SL	Decibels Sensation Level. The level of the stimulus above the threshold of the subject (to the stimulus) in dB.
dB p.e. SPL	Decibels Peak Equivalent Sound Pressure Level. A method for calibrating transient stimuli in which the sound pressure level equivalent to the peak amplitude is found (see Chapter 2 for details).
F_{sp}	F value at a single point. A statistic developed by Elberling and Don (1984) to estimate the quality of evoked responses. Based on the statistical F-test
MLR	Middle Latency Response. An Auditory Evoked Potential with typical latency 10-70 ms post stimulus. Also referred to as the MLAEP – Middle Latency Auditory Evoked Potential
MLS	Maximum Length Sequence (or Sentence). A form of Psuedorandom Binary Sequence. Has mathematical properties such that evoked potentials can be generated at high stimulation rates producing an overlap of responses. The overlapping responses can then be deconvolved to recover the response (requires linear superposition of responses)
N_a, P_a, N_b	Waves of the Middle Latency Response (Negative peak = N, Positive peak = P)
PAM response	Post Auricular Muscle response. A myogenic response to a loud acoustic stimulus (a form of AEP). Can appear as interference on a MLR recording
PRBS	Pseudorandom Binary Sequence. A binary sequence generated with a known function but with similar properties to a random sequence (an example is MLS)
SVR	Slow Vertex Response - an Auditory Evoked Potential with typical latency up to 500 ms post stimulus
VEP	Visual Evoked Potential - a neural potential evoked by a visual Stimulus
± difference	Plus/minus difference. A technique developed by Wong and Bickford (1980) to estimate the quality of AEPs based on comparing two subaverages of the AEP
Wave V	Wave five of the ABR. The largest wave of the ABR occuring at around 6 ms post stimulus.

CHAPTER 1

Introduction and Background

1.1 Introduction : Auditory Evoked Potentials and the problem of signal-to-noise ratio

Auditory Evoked Potentials (AEPs) represent the response of the auditory pathway to an auditory stimulus, typically a click presented through headphones. The response of the auditory pathway is recorded using surface electrodes placed on the scalp. AEPs vary in amplitude from tenths of a microvolt to a few microvolts and are embedded in the spontaneous Electroencephalogram (EEG) waveform which has an amplitude typically of 10 to 30 μV (Elkfafi et al, 1997). Thus the signal-to-noise ratio (SNR) is less that 1:10 (–20 dB). This poor SNR must be improved in order to obtain repeatable responses and this leads to a long acquistion time. The traditional method for improving the SNR of AEPs is to use a synchronised ensemble average of many successive responses, where the onset of the stimulus triggers the synchronisation process. Theoretically, for n averages the SNR

increases by a factor $\sqrt{n}$. Typically 1-2000 averages are needed in order to obtain a clear waveform. The large number of averages required results in a long acquisition time.

Reducing the recording time of AEPs is almost always desirable, either because there is limited time available to make a recording on a subject or because a large number of recordings have to be made. The question therefore arises as to whether the acquisition of AEPs can be improved. This question is the focus of this thesis.

A specific application of using AEPs where acquisition time of the response is critical, is the use of the AEP known as the Middle Latency Response (MLR) to indicate depth of anaesthesia during surgical procedures. Improving the acquisition of the MLR for this purpose has been a goal of this study. Therefore, much of the discussion regards the MLR.

1.1.1 The approach and structure of the Thesis

Once technical aspects of experimental design have been optimised, a number of techniques may be used to improve the acquisition of AEPs compared to conventional averaging using click stimulation. These fall into two broad categories : 1) signal processing techniques which aim to produce the best estimate of the underlying AEP and minimise the effects of noise; 2) signal generation techniques in which the evoking stimulus is optimised in order to generate a better AEP. A discussion of these techniques is covered below.

Any estimate of the underlying evoked potential will improve as more data are collected and so the invariant evoked response can be better extracted from the noise. However, ultimately any signal estimation technique will be fundamentally limited by the magnitude of the underlying response relative to the background noise. Therefore the approach of this study will be to focus on optimising the evoking stimulation which generates the AEP, as any improvement in the generation of the response will lead to an improvement in the estimate of the response. In particular the use of maximum length sequence and chirp stimulation to improve the generation of AEPs will be investigated.

Most of the work in the Thesis concerns improving acquisition of the Middle Latency Response (MLR) with a view to estimating depth of anaesthesia, although one investigation of the acquisition of the Auditory Brainstem Response (ABR) with band-limited stimuli is included. The structure of the thesis is as follows :

The rest of Chapter 1 is intended as background and describes the origins of AEPs and techniques that may be used to improve acquisition of AEPs.

Chapter 2 is a summary of the experimental methods used in the thesis.

Chapters 3 and 4 investigate the effects of different stimulation paradigms on the acquisition of the MLR. In Chapter 3 the effects of increasing conventional stimulation rate and the use of high MLS stimulation rates on the acquisition time of the MLR are investigated. Chapter 4 is an investigation of the MLR obtained with chirp stimuli designed to compensate for frequency delay on the basilar membrane and also the combination of MLS stimulation rates with such chirp stimuli is investigated.

In Chapter 5, the use of band-limited chirp stimuli to obtain the ABR is investigated.

Although most of the thesis is concerned with stimulus optimisation, Chapter 6 investigates the use of signal processing techniques to enhance AEPs. The properties of the EEG noise, which is present when recording AEPs, is investigated. A comparison of quality estimators is made and the potential use of Bayesian averaging and ARX modelling to improve acquisition of the MLR is investigated.

Chapter 7 is a feasibility study of the MLR as an indicator of anaesthetic depth. The optimal MLR stimulation paradigm found in Chapters 3 and 4 is used to record the MLR from patients undergoing general anaesthesia. The study investigates changes in the MLR as subjects pass between responding (conscious) and nonresponding (unconscious) states.

Finally, Chapter 8 summarises the findings and suggests future research leading on from the investigations that have been performed.

1.1.2 The contribution of the thesis

Although other authors have investigated the acquisition of the MLR using MLS stimulation rates, the rate-adaptation function of the MLR with conventional and MLS stimulation rates had not been fully explored. It is shown in this thesis that there is little adaptation of MLR amplitude with conventional stimulation rate up to 15 clicks/s, so the acquisition time of the MLR can be reduced by increasing conventional stimulation rate. However, a further reduction in acquisition time can be achieved using MLS stimulation rates, where the best stimulation rate found using MLS, out of those tested, is 167 click opportunities/s.

The acquisition of the MLR using chirps designed to compensate for frequency dispersion on the basilar membrane had not been previously investigated. Nor had the combination of such chirps with the MLS technique been explored. This is investigated in Chapter 4. A combination of the two techniques reduces acquisition time of the MLR by an order of magnitude compared to using conventional stimulation at 5 clicks/s.

These findings have been published in two papers in the Journal of the Acoustical Society of America (Bell et al, 2001, and 2002b).

A novel approach to acquiring the ABR using band-limited chirps with frequency-delay characteristics designed to compensate for frequency dispersion on the basilar membrane is explored in Chapter 5. The work was published in the International Journal of Audiology (Bell et al, 2002a). Whilst the approach was novel at the time it was performed, a similar study was carried out concurrently and published by Dau et al (2002).

In Chapter 6 the use of Bayesian techniques to acquire the MLR was investigated. This was found to produce a small reduction in the acquisition time of the MLR. The use of ARX modelling to acquire the MLR was investigated as a function of SNR. The findings suggest that ARX modelling estimates the MLR well for favourable SNR, but does not perform well as SNR reduces. It is possible that previous papers, which have suggested that ARX modelling can acquire the MLR very rapidly, may have had flawed methodology.

The effect of anaesthesia on the MLR evoked using chirps at MLS rates is explored in Chapter 7. This is a novel approach. Only a small number of subjects were included, however the findings point to a categorical change in the amplitude of the MLR with anaesthesia, not the graded change in N_b latency that had been reported in previous studies.

1.2 Background : The origins of Auditory Evoked Potentials

AEPs can be categorised into two types : those evoked by transient signals such as clicks or tone bursts, where the average response to the stimulus is viewed in the time domain, and those evoked by continuous stimuli such as pure tones or amplitude modulated tones, where the response is often viewed in the frequency domain. The former type of AEP might be referred to as transient-evoked auditory potentials and the latter type are often referred to as

steady state AEPs. For this thesis, the discussion will be limited to transient-evoked auditory potentials.

AEPs detected on the scalp represent the superposition of electrical fields arising from the synchronous firing of neurons along the auditory pathway. A transient stimulus such as a click will stimulate different sites along the pathway, each of which may contribute to an electric field detectable on the scalp. The further along the auditory pathway the site lies, the greater the latency of the response will be to the stimulus.

Figure 1.1 below shows how AEPs are typically characterised into the Auditory Brainstem Response (ABR), Middle Latency Response (MLR) and Slow Vertex Response (SVR) on the basis of latency. The ABR occurs from 1-10 ms after the stimulus. It has up to seven waves which are characterised by Roman numerals, the clearest of which are waves I, III and V. The MLR occurs from 11-70 ms after the stimulus. The waves are characterised by N for negative, P for positive and a subscript, with the clearest waves being N_a, P_a and N_b. Finally the SVR occurs up to 300 ms after the stimulus. The waves are characterised by N for negative, P for positive and a suffix. Waves P1, N1 and P2 are shown in Figure 1.1.

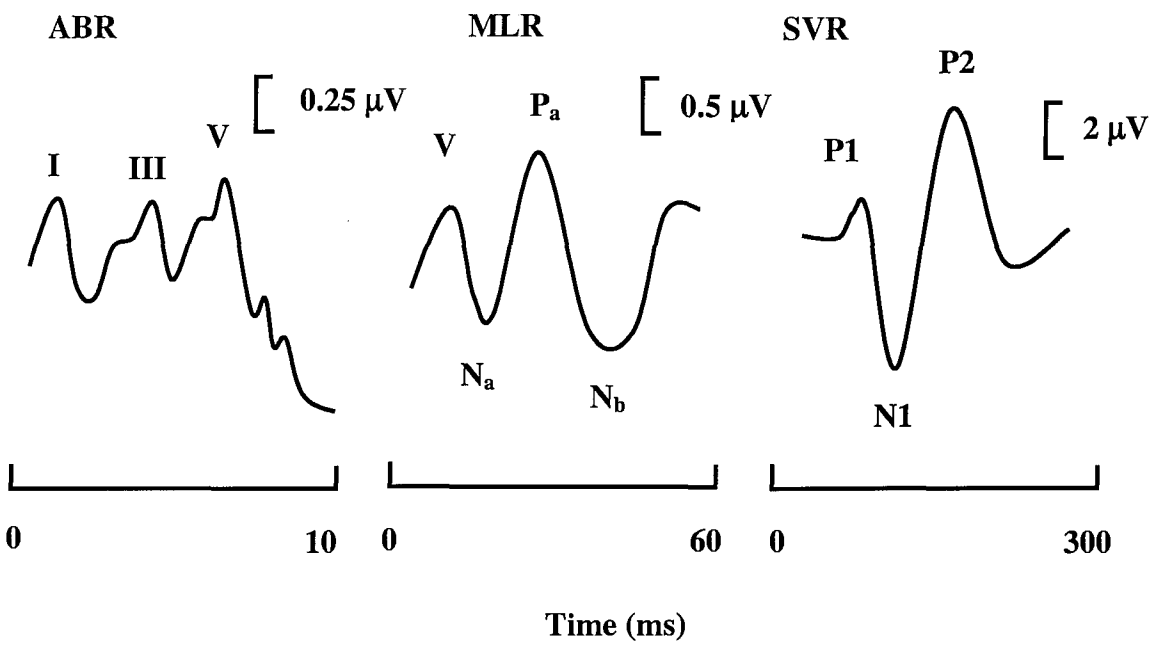
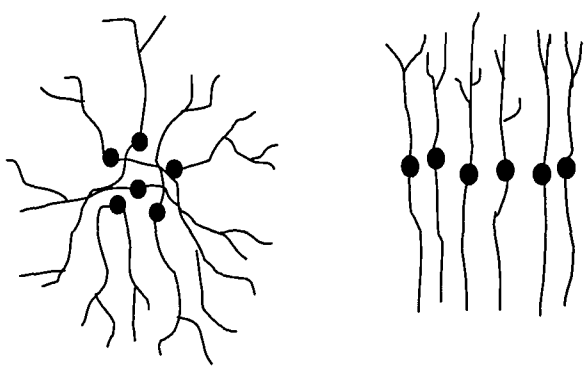


Figure 1.1 The common characterisation of AEPs on the basis of latency. Adapted from Hall (1992).

The neural centres which generate the components of AEPs are affected by the level of arousal of a subject to different extents. Some centres may represent the automatic processing

of sound by the brain, whereas others may be dependent on the state of arousal of the subject and involve conscious processing of sound. The early latency ABR probably represents the activity of autonomous auditory regions which are not under conscious control, as it is not affected by the state of attention of a subject or sleep. Later latency AEPs represent the activity of attention mediated centres. The MLR and SVR are larger in amplitude than the ABR and are affected by attention (Hall, 1992). The MLR may represent a mixture of unconscious and attention dependent auditory centres as it changes with sleep but is not abolished. The SVR is more likely to represent the activity of attention dependent centres only as it is abolished by sleep.

Populations of neurons (cell bodies and dendrites) in the auditory pathway can be considered as stationary electrical dipoles. The way in which the neurons are oriented will determine whether or not they will generate an electrical field that can be detected at the scalp (Cacace and McFarland, 2001). Groups of neurons can be characterised as closed or open field. Where neurons are orientated in many different directions, as shown on the Left panel of Figure 1.2 below, they are termed closed field. When the neurons fire synchronously, the electrical fields of the neurons cancel out, so it will not be possible to detect a far field response from the group of neurons. If instead the neurons are all oriented in similar directions as is shown on the Right panel of Figure 1.2, they will generate a strong electric field when they fire in synchrony which can more easily be detected at the scalp. They are therefore termed open field.



Closed field **Open field**

Figure 1.2 Closed and Open field configurations of neurons. Adapted from Cacace and McFarland (2001).

In auditory centres of the brain there may be a mixture of open and closed field neural orientations. The strength of the electrical field generated by a ground of neurons will decrease with distance, so the likelihood of detecting the field generated by a group of neurons using scalp electrodes will depend how far the recording electrodes are from the

source of the field. It should be easier to detect the field of neurons that lie close to the surface of the brain than those in the centre.

One way to determine the neural origin of AEPs is to insert depth electrodes into the brain. This is usually done on non-human primates and it is assumed that topographical organisation of the auditory pathway is similar, but not identical, to that of humans. In some surgical procedures it is necessary to insert depth electrodes into human brains, for example when trying to identify sources of epilepsy. Data from these procedures can help to identify the sources of human AEPs. The electrode position which generates the largest amplitude signal with the same latency as an evoked potential component can be located. If there is a single generation site for an AEP component, then when a depth electrode passes through the generation site, the polarity of that component should reverse as the electrode passes to the opposite side of the dipole generating the AEP.

For the short latency components of the ABR, the neural generation sites of the components have been identified and are thought to arise from specific generator sites along the auditory nerve and in the brainstem. Wave I arises from the distal portion of the afferent auditory nerves, Wave II from the proximal region of the eighth nerve as it enters the brainstem. Wave III is generated in the cochlear nucleus, wave IV in the superior olivary complex and wave V in the inferior colliculus (Hall, 1992).

For longer latency AEPs such as the MLR and SVR, the evidence for specific neural generation sites is less clear. It is likely that the components of the MLR originate from the primary auditory cortex and thalamus. However, the origin of the waves of MLR has been debated since it was first recorded by Geisler et al (1958). The components of the SVR are thought to originate in the cerebral cortex (Hall, 1992).

Lee et al (1984) attempted to localise the neural origin of the MLR in patients with seizure disorders, using an array of 16 subdural stainless steel disc electrodes during temporal craniotomies. They found that electrodes on the banks of the sylvian fissure (50 to 69 mm from the tip of the temporal lobe) demonstrated the largest auditory evoked response for latencies consistent with the P_a component of the MLR. Woods et al (1987) reviewed investigations of five patients with localised lesions in both temporal lobes. Their evidence suggests that the thalamic medial geniculate body may be the generator of the N_a component of the MLR. However, more recent studies with depth electrodes have failed to find specific origins for late latency AEPs (Cacace and McFarland, 2001). It is likely that the later latency

AEP components represent the superposition of activity from several regions of the brain, not just one specific region.

An alternative to using depth electrodes to identify the origins of AEP components is to use dipole modelling (Ponton et al., 2002). The AEP is recorded simultaneously from an array of electrodes over the head and a dipole source is mathematically identified which would produce a corresponding spread of electrical activity. The technique assumes a single dipole source for the components, which may not be true. However, dipole modelling of late latency AEPs suggests origins within the primary and secondary auditory cortices (Scherg and von Cramon, 1986).

1.3 Applications of Auditory Evoked Potentials:

1.3.1 The Middle Latency Response and measurement of anaesthetic depth

Monitoring the depth of anaesthesia of patients undergoing surgery is a major task for anaesthetists. It is used to prevent patient perception of pain, awareness and recall and it prevents untoward effects of excessively deep or light anaesthesia, minimises stress and facilitates prompt emergence from unconsciousness when required.

In the operating theatre, a patient undergoing surgery is generally given both a muscle relaxant, to prevent unwanted reflexes occurring to surgical stimulation, and an anaesthetic agent to induce a state of unconsciousness and hence prevent awareness of the surgical procedure. Once a patient is given a muscle relaxant, they are paralysed and would be unable to move and indicate if they regained awareness during surgery. It is therefore highly desirable to be able to monitor the state of consciousness of a patient to make sure that they are maintained at a sufficient depth of anaesthesia. In recent years there have been some rare but widely documented cases of patients that have reported being conscious during surgical procedures. This is particularly a risk in procedures where anaesthesia is kept to a minimum, such as caesarean section.

1.3.1.1 Defining depth of anaesthesia

Anaesthesia is defined as a loss of sensation (partial or complete), with or without loss of consciousness, which may be drug induced or due to disease or injury. An anaesthetic agent can either be intravenous or inhaled. The exact action of anaesthetic agents is still unknown and a large number of substances have an anaesthetic effect. Adequate anaesthesia can be defined as a sufficient level of analgesia, depression of autonomic reflexes, muscle relaxation and unconsciousness or amnesia, although not all of these are necessary during some types of surgery. For example some surgical procedures do not require a muscle relaxant to be administered. Depth of anaesthesia may be described according to different schema. According to one schema (Kaufmann, 1993) there are four stages of anaesthesia: 1 Analgesia (no feeling), 2 Delirium, 3 Surgical anaesthesia and 4 Medullary depression. In this schema a patient should be maintained at stage 3 during surgery. Stages 1 and 2 represent inadequate anaesthesia and stage 4 excessive anaesthesia.

Once a patient is unconscious, the extent of awareness is hard to define. The ability of a patient to repeatedly squeeze the anaesthetists hand on asking is one measure of awareness, but can only be used at a light stage of anaesthesia. Furthermore, if this technique is to be used in conjunction with a muscle relaxant, the blood supply to the arm must be stopped in order to prevent the relaxant affecting the arm muscles, the so called 'isolated arm technique' (Tunstall, 1977). However, this cannot be maintained for more than a few minutes due to risk of ischaemic paralysis to the arm.

At present clinical signs, such as heart rate, blood pressure and sweating are frequently used to indicate depth of anaesthesia in clinical practice. However, they cannot provide information regarding central processing capacity and therefore do not measure the level of awareness of a patient. A reliable measure of depth of anaesthesia would reduce the risk of a patient experiencing too light, or too heavy a depth of anaesthesia during surgery.

1.3.1.2 Desirable characteristics of a measure of anaesthetic depth

A measure of depth of anaesthesia needs to be sensitive to changes in depth of anaesthesia, even when a patient is unconscious. For many operations a measure would need to be unaffected by the injection of a muscle relaxant. If standardised values are to be taken to indicate when a subject is unconscious, then the measure would need to exhibit low inter-subject variability. However an alternative would be to calibrate the measure for each individual, for example the day before surgery or in theatre before a muscle relaxant is

introduced. In this case inter-subject variation is less critical, but intra-subject variability with anaesthetic depth needs to be low. Thornton and Newton (1989) suggest that a measure should 1) show graded changes with anaesthetic concentrations, 2) show similar changes for different agents, 3) show appropriate changes with surgical events and 4) indicate awareness or very light anaesthesia.

1.3.1.3 Electophysiological measures of neural activity and depth of anaesthesia.

Various electrophysiological measures of neural activity have been investigated with a view to providing an indicator of depth of anaesthesia. Early studies focused on the electroencephalogram (EEG) to try and provide such a measure. Interest in the EEG began when Emmons and Simon (1956) demonstrated that information presented during sleep could not be recalled upon awakening unless presentation coincided with EEG alpha activity, indicating that the EEG might indicate when learning has occurred. Subsequent to this, the potential use of auditory signals in determining state of awareness was highlighted when Oswald et al (1960) showed that subjects could discriminate between presented sounds even in the deepest stages of sleep. Hence AEPs have also been investigated as possible indicators of depth of anaesthesia.

A number of recent studies have found AEPs to be more reliable indicators of depth of unconsciousness than the EEG (Jones 1989, Thornton, 1991). For example Gajraj et al (1998) compared three indices derived from the EEG and one index derived from the MLR in their ability to distinguish the state of consciousness of patients as they passed repeatedly from consciousness to unconsciousness whilst undergoing orthopaedic surgery. The AEP index that they used is derived from the MLR and represents its configuration (Mantzaridis and Kenny, 1997). They found that only the AEP index demonstrated a significant difference on all mean values 1 minute before recovery of consciousness and all mean values 1 minute after recovery of consciousness. Furthermore the AEP index demonstrated the highest sensitivity of all the measures for detecting unconsciousness.

Anaesthetic agents produce differential effects on areas of the auditory pathway and their corresponding AEPs. Although the exact action of anaesthetics are unknown, they are thought to interrupt synaptic transmission (Kaufman, 1993). They should therefore have a greater effect on neuronal pathways with a larger number of synapses. Such pathways are found higher in the auditory pathway.

Responses dependent on the cochlea, auditory nerve and brainstem (ECochG and ABR), which are low in the auditory pathway, are not materially influenced by anaesthesia. Therefore they are unlikely to be sensitive to changes in anaesthetic depth. In contrast the far field, extralemniscal AEPs (MLR and SVR) involve multisynaptic nonlemniscal pathways and are sensitive to suppression by anaesthetic agents. The SVR is abolished when a patient becomes unconsciousness. It is therefore too sensitive to be used as a measure of depth of anaesthesia once a patient becomes unconscious.

The MLR remains when a patient becomes unconscious, but changes in configuration. The MLR therefore has potential in assessing depth of anaesthesia. A suitable measure of anaesthesia would need to be sensitive to changes in depth of anaesthesia and to have a midpoint at around the required depth. Figure 1.3 demonstrates sterotypical functions relating depth of anaesthesia to a suitable measure derived from the three AEPs. It is clear that the MLR changes most suitably at a moderate depth of anaesthesia.

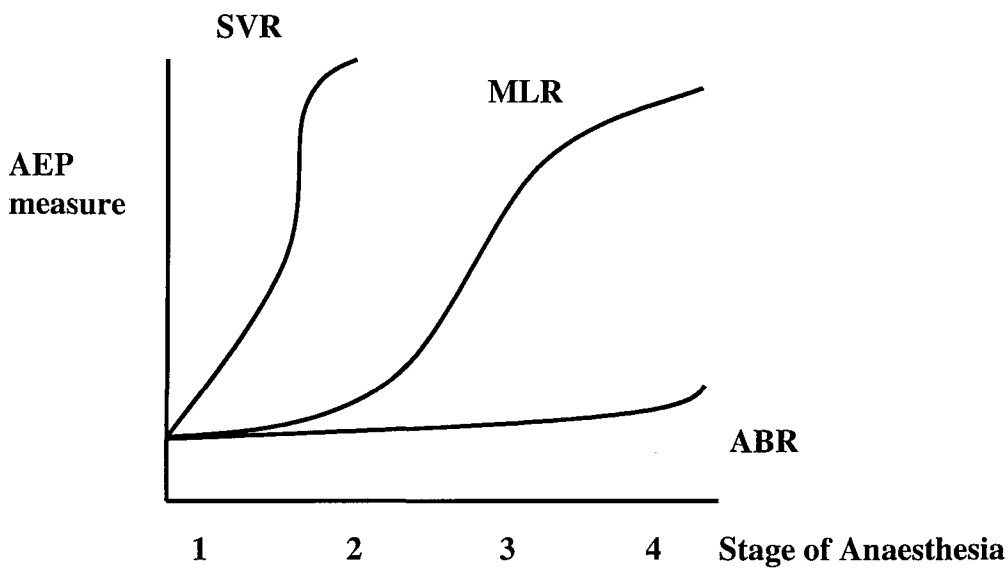


Figure 1.3 Possible relationships between AEP measures and anaesthetic depth

The function shown in Figure 1.3 might be expected if increasing concentration of anaesthetic in the brain progressively disrupts the generator sites of the MLR. An alternative hypothesis may be that the generation sites of the MLR are sensitive to the state of arousal of a subject. In which case the hypnotic action of an anaesthetic may produce a categorical change in the MLR between awake and sleep states. Such a hypothesis would imply that the MLR would be a suitable indicator of conscious awareness, but might not show the graded change with anaesthetic concentration that would make it a suitable indicator of anaesthetic depth.

The exact relationship between MLR components and awareness is unresolved (Jessop and Jones, 1992). Some papers report that anaesthetics induce a change in peak latency and others report a change in amplitude. However, Thornton and Newton (1989) have demonstrated that both the latencies and amplitudes of the midlatency waves change to both inhaled and intravenous agents. They found that, with increased anaesthetic dose, latency increases and amplitude decreases. Furthermore N_b latencies shorter than 44.5 ms appear to correspond to awareness as demonstrated with the isolated forearm technique. Also, the configuration of the waveform changes so that at light stages of anaesthesia all three peaks are seen, at a moderate depth of anaesthesia only P_a and P_b are seen and at a deeper level of anaesthesia than is desirable, none of the peaks are seen (Elkfafi et al, 1997). Several papers have demonstrated suitable indices that can be obtained from the MLR in order to represent its change in configuration (Elkfafi et al, 1997; Webb et al, 1996; Gajraj et al, 1998; Mantzaridis and Kenny, 1997). For example the AEPindex (Mantzaridis and Kenny, 1997) is calculated as the sum of the square roots of the absolute differences in amplitude between every two successive segments of the MLR.

The 40 Hz auditory steady state response is also an AEP and is seen as a sinusoidal signal when click stimuli are presented to a subject at 40 Hz. It is thought to be generated by the synchronisation of components of the MLR. Munglani et al (1993) have shown that, for volunteers breathing subanaesthetic doses of isoflurane, the optimal stimulating frequency needed to obtain a steady state response drops from 40 Hz with increasing anaesthetic concentration. This is thought to be due to the increased latency of the MLR. Whilst the 40 Hz steady state response may appear to present an alternative to the middle latency response in measuring depth of anaesthesia, Manglani et al found that the 40 Hz response was very sensitive to slight changes in anaesthetic depth. They concluded that it would be too sensitive to be used as a measure of the deeper stages of anaesthesia and that the response was probably too difficult to maintain in practical situations.

1.3.1.4 Factors affecting the Middle Latency Response

A number of factors can influence the configuration of the MLR. These need to be taken into account if the MLR is to be used as a measure of anaesthetic depth.

Stimulus intensity

As click intensity level increases up to 40-50 dB SL, the latency of the MLR systematically decreases, but above 50 dB SL the latency remains constant. ('SL' stands for sensation level

and refers to the level above the threshold of the subject at which the stimulus is presented.) MLR amplitude, however, increases steadily up to 70 dB SL (Madell and Goldstein 1972). When the MLR is used to measure depth of anaesthesia in surgery, it is desirable to obtain a clear trace, with large amplitude peaks; hence stimuli levels of 70 to 80 dB SL are typically used. However high stimulation levels should be used with caution as they may become uncomfortable for the subjects. Furthermore, such high stimulus levels may not be used in normal conscious subjects as the post-auricular muscle response (PAM) interferes with the measurement of the MLR at high stimulus intensities. It may therefore only be possible to use levels up to 60 dB SL in normal, conscious subjects.

Attention

In awake subjects, attention has been shown to affect amplitude of the N_a peak of the MLR. Picton et al (1974) summarise the effects of attention on the MLR. The amplitude of the MLR was measured as subjects either attended, or ignored, a stimulus. The results are shown in Table 1.1

Wave	latency (ms)	Amplitude Attend (μv)	Amplitude Ignore (μv)	Significance (p)
N_a	16	0.34	0.29	0.05
P_a	25	0.62	0.59	n.s.
N_b	36	0.49	0.49	n.s.

Table 1.1 Effect of attention on the MLR

It can be seen that for the N_a wave, there was a significant difference in amplitude between the conditions when subjects attended to the clicks stimuli and when they did not. When normative MLR experiments are to be done, it is therefore desirable to instruct all subjects the same way regarding attention (e.g. to relax, but to listen to the stimulus.)

Temperature

Hett et al (1995) have shown that MLR latency may be increased and amplitude decreases when the body is cooled to temperatures of 25°C or less during surgical procedures such as open heart surgery. Whilst this will not affect studies using normal, awake subjects, it will

need to be taken into account if the MLR is to be used to estimate depth of anaesthesia in patients undergoing such surgical procedures.

Sex

There is some evidence that MLR components are shorter in latency and larger in amplitude in female, compared to male subjects. However, the magnitude of the difference is small and has not always been shown to be statistically significant (Hall, 1992).

Age

There is some doubt as to whether a MLR can be reliably obtained in children under the age of 8 years and it is therefore doubtful whether it can be used as an indicator of depth of anaesthesia in such young children (O'Kelly et al, 1995). The amplitude of the MLR decreases with advancing age and the latency increases (Hall, 1992). Although this will not affect measurements taken from young, otologically normal subjects, it will need to be taken into account if the MLR is to be used as a measure of depth of anaesthesia in older adults.

Middle ear pressure

Middle ear pressure may alter with the use of certain anaesthetic agents. For example, O'Neill (1985) has shown that the middle ear pressure of patients undergoing general anaesthesia with nitrous oxide varies during the course of the operation and that post-operative middle ear pressure correlates with the theoretical partial pressure of nitrous oxide in the middle ear cleft. A change in middle ear pressure could effect the transmission of sound through the middle ear and hence may effect a MLR elicited using auditory stimuli.

1.3.1.5 Closed loop control systems and depth of anaesthesia

Closed loop control of depth of anaesthesia is a long term goal of research anaesthetists and biomedical control engineers. Once a measure of depth of anaesthesia has been obtained, it can be incorporated into a control system to control the rate of infusion of an intravenous anaesthetic. The system could be used to induce anaesthesia to a desired depth as quickly as possible and to maintain that level despite surgical stimulation. Progress has been made in using such automatic control systems in medical applications. Both blood pressure and muscle relaxation can be maintained at desired levels using such control techniques.

Webb et al (1996) have demonstrated the feasibility of an anaesthetic control system using the MLR. They demonstrated that a neural network has potential to obtain a measure of the N_b wave latency of a MLR waveform. This latency could then be input into a controller which could control the anaesthetic infusion rate to a patient. The applicability of such a closed loop control system will depend on the quality of the input it receives (the MLR waveform), in addition to other factors such as inter- and intra-subject reliability and the sensitivity of the index to the actual depth of anaesthesia. Hence, it is important to refine the measurement of the MLR before it is used for such a closed loop control system.

1.3.1.6 The problem of MLR acquisition time

The time it takes to obtain a good MLR recording will affect its responsiveness as an indicator to changes in anaesthesia. Typically to obtain an MLR trace when monitoring depth of anaesthesia in surgery, a rolling average of 1000 clicks is used which is regularly updated (say every 50 clicks). It is the responsiveness of the change in this moving average estimator to a change in anaesthesia that is crucial. At 6.12 clicks per second, averaging 1000 clicks to fully update the average takes 163 seconds. This is too slow for the purpose of a control system, which would need to respond rapidly to changes in the state of anaesthesia of a patient. If a closed loop control system is to be developed using the MLR, acquisition time needs to be reduced.

1.3.2 The Auditory Brainstem Response and assessment of hearing sensitivity

Objective testing of hearing sensitivity aims to estimate hearing thresholds in subjects without requiring their co-operation. This has practical application when they are unwilling or unable to co-operate with behavioural testing, perhaps because they have not yet reached a sufficient stage of development. The importance of objective testing in audiology is increasing with the introduction of universal neonatal hearing screening, which aims to detect children with a hearing impairment as young as 6 weeks. This screening typically takes the form of otoacoustic emission (OAE) testing followed by ABR testing using broadband click stimuli. Whilst these methods can give an indication of the overall level of hearing impairment, neither gives an unequivocal frequency-specific assessment of hearing threshold. Accurate frequency specific information can be obtained by using behavioural testing methods, such as distraction testing or visual reinforcement audiometry, which cannot be applied until around 6 months developmental age and which become more accurate with increasing age (Moore et al, 1977; Bamford and McSporran, 1993). This means that children who require a hearing aid may encounter a delay between the detection of hearing loss and

the age at which it is possible to obtain sufficient frequency-specific information to fit the aid accurately. It is therefore desirable to develop a frequency-specific objective test method for infants. To obtain low recording noise, responses need to be recorded from infants as they sleep. Responses which are abolished by sleep, such as the SVR, are not suitable for this application. However, the ABR is not affected by sleep.

The ABR is normally elicited using click stimuli and the objective threshold obtained using clicks has been shown to correspond best to behavioural thresholds in the 2-4 kHz frequency range (Coats and Martin, 1977). In order to produce a frequency-specific ABR, different stimulation paradigms have been used. These include tone bursts (Gorga et al, 1988; Hayes and Jerger, 1982), clicks presented simultaneously with ipsilateral high-pass noise (the 'derived response' technique: Teas et al, 1962; Eggermont and Don, 1982) and click or tone bursts presented in notched noise (Picton et al, 1979; Stapells and Picton 1981). ABR have also been recorded using tone bursts delivered by bone conduction (Kramer, 1992). Using these methods it is possible to obtain acceptable estimates of high frequency thresholds in the range 2-4 kHz. However, low frequency thresholds estimated using these methods do not agree well with behavioural thresholds and have a large variance. For example, Gorga at al (1988) obtained average thresholds of 10 dB SL (SD 5 dB) with high frequency tone bursts, but these increased to 35 dB SL (SD 15 dB) for low frequency tone bursts. There is also evidence that the responses to different frequency tone bursts at high stimulation levels arise from the same point on the cochlea as their latencies are the same (Burkard and Hecox, 1983). Hence, tone-burst stimuli may only assess the function of basal (high frequency) regions of the cochlea.

An improvement in the estimate of low frequency thresholds using the ABR has been reported when tone-bursts are presented in simultaneous high-pass noise (Stapells et al, 1990). The addition of high-pass noise prevents basal region of the cochlea responding to the tone-bursts. The authors report that responses to tone-bursts in high-pass noise are closer to threshold than those reported for unmasked tone-bursts. However these studies have not used an objective measurement of hearing threshold, but rather rely on the subjective estimate of threshold by authors. It is therefore unclear whether differences in thresholds reported between studies are due to differences in criterion for response presence between authors, or due to differences in the stimuli themselves. In clinical practice, the application of tone-bursts in high-pass noise is more problematic than the use of unmasked tone-bursts.

In general, when the ABR is used to estimate frequency specific hearing thresholds, the estimates of low frequency thresholds do not correspond as well with behavioural thresholds as those for high frequency. It may be possible to improve the transient signal which evokes the ABR in order to obtain a better estimate of low frequency hearing threshold. This idea is developed further in Chapter 5.

1.4 Methods to optimise the acquisition of Auditory Evoked Potentials

As mentioned above, the SNR of AEPs is typically low. The question therefore arises how may SNR be improved? There are a number of approaches to overcoming this problem. A fundamental step to improving SNR is to optimise the technical aspects of signal acquisition (e.g. electrode montage, filter settings). Once this is done then signal processing or the use of new signal generation techniques may further improve SNR.

1.4.1 Optimising technical aspects of signal acquisition

Many of the problems of recording auditory evoked potentials may be due technical aspects of experimental design. When recording AEPs it is important to take steps to eliminate possible noise sources.

1.4.1.1 Sources of noise

There are many sources of noise that can interfere with the recording of AEPs and these can be either physiological or non-physiological. Physiological sources of noise include the electroencephalogram (EEG) and the electromyogenic potential (EMP). Non-physiological sources of noise include electrostatic potentials, internal instrument noise, electromagnetic interference from radio signals, power line radiation and stimulus transducer radiation (Hyde, 1985). When AEPs are recorded in an operating theatre, much of the equipment in theatre may be a source of non-physiological noise.

Hansson et al (1998) has attempted to characterise the noise sources when recording AEPs during surgery. These are identified as :

i. The EEG - hundreds of microvolts in amplitude and decreases with anaesthetic depth.
ii. Electromyogenic activity - from eye blinks or other muscles. It increases in the conscious state and overloads amplifiers. During surgery it is reduced by muscle relaxants.

iii. Electrode polarisation - After a long time the conductive paste and the skin can act as a galvanic element. This is a low frequency, high amplitude disturbance which results in amplifier saturation.
i.v. Other electrical sources – (e.g. diathermy) at line frequency (50 Hz). This is at the same frequency as the MLR and also overloads A-D converters.
v. Sampling quantisation which introduces a small amount of white noise (and is probably small with modern sampling technology and reduces further with signal averaging.)

If non-physiological noise sources can be minimised from the experimental design, the physiological noise of the subject will still remain (e.g. electromyogenic activity and the EEG). Generally physiological noise reduces as a patient becomes unconscious.

1.4.1.2 Noise properties

If AEPs are to be extracted from background physiological noise, it is important to have some knowledge of the frequency distribution and statistical properties of the noise, the most significant of which is background EEG activity. The frequency content of the EEG lies between 0 to 100 Hz, although most of it lies between 1 to 20 Hz. Within it are characteristic frequency patterns : the delta wave from 0.5-4 Hz, the theta wave from 4-8 Hz, the alpha wave from 8-13 Hz and the beta wave from 13-22 Hz. Changes in the properties of the EEG are induced by changes in anaesthetic depth, however, studies have shown the MLR to be a more reliable indicator of anaesthetic depth than the EEG (see above).

Assessment of the statistical properties of the EEG has shown that the EEG generating process can be described as Gaussian two thirds of the time (Elul, 1969). It is usually assumed that the noise during AEP recordings is Gaussian (although one third of the time it is non-Gaussian). Bender (1992) suggests that the human EEG during anaesthesia can generally be considered the result of a Gaussian stochastic process.

McEwen and Anderson (1975) suggest that the EEG is stationary for short periods (less than 10 s). Short periods of the EEG that are stationary can be modelled by an autoregressive model with white noise input (Bromm and Spreckelsen, 1988). The stationarity of the EEG may depend on the task that a subject is performing. For example Popivanov and Mineva (1999) show that the EEG is non-stationary before and after a subject performs a mental task. Normally the MLR is recorded from a relaxed subject not performing any activity. Under such conditions variations in the EEG may be reduced.

The EEG is dependent on cortical activity, so it is thought to be independent of short latency AEPs arising from the auditory periphery and cortex. This may not be true for the SVR, which has long latency components which are also dependent on cortical activity.

1.4.1.3 Practical noise reduction techniques

Hall (1992) and Hyde (1985) summarise methods used to reduce noise when recording AEPs. These include removing noise sources, improved screening of the test room and connection cables, better electrode placement, relaxing the subject, differential amplification, band-pass filtering and artefact rejection. These are described in turn below. Thornton et al (1995) describe the use of a system for recording the MLR and somatosensory evoked potentials during surgery which utilises both radio frequency screening and fibre optic links to isolate the amplifiers electrically from preamplifiers. They report that such a system can significantly decrease interference from diathermy when recording AEPs during surgery.

1.4.1.4 Differental amplification

This technique is always used when recording AEPs. The signal from the reference electrode (relative to ground) is subtracted from the signal of the active electrode (relative to ground). When recording AEPs, the leads from the electrodes are placed close together, so non-physiological sources of noise, such as radio interference or mains interference, will induce almost identical signals in the active and reference electrodes. When the signals from the active and reference electrodes are subtracted from each other, such interference is almost completely eliminated.

1.4.1.5 Electrode impedance and placement

When the electrodes are placed on the scalp of the subject, it is important to reduce the impedance of the electrodes as much as possible and to balance the impedances (so that they have similar magnitudes), so that the AEP signal is well coupled with the isolation amplifier. This will reduce the amount of interference which is picked up by the isolation amplifier. The impedance is reduced by preparing the skin with an abrasive paste and then cleaning the skin with alcohol. An impedance of 5 kΩ or less is generally considered acceptable when recording AEPs, although the impedance that can be achieved in practice will depend on the skin of the subject. Ideally the impedances should be balanced to within 2 kΩ of each other.

The magnitude of AEPs on the scalp varies with position (Hall, 1992). In order to optimise the recording of a given AEP, it is important to place the active electrode where the response has greatest magnitude. The optimal position will depend on the type of response that is being recorded, though the optimal electrode positions for recording AEPs tend to be C_z (vertex of the head) for the active electrode with a non-encephalographic reference electrode.

1.4.1.6 Artefact reduction

When recording AEPs, muscle activity is a common physiological source of noise. Myogenic potentials are much larger in amplitude than neurogenic potentials, so the muscle activity is a recording artefact. Epochs containing such artefacts should not be included in the ensemble average. Therefore an artefact rejection algorithm should be employed, where epochs with a peak-to-peak amplitude above a specified value are discarded. The rejection criterion can either be set for all recordings, or varied acording to individual subject's noise levels. Typically a rejection criterion of a few μV is employed when recording AEPs.

1.4.1.7 Relaxing the subject

Physiological noise is increased if a subject is stressed or active. It is therefore desirable to make a subject comfortable and relax them as much as possible when recording AEPs. Also, the post auricular muscle will contract in response to high auditory stimulus intensities and this can be a strong source of physiological noise when high stimulus levels are to be used. It can be minimised by positioning the subject so that their neck is relaxed and slightly extended (but not so much that it is uncomfortable).

1.4.1.8 Band-pass filtering

In order to obtain an MLR trace, high and low-pass filters are used to exclude unwanted electrophysiological noise. However filter settings can greatly effect the morphology of the MLR. Distortion caused by filter settings can lead to reduced peak amplitude and latency shifts (Hall, 1992). Early studies of the MLR typically used settings of 30 to 100 Hz. However, most of the power of the MLR is in the 20-40 Hz region and Scherg (1982) has shown that such filter settings lead to significant distortion of the MLR. The high-pass filter cut off in particular is critical and needs to be sufficiently low so that the MLR is not distorted, but that EEG activity below 15 Hz is excluded. Hall (1992) suggests that optimal filter settings for recording the MLR using an on-line system are from 15 to 1500 Hz and that filters should have a relatively gradual slope (6 dB/octave). Hall suggests that using a low-

pass filter setting below 200 Hz may distort the MLR waveform. However, many authors have used a lower low-pass setting such as 150 Hz (Musiek and Lee, 1997). If an MLR is to be recorded during surgery with a view to measuring depth of anaesthesia, filter settings may be more critical as the amount of electromagnetic noise present in theatre may be high.

Whilst high and low-pass filters can be used to crudely separate the MLR from background noise, digital filters, such as ARMA or adaptive filters, which are described in detail later, can have much more complex frequency responses than simple high or low-pass analogue filters. Such filters can be optimised to separate the MLR from the background noise using algorithms such as least mean squares. If such digital filters are employed, then simple high and low-pass filters need only be utilised to exclude extremes of frequency from the data before optimal digital filtering of the data occurs.

1.4.2 Signal processing techniques

Once the technical aspects of experimental design have been optimised to produce the highest amplitude AEP and to minimise sources of noise during recording, the AEP will still be embedded in high levels of noise. The recorded signal must therefore be processed to extract the AEP. There are a number of signal processing techniques which may be used for this purpose.

1.4.2.1 Conventional ensemble averaging

The traditional method for improving the SNR when recording auditory evoked potentials is to use a synchronised mean of several successive responses, where the onset of the stimulus triggers the synchronisation process. The unwanted noise is assumed to be stationary and uncorrelated to the stimulus. Theoretically, for n averages, the SNR increases by a factor $\sqrt{n}$. An algorithm is used to exclude responses to stimuli that lie outside a specified range, for example muscle artefacts.

Conventional averaging makes no assumptions regarding the frequency content or morphology of the noise or the wanted signal. For a typical MLR recording a click stimulation rate of 6-9 clicks/s is used and around 1000-2000 averages are taken. It therefore takes between approximately 150 and 300 seconds to record an MLR once artefact rejection time is taken into account. This is considered too slow for the purpose of estimating changes in depth of anaesthesia during surgery. Sometimes a moving average of 1000 responses is utilised, which is updated every 50 sweeps or so. However, the moving average will contain

responses to stimuli presented approximately 3 minutes previously, so any rapid changes in the latency of the MLR will be blurred when current responses are averaged with the earlier data.

1.4.2.2 Other types of averaging

Although the conventional averaging approach to AEPs takes the mean of a number of ensembles, there is no reason why the mode or the median could not be taken. Median averaging may place less emphasis on outlying responses. Ozdamar and Kalayci (1999) have shown that the ABR can be successfully recorded using median averaging. They suggest that the waveforms obtained with median averaging are clearer and less susceptible to interference from recording artefacts. Such an approach could be used for the MLR, although it will not improve SNR.

The conventional averaging technique assumes that noise is stationary. However some studies suggest that this may not be the case for periods of more than 10 seconds (McEwen and Anderson, 1975). If the noise is non-stationary and the variance of the noise is varying with time, a Bayesian averaging approach may be beneficial (see below).

1.4.2.3 EEG correlated averaging

If the EEG noise is not stationary during an MLR recording, there may be some areas of the recording where the MLR is better distinguished from the EEG activity than in others. For example there may be regions with low overall EEG activity, or of low activity in certain frequency bands (such as low alpha wave activity.) It may be possible to correlate the averaging process to correspond with certain parameters associated with EEG activity.

Although no studies have looked at interactions between the EEG and AEPs, several studies (Brandt and Jansen; 1991, Brandt et al; 1991) have looked at interactions between the alpha wave component of the EEG and the visual evoked response (VEP). Brandt and Jansen (1991) recorded 1000 VEPs from each of seven subjects. The average VEP magnitude was found to be exponentially related to the magnitude of the pre-stimulus alpha wave activity, hence demonstrating an interaction between EEG and VEP.

It is likely that components of the EEG which contain similar frequencies to the MLR would interfere with acquisition of the MLR. The beta wave of the EEG is one such component and lies in the frequency region 13-22 Hz. This overlaps with the frequencies present in the MLR

(above 15 Hz). It might therefore be useful to carry out a study to investigate whether there is an interaction between the amplitude of the beta component of the EEG and the MLR.

By recording the MLR only when beta activity is below a threshold value, it may be possible to obtain the MLR in a smaller number of averages. Whilst such a technique may obtain a better estimate of the MLR, it may not result in an overall reduction in the acquisition time of the MLR from a subject as it will be necessary to pause the acquisition of the MLR when beta activity is too high, so increasing acquisition time.

1.4.2.4 Bayesian averaging

The process of ensemble averaging to reduce background noise is of most use if the background noise is considered to be stationary, so that the noise component added to each sweep collected is constant. However, in many clinical situations the background noise may be non-stationary. For example the state of relaxation of the subject may vary during a recording. When the subject is tense, noise levels due to muscle tension will be higher than when the subject is relaxed. Whilst artefact rejection will exclude very noisy traces from the average, it is an all-or-none approach, so the noise levels on traces that are accepted may still vary significantly.

If the background noise is non-stationary and varying in magnitude, it may be better to weight traces according to the level of the background noise. Elberling and Wahlgreen (1985) have shown that this can be achieved using Bayesian inference. Bayesian inference operates with three concepts: The *a priori* knowledge, the *likelihood function* and the *a posteriori* information. New information is added to the already acquired *a priori* knowledge through the *likelihood function* to produce updated *a posteriori* information. In the case of AEPs, the current average is the *a priori* knowledge and new sweeps are added to the average to produce *a posteriori* information. Bayesian inference formulates that the individual sweeps must be weighted according to their individual precision. If the background noise is considered to be gaussian distributed noise with a changing variance (where the changing variance represents the non-stationary nature of the noise), the precision of the individual sweep is inversely proportional to the magnitude of the variance when the sweep is acquired.

However, Elberling and Wahlgreen (1985) have shown that owing to the characteristics of the background noise, it is not possible to estimate with confidence the variance of the background noise from one sweep. Rather the variance can be estimated from a block of sweeps (for example 250) using the single point technique. Therefore, to produce a Bayes

estimate of the evoked potential, subaverages of each block of sweeps are calculated and a weighted average of the subaverages is calculated, with the contribution of each block being weighted by the reciprocal of the variance for that block.

Elberling and Wahlgreen (1985) recorded 50 ABRs from 10 consecutive patients at a level of 115 dB p.e. SPL (see Chapter 2 for a description of peak equivalent (p.e.) SPL). The quality of the recordings was estimated using the F_{sp} method (Elberling and Don, 1984) with an analysis time window from 1 to 11 ms. In none of the 50 recordings was the Bayes estimate inferior to the conventional average. In 30% of the cases a significant improvement in F_{sp} was seen and the average improvement in F_{sp} ranged from 1.1 to 2.4 times with a median of 1.47 times. They estimated that in 30% of the cases, 50% more sweeps would be required for the conventional average to obtain the same quality as the Bayesian estimate. Such an approach may reduce the acquisition time of AEPs, as a smaller number of sweeps would be required to produce the same signal quality when Bayesian averaging is used instead of conventional averaging.

1.4.2.5 Digital filtering

The process of extracting an AEP from noise can be considered as a process of filtering. Analogue band-pass filters are often used when recording AEPs to eliminate unwanted noise. By using digital filtering, it may be possible to calculate the optimal filter to extract the AEP from the background noise.

The principles of Autoregressive Moving Average (ARMA) digital filtering are described in a number of texts (e.g. Brown and Hwang, 1992). A general form of a digital filter is that an input signal x(n) is filtered by a system to give an output y(n), where n is the sample index (time in seconds = n times the sampling period). The response of the system to any input is described by the parameters a and b. The number of 'a' and 'b' parameters (Na+Nb) is termed the order of the filter. The input-output relationship is given by :

$$y(n) = \sum_{k=1}^{Na} a_k y(n-k) + \sum_{k=0}^{Nb} b_k x(n-k)$$

The output signal y(n) is a sum of filtered versions of previous inputs to the filter and previous outputs of the filter. A common use of such a filter is, given an input x(n), to make the output of the filter y(n) match a desired output $\underline{y}$(n). The mean squared error between the ideal output $\underline{y}$(n) and the true output y(n)is given by :

Error $L = \frac{1}{N}\sum e(n)^2$ where e(n)=y(n)-$\underline{y}$(n)

The problem of generating an optimum filter becomes a Wiener filtering problem (Brown and Hwang, 1992). The parameters of the filter are adjusted to minimise the error. The error is a function of each filter parameter and therefore forms a surface in n dimensional space where n is the number of filter parameters (the filter order). Therefore the problem of minimising the filter error is one of finding the minimum point on the surface. Commonly a least squares algorithm is used to achieve this, although other algorithms such as recursive least squares can be used. The minimum error achieved will depend on the order of the model used. Hence choice of the filter order is critical. One approach is to generate a matrix of models of different orders and to select the model which generates the minimum error.

One way in which such a digital filtering approach has been used to try and improve acquisition of the MLR is termed ARX modelling. A number of authors have used ARX modelling to extract the MLR from patients undergoing surgery (Jensen et al, 1996; Jensen et al, 1998; Cerutti et al, 1997; Elkfafi et al, 1997).

The concept of ARX modelling is that an Evoked potential (EP) in noise may be enhanced by modelling the EP as an ARMA filtered version of a reference EP. The reference signal might be the average of 1000 epochs. The optimum ARMA filter is calculated which, when applied to the reference gives the least squares error with the next measured noisy sweep. The filtered reference is then taken as an estimate of the underlying AEP (see Figure 1.4). This can be done for a number of different orders to find the optimal order. Also a variable delay between the input and output is introduced and the optimal delay is calculated. An increase in the latency of the response would correspond to an increase in the delay between noisy EP and the reference signal.

ARX is a technique for matching a template to recent data to see how closely the template matches the noisy data. In the ideal situation of no noise, when the recent data contains the same AEP as the template, the output of the filter will be the same as the template. When there is not an AEP present in the recent data, the output of the filter will be zero.

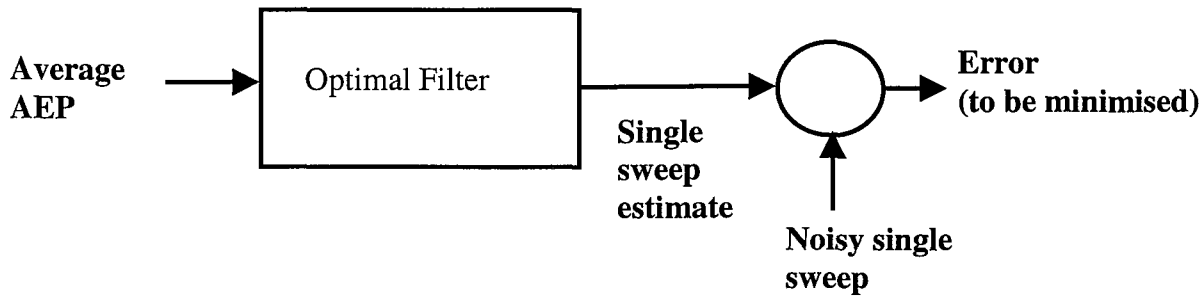


Figure 1.4 The ARX model

For example, Jensen et al (1996) used the average of 256 sweeps (taken from a moving average) as the input to a filter. The optimal model order had 5 Moving Average and 5 Autoregressive terms (order 10). They claim that this filter can produce a sweep by sweep estimate of the MLR. However the model still requires a template of the MLR which takes around 40 seconds to generate. It is unclear to what extent the underlying MLR is distorted by the filtering process. If the true MLR were to vary significantly from the template to the filter (for example if a patient rapidly regained consciousness), would the filter still be able to extract the MLR?

An assumption in the ARX approach is that the ARX modelling of the noisy data will match the embedded AEP signal better than the unwanted random noise. However, there is no formal justification for this assumption in the papers that have used the technique. Whilst AR modelling has been used to describe the EEG signal (Bromm et al, 1988; Cerutti et al, 1997), this does not justify the assumption that the ARX model will enhance the AEP and reduce the EEG noise. Furthermore, there has not been a systematic demonstration of how well the approach will fare for different SNR. At favourable SNR, the use of ARX modelling may well extract the most likely morphology of the AEP. However, when the noise amplitude is significantly higher then the signal, the ARX model will be trying to match the noise, rather than signal.

In general, using an optimised filter to extract an AEP from background noise may be useful if the AEP is stationary. However, the approach will not be able to track changes in the AEP as it has only been optimised for an AEP with a specific morphology. Such an optimised filtering approach is not likely to improve threshold estimation using AEPs either, as the morphology of the AEP depends on both stimulus frequency and level, so recording enough data to generate an optimal filter will take as long as the threshold estimation procedure itself.

Where the AEP is not constant, an adaptive filter may better be able to track changes in the AEP.

1.4.2.6 Adaptive filtering

An adaptive filter is one in which the filter parameters are constantly updated to follow changes in input. An impulse correlated adaptive filter ICAF is particularly appropriate for AEPs; the AEP of interest is always correlated to a stimulus such as a click, whereas the unwanted EEG noise is uncorrelated to the stimulus.

The ICAF filter can take the form of a digital ARMA filter as described above (although often only MA parameters are used for simplicity, in which case the number of MA parameters is critical to the performance of the filter). For application to AEPs the filter has two inputs; one consisting of an impulse train correlated to the stimulus (possibly the click stimulus itself) and the other consisting of the AEP signal in noise. A least squares algorithm is used to vary the filter parameters to maximise the signal correlated with the impulse train and minimise uncorrelated noise (this requires no assumption about the morphology of the AEP). Such a filter is shown below. Note that the output of the filter (the signal estimate) is subtracted from the true signal to give an error term *e* and it is the error which is minimised.

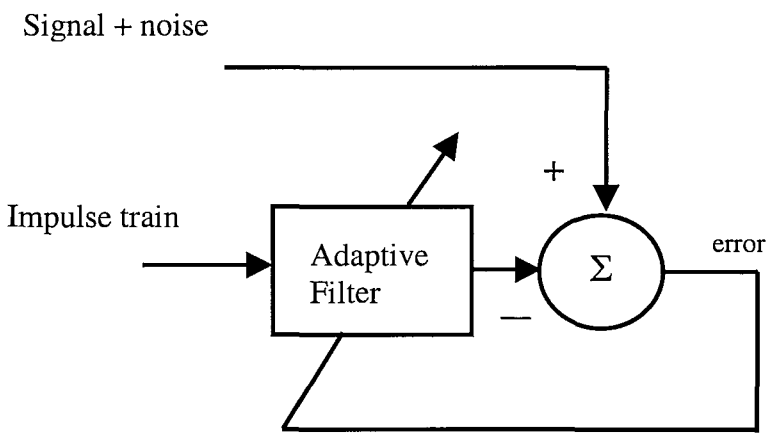


Figure 1.5 Configuration of an Impulse Correlated Adaptive Filter

The error term must be minimised with regard to the each filter parameter. However if the signal is non-stationary the optimum filter parameters will vary over time. Each time the filter adapts, an algorithm is used so that the filter parameters are adjusted towards the optimum solution. The adaptive filter adapts at a rate chosen by an adaptation parameter α. This determines the magnitude by which the filter parameters are adjusted on each adaptation. There is a trade off between the rate at which the filter adapts and the final SNR

the filter reaches (the steady state SNR after which SNR will not improve further). Selection of the α parameter may be critical to the extraction of an AEP for a given subject in specific noise conditions. If the SNR is poor and α is chosen incorrectly, the parameters of the AF may vary so much on each adaptation sweep that the filter does not converge.

A number of authors have used adaptive filtering to extract the ABR from background noise. (Thakor, 1987; Xu et al, 1994; Chan et al, 1995). Some averaging of the ABR is usually required to improve the SNR of the signal before filtering.

Laguna et al (1992) have used an ICAF for the ventricular late potential and a somatosensory potential. They have shown that the performance of the ICAF is equivalent to using an exponentially weighted average. They also demonstrated that when the input signal was stationary, the ICAF and a moving weighted average performed in a similar way in improving SNR, but when changes in the signal occurred, the ICAF was able to improve SNR more rapidly than averaging. It is the ability of the adaptive filter to adapt to changes in the input signal which makes it attractive for use in extracting the MLR during surgery. Such a filter may be able to adapt to changes in the latency of the MLR during an operation.

Lobb (1998) investigated the used of an ICAF to extract the MLR from background noise. Lobb demonstrated that an ICAF is able to extract an MLR from the EEG background noise and is able to adapt to changes in the MLR. He also investigated variation in the performance of the filter with choice of the α parameter and found a trade off between the rate at which SNR was reduced by the filter and the final SNR the filter achieved. However there was no comparison with other techniques such as conventional averaging or ARX and it is therefore unclear whether the ICAF performs better than other techniques to extract the MLR.

1.4.3 Improving the generation of Auditory Evoked Potentials

In general, the signal processing techniques outlined above aim to estimate the underlying AEP which is embedded in background noise. Ultimately, any signal estimation technique will be fundamentally limited by the magnitude of the underlying response relative to the background noise. It may therefore be better to focus on the way in which the AEP is generated to try and maximise the response, so less signal processing is then required to extract the signal from the noise.

1.4.3.1 The Maximum Length Sequence (MLS) Technique

The use of MLS with Auditory Evoked Potentials has been discussed by various authors including Eysholdt and Schreiner (1982), Thorton and Slaven (1993), Li et al (1988), Leung et al (1998), Musiek and Lee (1997) and Bell et al (2001). The following summarises the properties of maximum length sequences as applied to auditory evoked potentials.

Mathematically, MLS is a quasi-random binary sequence generated by a shift register of b bits. It consists of a series of +1 and −1 with a sum of −1.

The length L of MLS is given by: $L = 2^b - 1$

(as b is an integer, L can have values 3, 7, 15, 31 etc)

For application to Auditory Evoked Potentials, the **−1**s are represented by clicks in a stimulation sequence (effectively they are replaced by **+1**s) and the **+1**s are represented by silences (they are effectively replaced by **0**s). Therefore for an acoustic MLS of length L (order b):

the number of clicks: $(L+1)/2 = 2^{b-1}$

the number of silences: $(L-1)/2 = 2^{b-1} - 1$

making a total of $2^b - 1$ 'stimulation opportunities'

Thornton and Slaven (1993) give examples of stimulus sequences of different orders. These are shown in the following table:

Order	Length	Stimulation sequence
2	3	110
3	7	1101100
4	15	100110101111000
5	31	10010110011111000110111010100000

Table 1.2 MLS sequences of different order

Following stimulation, a deconvolution process is used to recover the overlapping responses to the stimulation sequence. For the deconvolution of the responses to a sequence, a recovery sequence of the same order and length as the stimulation sequence is used. The recovery sequence can be obtained by replacing each 0 in the corresponding stimulation sequence with a −1. Hence, if a MLS of length $L = 3$ has a sequence of (+1,+1,0), its corresponding recovery sequence will be (+1,+1,−1). Li et al (1988) have described four methods for data acquisition that can be used with the MLS technique, each involve averaging and deconvolution at some point and are mathematically equivalent. The important property of MLS is that the circular cross-correlation of the MLS sequence and the corresponding recovery sequence is a delta function. If the MLS sequence is put through a system with an impulse response h (e.g. the system could be the auditory pathway and h an AEP), then the output of the system is given by the convolution of the MLS sequence with h (to produce an overlapping sequence of h). Circular cross-correlation of the system output with the recovery sequence will produce a delta function convolved with h (i.e. h alone).

Marsh (1992) gives the following example of the deconvolution process:

Considering a simple MLS of order 2 (length 3), the stimulation sequence is 1 1 0. The sequence therefore consists of three consecutive steps. Steps 1 and 2 are clicks whilst step 3 is a silence. All responses synchronised to step 1 are averaged to form subaverage 1, those synchronised to step 2 form subaverage 2 and so on. It follows that subaverages 1 and 2 are synchronised to clicks, whilst subaverage 3 is synchronised to a silence (See Figures 1.6 and 1.7).

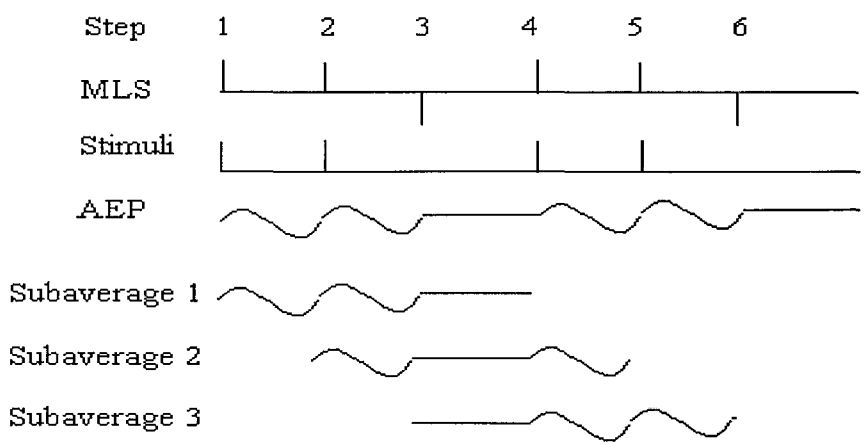


Figure 1.6 The subaverages of the MLS AER are synchronised to each stimulus opportunity (note non-overlapping responses are shown for simplicity)

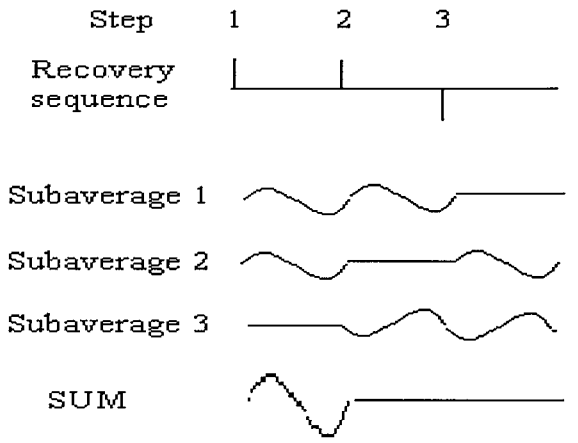


Figure 1.7 Stimuli are aligned (so that the subaverages 2 and 3 are synchronised and start at the same point as subaverage 1). They are then multiplied by the recovery sequence (1,1,–1) and the sum is calculated to give an amplified total response synchronised to step 1. (Note subaverage 3 has been multiplied by –1, so it is inverted). The amplitude of the sum is twice that of the subaverages, hence the SNR is improved.

This basic principle applies to sequences of higher order. Note that superposition of the subaverages is perfect, requiring that the system is linear. If nonlinearities are generated in the system, this recovery process will be compromised.

For application to AEPs, the MLS used for stimulation and recovery are interchanged compared with their use in traditional maximum length sequences (ie. a traditional MLS has stimulation sequence +1,+1,–1 and recovery sequence 1,1,0 whereas here the stimulation sequence is 1,1,0 and the recovery sequence is +1,+1,–1.) This is permissible as the stimulation and recovery sequences are commutative, so the net result is unchanged.

Terminology

The terminology for MLS parameters varies between authors. However, the following is a summary of the terms that have been used (as used in Eysholdt and Schreiner, 1982; Thorton and Slaven, 1993; Li et al 1988; Leung, 1996; Musiek and Lee, 1997.)

The **Order** is equal to the number of bits in the shift register used to generate a sequence.

The **Length** is defined as the total number of clicks and silence periods (or 'stimulus opportunities') in an MLS.

The **Interstimulus Interval (ISI)** is the period of silences within a MLS that separates the clicks and varies quasi-randomly with the Length L.

The **minimum interstimulus interval (MISI)**, or the **minimum pulse interval (MPI)**, is the time difference between two adjacent 'stimulation opportunities'. Note that the ISIs are integral multiples of the MISI.

The **average ISI** is the arithmetic mean of all ISIs within a sequence and approaches two times the MISI as the length of the MLS increases.

The **Stimulation rate** is usually expressed by either the maximum rate or the average rate.

The **maximum stimulation rate** is the inverse of the MISI

The **average stimulation rate** is the inverse of the average ISI

The **sequence repetition rate**, which is the number of sequences presented per second, is also sometimes used to express stimulation rate.

Maximum Rate vs Average rate

The stimulus rate of a MLS can be represented either by the maximum rate or the average rate. Whether the maximum or the average rate is more representative for the equivalent conventional rate is debatable. In conventional MLR, the rate at which stimuli are delivered is equal to the rate at which the corresponding responses are averaged. In MLS, the average rate only represents the number of stimuli which are delivered in a certain time and contribute to an evoked response. It does not reveal the rate at which averaging takes place. The maximum rate, however, indicates how fast the responses are averaged in the MLS analysis.

The relationship between conventional rate and MLS maximum or average rate is further complicated as the overlap between stimuli and responses to previous stimuli will vary in a given sequence. The effect of a stimulus on the response by a preceding stimulus within a sequence is determined by the actual interval between two consecutive stimuli (Burkard and Deegan, 1984). This varies quasi-randomly in an MLS sequence, as clicks will not be present in all the 'stimulus opportunities'.

From studies using MLS ABR, it is unclear exactly how the MLS maximum or average rate relates to that of conventional ABR (Leung, 1996). At present, no studies have attempted to relate the maximum or average rate for MLS MLR to that of conventional MLR. For convenience the maximum stimulation rate, r, for the MLS will be used in this report.

Defining the Signal to Noise Ratio improvement using MLS

Although MLS allows a higher stimulation rate so that more responses can be averaged in a given time period, a reduction in peak amplitude at high click rates due to neural adaptation limits the SNR improvement using MLS (Thornton and Slaven, 1993). The amount of neural adaptation can be described by k, where k is a function of click rate r and stimulus intensity I. It is defined as the ratio of peak amplitude at an MLS stimulus rate (r) to that at a given conventional rate (when the stimulus intensity at both rates is I). The value of k can be determined at different MLS rates using a normative experiment.

Leung (1996) has shown, based on a straightforward derivation by Hyde (1985) and Thornton and Slaven (1993), that for the same measurement time, the relative improvement in SNR obtained using MLS is given by:

Relative SNR $$\frac{SNR_{MLS}}{SNR_{CONV}} = ck\sqrt{\frac{r}{r_o}}$$

where

r = MLS click rate, r_0 = conventional click rate (6.12 clicks/s for MLR)

c = constant which is dependent on the order of the MLS, b, $\left(c = \frac{2^{b-1}}{2^b-1}\right)$

Furthermore, the value of k can also be used to determine the improvement in time taken to obtain a signal of equivalent SNR with the MLS technique.

$$T / T_o = \frac{r_o}{c^2 k^2 r}$$

where T = averaging time using MLS and T_0 = averaging time using conventional AER

For a given order of MLS, b (and hence constant c), a given MLS rate r, stimulus intensity I, and standard MLR rate r_o, a normative experiment is required to determine the neural adaptation factor k. One way to do this is to compare MLS MLR and conventional MLR signals obtained in different subjects using the same measurement time. Repeating this process for different r and I allows the function $k(r,I)$ to be described.

The function $k(r,I)$ can then be used to calculate the improvement in test time that MLS will bring for any combination of r and I. This techniques for measuring relative test speed can also be compared with direct estimates of waveform SNR, such as the ± difference technique (Wong and Bickford, 1980), or the F_{sp} technique (Elberling and Don, 1984).

Bell et al (2001) have shown that recording the MLR using MLS order 4 with a maximum rate of 89 stimulus opportunities/s, test speed is significantly improved relative to a conventional recording at 5 stimuli/s. However, it was not clear whether the test speed improvement with MLS was better than could be achieved by simply increasing conventional stimulation rate. This is an area for further investigation. Only three MLS rates were compared in the study, so the rate adaptation function for MLS stimulation was not fully mapped. Further study is necessary to identify the optimal MLS recording rate.

1.4.3.2 Alternative pseudorandom sequences

Maximum Length Sequences are not the only pseudorandom binary sequences available to obtain high stimulation rates. For example Legendre sequences are pseudorandom sequences that can be used to obtain high stimulation rates in auditory evoked potentials. Burkard et al (1990) compared the use of MLS and Legendre sequences to obtain the ABR and could find no significant difference between the responses obtained using each technique. There does not appear to be an advantage to be obtained from using different types of pseudorandom sequence.

1.4.3.3 The use of chirps to compensate for frequency dispertion on the basilar membrane

A recent advance in the generation of AEPs has been the use of chirp stimuli, which compensate for frequency-vs-delay characteristics of the basilar membrane. These have been used to record the compound action potential (Shore and Nuttall, 1985) and the ABR (Dau et al, 2000).

The peaks in AEP waveforms represent the synchronous firing of neurons in the auditory pathway. Click stimuli with a sharp onset are traditionally used in order to produce a synchronised response from the neurons innervating the cochlea. This is based on the assumption that the response occurs to the onset of the experiment. However, high frequency stimuli cause maximum displacement at basal regions of the basilar membrane whereas low frequency stimuli cause maximum displacement at the apex. As any stimulation of the basilar membrane will set up a travelling wave which takes time to pass from the base to the apex, thus low frequency regions of the cochlea will be stimulated after the high frequency regions resulting in a loss of synchrony between the firing of neurons which innervate different regions of the cochlea.

Dau et al (2000) calculated the frequency-delay characteristics of the cochlea based on a linear model of the cochlea (de Boer, 1980) and the place frequency mapping of the cochlea derived by Greenwood (1990). They showed that is takes approximately 10 ms for the peak of the travelling wave on the basilar membrane to travel from the base to the apex. Hence the neural response to a broad-band stimulus such as a click will be spread out in time. Dau et al (2000) calculated chirp stimuli which compensate for this delay. The low frequencies in the stimulus occur before the high frequencies, so all points on the basilar membrane should reach maximum amplitude simultaneously for that chirp, producing a synchronous neural response across the corresponding bundle of nerve fibres.

Dau et al (2000) recorded ABR waveforms from 10 subjects using a number of stimuli including a 0.8 ms click, an approximate chirp in which the speed of propagation of the travelling wave is construed to be independent of frequency, an 'exact' chirp, which includes some frequency dispersion and a reversed chirp with the opposite frequency-delay characteristics of the approximate chirp. There was little difference between the exact and the approximate chirp below 5 kHz. The time histories of the exact and approximate chirp are shown in figure 1.8 below.

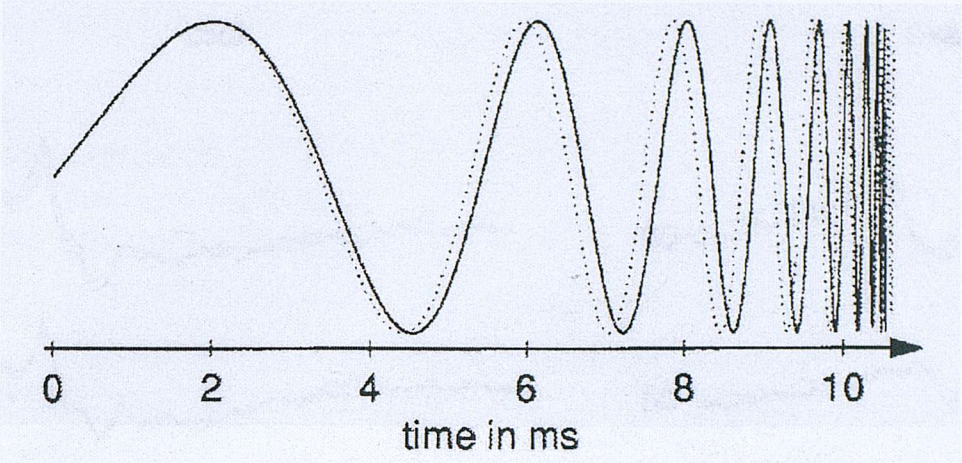


Figure 1.8 The time history of the exact (solid line) and approximate (dotted line) chirps used by Dau et al (2000). Reproduced with permission of the JASA editorial office and T.Dau.

They report a better defined ABR and a significant increase in ABR wave V amplitude for the approximate and exact chirp over the click stimuli. They also found that the latency of wave V of the ABR elicited with chirps was approximately 10 ms more than that for clicks (the length of the chirp stimuli). When a reversed chirp was used, wave V amplitude was significantly lower than that for clicks. The conclude that the ABR response is not simply an onset response, but represents the synchronous firing of neurons in response to the stimulus. As the chirp stimulus did not have the same flat spectrum as the click, they also investigated the use of a 'flat spectrum' chirp with the same spectrum as the click (see figure 1.9). However they found no significant difference in wave amplitude between the exact and flat spectrum chirps.

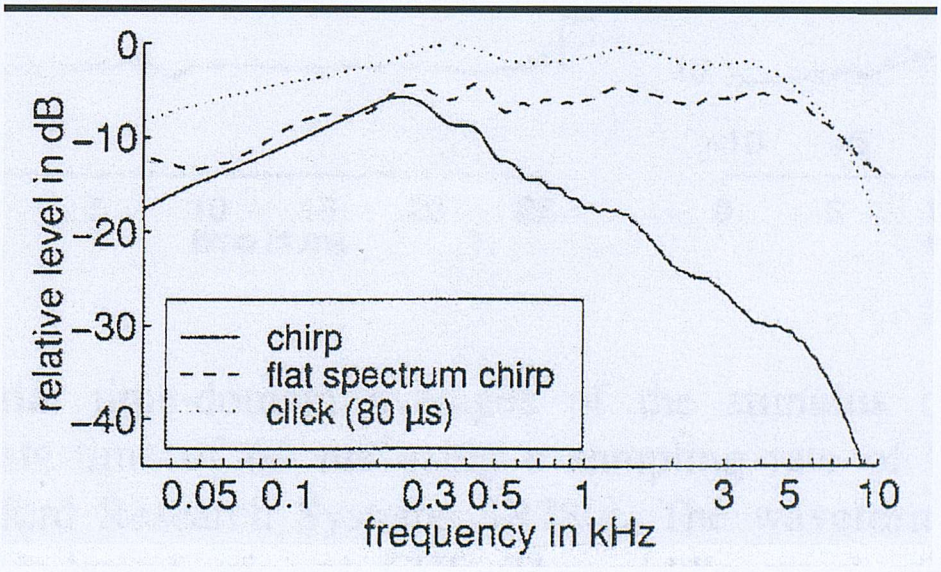


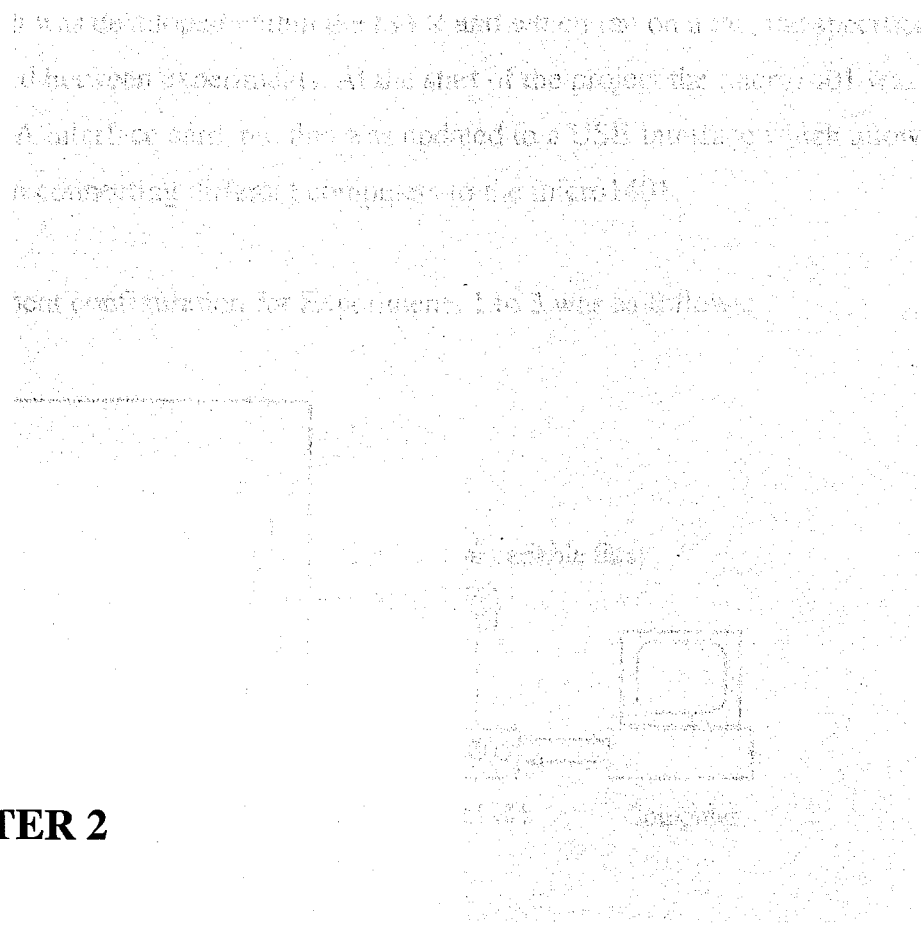
Figure 1.9 The spectra of the click, chirp and approximate chirp stimuli used by Dau et al (2000). Reproduced with permission of the JASA editorial office and T.Dau.

The use of a chirp stimulus which compensates for the frequency-delay characteristics of the cochlea appears to improve the acquisition of the ABR. However, the use of such stimuli to elicit other AEPs has not been investigated. It may well be the case that the generation of the MLR may be improved by using such stimuli.

It may be possible to generate a chirp over a limited band, with frequency-delay designed to compensate for frequency-dispersion on the basilar membrane. This may allow better objective estimation of frequency-specific hearing thresholds. Indeed, Wegner and Dau (2002) have investigated the use of such band-limited chirp stimuli to obtain the ABR. They report that the amplitude of the ABR obtained with low frequency band-limited chirps was greater than the amplitude to low frequency tone-bursts. However, they did not address the question of whether the band-limited chirps gave a better estimate of low frequency hearing threshold than tone-bursts.

In summary, once technical aspects of experimental design have been optimised, a number of techniques may be used to improve the acquisition of AEPs. These fall into two broad categories : 1) signal processing techniques which aim to produce the best estimate of the underlying AEP and minimise the effects of noise; 2) signal generation techniques in which the evoking stimulus is optimised in order to generate a better AEP.

Any estimate of the underlying evoked potential will improve as more data are collected and so the invariant evoked response can be better extracted from the noise. However, ultimately any signal estimation technique will be fundamentally limited by the magnitude of the underlying response relative to the background noise. Therefore the approach of this study will be to focus on optimising the evoking stimulation which generates the AEP, as any improvement in the generation of the response will lead to an improvement in the estimate of the response.



CHAPTER 2

Methodology

2.1 Experimental setup

Equipment for the generation and recording of AEPs is commercially available. For example Musiek and Lee (1997) used the commercial Nicolet Spirit Averager (Nicolet Corp, Madison, 1991) to generate click stimuli and record MLRs using MLS. This equipment is readily available and is already set up for using maximum length sequences. However, it is somewhat inflexible as there are a limited number of stimulation rates that can be used and the order of the MLS that the equipment utilises is dependent on the stimulation rate. Commercial equipment is not configured for using non-standard stimulation such as chirps.

It was desirable to have more control over the types of stimulation and the orders and rates of stimulation used, including MLS stimulation. It was therefore decided to develop a system for generating stimuli for the project. For this experiment, AEPs were generated and recorded

using a computer controlled Cambridge Electronic Design (CED) micro1401 laboratory interface (containing Analogue-to-Digital and Digital-to-Analogue converters) and CED1902 isolated biological amplifiers. This equipment was controlled using a program called MLS-MLR which was developed within the ISVR and which ran on a PC, the specification of which varied between experiments. At the start of the project the micro1401 was controlled using an ISA interface card, but this was updated to a USB interface which allowed more flexibility in connecting different computers to the micro1401.

The equipment configuration for Experiments 1 to 3 was as follows:

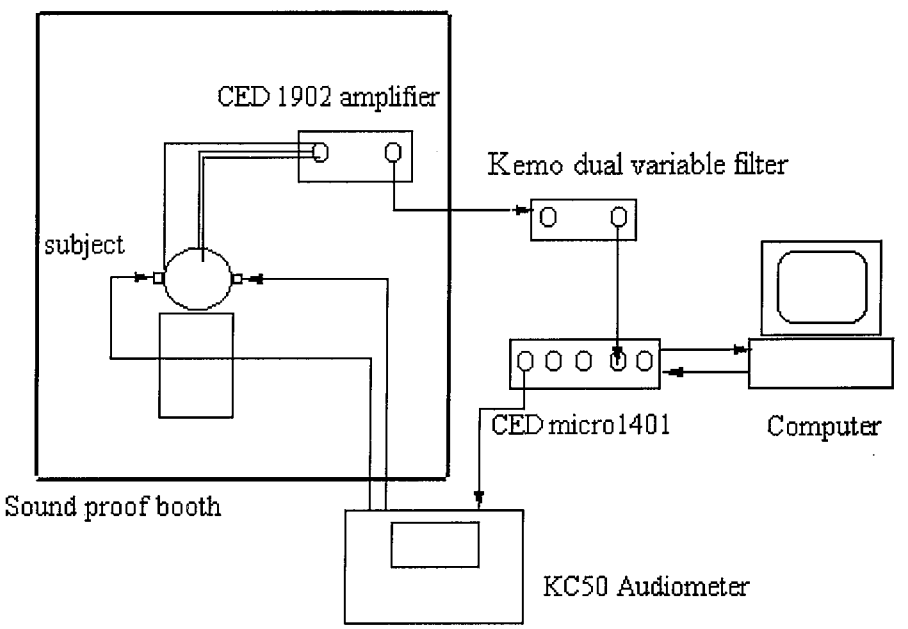


Figure 2.1 Equipment Configuration

The AEP is picked up by silver-silver chloride electrodes placed on the subject's scalp. This potential is sent to the CED 1902 biological amplifier via the isolated EEG input. The CED 1902 then amplifies the signal and either filters the signal, or the signal is passed to a Kemo dual variable filter for band-pass filtering. Following amplification and filtering, the signal is sent to the micro1401 Analogue-to-Digital converter and then in digital format to the computer. The signal is averaged by the MLS-MLR program and artefact rejection applied. As it is desirable to apply a number of statistics and averaging techniques to the data, the raw data from the micro1401 including artefacts is streamed to disk by MLS-MLR. The raw data can therefore be imported into other programs such as MATLAB for averaging and further analysis. MATLAB 'm' scripts used for data analysis are shown in Appendix 6.

2.1.1 Signal Generation and recording

The computer (PC) loads an appropriate waveform into the memory of the micro1401, which then continually reads out the buffer from the channel 0 Digital-to-Analogue converter to generate either a repeating stimulus such as a click or chirp, or a repeating maximum length sequence of stimuli. This analogue signal is sent to a Kamplex KC50 audiometer via the tape input, so that the level of the signal can be amplified and adjusted in level before it is sent to the subject via insert earphones.

2.1.2 Click generation

The click used consisted of a 0.1 ms 5V square wave output from the CED micro1401. The number of samples was sample rate dependent. For example the internal 1 MHz clock of the micro1401 is divided by 100 to give a sample frequency of 10 kHz corresponding to one sample every 0.1 ms, so a click was 1 sample long at this sample rate.

2.1.3 Chirp generation

Chirp stimuli were calculated in digital format in MATLAB and then imported into the MLS-MLR averaging software as ASCII files. Tosten Dau kindly provided a MATLAB 'm' file to generate the approximate chirp stimulus which was used by Dau et al (2000) (see Appendix 6). The approximate chirp generated had frequency content from 0.1 to 10 kHz. For Experiment 3, band-limited chirp stimuli were generated by applying Hanning windows to the approximate chirp in order to remove exact portions of the chirp corresponding to specific frequencies (see Chapter 6).

2.1.4 Maximum Length Sequences generation

When recording maximum length sequences, the sequences need to be generated contiguously, with no gaps between sequences. The way in which the MLS-MLR program accessed with micro1401 ensured there were no gaps between sequences. The program loaded the output buffer into the micro1401 which the micro1401 continuously repeats cyclically, so that if a maximum length sequence is put in the buffer, there is no break in the sequence during recording (this is a necessary condition when recording using maximum length sequences and is assumed for the deconvolution process).

In fact the output buffer of the micro1401 had two identical output sequences stored and each sequence was of equal length to the input buffers that the micro1401 used to store the

incoming AEP signal (for example a buffer length of 168 ms, corresponding to a repeat frequency of 5.95 Hz). This arrangement was purely a matter of convenience for utilising the micro1401 commands. Whilst the output buffer was sent to the D-to-A converter, the input buffer A of the micro1401 would fill with data whilst buffer B could be transferred to the PC. Then when the second output buffer was used, input buffer B of the micro1401 filled with data whilst buffer A was transferred to the PC. This meant the output sequences of the micro1401 remained synchronised to the input buffers (storing the corresponding AEP) and that the MLS repeated with no gaps.

The output sequence could either consist of a single stimulus (click or chirp) for conventional recording, or a maximum length sequence of order 3, 4 or 5 which contains several stimuli. The length of the output buffer needed to be a multiple of the length of the MLS sequence to be used and the length of 1 sample.

2.1.5 Sample Rate

For studies where only click stimuli were used, a sample rate of 10 kHz was sufficient to generate 0.1 ms clicks. However, when broadband chirp stimuli were used with a frequency content up to 10 kHz, it was necessary to increase the sample rate to 20 kHz in order to avoid aliasing of the chirp stimulus.

2.1.6 Filter settings and mains interference

Selection of appropriate filter settings is required to record clear AEP waveforms. The choice of band-pass between the high and low-pass filters is a compromise between excluding as much of the background EEG noise as possible (which is primarily low frequency) and including the maximum frequency content of the AEP.

A limited number of 12 dB/octave filter settings were available on the CED 1902 amplifier. For the studies of threshold ABR, the recommended filter settings are 30-3000 Hz with a notch filter at 50 Hz (Hall, 1992). These settings were available on the CED 1902 and were used for Experiment 3.

The MLR is a lower frequency response than the ABR, with most energy between 30 and 50 Hz (Kavanagh and Domico, 1986). The band-pass settings required to record the MLR are therefore lower than those for the ABR. Hall (1992) suggests that choice of high-pass filter setting is critical to obtaining a good MLR and that a setting of 15 Hz is optimal. As this

setting was not available on the 1902, for studies of the MLR a Kemo Dual variable 24 dB/octave filter was used instead of the those on the CED 1902 to filter the AEP signal between 15 and 250 Hz.

Mains interference is a significant problem when recording auditory evoked potentials. When recording the ABR, a 50 Hz notch filter can be applied to reduce mains interference. However, it is recommended that a notch filter is not applied online when recording the MLR as there is significant mains energy at similar frequencies in the signal so notch filtering may distort the response. In all the experiments carried out, steps were taken to reduce main frequency interference. These included moving mains transformers as far from the subjects as possible and using a battery powered torch instead of mains powered lighting for subjects to read by. Despite these measures, the FFT of MLR signals recorded without a notch filter applied online showed significant 50 Hz interference. A notch filter was therefore applied offline in MATLAB using a zero phase filter command, to avoid phase distortion of the signal.

2.1.7 Electrode placement (avoiding PAM interference)

AEPs were picked up by silver-silver chloride electrodes placed on the subject's scalp (disposable electrodes were used for Experiment 4). Placements are referred to using the ten twenty electrode system of the International Federation (Jasper, 1958). For the study of MLS MLR by Bell (2001), the electrode placement was : active (+ve) electrode at C_z (vertex of the head), reference electrode (-ve) at A1 (mastoid) and the ground electrode at F_z (forehead). The active electrode is placed on C_z as the magnitude of AEPs is found to be greatest along the centre line of the head and increases towards the vertex (Hall, 1992). Placement of the inverting electrode on the mastoid is standard practice for recording AEPs and has been used in many studies, for example Musiek and Lee (1997) used a mastoid reference placement to record MLS MLR. However, Hall (1992) suggests that Post Auricular Muscle (PAM) interference can be reduced by moving the reference electrode to a non-encephalographic position such as the nape of the neck. PAM interference occurs at around 15 ms after the stimulus. As this is of similar latency to the MLR, it is important to reduce any possible PAM when recording the MLR. In a pilot study, the effect of moving the reference electrode from the mastoid to the nape of the neck was investigated. A comparison of the two electrode positions for stimulation at a level of 60 dB SPL is shown in Figure 2.2 below. A recording with a mastoid reference electrode placement is shown on the right and a recording with placement on the nape of the neck on the left. The subject had their neck extended in order to maximise any PAM (which increases with neck tension). The PAM is seen as a large dip at

around 15 ms and it has a magnitude of approximately 5 μV, which is too large to be neural in origin. It also causes an apparent change in the morphology of the whole MLR, with the N_b wave of the MLR appearing to be at approximately 45 ms instead of 35 ms. It is clear that the PAM is reduced when the reference electrode is moved to the nape of the neck.

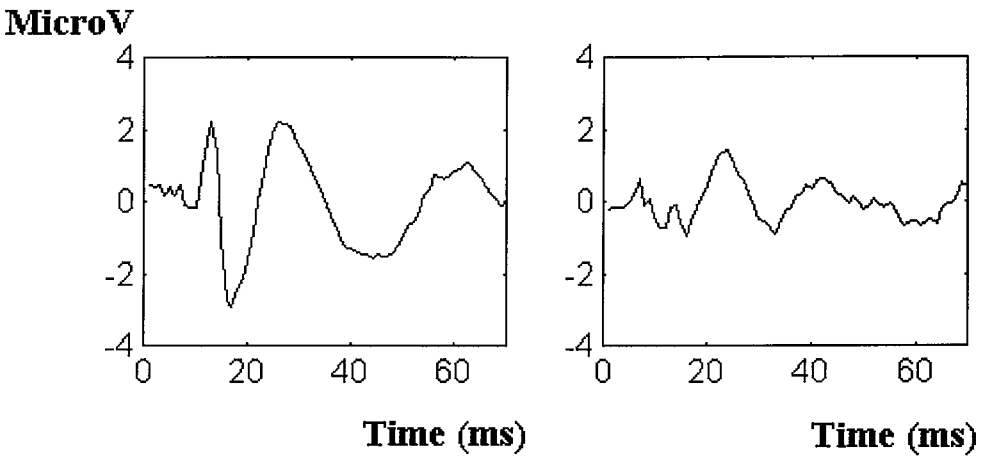


Figure 2.2 Effects of Electrode placement on the PAM (Vertex +ve). Recordings were made with the reference electrode placed either on the nape of the neck (right panel) or on the mastoid (left panel).

For all the subsequent studies performed, it was deemed desirable to reduce any possible PAM interference so the reference electrode was placed on the nape of the neck. The apparent latency shift resulting from the PAM may be of particular concern if the latency of the N_b wave is used to estimate depth of anaesthesia with the MLR. A non-encephalographic reference electrode placement was also used for the ABR study.

For Experiments 1 and 2, the active electrode was placed on C_z and the ground on F_z. For Experiment 3, it was found difficult for maintain electrode contact on C_z, so the active electrode was moved to a high centre forehead position. This is thought to only result in a small reduction in signal amplitude of around 15% (Hall, 1992).

2.1.8 Headphone selection

Two factors are important when choosing the transducers to generate AEPs : the frequency response of the transducers and the amount of stimulus artefact the headphones generate. Initially it was decided to use Etymotic ER-3A insert phones, which deliver the sound signal

via plastic tubes 25 cm long. These are less likely to generate stimulus artefacts than conventional headphones because the acoustic transducer is further away from the head.

When the approximate chirp stimuli of Dau et al (2000) was used, which contain frequencies up to 10 kHz, the high frequency response of the ER-3A was not adequate. Etymotic ER-2 insert phones were also available and manufacturer's specifications show that the ER-2 phones have a flatter frequency response than the ER-3A up to 10 kHz. The high frequency responses of the two types of insert phones were compared in a IEC 711 occluded ear simulator, using a fixed level peak-to-peak signal corresponding to 90 dB SPL at 1 kHz. The results are shown in the table below. The frequency response of the ER-3A varies over a 29 dB range between 1 and 8 kHz, whereas the ER-2 only varies by 10 dB over this range. It was therefore decided to use ER-2 phones for the comparison of clicks and chirps. However, the ER-2 phones need to be driven at a higher level than the ER-3A phones to obtain the same output sound pressure level. The increase in driving current was found to produce a large stimulus artefact. It was therefore necessary to cover the ER-2 insert phones in a grounded shield in order to eliminate electrically radiated stimulus artefact. The shield was connected to the ground on the audiometer.

Frequency (kHz)	ER-3A	ER-2A
1	90	90
2	93	91
3	94	95
4	92	97
5	93	100
6	79	103
7	67	93
8	65	90

Table 2.1. Variation in SPL recorded in IEC 711 occluded ear simulator for a fixed amplitude signal at different frequencies.

2.1.9 Artefact rejection

When recording AEPs, the signal will be contaminated by recording artefacts that are not neural in origin. The most common physiological artefact is muscle activity, which occurs when the subject is tense or restless and which is much greater in magnitude that the neural response. To exclude this contamination, artefact rejection is applied and responses with a peak-to-peak amplitude above a specified value are excluded from the ensemble average.

Either a fixed artefact rejection criterion can be used, or the criterion can be varied for different recordings. For Experiments 1 and 2, the main comparison of interest was SNR in a fixed time period. It was therefore decided to exclude the same percentage of data from all recordings, so the total recording time for data included in the ensemble average was constant. It was decided to exclude 10% of the data (± 2%) by examining the raw data from pilot recordings. As an artefact will affect the deconvolution of the response to an entire MLS sequence, where artefact rejection was applied, a block of data of equal length to an MLS sequence was excluded i.e. for MLS order 4, the response to 15 stimulus opportunities would be excluded. In general, it could be seen that less than 10% of the recordings were contaminated with muscle artefacts. The raw data from MLS-MLR including artefacts was streamed to disk for analysis in MATLAB. For each recording made, a MATLAB 'm' file calculated the artefact rejection level that corresponded to 10% rejection ± 2% (see Appendix 6). Epochs with peak values above this level were excluded from the average.

For Experiment 3, the main comparison involved threshold estimation, not recording duration. A fixed artefact rejection criterion was applied and the average waveforms were calculated using the MLS-MLR software. A peak-to-peak amplitude of 27 μV was used as the criterion and responses with peak-to-peak amplitudes above this were excluded from the analysis.

2.1.10 Subject Screening

For the studies performed on normal hearing volunteers, it was required that the subjects were young and otologically normal. Young was defined as being aged between 18 and 30. Otological normality was defined as having normal hearing and no history of ear disease or undue noise exposure. In order to check that subjects met this criterion, each subject was screened using a questionnaire (see Appendix 4), pure tone audiometry and typanometry. Subjects were required to have pure tone thresholds no greater than 20 dB HL in the range 250 to 8000 Hz and middle ear pressure and compliance within normal adult limits (middle ear pressure between −50 and 50 daPa, compliance between 0.35 and 1.4 ml).

2.2 Calibration of equipment

For each of the experiments conducted, three calibration procedures were carried out. The amplification of the CED amplifiers was checked, the stimuli were calibrated in terms of

peak-equivalent SPL and a biological calibration was performed for each subject to determine the sensation level of the stimuli.

2.2.1 Calibration of the CED 1902 biological amplifiers

In order to calculate the magnitude of the AEPs correctly, it was necessary to know the gain of the CED 1902 amplifiers. The gain of the amplifier may drift over time, so the calibration was performed for each experiment.

The MLS-MLR program was able to generate a calibration sine burst from the micro1401 analogue output. This sine burst was generated in phase with the averaging sweeps of the program so that it could be fed back into the program and averaged for calibration purposes.

The calibration of the CED 1902 amplifier was in two stages. First the relationship between the voltage input to the micro1401 A-D converter and the scale on MLS-MLR had to be calculated. A 2V peak-to-peak sine burst was generated by MLS-MLR and this was fed directly from the analogue output of the micro1401 back to the analogue input. The level of the sine burst was verified with an oscilloscope. The sine burst was averaged by MLS-MLR for 100 sweeps and the peak-to-peak amplitude read off. For Experiment 1, a peak-to-peak amplitude of 12767 scale units was recorded, which meant that IV corresponds to 6384 MLS-MLR scale units, or that 1 scale unit corresponds to 0.157 mV at the input to the micro1401.

Next the 2V sine burst was attenuated by 100 dB and the signal was fed to the CED 1902 amplifier set to a nominal gain of 30,000. A 610 ohm resistor was placed across the output of the attenuator to balance the 600 ohm impedance of the attenuator. The output of the CED 1902 was then fed back to the micro1401 and the sine burst was again averaged for 100 sweeps by MLS-MLR and the peak-to-peak amplitude read off. For experiment 1 the value obtained was 3914 scale units.

This meant that the true gain of the CED1902 for Experiment 1 was 3914/12767*100,000, or 30,657. This in turn means that 1 scale unit on the MLS-MLR display corresponds to a potential difference of $5.12*10^{-9}$ V at the input of the CED1902. The 1902 gain settings for each of the experiments are shown in Table 2.2. The measured gain was found to vary by up to 20 % from the nominal value.

	1902 Gain setting	Measured Gain	Voltage corresponding to 1 MLS-MLR scale unit (μV)
Experiment 1	30000	30,657	$5.12*10^{-3}$
Experiment 2	30000	36,009	$4.23*10^{-3}$
Experiment 3	30000	34,279	$4.45*10^{-3}$
Experiment 4*	10000	10,095	$1.51*10^{-2}$

* For Experiment 4, the CED 1902 was set on a gain setting of 1000 and a CED 1902-10 battery powered pre-amp was used with a gain setting of 10

Table 2.2 Gain settings for the 1902

2.2.2 Setting up the input level of the audiometer

All signals from the micro1401 were routed through the tape input of the audiometer. They were then attenuated by the audiometer and the signal was then routed to the earphone connected to the subject (see Figure 2.1). A change of the gain of the tape input of the audiometer would result in a change of the stimulus level. It was therefore important to set the gain of the tape input of the audiometer before any measurements were made on a subject or any calibration was performed.

The tape input of the audiometer was set by using a 2V peak-to-peak sine wave generated by the micro1401. Before any measurements were made on a subject, the setting of the tape input was checked using this calibration signal and adjusted so the LCD display for the tape input level on the audiometer read 0 dB.

2.2.3 Calibration of the Stimuli in dB p.e. SPL

Calibration of clicks

The insert earphone was connected to a Brüel and Kjær 2112 spectrometer and an oscilloscope via a IEC 126 '2cc' coupler with a 1 inch microphone as specified in International Standard ISO 389. The scale of the spectrometer was set up using a reference calibration piston. The piston generates a fixed SPL and the input gain of the spectrometer is adjusted until the spectrometer dial gives the same reference level. The output of the spectrometer was routed back to the micro1401. A clear click response was recorded from

the coupler by averaging 100 click stimuli using the MLS-MLR program. The amplitude and half period of the first going positive cycle of the click were estimated from the recording.

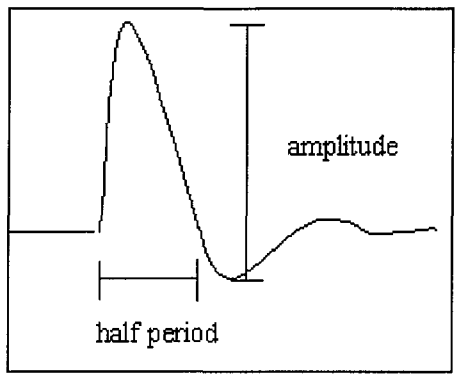


Figure 2.3 A typical click captured by MLS-MLR

For the purpose of calibration, the frequency of the click is assumed to be one over twice the half period measured. A sine wave of peak-to-peak amplitude equivalent to the peak-to-peak amplitude of the click and of equal frequency to that calculated is then fed into the microphone input of a spectrometer and the rms SPL is read off the meter. This is defined to be the p.e. SPL of the click.

Calibration of chirps in dB p.e. SPL

For chirp calibration, the equipment was connected as described above for click calibration. A clear chirp response was recorded from the coupler by averaging 100 click stimuli using the MLS-MLR program. The maximum amplitude cycle of the chirp is estimated from the MLS-MLR program (see figure 2.4 below). As the chirp waveform is almost symmetrical, a sine wave of peak-to-peak amplitude equivalent to the peak-to-peak amplitude of the greatest cycle of the chirp is used. The delay of the greatest amplitude cycle can be read from the MLS-MLR display. As the frequency-delay characteristics of the approximate chirp are known (see Chapter 6), for the approximate chirp, the frequency corresponding to the delay to the point of greatest amplitude can be estimated (taking into account the delay introduced by the use of insert phones). For the band-limited chirps of Chapter 6, the geometric mean frequency of the chirp is used. A sine wave with the same frequency and peak-to-peak amplitude as that estimated for the greatest cycle of the chirp is then fed into the microphone input of the spectrometer and the level in SPL is read off the meter. This is defined to be the dB p.e. SPL of the chirp.

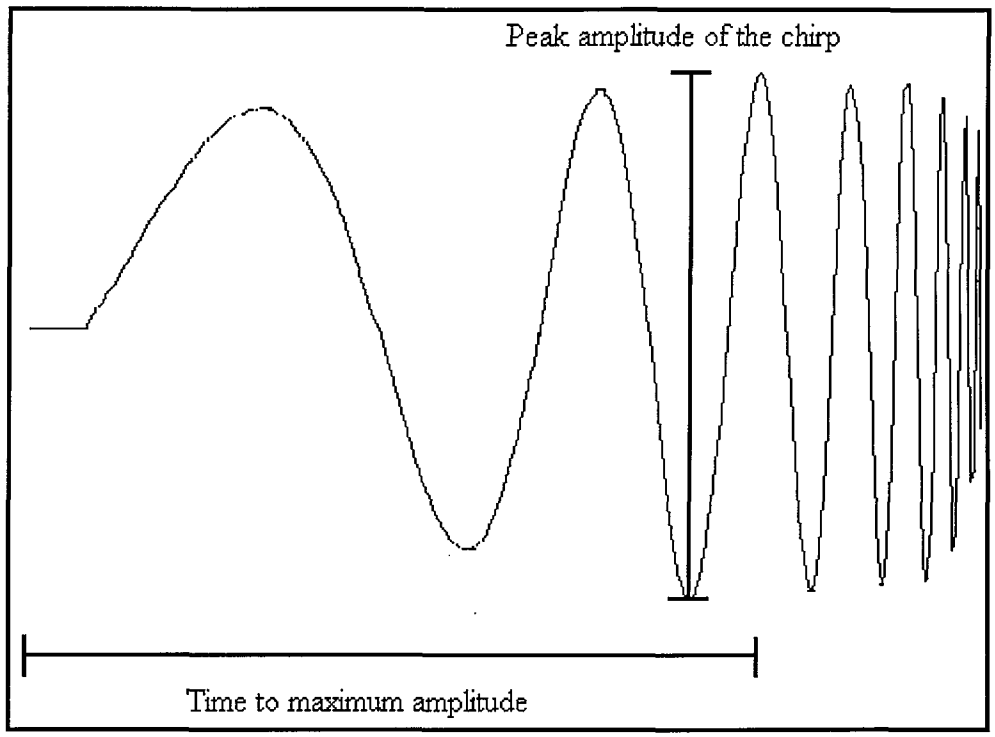


Figure 2.4 Estimating the greatest amplitude cycle of the chirp.

The calibration levels for each experiment and each stimulus type in dB p.e. SPL are shown below in Table 2.2. The mean threshold values in dB p.e. SPL are also shown (which corresponds to 0 dB SL). For experiments 1 and 3, stimuli were routed through a KC-50 Audiometer. For experiments 2 and 4 a GSI-16 Audiometer was used which had a slightly higher gain on the tape input.

Experiment	Stimulus type	Transducer	Ear	Audiometer Dial setting	dB p.e. SPL	Mean Threshold dB p.e. SPL
1	Click	ER-3A	R	90	88	38 Group 1 39 Group 2
			L		87	40 Group 1 38 Group 2
2 & 4	Click	ER-2	R	100	92	44
			L		92.5	44
	Chirp	ER-2	R		93.5	20
			L		95	22
3	0.5 kHz Chirp	ER-3A	R	60	55	21
	1 kHz Chirp		R		63	24
	2 kHz Chirp		R		59	21
	4 kHz Chirp		R		58	24

Table 2.2 Calibration values for the different Experiments

The calibration for Experiment 4 was the same as for Experiment 2. The mean threshold for chirps of 19 dB p.e. SPL from Experiment 2 was taken as 0 dB nHL and stimuli were presented dicotically at +60 dB nHL (79 p.e.SPL).

2.2.4 Checking the audiometer attenuator linearity

The audiometer dial setting was used to set the stimulus levels for the different experiments. It was therefore important that the attenuator was linear over its range. Although this is checked when the audiometer is calibrated each year and the audiometer was within its calibration period, the attenuator linearity was also checked before each experiment. A calibration sine wave was routed through the insert phones and a "2cc" coupler to a Brüel and Kjær 2112 spectrometer. The dial setting on the audiometer was varied and the corresponding variation in dB SPL of the reference tone was checked. The variation was less than 4 dB over an 80 dB range.

2.2.5 Calibration of the Stimuli in dB SL

Stimuli were presented at a sensation level above the threshold for the subject in each ear (most commonly at 60 dB SL). The threshold of the subject to the stimulus was found in each ear using a conventional audiometric procedure with 5 dB steps. (British Journal of Audiology, 1981). Stimuli were then presented at a fixed value above the threshold dial setting. For example, a typical threshold dial setting might be 30 dB and so stimuli would be presented at 90 dB dial to give 60 dB SL.

As the relationship between the dial setting and the stimulus level in dB p.e. SPL was known, the relationship between dB SL and dB p.e. SPL could also be calculated. In the above example, if stimuli at 100 dB dial had a p.e. SPL of 83, then a 60 dB SL at 90 dB dial corresponds to 73 dB p.e. SPL.

2.3 Quality Estimators for Auditory Evoked Potentials

In order to assess improvements in the acquisition of AEPs using different techniques, it is important to have a reliable measurement of SNR. Wong and Bickford (1980) suggested a technique called the plus minus difference (± difference). For this technique, when an AEP is averaged alternate sweeps are put into different buffers to generate two averages (alternatively the AEP can be acquired twice to produce two averages). The sum term is

calculated as the sum of the two averages (a signal estimate) and the difference term is the difference between the two averages (a noise estimate). The ± difference is defined as :

$$+/- difference = \frac{std(SUM)}{std(DIFF)}$$

Where std = standard deviation, SUM = addition of the two averages, DIFF = difference of the two averages.

However, this is not directly a measure of SNR as the sum term includes the difference signal (Mason, 1983). It is only a statistic to be used to indicate wave presence. If the two averaged signals contains the signal of variance S and random noises n1 and n2. When the variance of n1=n2=n and the noise is white, the variance of the sum term will be 4S+2n and the variance of the difference term will be 2n (the signal variance increases with the square of the number of additions and the random noise variance increases with the number of additions). It follows that an rms measure of SNR is given by :

$$SNR = \sqrt{\frac{\text{var}(SUM) - \text{var}(DIFF)}{2\,\text{var}(DIFF)}}$$

Elberling and Don (1984) suggest that when the signal contains a large amount of low frequency components, the amount of unknown random variability in the ± difference due to low frequency components becomes large, so the ± difference method may not estimate SNR accurately. They suggest that the F_{sp} statistic is a better unbiased estimate of SNR. Arnold (1985) also recommends the F_{sp}. The F_{sp} statistic is defined as :

F_{sp} = var (S) / var (SP)

where var (S) is the variance within the averaged MLR between 25 and 45 ms after the onset of the stimulus and var (SP) is the variance of a single point 35 ms after stimulus onset calculated across all the epochs recorded and divided by the number of epochs[2]. As the N_b wave was the MLR feature of most interest, the latency of the single point (35 ms) was chosen to correspond to the expected latency of N_b and the variance of the MLR was measured 10 ms either side of that point. The F_{sp} tends to 1 as SNR tends to zero, so an rms measure of SNR is given by $\sqrt{F_{sp} - 1}$ (Elberling and Don 1984).

The effect of low frequency noise is more of an issue when recording the MLR than when recording the ABR, as the high-pass filter is set lower for MLR than for ABR recordings (typically 15 Hz for the MLR and 30 or 100 Hz for the ABR). The effects of low-pass noise on the ± difference and F_{sp} quality estimators is investigated further in Chapter 6. Experiments 1, 2 and 4 investigated the MLR, so low frequency noise levels in the signals were likely to be high. The F_{sp} SNR estimator was therefore used. In Experiment 3, which investigated the ABR acquired with band-limited chirps, low frequency noise was reduced by high-pass filtering. Furthermore, the low-pass filter setting in Experiment 3 was 3000 Hz, so the minimum sample rate of 6000 Hz to avoid aliasing was higher than in experiments 1, 2 and 4 (which used a sample rate of 1000 Hz). The resulting file sizes meant that implementing the F_{sp} in MATLAB for Experiment 3 was more problematic than for Experiments 1, 2 and 4, whereas calculating the ± difference from two replications of the same condition was straightforward. The ± difference estimate of SNR was therefore used for Experiment 3. MATLAB 'm' scripts for calculating the ± difference and F_{sp} are given in Appendix 6.

CHAPTER 3

Experiment 1. Mapping rate-adaptation of the MLR with conventional and MLS stimulation

3.1 Introduction

Reducing the recording time of AEPs is almost always desirable, either because there is limited time available to make a recording on a subject or because a large number of recordings have to be made. One way in which the acquisition time of the MLR may be improved is simply by increasing the stimulus rate. In conventional MLR recording, successive responses do not overlap. For an analysis time window of 70 ms, a conventional click stimulation pattern with a rate of up to 14 clicks/s might be used. Above this rate, responses would overlap. However, most studies that attempt to measure depth of anaesthesia using the MLR have used lower click rates such as 6 clicks/s (e.g. Elkfafi et al, 1997). It is unclear whether this is because the MLR is thought to adapt and reduce in amplitude at higher click rates, or whether authors have simply followed the protocol of the first paper to investigate depth of anaesthesia using the MLR (Thornton, 1989)

Another way in which the acquisition time of the MLR may be improved is by using an alternative pattern of click stimulation such as the maximum length sequence (MLS) technique (Eysholdt and Schreiner, 1982). Bell et al (2001) have demonstrated that MLS can reduce the acquisition time of the MLR by a factor of 4 when compared to conventional click stimulation at a rate of 6 clicks/s. However it is unclear whether the estimated test time reduction they achieved using MLS is greater than could be achieved by simply increasing the conventional click rate. Indeed, van Veen and Lasky (1993) have demonstrated that for

the ABR, MLS reduces recording time no more than can be achieved by using the optimal conventional recording rate.

MLS allow a higher stimulation rate to be used than for conventional MLR by overlapping successive recording epochs. A particular deconvolution technique is then used to extract the responses which overlap in time (see Chapter 1). A MLS sequence of order b (where b is an integer) is of length 2^b-1 (stimulus opportunities) and contains $2^{(b-1)}$ stimuli. MLS has been used to improve the recording time of transient evoked otoacoustic emissions (Thornton, 1993) and it has been demonstrated that MLS can been used to record auditory evoked potentials such as the auditory brainstem response (ABR) (Burkard, Shi and Hecox 1990, Burkard 1991, Lina-Grande 1994, Jiang 1999) and the MLR (Picton, Champagne and Kellett 1992, Musiek and Lee 1997).

The amplitude and hence the SNR of recordings made with binaural stimulation should be greater that than from monaural stimulation (Kadobayashi et al, 1984). Binaural stimulation should therefore result in a reduction in test time for given quality of recording. The inclusion of some conditions with monaural stimulation would assess the magnitude of this effect.

The aims of this study were as follows : 1) To investigate the extent to which the acquisition time of the MLR might be improved by increasing the rate for conventional click stimulation, 2) to explore a range of rates using MLS stimulation with a view to optimisation of test speed, and 3) to investigate the binaural/monaural stimulation advantage when using conventional and MLS stimulation. The experiment was performed on two groups of subjects, as described below.

3.2 Method

Subjects with normal hearing participated and the MLR was recorded at a fixed stimulus level for equal time periods. The SNR of recordings were estimated directly using the F_{sp} technique (Elberling and Don, 1984) and also the relative SNR of recordings were obtained from the peak amplitudes of the traces. These estimates of SNR were used to infer the relative test speeds of recordings.

3.2.1 Subjects

Subjects were taken from a student population at the University of Southampton. Group 1 included 6 male and 8 female subjects. Group 2 included 6 male and 5 female subjects (the same group of subjects was not available for both experiments). The standard deviation of MLR amplitude measurements from Bell et al (2001) was estimated to be 0.25 μV. A power calculation revealed that 10 subjects would be required to detect an amplitude difference of 0.2 μV with a power of 80%. To minimise effects of age and hearing impairment, subjects included in the study were required to be otologically normal. They were aged between 18 and 30 years with hearing threshold levels better than 20 dB throughout the range 250-8000 Hz in each ear and all had normal tympanograms. No subjects had a history of ear disease or undue noise exposure (see Appendix 4 for the screening questionnaire used). The mean age was 25.4 years for group 1 and 24.3 years for group 2.

3.2.2 Stimuli

For both experiments, a stimulus level of 60 dB SL was used. Here 'dB SL' refers to the level of the stimulus above the threshold level of the subject, as determined from audiometry (see below). In both experiments, the order of stimulation was randomised among subjects.

The same duration of 185 seconds was used for all recordings. Artefact rejection was applied offline to exclude epochs that may contain excessive noise. For each recording made, a criterion was calculated so that so that the extreme 10% of epochs (± 2%) were rejected. This results in an equal amount of data being rejected from all recordings, so maintaining parity of recording duration.

Group 1

All recordings were made using rectangular click stimuli with duration of 0.1 ms. The majority of recordings used binaural stimulation although restricted monaural stimuli were included. For binaural stimulation, six conventional stimulation rates of 5, 7, 9, 11, 13 and 15 clicks/s were used and six MLS stimulation rates of 50, 70, 90, 111, 143 and 167 stimulus opportunities/s. Monaural recordings were also made at 5 and 90 clicks/s to allow a comparison between monaural and binaural stimulation.

Group 2

The recordings made from group 1 did not fully map the rate-adaptation function of the MLR. Further recordings were made at higher rates on a second subject group. All recordings were made using binaural stimulation. Ten recordings were made using the same click stimuli as for Experiment 1; three conventional recording rates of 5, 15 and 19 clicks/s were used and seven MLS stimulation rates of 70, 111, 143, 167, 200, 250 and 333 clicks/s.

3.3 Equipment

The study was carried out with the subject seated in a sound proof booth. Stimuli were delivered through insert earphones (Etymotic ER-3A) via a Kamplex KC50 audiometer. Stimuli were either monaural or binaural. For monaural presentation, stimuli were delivered to the right ear and to prevent cross-hearing the left ear received a broadband masking noise at 52 dB SPL through a similar insert earphone. Relaxed subjects produce less electrophysiological noise and hence they were sat in a comfortable chair with a head rest. All subjects were awake and reading. To reduce electrical interference, screened cables were used and the biological amplifier (see below) was placed near the subject. For group 1 a table lamp was used to provide light for reading and for group 2 a battery powered torch was used instead to minimise electrical interference.

Stimuli were presented at a level of 60 dB SL to each ear. Here sensation level is referenced to the detection threshold for clicks presented at a rate of 5/s. For group 1, the mean threshold for clicks was 38 dB peak equivalent (pe) SPL for the R ear and 40 dB pe SPL for the L ear. For group 2, the corresponding values were 39 and 38 dB pe SPL. The generation of stimuli is described in Chapter 2. Data were down-sampled to 1 kHz for offline analysis in MATLAB.

For recording, the band-pass filters were set to 15 Hz (high-pass) and 250 Hz (low-pass). Despite attempts to reduce 50 Hz mains interference on recordings, including using a torch for subjects to read instead of a table lamp, the FFTs of the raw data from both studies showed a significant 50 Hz component. Recordings were therefore zero phase 50-Hz notch-filtered in MATLAB before analysis.

3.3.1 Recording the MLR

The MLR was picked up by three silver-silver chloride electrodes placed on the skin after skin preparation: active electrode on the vertex of the head, ground electrode on the forehead and reference electrode on the nape of the neck. Recordings were made with impedances of less than 5 kΩ at 1 kHz between all pairs of the electrode array.

An important consideration identified in a pilot study was the position of the reference electrode. When recordings were made with the reference electrode on the mastoid, a large PAM response was seen. This was reduced significantly when the reference electrode was moved to the nape of the neck (see Chapter 2 for further discussion). All recordings for this experiments were made with the reference electrode on the nape of the neck.

3.3.2 Determination of signal-to-noise ratio

a) Using the F_{sp} Technique

Sampled data comprised contiguous epochs from the recording electrodes synchronised with stimulation and were streamed to disk. This allowed the use of the F_{sp} statistic to estimate SNR (see Chapter 2). For the present study, F_{sp} statistic was defined by :

F_{sp} = var (S) / var (SP)

where var (S) is the variance within the averaged MLR between 25 and 45 ms after the onset of the stimulus and var (SP) is the variance of a single point 35 ms after stimulus onset calculated across all the epochs recorded and divided by the number of epochs[2]. As a measure of SNR was required for comparison with the Thornton derivation of relative SNR between recordings, in this study SNR is defined by $\sqrt{F_{sp}-1}$.

b) Using Wave Amplitudes

With conventional averaging, if a signal of amplitude *S* embedded in random noise of amplitude *N* is averaged over *n* sweeps, the resultant SNR is approximated by :

$$\frac{S\sqrt{n}}{N}$$

When using high stimulation rates, the response S may be reduced by a factor k due to neural adaptation, so the SNR is also reduced by a factor of k. Furthermore, each sequence of MLS contains noise from 2^b-1 stimulus opportunities but only $2^{(b-1)}$ stimuli, so the SNR for MLS stimulation is further reduced by a factor $c=2^{(b-1)}/(2^b-1)$. If averaged over m stimulus opportunities, the SNR using MLS is approximated by $ck\sqrt{m}S/N$.

If the conventional recording rate is r_0, the MLS stimulation rate is r and the recording time used is t, then $n=r_0t$ and $m=rt$. (Note that here the MLS stimulation rate used is the peak stimulation rate or stimulus opportunity rate, or in other words the inverse of the minimum interval between clicks in the sequence.)

Then the relative SNR (MLS to conventional) is given by $$\frac{SNR_{MLS}}{SNR_{CONV}} = ck\sqrt{\frac{r}{r_o}} \qquad (1)$$

(Thornton and Slaven, 1993; Thornton, 1993)

By measuring k (the ratio of the MLS amplitude to that of the conventional amplitude), the SNR of the conventional and MLS recordings can be compared. In the present study, the P_a-N_b amplitude (peak-to-peak) was used (as it is the N_b wave which is thought to be of most use for measuring depth of anaesthesia). For each MLS recording, the amount of neural adaptation, k, was determined by dividing the MLS amplitude by the amplitude obtained for conventional stimulation at 5 clicks/s.

3.4 Results

3.4.1 Waveform morphology

Example waveforms from subject OB are shown in Figure 3.1 for stimulation at 5 clicks/s. 15 clicks/s and clicks at MLS rate 167 opportunities/s. The peaks of the MLR have been identified. The recordings made at 5 and 15 clicks/s are similar. For the recording at 167 opportunities/s, there is a reduction in MLR amplitude due to neural adaptation. For this subject N_b latency has reduced for the MLS recording compared to the conventional recordings.

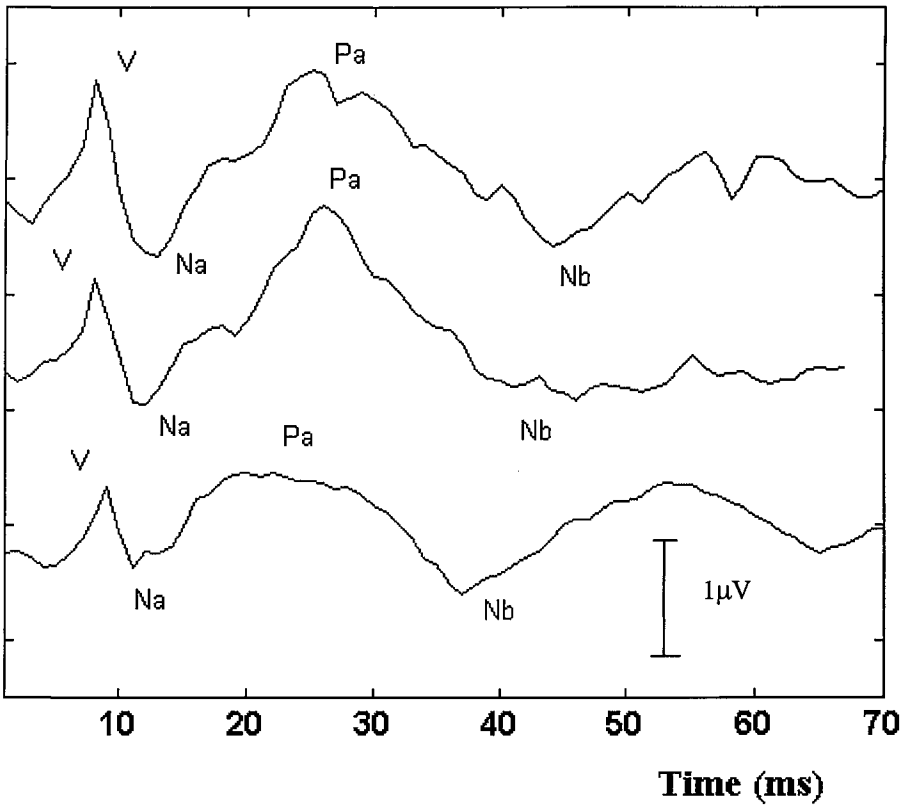


Figure 3.1. Example MLR recordings for subject OB at 5 clicks/s (top), 15 clicks/s (middle) and clicks at MLS rate 167 opportunities/s (bottom).

3.4.2 Variation in P_a-N_b wave amplitude with stimulus condition

Group 1

The variation in P_a-N_b amplitude with rate is shown in Figures 3.2i (conventional stimulation) and 3.2ii (MLS stimulation). For conventional click rates (5 to 15 Hz) all stimulus opportunities are filled. Repeated measures analysis of variance was performed separately with either conventional stimulation rate or MLS stimulation rate as the within subject factor. There was no significant effect of conventional stimulation rate, but there was a significant cubic effect with MLS stimulation rate shown by the sigmoid trend in Figure 3.2ii. Average MLR waveforms across Group 1 subjects for each stimulation condition are shown in Appendix 1.

Group 2

The variation in P_a-N_b amplitude for group 2 is also shown in Figures 3.2i (conventional recording rates) and 3.2ii (MLS recording rates). Repeated measures analysis of variance was performed separately with either conventional stimulation rate or MLS stimulation rate as the within subject factor. Only the MLS recordings showed a significant rate effect. The analysis of variance involved polynomial contrasts to examine the effects of rate. For group 2 there were significant linear and quadratic effects shown by the accelerating downward trend in Figure 3.2ii. It appears that there is little adaptation of response amplitude with conventional stimulation at rates below 20/s, but there is with MLS where rates are higher. From figure 3.2ii, it appears that as the MLS stimulation rate increases above 167 opportunities/s, the response amplitude decreases. Average MLR waveforms across Group 2 for each stimulation condition are shown in Appendix 1.

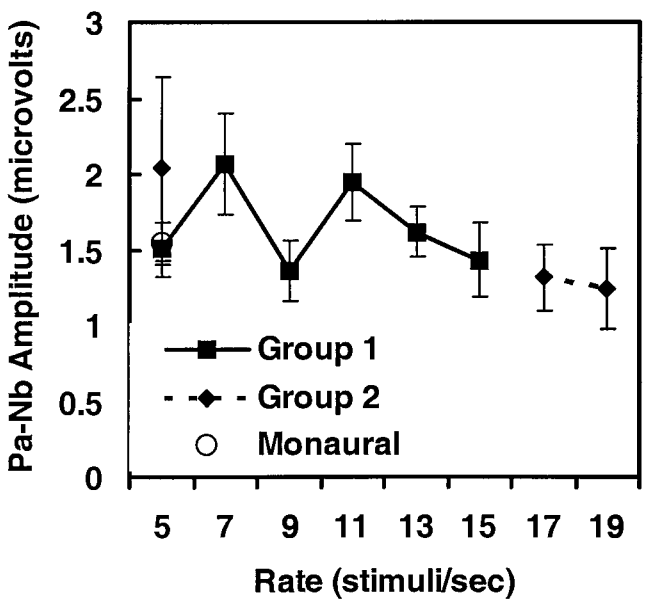


Figure 3.2i Variation in P_a-N_b wave amplitude with conventional stimulation rate. Error bars represent 1 s.e. of the mean

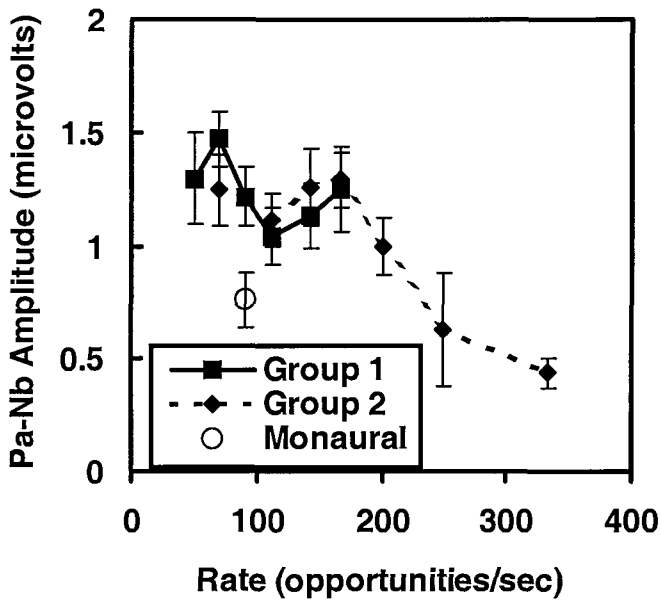


Figure 3.2ii Variation in P_a-N_b wave amplitude with MLS stimulation rate. Error bars represent 1 s.e. of the mean

3.4.3 Variation in wave latency with stimulus condition

Table 3.1 shows the variation in N_a, P_a and N_b wave latency for the stimulation conditions of groups 1 and 2. Repeated measures analysis of variance shows no overall effect of rate on wave latency for either conventional or MLS stimulation for either group.

Experiment 1			
Rate	N_a latency	P_a latency	N_b latency
5	15.7 (3.6)	25.1 (2.1)	37.0 (4.8)
7	14.5 (3.3)	24.8 (2.0)	35.5 (4.8)
9	14.1 (2.5)	25.8 (2.9)	35.5 (3.3)
11	13.1 (2.5)	24.5 (1.6)	36.3 (3.9)
13	12.9 (1.5)	26.2 (2.0)	37.4 (3.2)
15	12.8 (1.6)	26.0 (2.5)	36.0 (3.3)
50	12.1 (2.0)	24.8 (2.9)	35.5 (3.3)
70	12.3 (1.8)	25.2 (1.4)	37.5 (3.1)
90	11.8 (1.1)	25.5 (1.4)	36.9 (2.2)
111	13.2 (2.1)	24.3 (1.5)	35.6 (2.8)
143	14.2 (2.2)	23.4 (2.8)	35.0 (2.4)
167	12.1 (1.5)	22.2 (2.3)	36.8 (1.7)
5 (monaural)	13.8 (2.1)	23.5 (3.2)	35.1 (2.8)
90 (monaural)	14.6 (3.7)	25.2 (3.3)	35.2 (2.6)
Experiment 2			
Rate	N_a	P_a	N_b
5	12.7 (2.6)	22.3 (1.8)	33.4 (4.8)
15	12.2 (2.8)	24.5 (2.3)	34.2 (5.4)
19	14.1 (3.5)	24.3 (1.5)	32.4 (2.0)
70	11.2 (1.5)	23.5 (2.6)	34.1 (3.2)
111	11.2 (1.3)	23.5 (2.7)	34.0 (3.8)
143	11.2 (2.2)	23.1 (2.5)	34.2 (3.5)
167	10.8 (1.3)	21.3 (1.7)	33.8 (2.1)
200	10.4 (0.7)	22.2 (2.9)	34.1 (1.9)
250	13.1 (4.9)	26.7 (1.5)	39.8 (7.1)
333	11.8 (3.4)	19.9 (5.2)	26.3 (6.0)

Table 3.1 Wave latency variation with rate

3.4.4 Variation in SNR with stimulus condition

Figures 3.3i and 3.3ii show the variation in SNR estimated using the F_{sp} technique for the conventional stimulus rates and the MLS stimulus rates respectively (the data from the two groups have been overlaid). For the conventional stimulation rates, SNR increases with rate. Repeated measures analysis of variance on the data from group 1 showed the linear effect of rate to be significant ($p<0.001$). For the MLS stimulation, significant linear, cubic and quadratic effects of rate on SNR were found for group 1 ($p<0.05$) and a significant quadratic effect was seen for group 2 ($p<0.005$), where the SNR increases up to around 143-167 clicks/s and then decreases at higher rates. The reason for this is that the noise estimate

reduces with increasing number of stimuli to a greater extent than the reduction in signal amplitude shown in Figure 3.1.

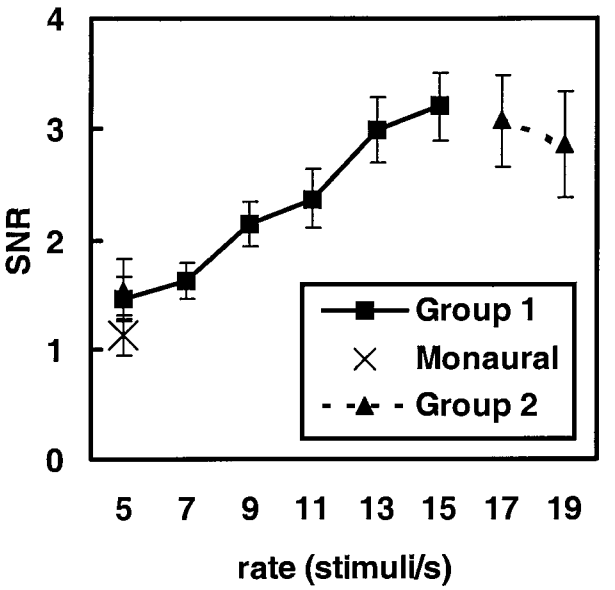


Figure 3.3i Variation in the F_{sp} estimate of SNR with conventional stimulation rate. Error bars represent 1 s.e. of the mean.

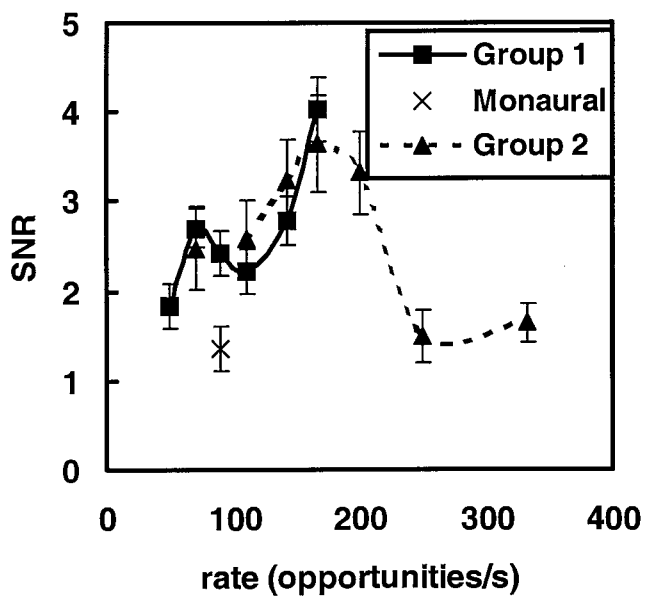


Figure 3.3ii Variation in the F_{sp} estimate of SNR with MLS stimulation rate. Error bars represent 1 s.e. of the mean.

3.4.5 A comparison of the wave amplitude estimate and the F_{sp} estimate of SNR

For all recordings made on the two groups, two estimates of SNR were made. The F_{sp} estimate of SNR was computed and the relative SNR between all recordings and the recording at 5 clicks/s was calculated. The correlation between the two methods was high (0.87 for Group 1 and 0.84 for Group 2; $p<0.005$). Both methods showed that SNR increases with conventional stimulation rate. For MLS stimulation, SNR increases with rate up to 167 clicks/s and then starts to decrease. The monaural recordings had a lower SNR than the equivalent binaural recordings.

3.4.6 Variation in wave presence with stimulus condition

N_a, P_a and N_b wave presence was assessed for all recordings made. The author estimated whether each wave could be identified. Table 3.2 shows wave detectability for both subject groups. For the recordings made with click stimuli, wave presence increased with the SNR. Recordings made using MLS clicks at 167 opportunities/s had 100% wave presence of the N_b wave for both subject groups.

Group 1			
Rate	N_a	P_a	N_b
5	86%	93%	86%
7	93%	100%	86%
9	100%	93%	100%
11	86%	100%	100%
13	93%	93%	100%
15	93%	93%	79%
50	100%	93%	93%
70	93%	100%	100%
90	100%	100%	100%
111	100%	100%	100%
143	100%	100%	100%
167	92%	100%	100%
5 (monaural)	79%	71%	79%
90 (monaural)	86%	93%	100%
Group 2			
Rate	N_a	P_a	N_b
5	90%	90%	90%
15	100%	100%	91%
19	73%	64%	82%
70	91%	91%	100%
111	82%	100%	100%
143	100%	100%	91%
167	100%	100%	100%
200	91%	100%	100%
250	73%	36%	36%
333	100%	91%	82%

Table 3.2 Wave detectability as a function of rate

3.5 Discussion

3.5.1 Avoiding PAM interference when recording the MLR

Whilst conducting the pilot study, the effect of moving the inverting electrode from a mastoid to a non-encephalographic position at the nape of the neck was investigated. Hall (1992) suggests that this should reduce PAM interference. However, many studies of the MLR have used a mastoid reference (Beer et al, 1996; Musiek and Lee, 1997; Bell et al, 2001). Despite the fact that PAM interference will be reduced in surgery where muscle relaxant is administered, it would appear to be good practice to use a non-encephalographic reference electrode in all studies of the MLR.

3.5.2 A comparison of methods for estimating relative SNRs

The relative SNR of AEPs can either be assessed using wave amplitudes as suggested by Thornton (1993), or using the SNR directly estimated from recordings using the F_{sp} technique. The correlation between the two methods is high (0.85 for group 1 and 0.835 for group 2; $p<0.005$) for both subject groups. It therefore appears that it is valid to use either method.

3.5.3 Test speed improvement by increasing the conventional stimulation rate

One of the aims of this study was to investigate whether increasing the conventional recording rate could improve the acquisition of the MLR. Figure 3.3i shows the variation in the SNR of recordings with conventional stimulation. SNR increases significantly with rate. As recording time of conventional recordings is inversely proportional to the square of the SNR, the test time of a recording relative to that of a recording made at 5 clicks/s can be estimated. The test speed increase is almost linear with rate. For example, for group 2 in Figure 3.3i it can be seen that recordings made at 19 clicks/s have a mean SNR of 2.86 and recordings made at 5 clicks/s have a mean SNR of 1.54. The ratio of test speeds is given by $(2.86/1.54)^2 = 3.45$. This is almost as much as would be expected under the assumption that the response does not adapt with increasing rate.

The limit to increasing the conventional recording rate is overlapping of successive responses, which occurs when the response duration exceeds the reciprocal of the rate used. To identify the latency of a peak in an auditory response, it is necessary to view some of the response beyond the peak. If the N_b latency increases to around 50 ms due to increasing depth of anaesthesia (Thornton 1989), then the analysis time window should not be shortened much below 70 ms for correct identification of the wave. At 15 clicks/s, the time window is 67 ms. The SNR data show that this corresponds to a reduction in estimated test time by a factor of 3 relative to a recording made at 5 clicks/s.

3.5.4 The test speed improvement with rate of MLS stimulation

The SNR of MLS recordings from groups 1 and 2 are shown in Figure 3.3ii. It can be seen that the SNR increases up to around 143-167 click opportunities/s and then decreases above this rate. It appears that a rate of 143-167 opportunities/s represent the best trade off between a reduction in averaged noise to an increasing number of averages and a decrease in signal

due to adaptation of the response amplitude. This is consistent with the P_a-N_b amplitudes shown in Figure 3.2ii, where the wave amplitude is seen to drop off above 167 opportunities/s. The optimal MLS stimulation rate found in this study is somewhat higher than that found by Bell et al (2001). However, the electrode placement used in the previous study may have resulted in PAM interference on the responses recorded (see above), resulting in increased variability of recordings. The optimal stimulation rate of 167 opportunities/s is consistent with the results reported by Leung et al (1998), who investigated the rate-adaptation of the ABR with MLS sequences and who reported an increase in SNR with MLS rate up to approximately 200 opportunities/s at 60 dB nHL, after which the SNR decreases with rate as the response adapts.

The mean SNR at 167 opportunities/s from groups 1 and 2 is 3.84. If this is compared to the mean SNR of 1.5 at 5 clicks/s from groups 1 and 2, the test speed improvement is 6.5 times. This is almost twice the improvement in test speed that can be achieved by increasing the conventional stimulation rate. This would appear to contradict the findings of van Veen and Lasky (1994), who suggested that MLS cannot be used to improve the SNR of recordings above that of a conventional recording. However, their findings were based on ABR data from other studies and they may not have taken into account the limitation of having a sufficient time window for wave analysis (at 167 click/s, the analysis time window available is 90 ms using an MLS of order 4). The limit on conventional averaging rate for ABR recording is higher than that for MLR recording (100 stimuli/s for ABR vs 15 stimuli/s for MLR). The rate at which neural adaptation reduces SNR for MLS recording is at around 150-200 stimuli/s for both ABR and MLR recording. This is a lot higher than the maximum conventional rate for MLR recording, but not much higher than the maximum conventional rate for ABR recording. The rate increase that can be achieved using MLS before neural adaptation occurs is therefore higher for MLR than ABR recording, so the technique may improve SNR more for MLR than ABR.

3.5.5 Latency variation with rate

There was found to be no significant variation in wave latency with either increasing MLS or conventional recording rates. This finding contradicts previous studies which appear to have found a change in wave latency with rate (Bell et al, 2001; Picton et al, 1991). However, both these studies used a mastoid reference electrode at A1. As mentioned above, PAM interference appears to produce a shift in wave latency and this effect may account for apparent latency shifts in these two studies. If the PAM adapts differently with rate than the

MLR and the PAM is recorded, there might be an apparent rate induced latency shift which reflects adaptation of the PAM, not the MLR.

If the MLR is to be used as a measure of anaesthetic depth, it will be necessary to investigate whether other parameters such as subject age, body temperature and hearing threshold can have a significant effect on the latencies of the MLR waves.

3.5.6 The usefulness of the MLR in assessing anaesthetic depth

If the MLR is to be used as a measure of anaesthetic depth, an important consideration is whether it is possible to record an MLR from all subjects undergoing operations. Table 3.2 shows the presence of the MLR waves from the two experiments performed. Overall the wave presence was high in both experiments, which is encouraging if the MLR is to be used as a measure of anaesthetic depth, although it may not be possible to record an MLR from subjects who do not have normal hearing, or from young children in whom the MLR response is not fully developed (Hall, 1992). In both groups, it was possible to record an N_b wave from all subjects at 167 opportunities/s. This was not true for any of the conventional recording rates and is consistent with the recordings at 167 opportunities/s having a higher SNR than the conventional recordings. Of course, wave presence may be increased if the averaging process is continued for a longer time period, but in these experiments the recording time was fixed.

The electrode placement in the experiments appears to have reduced PAM interference and may account for the high wave presence in both studies. In operations in which a muscle relaxant is given to a patient, such muscle activity is minimised, so electrode placement is not as critical, although it will still be necessary to use a non-encephalographic inverting electrode if baseline MLR measurements are to be made on subjects before they are anaesthetised.

3.6 Summary and conclusions

This study investigated the effect of varying the conventional stimulation rate and varying the MLS stimulation rate on the MLR. MLR recordings can be reliably recorded using conventional stimulation rate clicks and high MLS stimulation rate clicks. The same time period of 185 s was used for all recordings. It was possible to record an N_b wave from all subjects at an MLS stimulation rate of 167 clicks opportunities/s.

In a pilot study, the amplitude of PAM interference was significantly reduced by moving the inverting electrode to a non-encephalographic position. It would appear that such an electrode configuration should be used in all studies of the MLR. Presence of the PAM response can produce an apparent shift in the latencies of the MLR waves.

Experiment 1 compared binaural and monaural presentation of stimuli. Binaural presentation increases the SNR of recordings compared to monaural presentation and results in a reduction in test time by a factor of approximately 2.

SNR was found to increase almost linearly with increasing conventional click rate, so a reduction in test time by a factor of 3 can be expected by increasing the conventional click rate from 5 to 15 click/s. The length of the analysis time window available for correctly identifying a N_b wave, which may be shifted in latency due to the action of anaesthetics, limits the amount by which the conventional click rate can be increased to approximately 15/s.

SNR was found to increase with MLS stimulation rate up to 167 opportunities/s, after which SNR reduced with rate. The test speed improvement that can be expected with MLS clicks is 6.5 times, which is twice as much as can be achieved by simply increasing the conventional click rate.

Wave latency was not found to vary significantly with rate of presentation. P_a-N_b Wave amplitude does not reduce significantly as conventional stimulation rate is increased, but does decrease at MLS stimulation rates above 167 opportunities/s.

CHAPTER 4

Experiment 2. A comparison of click and chirp stimuli to elicit the MLR

4.1 Introduction

Experiment 1 mapped the rate-adaptation effects on the MLR for conventional and MLS sequences of click stimulation. The acquisition time of the MLR reduces near linearly with conventional stimulation rate and could be improved by a factor of three times by increasing the conventional stimulation rate from 5 to 15 clicks/s. The limit of the conventional stimulation rate is the reciprocal of the analysis time window required. The use of MLS overcomes this limit on stimulation rate and allows higher stimulation rates to be used. However, the improvement in acquisition time with increasing rate is limited by adaptation of the response. By mapping the adaptation-rate function of the MLR, the optimal stimulation rate found was 167 stimulus opportunities/s, which corresponds to a reduction in test time of six times over conventional stimulation at 5 clicks/s.

A new stimulation technique that may improve the acquisition of AEPs has been suggested by Dau et al (2000) and involves the use of chirp stimuli to compensate for temporal

dispersion occurring in the response of the basilar membrane for stimuli at different frequencies. Click stimuli are commonly used to elicit AEPs as they have a wide band frequency spectrum and so stimulate a large portion of the cochlea. However, a click will take time to travel along the basilar membrane, so low frequency regions at the apex of the cochlea will be stimulated up to 10 ms later than high frequency regions at the base of the cochlea. The response of the auditory nerve to a click will therefore be spread out in time. Dau et al (2000) generated chirps that compensate for the place-frequency mapping of the cochlea, sweeping from low to high frequency within 10 ms. They demonstrated that ABR elicited using such chirps have a larger amplitude than ABR elicited using clicks. However, no published study has investigated whether such chirps might improve the acquisition of other AEPs, such as the MLR. Assuming the system is linear, it should be possible to replace the click stimuli with chirps to generate the MLR. The aim of experiment 2 was to investigate whether the amplitude of the MLR might be increased by using such a chirp stimulation for the optimal stimulation rates found in Experiment 1. An increase in amplitude would correspond to an increase in SNR. This should in turn further reduce the acquisition time for the MLR.

The aim of the experiment was to investigate whether using the approximate chirp stimuli of Dau et al. (2000) might further improve the acquisition time of the MLR, both for conventional stimulation rates and for higher MLS stimulation rates. A direct comparison between clicks and chirps was made at two conventional recording rates and two MLS recording rates.

4.2 Method

Subjects with normal hearing participated and the MLR was recorded at a fixed stimulus level for equal time periods. Experiment 1 had demonstrated that the relative SNR of recordings obtained from wave amplitudes agreed well with the direct estimate of SNR using the F_{sp} technique (Elberling and Don, 1984). For this experiment direct estimates of SNR using the F_{sp} technique were used to infer the relative test speeds of recordings (see Chapter 3). The F_{sp} analysis time window was 25-45 ms for click stimulation and 35-55 ms for chirp stimulation. The single point was taken 35 ms after the start of the clicks and 45 ms after the start of the chirp. Dau et al report that the response occurs at the offset of the chirp stimulus. As the chirp is 10.4 ms in length, the chirps should produce a latency shift of approximately 10 ms in the response; hence the analysis time window was moved by 10 ms.

4.2.1 Subjects

Subjects were taken from a student population at the University of Southampton; five males and five females were included (the same group of subjects used as for Experiment 1 was not available). To minimise effects of age and hearing impairment, subjects included in the study were required to be otologically normal. They were aged between 18 and 30 years with hearing threshold levels better than 20 dB throughout the range 250-8000 Hz in each ear and all had normal tympanograms. No subjects had a history of ear disease or undue noise exposure (see Appendix 4). The mean age was 24 years.

4.2.2 Stimuli

Stimuli consisted of either 0.1 ms rectangular clicks (2 samples long at 20 kHz), or 'approximate' chirps of length 10.4 ms. Stimuli were presented at a level of 60 dB SL to each ear. Here sensation level is referenced to the detection threshold for clicks or chirps presented at a rate of 5/s. The mean threshold for clicks was 44 dB peak equivalent (pe) SPL for both ears. For chirps, the corresponding values were 20 and 22 dB pe SPL for right and left ears. The order of stimulation was randomised among subjects.

The same duration of 185 seconds was used for all recordings. Artefact rejection was applied off line to exclude epochs that may contain excessive noise. For each recording made, a criterion was calculated so that so that the extreme 10% of epochs ($\pm$ 2%) were rejected.

4.2.3 Specification of the approximate chirp stimuli

The chirps used in this experiment were the approximate chirps used by Dau et al. (2000). The approximate chirps were generated in MATLAB using an 'm' file supplied by Tosten Dau (see Appendix 6). Dau et al (2000) used two types of chirp: an 'exact chirp' in which the speed of propagation of a travelling wave on the basilar membrane is frequency dependent and an 'approximate chirp' in which the propagation constant is not frequency dependent. They report that the frequency independent expression used for the approximate chirp is not valid at low frequencies near the cochlea windows, but that the effect is not large. Chirps with a frequency range from 100-10000 Hz were generated using the same specification as Dau et al. These waveforms would be replayed via insert earphones to obtain the MLR. The waveform of the approximate chirp generated in MATLAB is shown in Figure 4.1i. In order to verify the chirps, the output from the insert earphones was delivered to a IEC 711 occluded ear simulator, the microphone of which was in turn connected to a Brüel and Kjær 2112

spectrometer. The output of the spectrometer was averaged during presentation of 100 chirps to obtain a clear representation of the waveform. The FFTs of the averaged chirp and the averaged click are shown in Figure 4.1ii. The frequency spectrum of the averaged chirps is reasonably flat. As a calibration reference for the scale of figure 4.1ii in dB SPL, the FFT of a 1 kHz sine wave was used. This was generated with a sound calibrator (Brüel and Kjær 4230) placed on the microphone of the occluded ear simulator, which generates a sound pressure level of 93.8 dB.

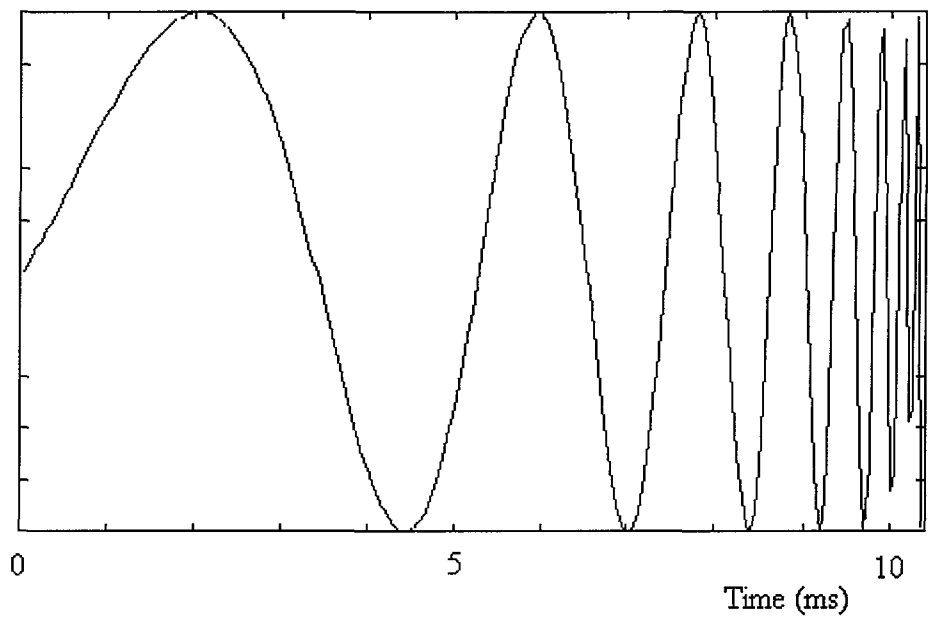


Figure 4.1i The time history of the approximate chirp as defined in Matlab.

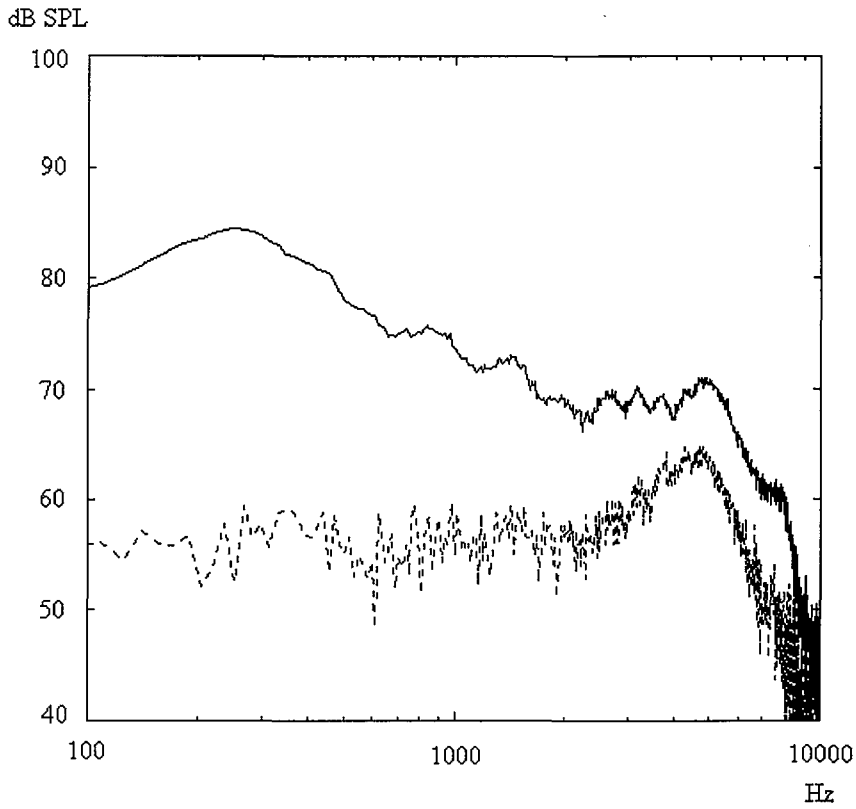


Figure 4.1ii The frequency spectrum of the approximate chirp (continuous line) and the click (dotted line), at the same dial setting.

4.2.4 Equipment and recording conditions

Apart from the headphones used, the equipment configuration was identical to that for Experiment 1. The headphones used were ER-2 insert phones instead of the ER-3A insert phones used in Experiment 1. ER-2 insert phones were used by Dau et al (2000) and have a flatter frequency response than ER-3A insert phones (see Chapter 2). This was considered important as the chirp stimulus should excite the cochlea over a wide frequency band. The ER-2 insert phones require a higher driving current that the ER-3As, so a Gason Stadler GSI-16 audiometer, which generated a higher output level, was used instead of a Kamplex KC50 to drive the insert phones. Subjects were awake, sitting in a comfortable chair and reading. Electrode placement was the same as for Experiment 1 and recordings were made with an impedance < 5 kΩ

4.3 Results

4.3.1 Waveform Morphology

Example waveforms from subject JH are shown in Figure 4.2 for stimulation of 5 clicks/s, 5 chirps/s and chirps at MLS rate 167 stimulus opportunities/s. Wave V of the ABR and waves N_a, P_a and N_b of the MLR have been identified for each waveform. Use of the chirp stimulation produces approximately a 10 ms increase in the latency of the MLR waves compared to click stimulation. N_b amplitude is greatest for chirp stimulation at 167 stimulus opportunities/s. For stimulation of 5 chirps/s an additional peak is seen before wave V at approximately 9 ms, although it is not seen for this subjects using MLS chirp stimulation. Dau et al (2000) reported a similar feature at high stimulation levels when recording the ABR using the approximate chirp. They suggest that the feature is a result of early low frequency energy in the chirp.

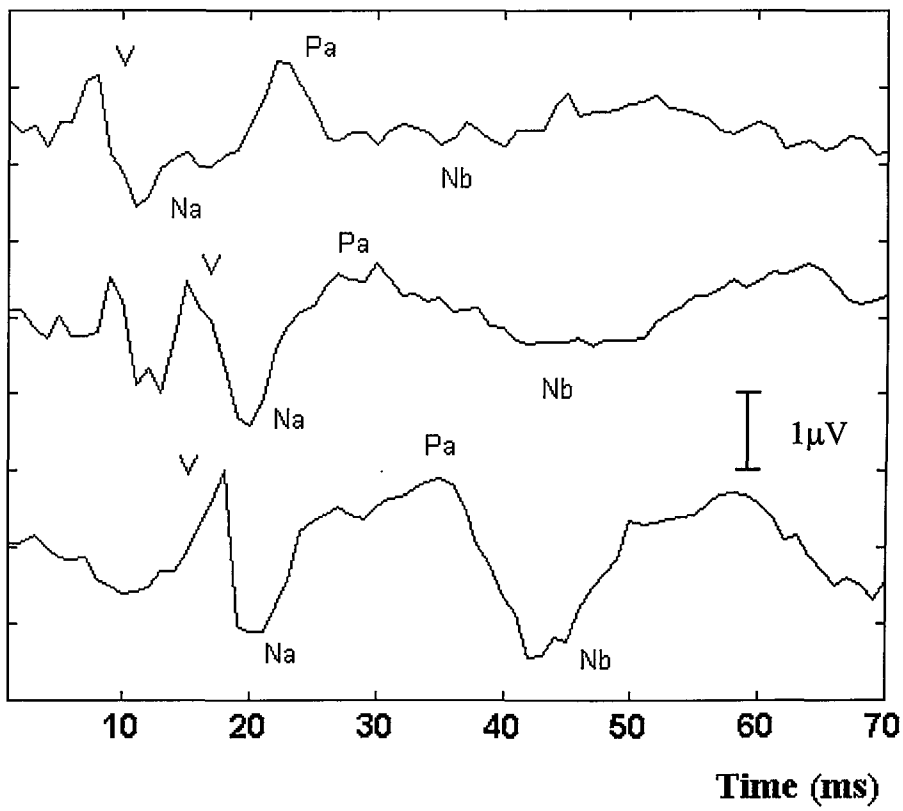


Figure 4.2. MLR Waveforms from subject JH using stimulation at 5 clicks/s (top), 5 chirps/s (middle) and chirps at MLS rate 167 stimulus opportunities/s (bottom).

4.3.2 Variation in wave latency with stimulus condition

Latencies for wave V of the ABR and the N_a, P_a and N_b waves of the MLR were estimated by the author for each of the recordings made. The variation in mean wave latency with stimulus type is shown in Figure 4.3. Repeated measures analysis of variance demonstrated a significant effect of chirp type for all the waves ($p<0.002$). The effect of rate was only significant for wave V ($p<0.01$) where latency increases with rate. The average increase in latency between chirps and clicks was 8.9 ms. Average MLR waveforms across subjects for each stimulation condition of Experiment 2 are shown in Appendix 2.

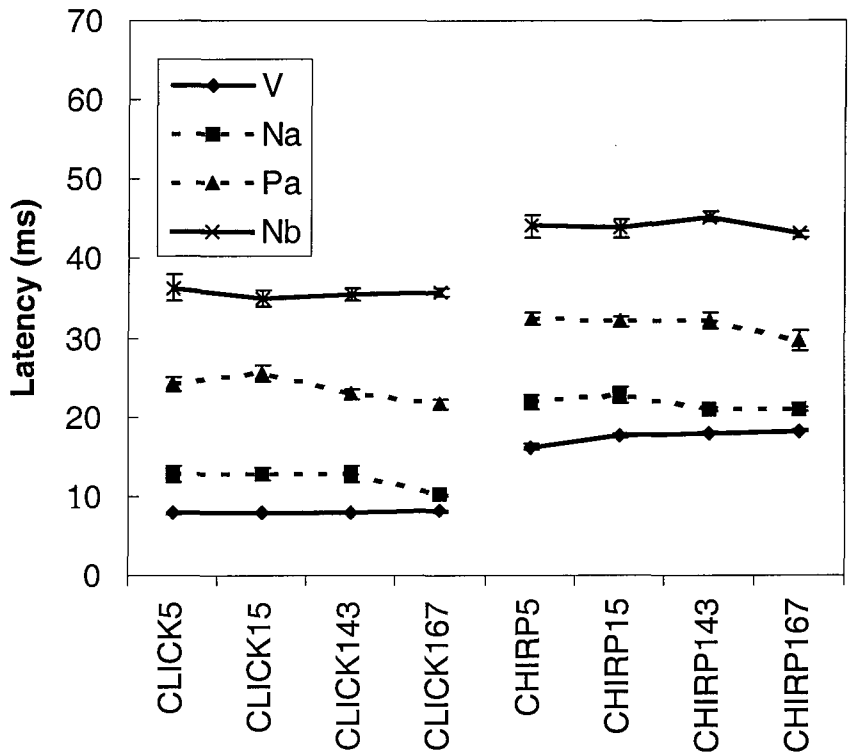


Figure 4.3 Variation in mean wave latency with different stimulus types. Error bars represent one standard error of the mean.

4.3.3 Variation in wave amplitude with stimulus type

Wave amplitude was estimated by the author for all recordings. The variation in P_a-N_b amplitude with stimulus type and rate is shown in Figure 4.4 and the variation for wave V-N_a amplitude with stimulus type and rate is shown in Figure 4.5.

For the P_a-N_b amplitude, repeated measures analysis of variance showed no overall effect of stimulus type (click vs chirp) on amplitude. There was a significant effect of rate on

amplitude ($p<0.05$). Paired samples T-tests were used to compare clicks and chirps at each rate and the only significant difference was at 167 stimuli opportunities/s, with a significantly higher amplitude for chirps than clicks.

For the wave V-N_a amplitude, repeated measures analysis of variance showed that there was an overall effect of stimulus type on amplitude ($p<0.05$) with the chirp recordings having significantly larger amplitudes than those using clicks. There was no significant effect of rate on amplitude. Paired samples T-tests showed a significant higher amplitude for chirps over clicks at 5, 143 and 167 stimulus opportunities/s.

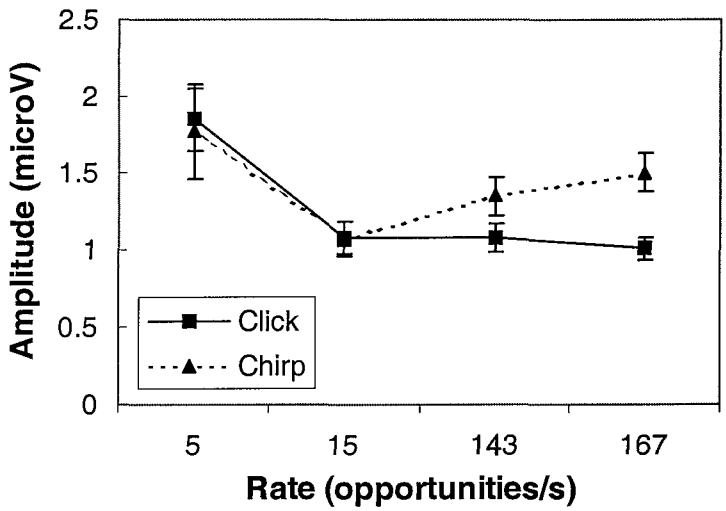


Figure 4.4. Variation in P_a-N_b amplitude with stimulus type and rate. Error bars represent one standard error of the mean.

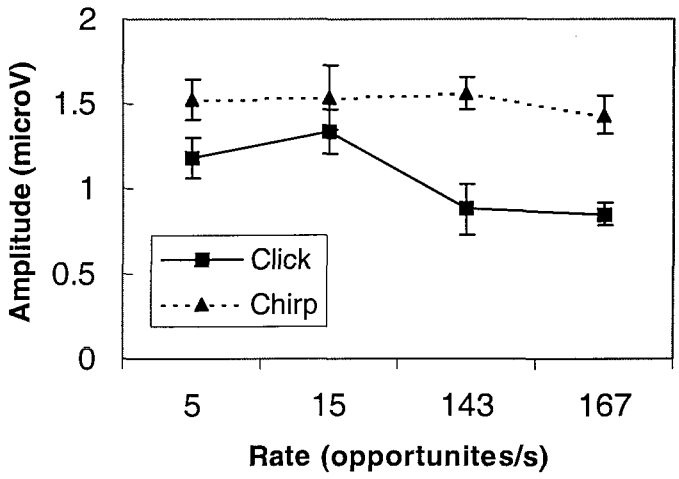


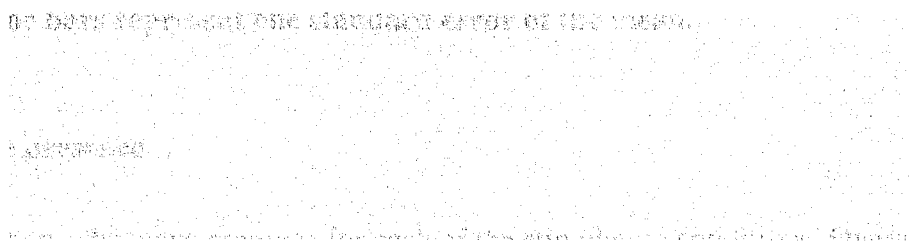
Figure 4.5. Variation in Wave V-N_a amplitude with stimulus type and rate. Error bars represent one standard error of the mean.

4.3.4 Variation in SNR with stimulus condition

SNR was estimated from recordings using the F_{sp} technique (Elberling and Don, 1984). This was performed for regions corresponding to the N_b region of the MLR (25-45 ms after the stimulus onset for clicks and 35-55 ms for chirps) and wave V of the ABR (5-15 ms after stimulus onset for clicks and 15-25 ms for chirps). The variation in SNR for the N_b region with stimulus type and rate is shown in Figure 4.6. The variation for the wave V region is shown in Figure 4.7.

Repeated measure analysis of variance showed significant effects of both stimulus type and rate on the SNR for the N_b region of the MLR ($p<0.001$). The highest SNR is seen at 167 stimulus opportunities/s for both stimulus types. Paired T-tests showed significant difference between clicks and chirps at 15, 143 and 167 stimulus opportunities/s ($p<0.05$). At 143 and 167 stimulus opportunities/s the SNR was significantly higher for chirps than clicks, but at 15 stimulus opportunities/s the SNR was significantly smaller.

Repeated measure analysis of variance showed significant effects of both stimulus type and rate on the SNR for the wave V region of the ABR ($p<0.005$). Paired T-tests showed a significantly greater SNR for chirps than clicks at all rates ($p<0.01$). For the wave V region of the ABR, the greatest SNR is seen at 143 stimuli/s for both stimulus types.



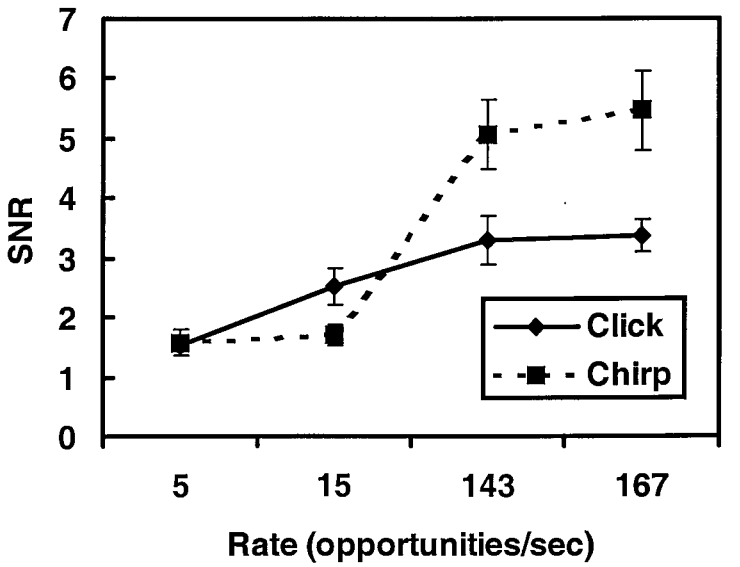


Figure 4.6 Variation in SNR with stimulus type for the N_b region of the MLR. Error bars represent one standard error of the mean.

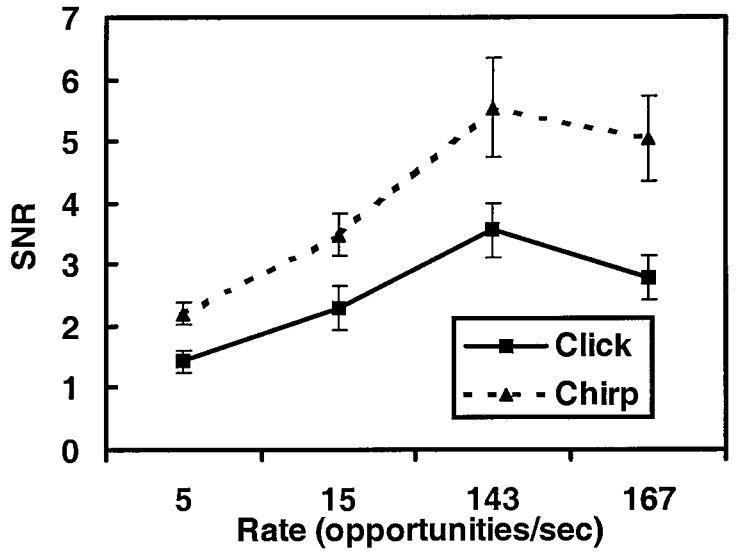


Figure 4.7 Variation in SNR with stimulus type and rate for the wave V region of the MLR. Error bars represent one standard error of the mean.

4.3.5 Wave presence

Table 4.1 shows the wave presence for each of the stimulation conditions. Overall wave presence is higher for clicks than for chirps. However N_b wave presence is 100% for all MLS recordings at rates of 143 and 167 stimuli/s.

	V	N_a	P_a	N_b	Average
5 clicks/s	70%	80%	100%	80%	83%
15 clicks/s	100%	100%	100%	100%	100%
143 clicks/s	100%	100%	100%	100%	100%
167 clicks/s	100%	100%	100%	100%	100%
5 chirps/s	60%	90%	70%	70%	73%
15 chirps/s	70%	90%	90%	90%	85%
143 chirps/s	100%	100%	100%	100%	100%
167 chirps/s	100%	100%	90%	100%	98%

Table 4.1. Wave presence in Experiment 2

4.5 Discussion

4.5.1 Test speed improvement using chirps

For Experiment 2, the approximate chirp stimuli specified above were used at both conventional and MLS stimulation rates. For MLS chirp recordings, the assumption has been made that the measurement system is linear, so both the input sequence as well as the output response can be convolved in time. At 143 and 167 opportunities/s some of the chirp stimuli will overlap in time.

Figure 4.6 shows the SNR from the recordings for the N_b region of the MLR. Chirps produced a significantly higher SNR than clicks at 143 and 167 stimuli/s and the greatest SNR is obtained at 167 clicks/s. The SNR at 167 chirps/s is 5.35. This compared to the SNR of 1.39 at 5 clicks/s and corresponds to a test speed improvement of 14.9 times (assuming SNR improves as the square root of test duration). It would therefore appear that by combining MLS stimulation rates with chirp stimuli, a greater reduction in test time can be achieved than the use of MLS stimulation rates with clicks.

However there was no significant difference in SNR between clicks and chirps at 5 stimuli/s for the N_b region of the MLR and the SNR was significantly lower for chirps than clicks at 15 stimuli/s. The SNR advantage of chirps over clicks seen at MLS rates is not seen at conventional stimulation rates for this region of the waveform. These results contrast with the SNR results for the wave V region of the ABR shown in Figure 4.7, where a significantly higher SNR is seen for all stimulation rates (MLS and conventional) and would be consistent with the results of Dau et al (2000) who reported an increased amplitude of wave V using chirps instead of clicks. It had been assumed for this study that the rate-adaptation effects for

clicks and chirps would be the same. However, it would appear that the rate-adaptation effects for the N_b region of the MLR are not the same for chirps as for clicks at conventional stimulation rates. The SNR does not improve when the rate is increased from 5 to 15 chirps/s, although an improvement is seen for 15 clicks/s over 5 clicks/s. Whilst this experiment has shown that test speed may be improved by using MLS chirp stimulation instead of MLS clicks, it would appear that more research is necessary to fully understand rate-adaptation effects for chirp stimuli.

4.5.2 Variation in wave presence with stimulus condition

If the MLS is to be used as an indicator of anaesthetic depth, it is important that the appropriate waves are present in the recordings. The overall wave presence for chirps across recordings was slightly lower than that for clicks. However the N_b wave presence was 100% for all MLS chirp recordings made and it is the N_b wave which is thought to be most useful as an indicator of anaesthetic depth.

4.5.3 Latency variation with stimulus type

Dau et al (2000) reported that when chirps are used instead of clicks, the latency of wave V of the ABR is shifted by 10.5 ms which corresponds to the length of the chirp. They concluded that the response occurred at the offset of the stimulus by which time the lowest frequencies in the chirp have time to travel to the apex of the cochlea. In this study, the average latency shift of waves was 8.9 ms. This is consistent with the response not occurring until near the offset of the stimulus. However, it is slightly shorter than the full length of the chirp (10.4 ms). Whilst the difference is small, it may imply that, for the subjects in this study, either the delay of the lowest frequencies in the chirp are slightly longer than the actual travel time for those frequencies to reach the apical regions of the cochlea, or that the lowest frequencies in the chirp are exciting a response more basally of the cochlea than assumed and hence the latency of the response is reduced.

4.6 Summary and conclusions

This study compared the MLR elicited using chirps and clicks at conventional rates of 5 and 15 stimuli/s and MLS rates of 143 and 167 stimulus opportunities/s. All recordings were made in the same time period of 185 s and the SNR of recordings was compared using the F_{sp} technique.

The best SNR was obtained using MLS chirps at 167 stimulus opportunities/s. If this is compared to stimulation at 5 clicks/s, it represents an improvement in test speed of 14.9 times. This is a further improvement in test speed over that obtained using MLS clicks in Experiment 1 and may represent a significant reduction in test time if the MLR is to be used as a measure of anaesthetic depth.

Whilst the SNR of recordings obtained using MLS chirps is greater than that for MLS clicks for the N_b region of the MLR, when conventional stimulation rates of 5 and 15 stimuli/s are used there is no improvement in SNR for chirps over clicks. Indeed, the SNR for 15 chirps/s is significantly worse than that for 15 clicks/s. It would appear that the rate-adaptation effects of the MLR elicited with chirps are not the same as for the MLR elicited with clicks and this may require further investigation. If SNR is calculated for the wave V region of the ABR, all chirp recordings show an increased SNR over clicks recordings. This implies that rate-adaptation effects with chirp stimulation are different for different types of AEP.

The average increase in wave latency using chirps instead of clicks was 8.9 ms, which is slightly less than the length of the chirp. The discrepancy may imply that the true frequency-vs-delay characteristics of the cochlea at 60 dB SL are not exactly those predicted from the linear cochlea model of de Boer on which the approximate chirp stimulus was based.

4.7 Chapter 4 Addendum

4.7.1 A supplementary investigation of the interaction between rate and the SNR advantage of chirps over clicks

Experiment 2 demonstrated that, for a fixed acquisition time, SNR for the N_b region of the MLR is greatest when using chirp stimuli presented at an MLS stimulation rate of 167 chirps/s. This would appear to be the stimulation of choice when making clinical measurements of the MLR for estimating depth of anaesthesia as it results in the highest signal quality for a given acquisition time. However, the results of Experiment 2 also show that there is an unexpected interaction between rate of stimulation and the SNR advantage of chirps over clicks. Figure 4.6 shows SNR with stimulation type for the N_b region of the MLR. Whilst the SNR of chirps is higher than for clicks at MLS stimulation rates of 143 and 167 stimuli/s, there is no such increase in SNR for conventional stimulation rates of 5 and 15 stimuli/s. Indeed at 15 stimuli/s, SNR is smaller for chirps than clicks. This effect is also seen in the P_a-N_b amplitude data shown in Figure 4.4. The P_a-N_b amplitude is greater for chirps

than clicks at MLS stimulation rates, but at conventional rates there is no significant difference.

There are two possible explanations for this interaction between rate of stimulation and the SNR advantage of chirps over clicks. One is that MLS is fundamentally different from conventional stimulation as it is pseudo-random. The response of the auditory pathway to a regular train of stimuli may be different to that when stimuli are in an unpredictable MLS sequence. The magnitude of this effect might be different for click and chirp stimuli as the chirps stimulate a wider frequency region of the auditory pathway.

An alternative explanation is that the rate-adaptation function for chirp stimulation may not be the same as for click stimulation. Experiment 1 mapped the rate-adaptation function for the MLR using conventional and MLS stimulation. In Experiment 2 it was assumed that the optimal stimulation rate for chirps would be the same as that found for clicks. However, this might not be the case. If the amplitude of the MLR obtained with clicks drops away with rate faster than the amplitude obtained with chirps, then the MLR amplitude may be higher for chirps than clicks at high stimulation rates, but not at low rates.

To investigate these possible effects further, two pilot experiments have been completed. The first experiment compared the amplitude of MLR obtained using conventional and MLS chirp stimulation at the same rate; that is, the experiment addressed the question of whether conventional chirp stimulation would produce the same response as pseudo-random chirp stimulation when the rate was the same. The second experiment attempted to compare the rate-adaptation functions for chirp and click stimuli. Differences in MLR amplitudes and SNR for click and chirp stimuli were measured as a function of stimulation rate.

For both supplementary experiments the equipment was the same as that used in Experiment 2. All stimuli were presented at a level of 60 dB SL. All subjects were otologically normal.

4.7.2 Supplementary experiment 1

Chirp and click stimuli were presented at a conventional rate of 15 stimuli/s. In addition chirps were presented using MLS order 3 with the same average stimulation rate of 15/s. An MLS order 3 contains four stimuli and seven stimulus opportunities. A buffer length of 0.268 s gives a maximum rate of 26 stimuli/s and average rate of 15 stimuli/s. MLS order 4 could not be used as the desired buffer size became too large for the memory available on the micro1401 using the current software configuration. The SNR obtained using MLS will be

worse than that for equivalent average rate conventional stimulation as not all stimulus opportunities in the MLS sequence are filled. The recording time was therefore increased to 9 minutes in order to obtain favourable SNR using slow MLS rates. Four subjects participated in this pilot.

The results from the first supplementary experiment are shown in Figure 4.8. For conventional stimulation at 15 stimuli/s, wave V-N_a amplitude is smaller for click than for chirp stimulation, whereas there is little difference in P_a-N_b amplitude between click and chirp stimulation. This replicates the finding of Experiment 2.

There is little difference in amplitude between conventional chirp and MLS chirp stimulation. There is a possible difference between MLS and conventional chirp stimulation for the N_a-P_a amplitude, but none for V-N_a and P_a-N_b amplitudes.

Whilst the number of subjects is small, it does not appear likely that the pattern of wave amplitude results from Experiment 2 is due to a difference between conventional and MLS chirp stimulation. (The average standard deviation on the data is around 0.5 μV but has not been shown on the figure for clarity).

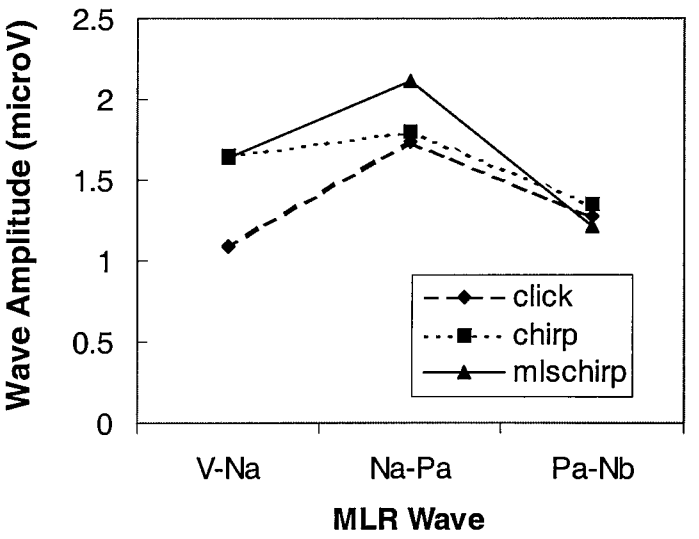


Figure 4.8 Wave amplitudes obtained using click, chirp and MLS chirp stimulation at the same average rate.

4.7.3 Supplementary experiment 2

MLR recordings were obtained using both click and chirp stimulation at a number of different rates. Conventional rates of 15 stimuli/s and MLS rates of 50, 90 167, 200, 250 and 333 stimuli/s were used. A fixed recording duration of 218 s was used.

Figure 4.9 shows the effect of rate on P_a-N_b amplitude for click and chirp stimulation. Although the number of subject is small, it appears that the adaptation of the click response with rate is faster than the adaptation of the chirp response. At 15 stimuli/s there is little difference in P_a-N_b amplitude between click and chirp stimuli. However, by 90 stimuli/s the click response has adapted more with rate than the chirp response. The P_a-N_b amplitude at higher rates is therefore greater for chirps than for clicks.

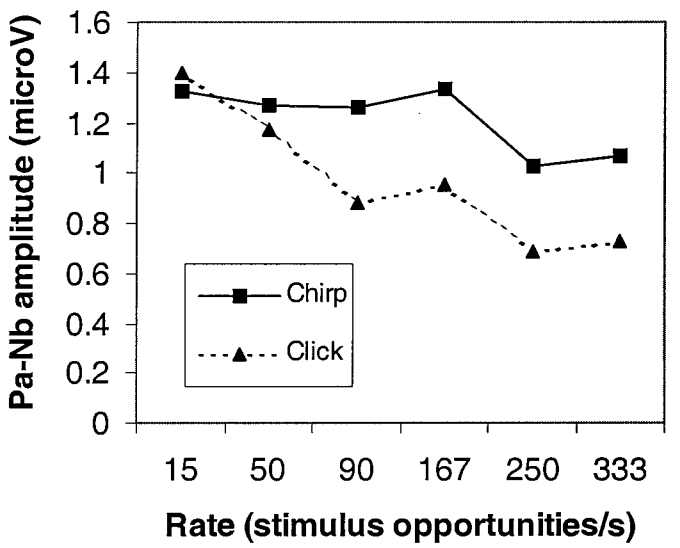


Figure 4.9 P_a-N_b amplitude as a function of rate for chirp and click stimulation

These two supplementary studies were intended to investigate the effect found in Experiment 2 further, whereby P_a-N_b amplitude (and the corresponding SNR) was greater for chirps than clicks at high stimulation rates, but not at low rates. These were not full experiments and subject numbers are too small for statistical analysis. However, it appears that the explanation for the effect is that adaptation of the MLR response with rate is faster for click than for chirp stimulation. This may be a consequence of the chirp stimulating a wider bandwidth of the auditory pathway. A full experiment with a larger sample size is necessary to confirm this finding.

CHAPTER 5

Experiment 3. An investigation of the use of band-limited chirp stimuli to elicit the ABR.

5.1 Introduction

Objective testing of hearing sensitivity aims to estimate hearing thresholds in subjects without requiring their co-operation. This has practical application when they are unwilling or unable to co-operate with behavioural testing, perhaps because they have not yet reached a sufficient stage of development. The importance of objective testing in audiology is increasing with the introduction of universal neonatal hearing screening, which aims to detect children with a hearing impairment as young as 6 weeks. This screening typically takes the form of otoacoustic emission (OAE) testing followed by auditory brainstem response testing (ABR) using broadband click stimuli. Whilst these methods can give an indication of the overall level of hearing impairment, neither gives an unequivocal frequency-specific assessment of hearing threshold. Accurate frequency specific information can be obtained by using behavioural testing methods, such as distraction testing or visual reinforcement audiometry, which cannot be applied until around 6 months developmental age and which become more accurate with increasing age (Moore et al, 1977; Bamford and McSporran, 1993). This means that children who require a hearing aid may encounter a delay between the detection of hearing loss and the age at which it is possible to obtain sufficient frequency-specific information to fit the aid accurately. It is therefore desirable to improve the frequency specificity of objective test methods.

The ABR is normally elicited using click stimuli and the objective threshold obtained using clicks has been shown to correspond best to behavioural thresholds in the 2-4 kHz frequency range (Coats and Martin, 1977). Techniques that have been developed to make ABR testing frequency specific are described in Chapter 1. Using these methods it is possible to obtain acceptable estimates of high frequency thresholds in the range 2-4 kHz. However, low-frequency thresholds estimated using these methods do not agree well with behavioural thresholds and have a large variance.

A recent advance in the generation of AEPs has been the use of chirp stimuli, which compensate for frequency-vs-delay characteristics of the basilar membrane (see Chapters 1 and 4). As there is an approximately exponential rise in frequency with delay on the basilar membrane, the delay effect is more pronounced for low than high frequencies, so the issue of lack of neural synchrony due to frequency dispersion is more critical when attempting to measure low frequency brainstem responses. If chirps are generated with corresponding frequency-vs-delay characteristic over a restricted range of frequencies, it may be possible to generate better frequency specificity for the ABR than is achieved for tone bursts and thus estimate hearing thresholds better. The present study develops suitable frequency-specific chirps and investigates their feasibility to evoke the ABR in normal hearing subjects. Although this study is a departure from the rest of the thesis, which concerns the acquisition of the MLR (not the ABR), it is included as it investigates a novel method to obtain an AEP with potential clinical application. The study was designed as a preliminary investigation and anticipates the need for further investigation of subjects with hearing impairment if results from normal ears are promising.

Wegner and Dau (2002) have also investigated the use of band-limited chirp stimuli to obtain the ABR. The study was performed concurrently to the present study. The chirp stimuli used in the study were generated by using rectangular windows to remove portions of the 'flat spectrum chirp' (a chirp stimulus with a flat spectrum designed to compensate for frequency-dispersion on the Basilar mambrane) used by Dau et al (2001). In the current study Hanning windows were used to remove portions of the 'Approximate Chirp' used by Dau et al (2001), which does not have a flat spectrum. Wegner and Dau (2002) report that the amplitude of the ABR obtained with low frequency band-limited chirps was greater than the amplitude to low frequency tone-bursts. However, they did not address the question of whether the band-limited chirps gave a better estimate of low frequency hearing threshold than tone-bursts.

5.2 Method

5.2.1 Subjects

Subjects were drawn from the student population at the University of Southampton and included 5 male and 5 female subjects. A power calculation revealed that, assuming a standard deviation of ABR amplitude measurements of 0.25 μV, 10 subjects would be required to detect an amplitude difference of 0.2 μV with a power of 80% (the average difference between click and chirp wave V amplitudes found by Dau et al (2001) was approximately 0.3 μV). To minimise effects of hearing disorder, subjects included in the study were required to be otologically normal. They were aged between 18 and 30 years with hearing threshold levels better than 20 dB throughout the range 250-8000 Hz in each ear. No subjects had a history of ear disease or undue noise exposure (see Appendix 4). The mean age was 23 years.

5.2.2 Stimulus conditions

Four types of chirp were defined and used as stimuli. For each type a total of 10 recordings were made for each subject. Two recordings were made at each stimulus level, ranging from 50 down to 10 dB SL. Sensation level is referenced to the detection threshold for chirps presented at a rate of 30.3/s. The mean detection thresholds for the chirps were 21, 24, 21 and 24 dB p.e. SPL from low to high frequency respectively. The order of the chirps was balanced using a Latin square design.

A fixed rejection criterion of 27 μV peak-to-peak was applied online for all recordings to exclude sweeps containing excessive amplitudes (artefacts), which might arise from unwanted muscle activity and has a much greater amplitude than the evoked response of interest. This resulted in a mean artefact rejection rate of 3%.

The number of sweeps contributing to each averaged response was between 1000 and 2000 for stimuli at 40 and 50 dB SL; 2000 and 4000 for stimuli between 10 and 30 dB SL. This corresponded to recording durations of 30-60 s and 1-2 minutes respectively (not including artefact rejection). The total recording time including artefacts was approximately 70 minutes for 40 stimulus conditions per subject.

Due to unusual weather conditions, temperature control in the testing booth proved to be inadequate and three subjects complained of being cold during the recordings. It was found

that these subjects had poor recordings with unusually high noise levels. This was thought to be due to the subjects shivering. It was desirable to repeat the recordings on these subjects, but due to time limitations, it was only possible to repeat half the recordings for two of the three subjects. For these two subjects, the low frequency recordings were repeated as it was expected that the low frequency stimuli would produce a lower amplitude of response than the high frequency stimuli and so are more likely to be abolished by high levels of subject noise.

5.2.3 Specification of the chirp stimuli

The chirps used in this experiment were derived from the "approximate chirp" used by Dau et al. (2000). A chirp with a frequency range from 100-10000 Hz was generated using the same specification as Dau et al. Windowing in the time domain was used to extract frequency-specific chirps from this signal covering approximately octave bands. The time delays corresponding to the boundary frequencies of 375, 750, 1500, 3000 and 6000 Hz were calculated and Hanning windows with upper and lower –3 dB points corresponding to these frequencies were applied to the approximate chirp to produce the frequency-specific chirp stimuli. This process is shown in Figure 5.1. The approximate chirp is illustrated at the top of the figure along with the frequency-vs-delay mapping (calculated by generating chirps with different upper frequencies from 100 to 10000 Hz). The vertical dashed lines correspond to the frequencies where the –3 dB points of the Hanning window were applied and the chirps produced after windowing are shown at the bottom of the figure. The four stimuli produced covered frequency ranges from 375-750, 750-1500, 1500-3000 and 3000-6000 Hz (geometric centre frequencies 530, 1061, 2121 and 4243 Hz).

These signals were replayed via insert earphones to obtain the ABR. In order to verify the chirps, the output from the insert earphones was delivered to a "2-cc" coupler complying with IEC 126, the microphone of which was in turn connected to a Brüel and Kjær 2112 spectrometer. The output of the spectrometer was averaged during presentation of 100 stimuli to obtain a clear representation of the waveform of each of the four chirps. The spectra of the averaged chirps are shown in Figure 5.2. As a calibration reference for Figure 5.2, the FFT of a 1 kHz sine wave was used. This was generated with a sound calibrator (Brüel and Kjær type 4230) placed on the microphone of the 2-cc coupler, which generates a sound pressure level of 93.8 dB. Low frequency stimuli contain more energy as this is proportional to the product of amplitude squared and duration (which is greater for the low frequency stimuli). A comparison of the spectra of 530 and 4243 Hz chirps with 500 and 4000 Hz linear ramp 2:1:2

tone bursts is shown in Figure 5.3. It can be seen that the spectral spread of the band-limited chirps is greater than that for tone-bursts.

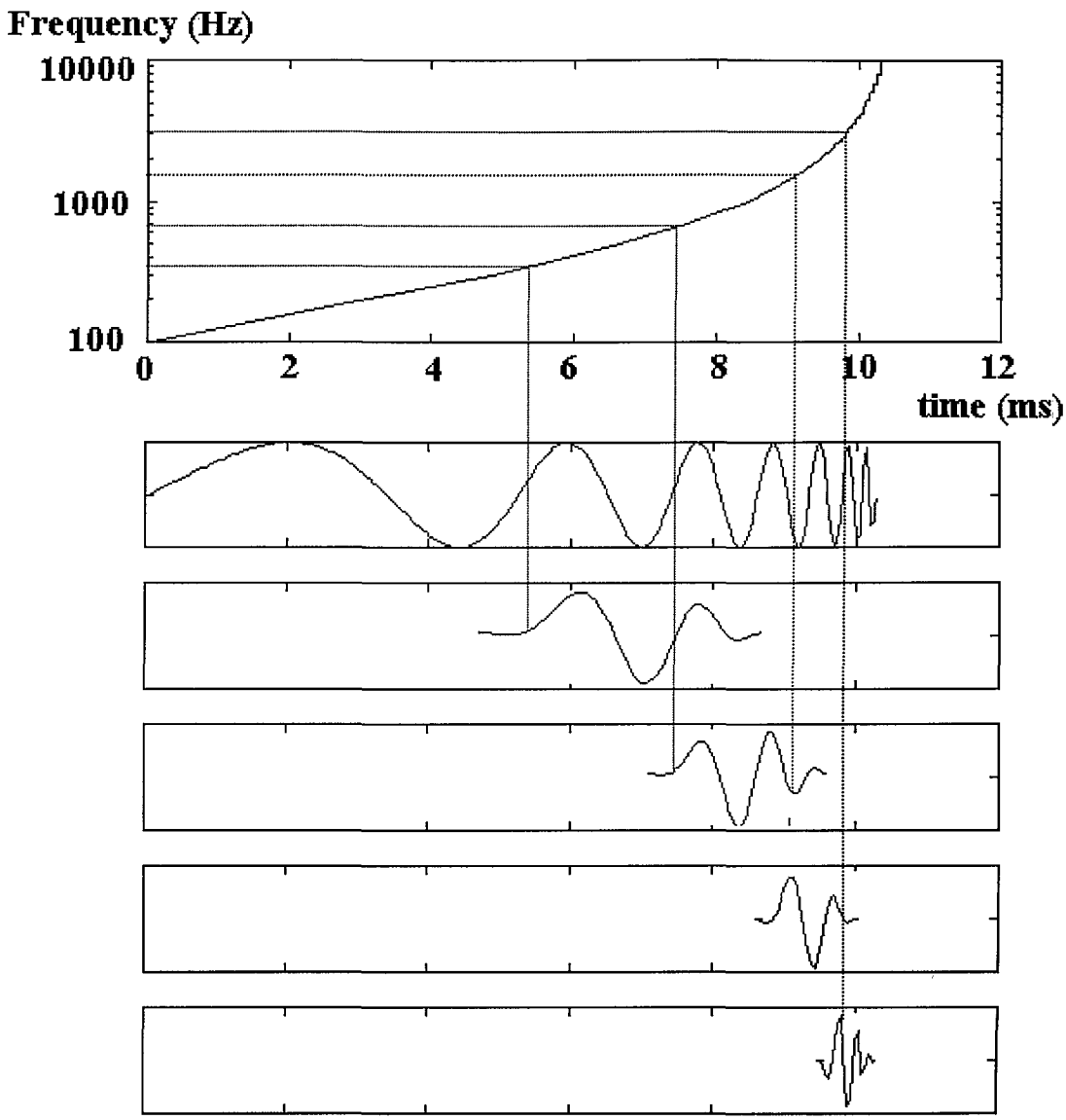


Figure 5.1 The frequency-vs-delay characteristic of the approximate chirp and the chirps used in the current study. The dotted lines correspond to the windowing frequencies

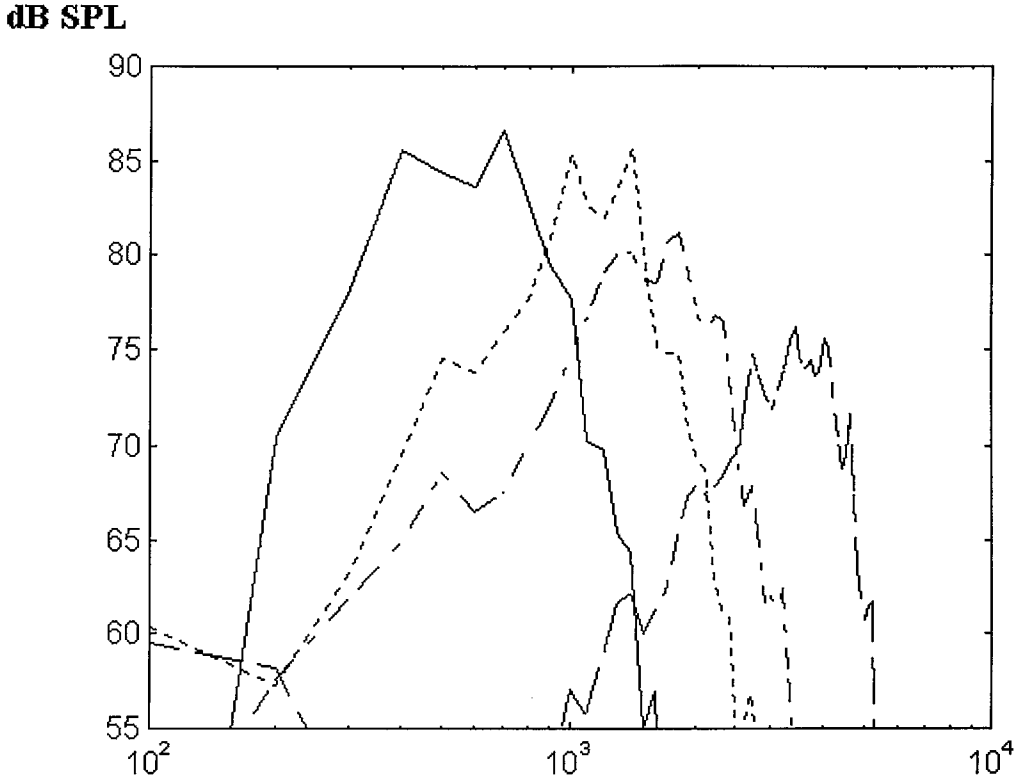


Figure 5.2 The FFT of the band-limited chirp stimuli

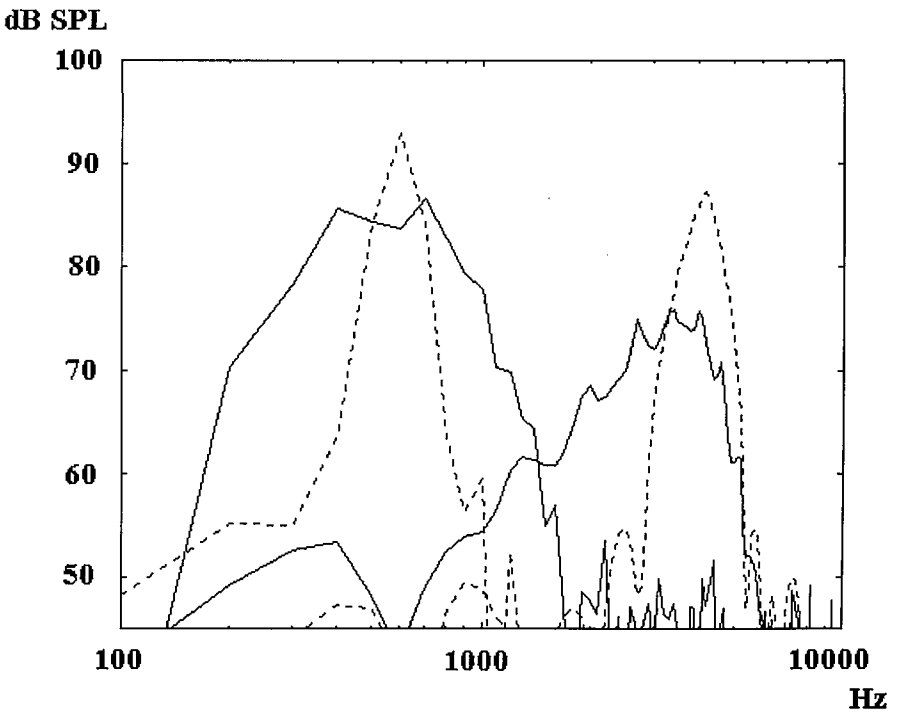


Figure 5.3 A comparison of the acoustic spectra of band-limited chirps (solid) and 2:1:2 tone-bursts (dashed).

5.2.4 Equipment

The study was carried out with the subject seated in a sound isolated booth. Chirp stimuli were delivered to the right ear of each subject through the insert earphones (Etymotic ER-3A) via a Kamplex KC50 audiometer. Relaxed subjects produce less electrophysiological noise and hence they reclined in a comfortable chair with a head rest. The lights were turned off and subjects were told to relax and sleep if possible. To reduce electrical interference, screened cables were used and the biological amplifier (see below) was placed near the subject.

All stimuli were produced from digitally defined waveforms using the CED micro1401 laboratory interface described in Chapter 2. Responses were recorded synchronously by the same interface from recording electrodes connected via the CED 1902 biological amplifier. For each experimental condition, an appropriate waveform was loaded into a memory buffer in the micro1401 and this was replayed cyclically at a sample rate of 20 kHz. A buffer length of 660 samples was used corresponding to a repeat rate of 30.3 Hz.

5.2.5 Recording the ABR

For both experiments, auditory evoked responses to the clicks were obtained using three silver/silver-chloride electrodes placed on the skin after skin preparation: active electrode high forehead at F_z, ground electrode on the lower forehead and reference electrode on the nape of the neck. Recordings were made with impedances less than 5 kΩ at 1 kHz between all pairs of the electrode array. For recording, band-pass filters within the 1902 were set to 30 Hz (high-pass) and 3000 Hz (low-pass) with a notch filter applied at 50 Hz (mains frequency).

5.2.6 Objective assessment of threshold

The ± difference method (Wong and Bickford, 1980) was used to give an objective measure of response presence. The procedure was performed on 7-ms segments of the response (140 samples). As wave V and the SN10 following it were considered the features of interest when defining threshold, the start of each analysis segment was defined to be 3 ms before the wave V latency expected from Figure 5.1 (i.e. the start of the analysis window was dependent on chirp type and stimulus level.)

For each stimulus type and level, two recordings were repeated consecutively and the average responses were calculated. The ± difference was defined as the variance of the sum of the averages divided by the variance of the difference between the averages. This assumes that the noise conditions were constant over the duration of the two consecutive recordings. The effect of high-pass filtering the ABR waveforms at 100 Hz on the ± difference was investigated.

5.3 Results

5.3.1 Waveform clarity

Example waveforms from one subject (DD) are shown in Figure 5.4 for low frequency (375-750 Hz) and high frequency chirps (3000-6000 Hz). With high frequency stimulation, wave V of the ABR is seen at 7 ms for stimuli at 50 dB SL increasing in latency to 9 ms at 10 dB SL. For low frequency stimulation, wave V is seen at approximately 10 ms at 50 dB SL, with latency increasing to 13 ms at 20 dB SL. There is a suggestion of a peak at 10 dB SL at 14 ms, but it is not definite.

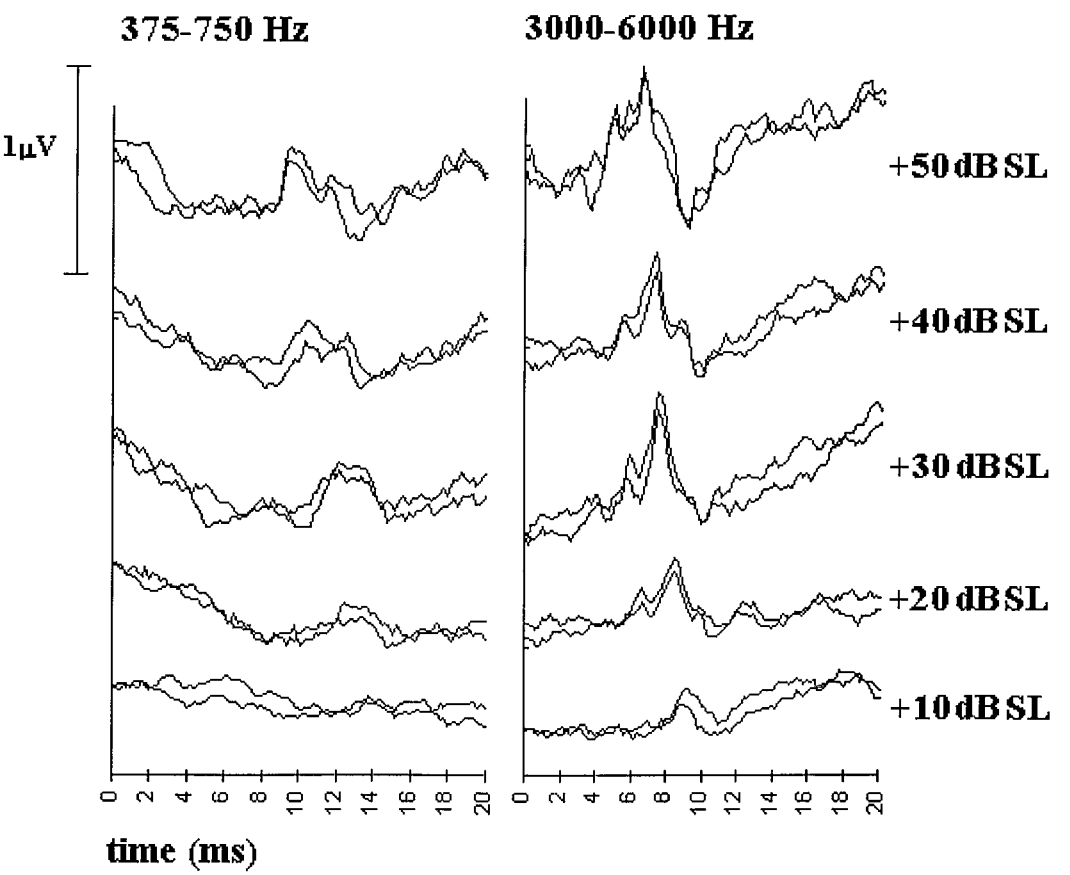
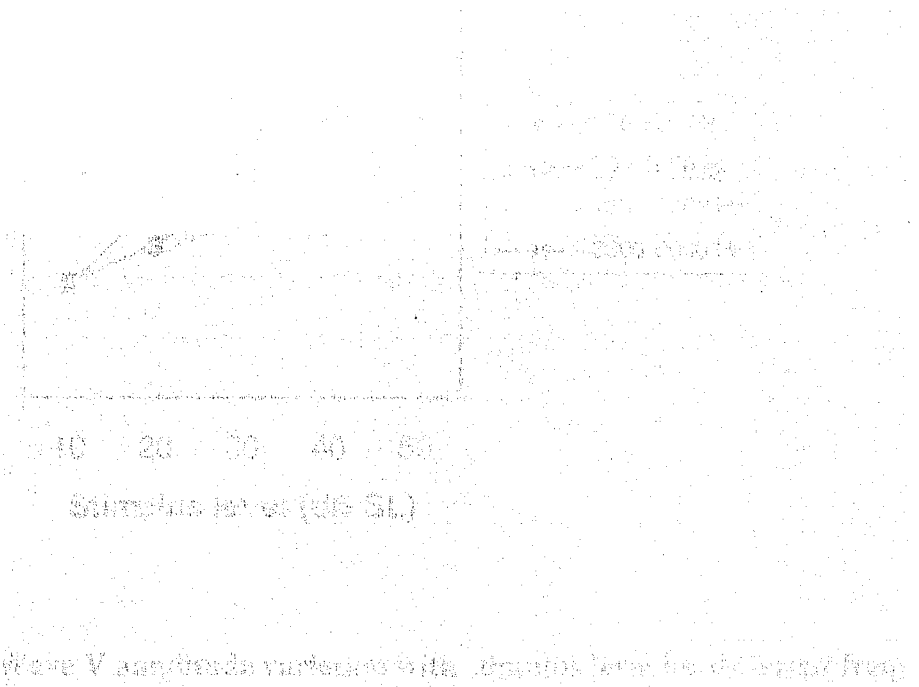


Figure 5.4 Example waveforms to high and low frequency chirp stimuli at different stimulation levels

5.3.2 Variation in wave amplitude and latency with chirp type and stimulus level

For all recordings where wave V was considered to be present and repeatable on the two recordings, the amplitude and latency were estimated by the author (the mean of the two recordings made). For the lowest frequency chirp (375-750 Hz), it was not possible to record a wave V at 10 dB SL in any subject. Figure 5.5 shows the variation in latency with chirp type and sensation level. Repeated measures analysis of variance demonstrated a significant linear effect ($p<0.05$) of stimulus level on wave latency for each of the four chirps. There was also a significant effect of chirp frequency on latency ($p<0.005$) for stimulation levels 20-50 dB SL, as expected.

Figure 5.6 shows the variation in wave V amplitude with chirp type and sensation level. Repeated measures analysis of variance demonstrated an overall significant effect of stimulus level ($p<0.05$) on wave V amplitude for only two of the chirps (750-1500 and 3000-6000 Hz). However, from Figure 5.5 it would appear that there is a trend for amplitude to decrease with stimulus level for all of the chirps.



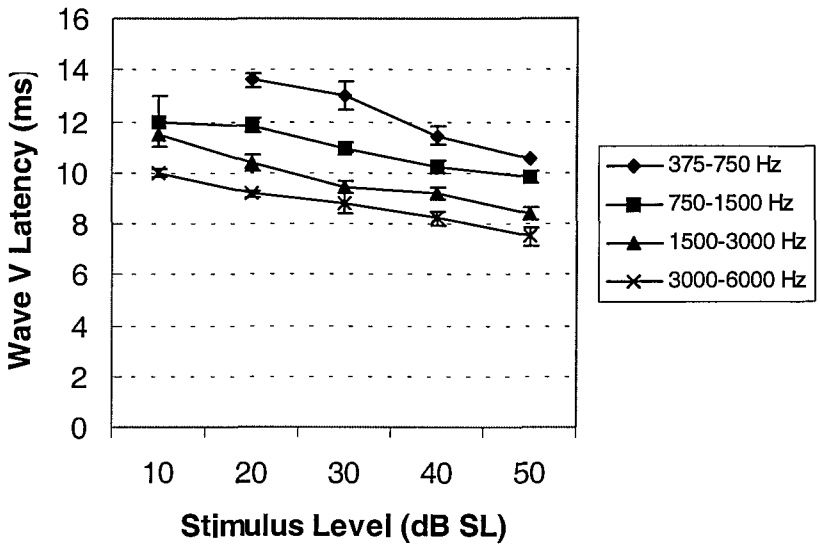


Figure 5.5 Wave V latency variation with stimulus level. Error bars represent one standard error of the mean.

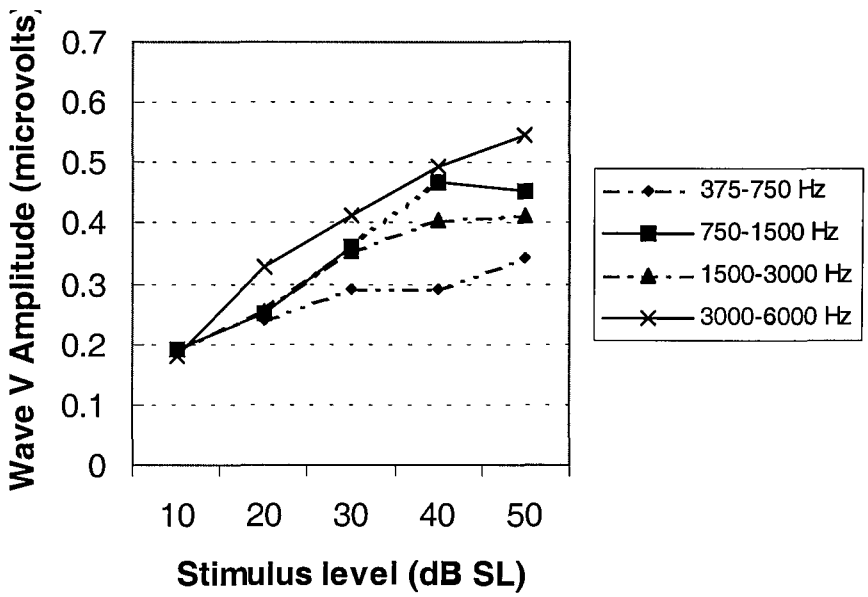


Figure 5.6 Wave V amplitude variation with stimulus level for different frequency stimuli. Error bars represent one standard error of the mean.

5.3.3 Estimation of threshold

i. Observer estimation of threshold

For each subject and each chirp type, the ABR threshold was defined as the lowest sensation level at which a wave V was determined to be repeatable by the author. The mean and standard deviation for thresholds across subjects are shown in Table 5.1 for each chirp centre frequency.

ii. Use of the ± difference statistic to estimate threshold

For each subject and each stimulus type, the ABR threshold level was taken as the lowest stimulus level with a ± difference value above 2.0. This cut off value was suggested by Wong and Bickford (1980) to define response presence. Values obtained in this way are termed objective thresholds here. The average objective thresholds are shown in Table 5.1. The method was applied both with no high-pass filtering of the waveform and with a 100 Hz high-pass filter.

When the ± difference is applied with no high-pass filtering of the waveforms, the objective thresholds obtained are lower than those subjectively estimated by the author. Whilst the author was estimating the presence of wave V of the ABR, which is a relatively high frequency feature of the waveforms, it is possible that the ± difference technique is detecting lower frequency features in the ABR waveforms. If the waveforms are high-pass filtered at 100 Hz to exclude low frequency components before objective estimation, the agreement between objective and subjective estimates of threshold is better. Using the ± method with no high-pass filter, ABR thresholds were estimated within 10 dB SL of the observer estimated ABR thresholds for 85% of recordings. When a 100 Hz high-pass filter is applied, the agreement increases to 93%.

Geometric mean frequency (Hz)	Mean subjective thresholds	Mean Objective threshold (no h.p. filter)	Mean objective threshold (100 Hz h.p. filter)
530	25.0 (5.3)	24.0 (10.7)	19.0 (8.8)
1061	21.0 (7.1)	17.0 (8.2)	18.0 (7.9)
2121	22.0 (9.7)	18.0 (7.9)	13.0 (4.8)
4243	16.0 (5.3)	16.7 (7.1)	14.4 (5.3)

Table 5.1 Mean thresholds estimated subjectively from response repeatability and objectively using the ± difference method (dB SL)

5.4 Discussion

The low frequency objective thresholds found in this study (19 ± 9 dB SL at 530 Hz) appear to be significantly lower and have a smaller variance than those achieved using tone burst stimuli (34 ± 16 dB SL at 500 Hz; Gorga et al, 1988). However, they are not as close to threshold as those reported for tone-bursts in high-pass noise (14 ± 12 dB SL at 500 Hz; Stapells et al, 1990). In both these studies, wave presence was subjectively rated by the authors; they did not use an objective measure of wave presence such as the ± difference technique used in this study. The discrepancy in the findings could either be due to a difference in stimuli or to a difference in threshold criterion. It is also unclear why the addition of high-pass masking to a low frequency tone-burst should increase response amplitude and therefore result in a better measurement of threshold as found by Stapells et al (1990) when compared to unmasked tonebursts (Gorga et al, 1988).

When 100 Hz high-pass filtering is applied to the ABR waveforms before objective estimation of threshold, the objective estimates of threshold increase and agree better with subjective estimates of threshold. It is possible that the ± difference statistic is sensitive to a lower frequency component in the ABR waveform than the wave V which was used to subjectively estimate thresholds, so when the low frequency component is removed, the objective and subjective estimates show closer agreement.

The example waveforms for low frequency tone bursts in high-pass noise shown by Stapells et al (1990) do not appear to show a wave V at low stimulation levels. Instead they reported a repeatable low frequency component in responses to low frequency stimulation. The example waveforms from the current study shown in Figure 5.4 would appear to show a wave V for

the chirp with centre frequency 530 Hz down to 20 dB SL. The presence of the wave V for low frequency stimuli found in the current study may be a consequence of the increased neural synchrony that would be expected from the frequency-vs-delay characteristics of the chirp stimuli.

The frequency range of the band-limited chirp stimuli is wider than that of tone bursts (Figure 5.3). A similar spectral spread was found for the band-limited chirp stimuli used by Wegner and Dau (2002). In this study it was arbitrarily decided to use stimuli with half-power points spanning octave bands. As the rise in frequency with time of the original chirp used by Dau (2000) is very rapid (see Figure 5.1), in order for the chirps to maintain the same frequency-delay characteristics as the original chirp but to cover frequency specific bands, the stimuli had to be of very short duration. Hence the stimuli show a further significant spectral spread compared to tone-bursts (Figure 5.3). If the stimulation of the cochlea elicited by the band-limited chirps was limited to octave bands then it would be possible to obtain a good objective estimate of an audiogram. However, the further spectral spread will result in the band-limited chirps stimulating frequency regions wider than an octave. This spread of excitation means it will be unclear which region of the cochlea a response is generated from.

The chirps should have the advantage that they produce neural synchrony across a larger number of nerve fibres. Therefore, they should produce a better defined wave V. There is a trade off between the frequency specificity of the response and the length of the basilar membrane which is stimulated. The issue of neural synchrony may be more critical for low frequency than high frequency stimulation as the approximate chirp from which the stimuli in this experiment are derived has an approximately exponential rise in frequency with time (see Figure 5.1).

Chirp type was found to have a significant effect on wave latency, with lower frequency stimulation resulting in an increase in latency. This is consistent with the low frequency response arising from a more apical region of the cochlea. The latency differences are also consistent with the expected travel times of the chirps to the point where the lowest frequency in the chirp causes maximum stimulation. For example, the highest frequency chirp is from 3000-6000 Hz and the lowest frequency chirp from 375-750 Hz. From the frequency delay mapping shown in Figure 5.1, it should take 4.1 ms for the travelling wave to move from the point on the basilar membrane with maximum displacement to 3000 Hz to that with maximum displacement to 375 Hz. This is consistent with the difference in latencies of the high and low frequency chirps shown in Figure 5.5.

Neely et al (1988) investigated the wave V latency of different frequency tonebursts and also found an increased latency for lower frequency stimuli. They suggest that the latency of an ABR is due to two components: the mechanical travel time of the stimulus to the point of maximum amplitude and the delay due to the onset of the neural response. The neural component of the delay is constant, but the mechanical delay is dependent on place-frequency mapping which is itself dependent on stimulus intensity and frequency. They suggest that an increase of 18 dB in stimulus level would result in the same basal shift in the point of maximum amplitude on the basilar membrane (and hence decrease in response latency) as a doubling of stimulus frequency. The latency values found in this study shown in Figure 5.6 are consistent with this, with a 20 dB increase in stimulation level being roughly equivalent to a doubling of stimulus frequency.

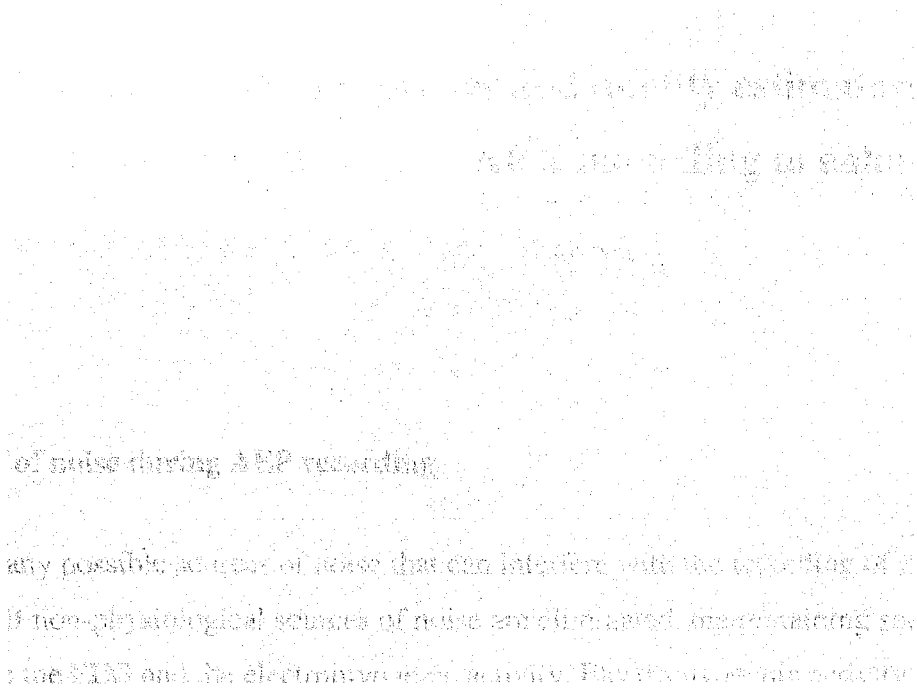
5.5 Summary and Conclusions

Band-limited chirp stimuli were generated with frequency-vs-delay characteristics matching those estimated using a model of the basilar membrane mechanics (Dau et al, 2000). The half-power points of the chirps covered four approximately octave bands ranging from 375 to 6000 Hz. It was possible to record ABR from all subjects using these chirp stimuli with a maximum of 4000 response averages. Wave presence was estimated both subjectively by the author and objectively using the ± technique and the two estimates agreed well. Objective ABR thresholds were compared with behavioural thresholds to the chirp stimuli. The average objective ABR thresholds were within 16 dB of behavioural thresholds at high frequency, increasing to 25 dB at low frequency. This agreement appears to be better than that reported for tone burst stimuli (Gorga et al, 1988). However, it is not as good as that reported for tone-bursts in high-pass noise (Stapells et al, 1990).

It is hypothesised that neural synchrony is more critical for low frequency than high frequency stimuli as the variation in place-vs-frequency mapping corresponding to place frequency mapping on the basilar membrane and travelling wave velocity is greater for low than high frequencies. There will be a trade off between the frequency specificity of stimuli used to generate the ABR and the length of the basilar membrane that is stimulated. Whilst the use of a chirp stimulus may improve neural synchrony, the rapid frequency-delay characteristics required to compensate for cochlear delay limit the frequency specificity of the chirps. The spectral spread of such short duration stimuli means they may have limited clinical utility.

Wave V amplitude increases with stimulus frequency and latency decreases. The decrease in wave V latency is consistent with the low frequency responses arising from more apical regions of the cochlea. The noise level of the subject and the amplitude of the ABR determine how long the averaging process must be continued in order to achieve a clear waveform. With a maximum recording duration of 2 minutes (excluding artefacts), it was not possible to record a repeatable ABR at 10 dB SL for the lowest frequency chirp in any subject.

The wave V amplitude for the lowest frequency chirp at 50 dB SL was 0.35 μV, which compares to 0.6 μV for an average adult click evoked ABR and would correspond to a test time increase of 2.5 times given the same noise conditions. It appears that the use of chirp stimuli in preference to unmasked tone-bursts may improve the objective estimation hearing thresholds from the ABR in normal hearing adults. However, the spectral spread of the stimuli leads to uncertainty as to where the response is generated in the cochlea, so they may have limited application in clinical practice.



CHAPTER 6

An investigation of EEG properties and quality estimators. The efficacy of Bayesian methods and ARX modelling to enhance the MLR.

6.1 Sources of noise during AEP recording

There are many possible sources of noise that can interfere with the recording of AEPs (see Chapter 1). If non-physiological sources of noise are eliminated, the remaining sources of noise will be the EEG and the electromyogenic activity. Electromyogenic activity causes voltage spikes that can best be eliminated using artefact rejection. Once artefact rejection is completed, the EEG will be the main noise source on the AEP recording. It is therefore useful to have some understanding of the properties of the EEG.

6.2 Assessing EEG properties

If the techniques are to be used to extract the MLR from background noise, it is important to have some knowledge of the frequency distribution and statistical properties of the noise, specifically background EEG activity. The frequency content of the EEG lies primarily between 0 and 100 Hz, although most of it lies between 1 to 20 Hz. Within it are characteristic frequency patterns; the delta wave from 0.5-4 Hz, the theta wave from 4-8 Hz, the alpha wave from 8-13 Hz and the beta wave from 13-22 Hz (see Chapter 1 for a description of the origins of the EEG).

In order to assess the low frequency properties of the EEG, as part of a pilot study for Experiment 1, some EEG data were recorded with no stimulus present and with the high-pass filter set at 1 Hz. The following shows 10 seconds of raw EEG data. The signal was sampled at 1000 Hz with a 100 Hz low-pass and 1 Hz high-pass filter. The rms amplitude is 1.42 μV.

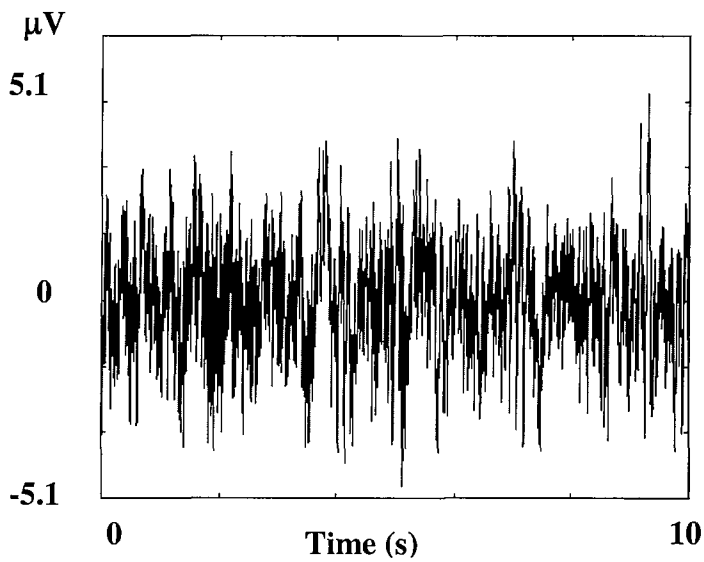


Figure 6.1 A time series of typical EEG data

The Average FFT of the EEG data is shown below (average of the FFT of seventy 10 second blocks). It is clear that the energy is greatest at low frequencies and the majority of the energy is below 20 Hz.

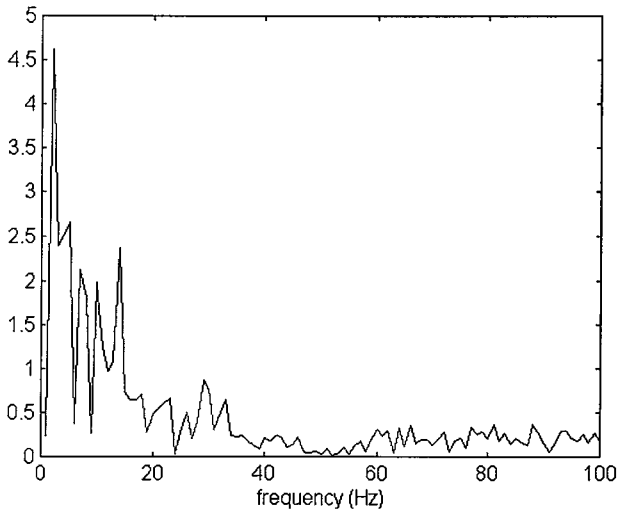


Figure 6.2 The FFT of typical EEG data

As the EEG noise is primarily low frequency, a high-pass filter should help to separate the EEG noise from the AEP of interest. However, it is not possible to separate the AEP from the EEG completely using a high-pass filter as the spectra of the two signals overlap. Most of the power of the MLR is in the 20-40 Hz region. The high-pass filter cut off frequency is critical and needs to be sufficiently low so that the MLR is not distorted, but that maximum amount of EEG is excluded. Hall (1992) suggests that optimal high-pass filter setting for recording the MLR using an online system is 15 Hz.

6.3 The effect of averaging on uncorrelated noise

When an ensemble average of uncorrelated noise is taken, the rms amplitude reduces (on average) as the square root of the number of ensembles. This can be demonstrated for both white noise and for typical noise from a subject in study 1. Figure 6.3 below shows the effect of averaging on the SD of white noise (solid line) generated in Matlab using the 'randn' function (initially with SD 1.0). Also shown is the effect of averaging on the SD of noise data from a subject in study 1 (AH – dashed line) sampled at 1000 Hz, with band-pass 15-250 Hz and a 50 Hz notch filter applied. The averaging time window was 197 ms. The noise data has been normalized by dividing by the SD of the noise. A plot of a theoretical decrease as the square root of the number of sweeps (dotted line) is also shown. The SD for both white noise and real subject noise closely match the reciprocal of the square root of the number of sweeps.

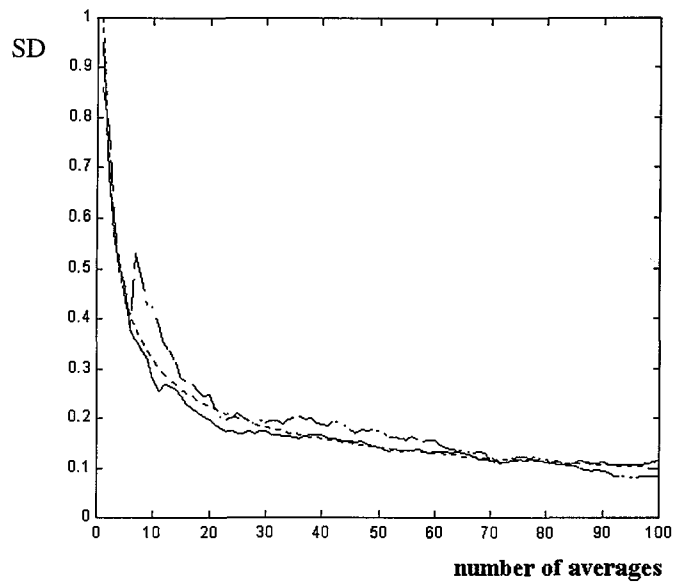


Figure 6.3 The effect of averaging on the standard deviation of white noise.

6.4 An investigation of the properties of quality estimators

In order to assess improvements in the acquisition of AEPs using different techniques, it is important to have a reliable measurement of SNR. Two possible estimators of SNR that may be used to assess signal quality are outlined in Chapter 2. The ± difference estimator was developed by Wong and Bickford (1980) and the F_{sp} statistic was developed by Elberling and Don (1984).

Elberling and Don suggest that when a signal contains a large amount of low frequency components, the amount of unknown random variability in the ± difference due to low frequency components becomes large, so the ± difference method may not estimate SNR accurately. They suggest that the F_{sp} statistic would be a better, unbiased estimate of SNR. The effects of low frequency components on these two measures of SNR has been investigated. Figure 6.4 compares the ± difference and F_{sp} estimates of SNR. First a 55 Hz sine wave was embedded in white noise at a sample rate of 1000 Hz and averaged with a time window of 90 ms. The sine wave and noise had the same SD, so SNR = 1. The F_{sp} and ± difference (dotted) estimates of SNR give similar estimates. After 500 averages, the SNR should be $\sqrt{500}$ or 22.4 as the noise has reduced by $\sqrt{500}$. The F_{sp} estimate is closest to this value.

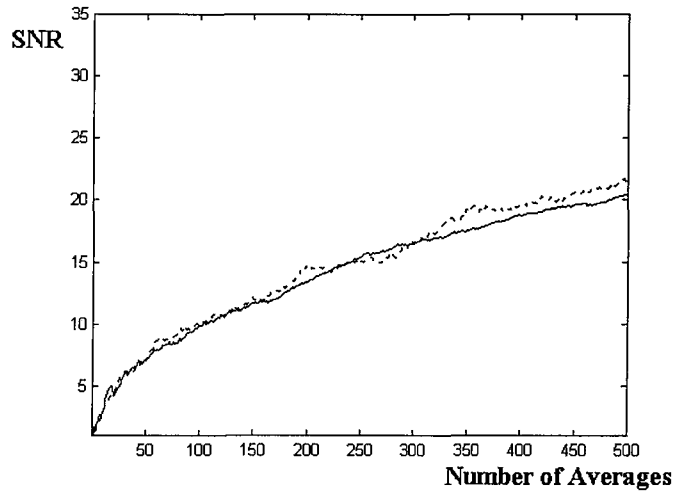


Figure 6.4 A comparison of the effect of averaging on the F_{sp} (solid line) and ± difference (dotted line) estimates of SNR for a sine wave in white noise

Next the sine wave was embedded in noise low-pass filtered at 100 Hz with a 5^{th} order Butterworth filter. The ± difference estimate (dotted) now shows more variation than the F_{sp} estimate (solid).

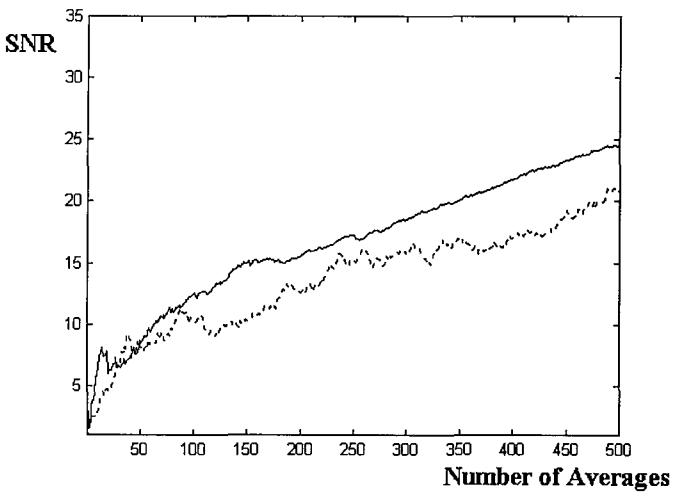


Figure 6.5 A comparison of the effects of averaging on the F_{sp} (solid line) and ± difference (dotted line) estimates of SNR for a sine wave in low-pass filtered noise

Finally the sine wave was embedded in real EEG noise from a subject in experiment 1 (AH). The ± difference estimate of SNR (dotted) is now much less stable than the F_{sp} estimate of SNR (solid).

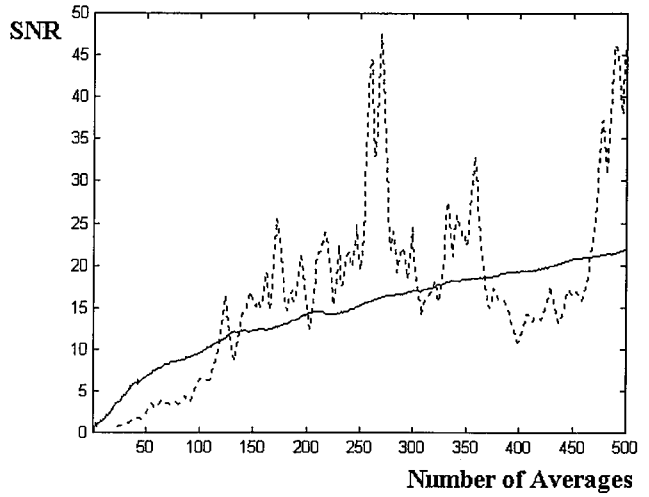


Figure 6.6 A comparison of the effects of averaging on the F_{sp} (solid line) and ± difference (dotted line) estimates of SNR for a sine wave in experimental EEG noise

As the MLR contains substantial low frequency components, the F_{sp} statistic was used in preference to the ± difference technique for Experiments 1 and 2. For Experiment 3, band-pass filter setting were higher, so low frequency noise was reduced. (Also file sizes were large due to the higher sample rate, so the ± difference technique was used as it is easier to implement on large files.)

6.5 Assessing the stationarity of background noise

The EEG data from Experiment 1 was examined to see if it could be considered stationary. Various authors have assessed the statistical properties of the EEG (see Chapter 1). McEwen and Anderson (1975) suggest that the EEG is stationary for short periods (less than 10 s). The stationarity of the EEG may depend on the task that a subject is performing. For example Popivanov and Mineva (1999) show that the EEG is non-stationary before and after a subject performs a mental task. Normally the MLR is recorded from a relaxed subject not performing any activity. Under such conditions variations in the EEG may be reduced.

If the noise data from individual subjects are investigated, muscle activity can be seen as an obvious non-stationary process. EEG data from a subject in Experiment 1 (BL) are shown in Figure 6.7. Muscle activity can be seen in three regions at approximately 20 s, 60 s and 250 s. A fixed artefact rejection criterion such as ± 30 μV could be used to eliminate those artefacts

when averaging the data. Any sweeps with amplitude above or below the criterion would not be included in the average.

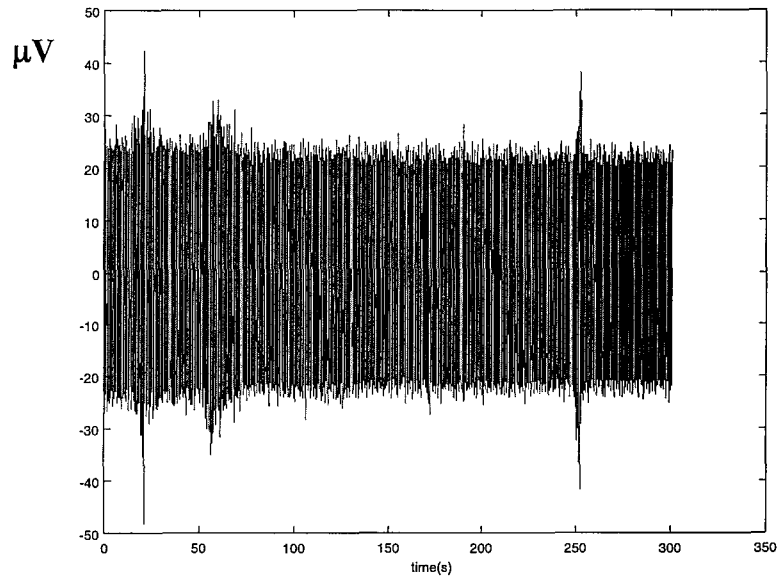
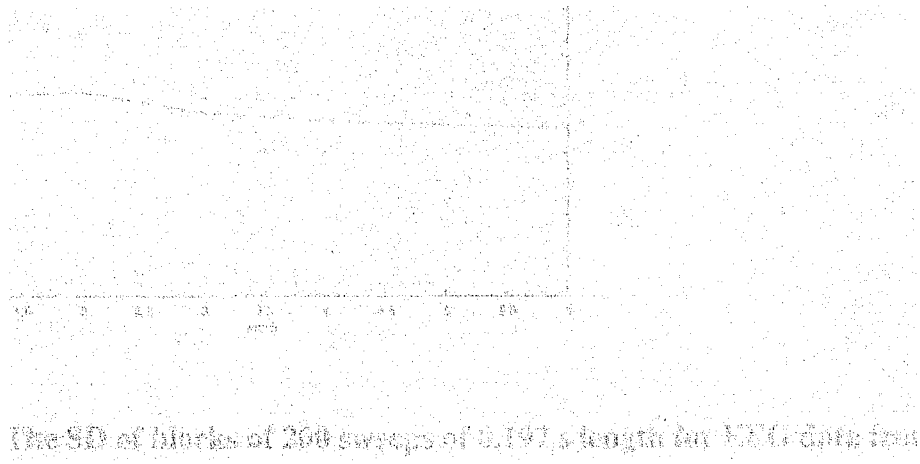


Figure 6.7 Time series EEG data from subject BL

The effect of aftefact rejection on the data from BL is shown in Figure 6.8. The 10% of the data with the largest amplitude has been removed. It can be seen that the waveform is much smoother (the large spikes have been removed) :



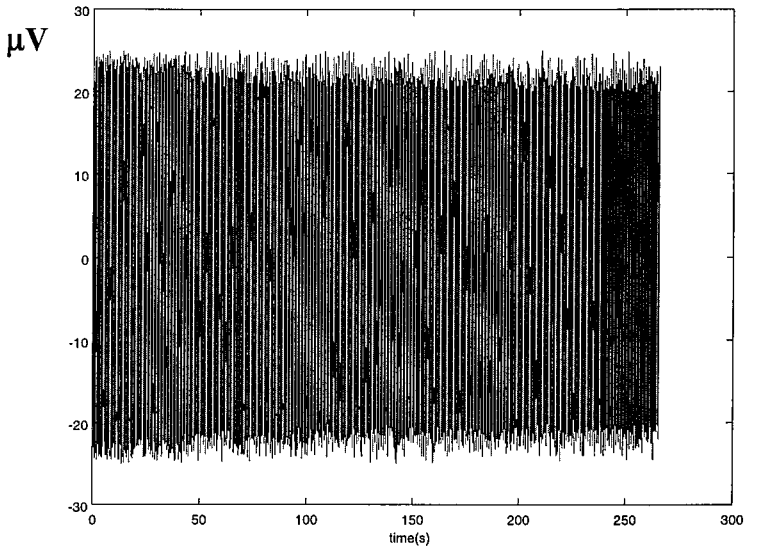


Figure 6.8 The effect of 10% artefact rejection on the EEG data from subject BL

Once artefact rejection has been performed, the question arises whether the EEG noise is stationary. This can be assessed by splitting the signal into blocks and comparing the SD of different blocks. Elberling and Don (1984) suggested for the ABR using a block size of 200 sweeps will give a good estimate of SNR. Figure 6.9 shows the results if this is done with the EEG data from BL above. It can be seen that there is little variation between the blocks.

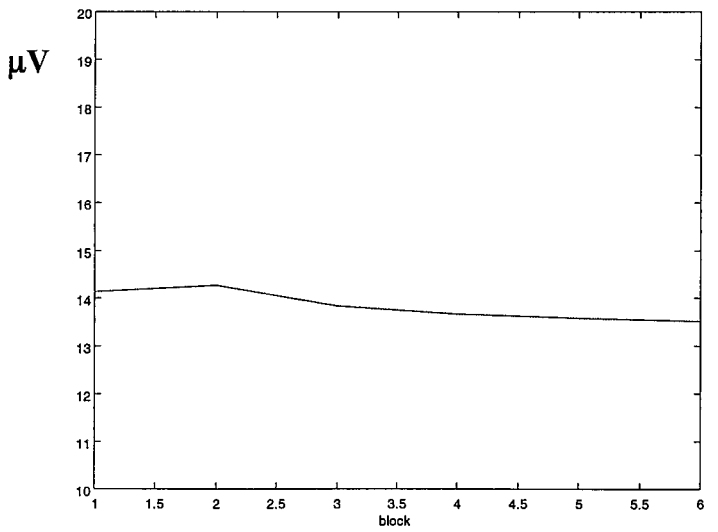


Figure 6.9 The SD of blocks of 200 sweeps of 0.197 s length for EEG data from subject BL

The size of the blocks may be too large to demonstrate much variation in the stationarity of the EEG when sweeps of long duration typical for recording the MLR are used. For the ABR

a sweep is typically 10 ms long, but when recording the MLR a sweep is much longer in duration. When recording the MLR at 5.95 Hz one sweep is 197 ms long. A block of 200 sweeps is almost 40 s in length.

If instead, the SD of individual sweeps is compared, more variation in the signal can be seen. This is shown in Figure 6.10.

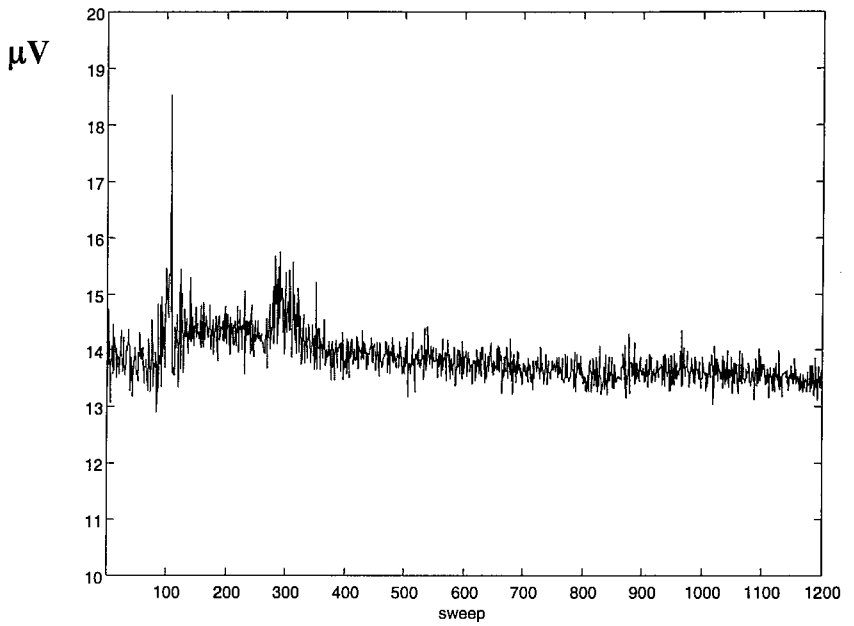


Figure 6.10 The SD of individual sweeps of length 0.197 s for EEG data from subject BL

Whilst a single averaging sweep of the ABR may not be of sufficient duration to give an accurate estimate of signal variance, the duration of a single averaging sweep for the MLR is an order of magnitude longer and will therefore produce a better estimate of signal variance. The variance of the noise data appears to show significant variation between epochs.

6.6 The use of Bayesian averaging to improve SNR

Whilst artefact rejection will exclude very noisy traces from the average, it is a binary approach, so the noise levels on traces that are accepted may still vary significantly. Where the background noise is non-stationary and varying in magnitude, it may be better to weight traces according to the level of the background noise. This is a form of Bayesian inference (see Chapter 1).

The use of Bayesian inference can improve signal quality for the ABR (Elberling and Wahlgreen, 1985). The approach has not been tried for MLR data.

To calculate the average MLR in MATLAB, an array of 'good' sweeps (sweeps with a variance smaller that the artefact rejection criterion) is generated. The average MLR is simply the mean of the array. In order to implement a Bayesian averaging approach, each sweep is multiplied by the reciprocal of the sweep variance; that is, sweeps with a higher variance have smaller weighting in the Bayesian average. The whole array is then multiplied by the inverse of the sum of the reciprocals of sweep variances. The Bayesian average is the mean of the new array. In summary, the algorithm can be written as follows :

If S_n is the waveform of the n^{th} sweep, V_n is the variance of the n^{th} sweep and C_n is the sum of the reciprocals of the variances of n blocks.

After the first sweep :

$$AEP = \frac{S_1}{V_1}.\frac{1}{C_1}; where C_1 = \frac{1}{V_1}$$

After the second sweep :

$$AEP = (\frac{S_1}{V_1} + \frac{S_2}{V_2}).\frac{1}{C_2}; where C_2 = \frac{1}{V_1} + \frac{1}{V_2}$$

And after the n^{th} sweep :

$$AEP = (\frac{S_1}{V_1} + \frac{S_2}{V_2} + ... + \frac{S_n}{V_n}).\frac{1}{C_n}; where C_n = \frac{1}{V_1} + \frac{1}{V_2} + ... + \frac{1}{V_n}$$

For the data from Experiment 2, the Bayesian averaging approach was compared with the conventional averaging approach. The Figure 6.11 shows the results. There is a slight improvement in the SNR obtained with the Bayesian averaging approach over that obtained with conventional averaging for all stimulation conditions. However, the improvement in

SNR is small compared to that which can be achieved by changing the stimulus which evokes the MLR (e.g. using chirps instead of clicks.)

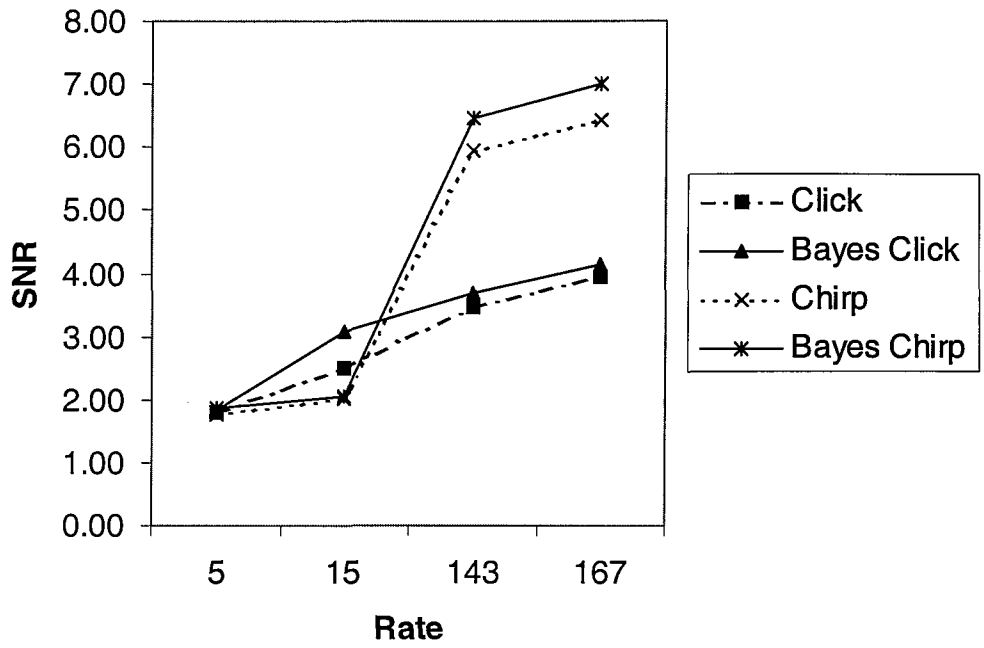


Figure 6.11 A comparison of Bayesian and conventional averaging on the results of Experiment 2

6.7 An investigation of ARX enhancement of the MLR

A concept that has been referred to in several papers is using 'ARX' modelling to extract an evoked potential from a noisy signal. The concept is outlined in Chapter 1. There has not been a systematic demonstration of how well the approach will fare for different SNR. At favourable SNR, the use of ARX modelling may well extract the most likely morphology of the AEP. However, when the noise amplitude is significantly higher then the signal, the ARX model will be trying to match the noise, rather than signal. Despite this, some very impressive claims have been made regarding the efficacy of ARX models. It is suggested that the acquisition of the MLR can be speeded up by taking the average of fewer epochs, but then using an ARX model to extract the MLR from the noisy average.

Cerutti et al (1988) used parametric (ARX) estimation to extract visual evoked potentials (VEP) from background noise on a sweep by sweep basis. However VEP are much larger in amplitude than the MLR (tens of μV vs tenths of μV) and hence the SNR is much better. If

the technique is to be applied to the MLR, some averaging of the noisy signal must be carried out in order to improve SNR before the ARX technique is applied.

The numbers of averages used in the reference and noisy signals vary between authors. Elkfafi et al (1997) used a reference of 1000 averages to 'enhance' the noisy average of 192 sweeps. The typical SNR of the MLR is less than –20 dB, so even after the SNR is improved by 14 times ($\sqrt{192}$) by averaging, the signal will be quite noisy (the rms SNR will only be around 1). Whilst the ARX model may give an estimate of where the MLR probably is, it would be better to average the response for a longer time, or to improve the stimulus in order to obtain a better SNR.

More surprising are the papers by Jensen et al (1996) and Capitano et al (1997). They claim to use a reference signal of 256 sweeps to enhance a noisy AEP of only 15 averages (3 s of data). After 15 averages, SNR is only increased by approximately 4 times, so the SNR will still be less than 0.4. It is hard to see how the ARX model could be matching anything other than the noise on the signal.

A possible explanation is the electrode configuration in these papers: Jensen et al (1998) positioned the active electrode on the right side of the forehead, the reference electrode on the left side of the forehead and the negative electrode on the left mastoid. A pitfall when recording the MLR is PAM interference. This is a problem when a mastoid reference electrode is used and this is why Hall (1992) recommends using a non-encephalographic reference when recording the MLR. The position of the positive electrode on the side of the forehead is also not optimal, a vertex placement would give a larger response.

Example AEPs are shown in both papers, but the scale is not shown. The data shown in the two papers is identical and appears to be from the same study. The AEP shows a large peak at 15 ms, which is characteristic of the PAM. It appears that Jensen et al have recorded the PAM, not the MLR. The PAM is much larger in amplitude that the MLR (several μV vs a few tenths of μV) and this would explain why the response could be extracted with such a small number of averages. The PAM response will be abolished by the anaesthetic as the patient relaxes and Capitano et al (1997) demonstrate that the output of the ARX model decreases rapidly with anaesthesia. However, the PAM will also be abolished by the use of a muscle relaxant, so the PAM response is not a good indicator of conscious awareness. It is likely that the impressive claims made by Capitano et al for the ARX extracted AEP are a consequence of poor electrode placement (i.e. they have recorded the PAM, not the MLR).

Whilst ARX modelling will estimate the most probable EP in a noisy signal, the match between the estimate and the underlying AEP will be limited by the SNR of the signal. The effect of SNR on the stability of the technique has not been properly investigated. The technique is based on the assumption that the EP being measured is similar in morphology to the reference signal. However this assumption may not always be justified. Some of the impressive claims that have been made for using ARX to extract the MLR in seconds appear to be a consequence of methodology in the recording of the MLR. It appears that the authors may have inadvertently recorded a PAM response, which has a much larger amplitude than the MLR and hence can be extracted with a much smaller number of averages than would be needed to record the MLR.

The efficacy of ARX in estimating the MLR as a function of SNR

The following investigation was intended to evaluate how well ARX modelling could extract a MLR from background noise as a function of SNR. The methodology is similar to that used by Capitano et al (1997) to evaluate the efficacy of ARX in extracting VEP from simulated noise.

The System Identification Toolbox in Matlab was used to calculate an ARX model for given input and output data. The order of the model can be selected, or the calculation can be performed for a number of different model orders and the mean squared error between input and output can be compared for the different orders.

The ARX model is given by

$$y(n) = \sum_{k=1}^{Na} a_k\, y(n-k) + \sum_{k=0}^{Nb} b_k\, x(n-k-d) + e(n)$$

Which relates the current output $y(n)$ to a weighted sum of the N_a previous outputs ($y(n-k)$) and N_b previous inputs ($x(n-k)$) delayed by d samples. $e(n)$ is the error between the output of the model and the desired output (in this case the desired output is the noisy MLR).

This can be expressed as

$$y(n) = \varphi^T[n]\theta + e[n]$$

where

$$\varphi^T[n] = (-y[n-1],...,-y[n-N_a], x[n-d],....,x[n-N_b-d])$$

$$\theta = (a_1,.....,a_{Na},b_0,....,b_{Nb})^T$$

The mean squared error E_N over N data points

$$E_N(\theta) = \frac{1}{N}\sum_1^N e^2[n]$$

is minimised when

$$\theta = \left[\frac{1}{N}\sum_1^N \varphi[n]\varphi^T[n]\right]^{-1}\left[\frac{1}{N}\sum_1^N \varphi[n]y[n]\right]$$

This approach is termed the equation error approach (a filtered version of the input is compared to a filtered version of the output). This is not the only method that can be used to find the optimum ARX model parameters. For example, an output error approach could alternatively be used in which only the reference signal is filtered and the filtered reference is compared to a desired signal. It is possible that an alternative approach to the one specified above may produce a better fit to the data.

In general, a higher order model will produce a lower mean squared error. However, a higher order model may not be a better model, as the higher parameters may simply be matching the measurement noise better (not the signal of interest). There are a number of techniques for comparing models of different order which take into account the effect of the error decreasing as the model order increases. For this investigation, Akaike's Information Theoretic Criterion was used to select the optimal model order (Akaike, 1970).

In order to assess the efficacy of the technique, a MLR recorded from subject FC at 15 clicks/s in Experiment 2 was used as a reference signal. After 2000 averages, the rms SNR was 2.29. The reference signal was normalised (divided by its standard deviation) and delayed by 4 samples (4 ms) to simulate a possible shift in the latency of the data as might be induced by an increased anaesthetic depth. This is the desired signal for the model to identify.

The desired signal was corrupted by adding different amounts of unaveraged EEG data from the same subject. The reference and corrupted MLR were imported into the Matlab System Identification Toolbox and the optimal ARX model calculated with the orders of *a*, *b* and delay parameters ranging from 1 to 10. The model which produced the lowest value of the Information Theoretic Criterion (Akaike, 1970) was selected. This model was used to filter the reference signal to produce an estimate of the MLR.

It was desirable to have a measure of the fit between the desired signal (the shifted reference signal) and the filtered reference signal. A measure of fit was calculated by dividing the variance of the desired signal by the variance of the difference between the desired and filtered reference signals.

$$Fit = \frac{Var(Shiftedreference)}{Var(difference)}$$

This process is demonstrated below for a SNR of 2. Figure 6.12 shows the average of 2000 MLR epochs from subject FC. Figure 6.13 shows the average shifted by 4 ms (solid line) and the shifted signal corrupted by EEG noise with equal variance to give a SNR of 1 (dotted line). The optimal ARX order and model was estimated using the Matlab System Identification Toolbox. The optimal order was Na=1, Nb = 2, Delay=4. Note that the best fit model correctly identifies the shift between reference and the corrupted signal output as 4 ms. Figure 6.14 shows the match between the shifted reference signal (the desired signal to be extracted from noise) and the filtered reference signal. The match is good with a fit of 37.

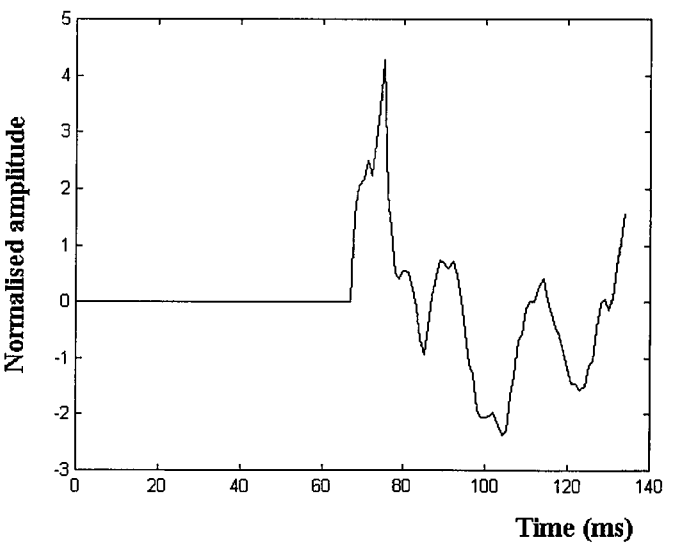


Figure 6.12 The reference MLR

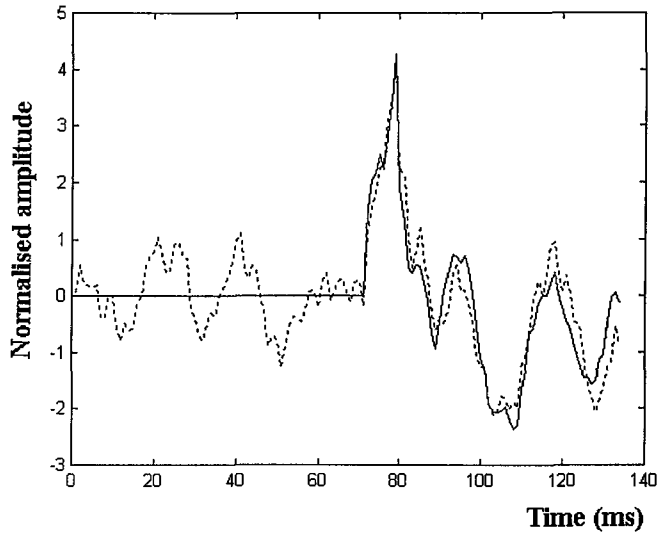


Figure 6.13. The desired shifted reference signal (solid line) and corrupted signal (dotted line) at SNR 2

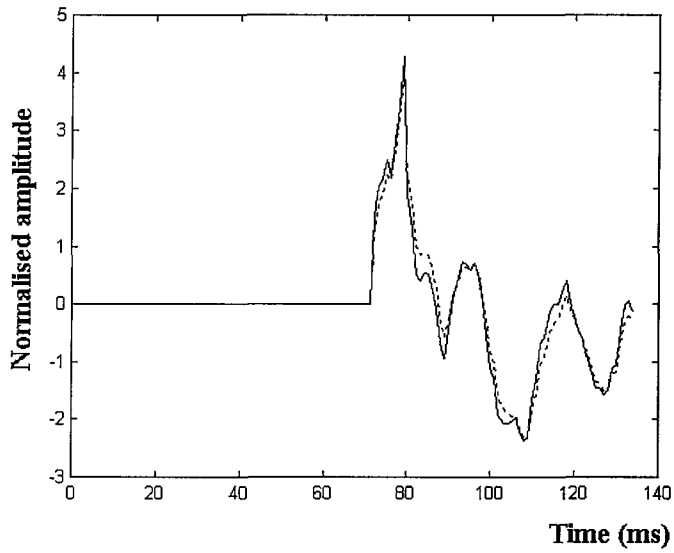


Figure 6.14 The desired shifted reference signal (solid) and ARX filtered reference signal (dotted line) at SNR 2

The process was repeated with the level of EEG noise added to the reference signal varied to produce different SNRs.

Table 6.1 summarises the match between the model output and the desired signal as a function of SNR. The optimal model order is shown as a function of SNR.

SNR (noisy AEP)	Optimal model order (na,nb,delay)	Fit (filtered reference vs shifted AEP)
2	1,2,4	37
1	10,7,4	3
0.5	10,5,6	0.777
0.33	10,5,6	0.543
0.25	10,5,6	0.379
0.1	10,8,4	0.054

Table 6.1 ARX estimation as a function of SNR.

At favourable SNR, the ARX model extracts the desired AEP well from the EEG noise. However, as the SNR decreases, the fit between the filtered reference signal and the desired signal (the shifted reference) becomes poorer. The model does not perform very well for SNR below 1. Note that the original signal from FC had a SNR of 2.29 after 2000 averages. Assuming that SNR increases as the root of the number of averages, the SNR would be around 1 after approximately 400 sweeps. However, if only 15 sweeps were used as suggested by Jensen et al (1996), the SNR would only be around 0.2, so the match between the filtered reference signal and the desired signal would be poor.

Figure 6.15 shows the match between the shifted reference and the filtered reference at a SNR of 0.5. The optimal model order was [10,5,6]. It is clear that the filtered reference signal does not match the desired signal as well as in Figure 6.14 and the identified shift between reference and noisy signal is over estimated at 6 ms. The fit between desired signal and model output was 0.777.

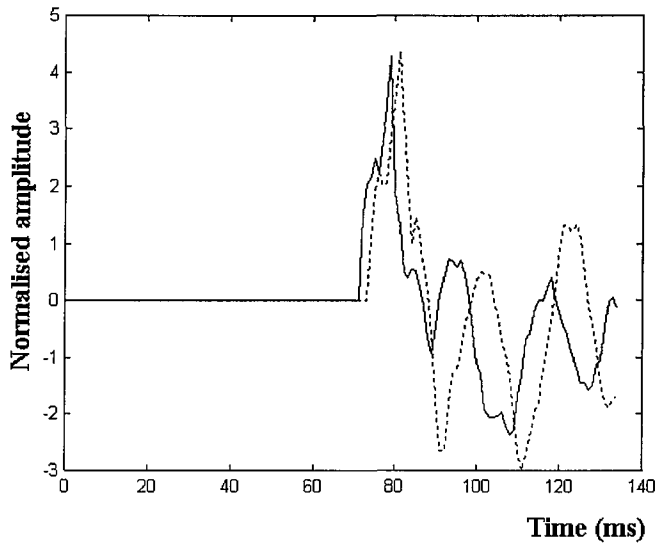


Figure 6.15 The match between the desired signal (solid line) and filtered reference signal at SNR 0.5

ARX may be a way of extracting the most likely AEP from a noisy signal and hence reducing the need for averaging as many sweeps. However, the technique is limited by the SNR of the signal. As the SNR increases, the match between the filtered reference signal and the underlying AEP will improve. The technique will also be limited by the match between the reference signal and the AEP being measured. The claims of Jensen et al (1996) that ARX modelling can extract the MLR from 15 averages are not supported by the simulation above. It would appear likely that the response recorded by Jensen et al was not the MLR, but rather the PAM which would have a favourable SNR after only 15 averages.

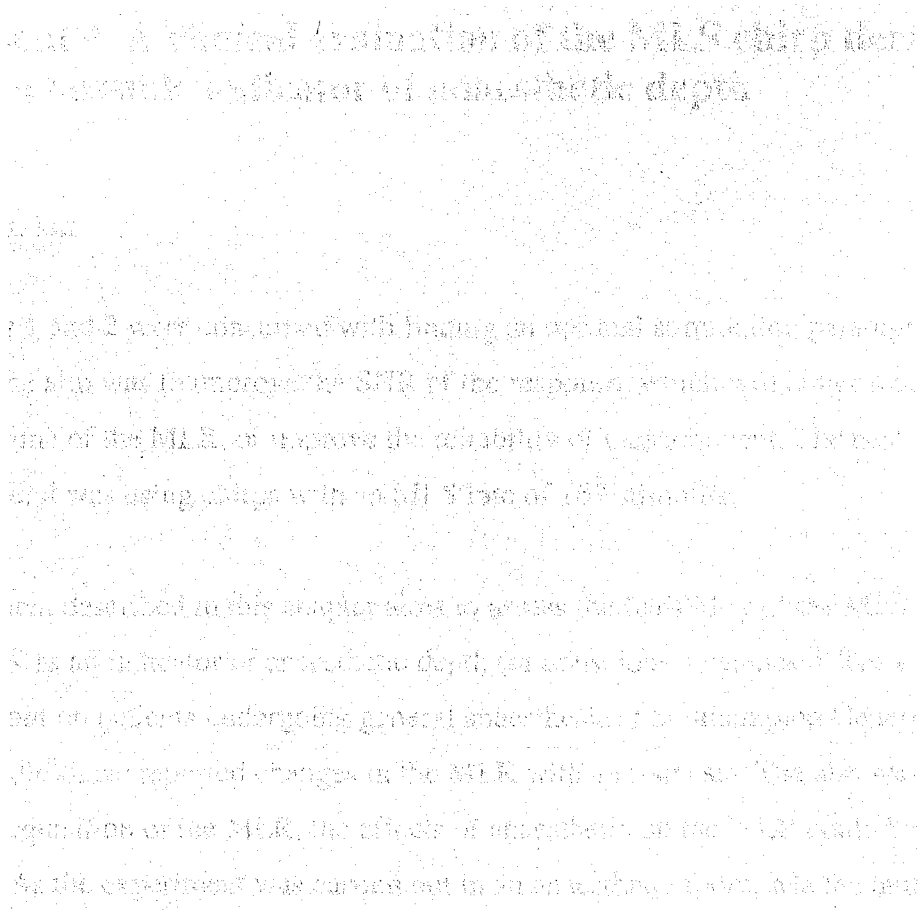
6.8 Summary

This chapter has gone some way towards investigating the use of signal processing techniques to enhance AEPs. In the first section, the properties of the EEG noise, which is present when recording AEPs, is investigated. A comparison of quality estimators was made which demonstrated that the ± difference estimator of SNR is less stable than the F_{sp} estimator when low frequency noise is present on the recording.

In the latter part of the chapter, the potential use of Bayesian averaging and ARX modelling to improve acquisition of the MLR was investigated. It was found that there is a slight improvement in the SNR obtained with the Bayesian averaging approach over that obtained with conventional averaging for all stimulation conditions. However, the improvement in

SNR is small compared to that which can be achieved by changing the stimulus which evokes the MLR (e.g. using chirps instead of clicks.)

The investigation of ARX modelling to enhance an AEP showed that ARX may be a way of extracting the most likely AEP from a noisy signal and hence reducing the need for averaging as many sweeps. However, the technique is limited by the SNR of the signal. As the SNR decreases, the match between the filtered reference signal and the underlying AEP will deteriorate. The claims of Jensen et al (1996) that ARX modelling can extract the MLR from 15 averages were not supported by the simulations performed. It is possible that the response recorded by Jensen et al was not the MLR, but rather the PAM, which would have a favourable SNR after only 15 averages. This may explain their impressive claims for the ARX approach.



CHAPTER 7

Experiment 4. A clinical evaluation of the MLS chirp derived MLR as a possible indicator of anaesthetic depth

7.1 Introduction

Experiments 1 and 2 were concerned with finding an optimal stimulation paradigm to acquire the MLR. The aim was to improve the SNR of the response, which will either reduce the acquisition time of the MLR, or improve the reliability of measurement. The best stimulation paradigm found was using chirps with an MLS rate of 167 stimuli/s.

The experiment described in this chapter aims to assess the feasibility of the MLS chirp derived MLR as an indicator of anaesthetic depth (or conscious awareness). The experiment was carried out on patients undergoing general anaesthesia at Southampton General Hospital. Previous studies have reported changes in the MLR with anaesthesia. The aim was that by improving acquisition of the MLR, the effects of anaesthetic on the MLR could be better understood. As the experiment was carried out in an anaesthetic room, which contains many sources of electrical interference, and not in a sound proofed booth, it was possible to assess some of the problems associated with recording AEPs in a more challenging recording environment.

7.2 Method

7.2.1 Subjects

All subjects were due to have heart surgery at Southampton General Hospital. A consultant anaesthetist was responsible for deciding if subjects should be excluded from the experiment on medical grounds. Due to the sex bias for patients having heart surgery, all subjects were male. The average age was 60.2 years. None of the subjects could be described as otologically normal (hearing thresholds better than 20 dB HL at all frequencies). Table 7.1 summarises the age and hearing thresholds for subjects who participated in the experiment. Pure tone audiometry was carried out in the anaesthetic room prior to the study. The rooms were quiet, but not sound proofed. The insert earphones provide some attenutation of background noise. For each ear the category of hearing impairment is shown (normal, mild, moderate, severe or profound). For the four subjects from whom 'good' data were collected (JC, PB, SM and DM) the average age was 63.5 years and the average hearing loss was moderate.

			Frequency (kHz)						Descriptor of hearing loss
Subject	**Age**	**Ear**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	
JC	73	R	30	30	25	20	45	30	Mild
		L	25	30	30	20	55	50	Mild-Mod
PB	62	R	55	50	40	30	40	65	Moderate
		L	40	40	30	25	45	50	Moderate
SM	56	R	60	55	40	15	20	55	Moderate
		L	25	25	25	20	30	65	Moderate
DM	63	R	40	45	30	30	55	50	Mild-mod
		L	35	35	35	35	50	50	Mild-mod
PM	37	R	25	25	25	10	10	0	Mild
		L	30	30	25	15	15	10	Mild
MD	64	R	35	40	30	35	40	70	Mild-mod
		L	45	45	35	25	50	70	Mod-mod
RM	61	R	45	55	95	90	95	95	Profound
		L	35	45	40	30	65	45	Mild-mod
LH	60	R	20	25	30	15	35	25	Mild
		L	25	25	25	25	20	20	Mild
FB	66	R	20	30	25	30	30	25	Mild
		L	25	30	35	45	30	15	Mild

Table 7.1 Summary of ages and hearing thresholds of subjects in dB HL.

7.2.2 Equipment

The equipment was mains safety tested and health and safety inspected before the experiment commenced. Ethics approval for the study was obtained from the ISVR Human Experimentation Safety and Ethics Committee and from the South and West Hants Local Research Ethics Committee (covering Southampton General Hospital).

The equipment configuration was the same as that used in Experiment 2, but with the equipment placed on a trolley for portability. The trolley is shown in Figure 7.1. The equipment on the trolley comprised: Laptop PC with a 500 MHz Intel Celeron processor; CED micro1401 Laboratory Interface; Kemo Dual Variable 48 dB/octave filter with band-pass set from 15 to 250 Hz; CED 1902 isolated EEG amplifier with band-pass set from 1 to 3000 Hz, a gain of 30000 and ac coupled; GSI-16 audiometer. ER-2 insert phones were used with a metal shielding cable connected to ground.

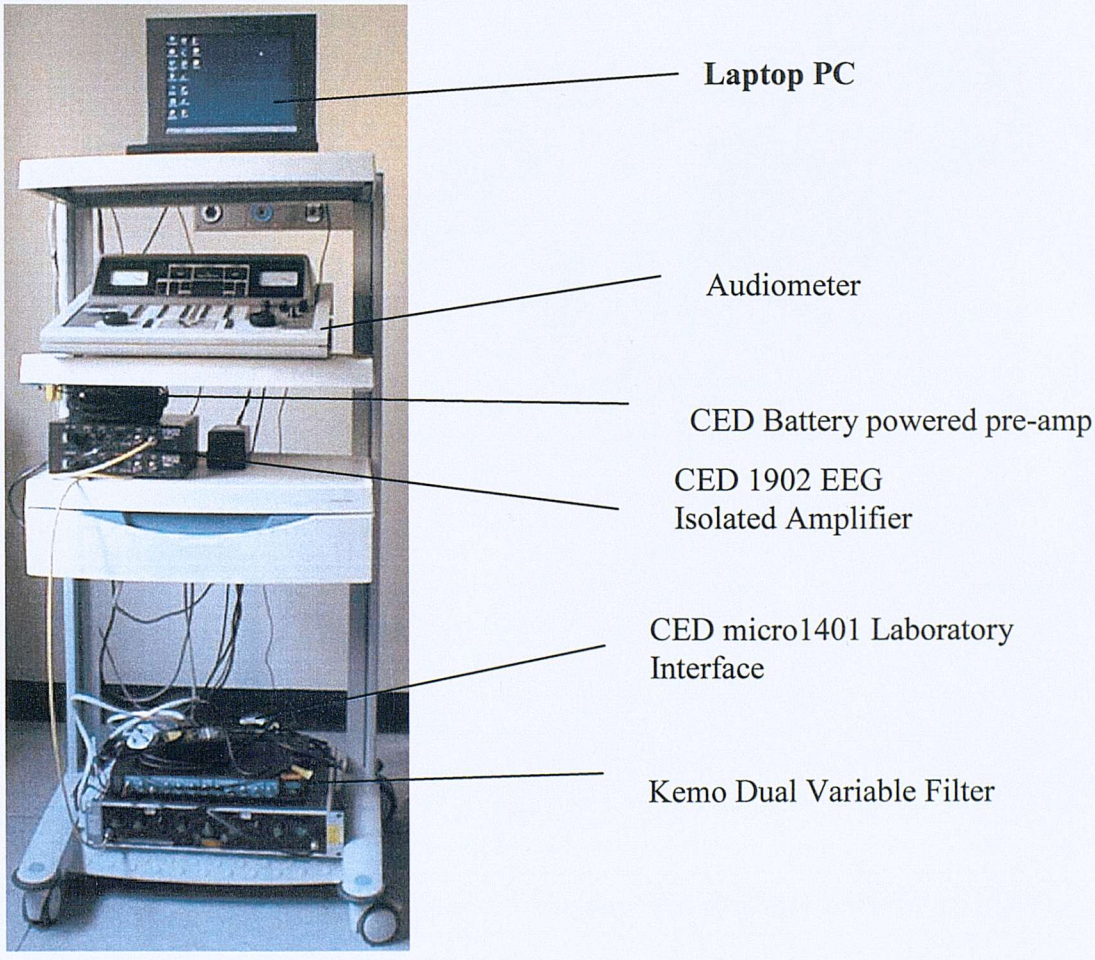


Figure 7.1 Equipment for recording the AEP and performing audiometry

At the start of the experiment, the electrodes were connected directly to the isolated EEG input of the CED 1902 biological amplifier, but problems were experienced due to high

levels of mains interference from equipment in the anaesthetics room. Part way through the experiment, a CED battery powered pre-amplifier (model 1902-10-HS2) was purchased in order to reduce the amount of cable exposed before amplification. The pre-amp could be placed nearer the patient (and hence further away from possible sources of mains interference) than the 1902 amplifier. This helped to reduce mains interference and was used for the remainder of the experiment. The gain setting on the headbox was 10, with the gain on the CED 1902 set to 1000, giving a total gain of 10000.

The electrode configuration is shown in Figure 7.2. The active and ground electrodes can be seen on the patient's forehead and the reference on the sternum. The electrodes attach to the pre-amplifier (top left). The ER-2 transducers can been seen above the patients head with sound tubes connected to each ear. Also seen is an ECG monitoring electrode on the patient's chest and the intubation/ventilation tube in the patient's mouth.

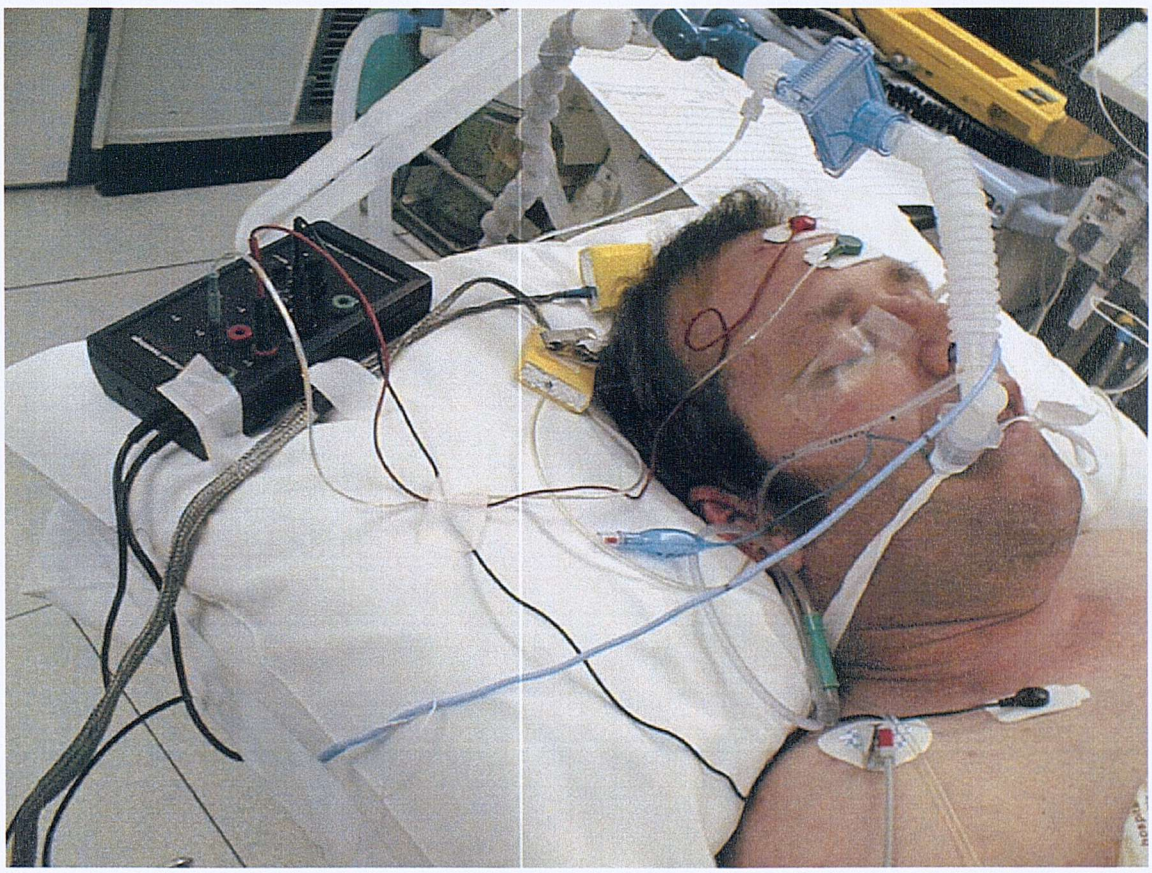


Figure 7.2 Electrode configuration. Consent was obtained from the subject to use this photograph.

7.2.3 Procedure

The written consent from subjects to participate in the experiment was obtained by the consultant anaesthetist on the day of arrival (typically the day before the operation). An information sheet was given to the patient which made clear the procedures in the experiment and that there was no obligation for them to participate (see Appendix 5).

The patient was brought into the anaesthetics room on a trolley after being given pre-med injection (10-15 mg of diazepam, 10 mg of morphine and 12.5 mg of prochlorperazine). The patient was brought in early in order to allow time for the experiment to be carried out prior to surgery. However, it is common practice for patients undergoing heart surgery to be anaesthetised in readiness for the previous operation to finish as this makes best use of theatre time. This can take several hours if there is a delay with the previous operation.

When the patient entered the anaesthetic room, disposable electrodes were attached to the patient for ECG monitoring. The AEP recording electrodes were attached. The ground electrode was placed on the low forehead, the active on F_z and the reference on the sternum. Pure tone audiometry was carried out using ER-2 insert phones and then a baseline recording of 2000 sweeps was made using bilateral approximate chirp stimuli at 60 dB nHL (a dial setting of 85 dB as determined from Experiment 2) using MLS order 4 with a maximum rate of 167 stimuli/s. It was explained to the patient that there would be a fairly loud noise for 2-3 minutes and that they should relax and do nothing. It was stressed that subjects should inform the experimenter if they felt the sound to be uncomfortably loud (no one did).

After the baseline AEP recording had been completed, an orthopaedic tourniquet was attached to the patient's left arm (to allow use of the isolated forearm technique – see below). An intravenous line, arterial blood pressure monitor and pulse oximeter were attached to the patient's right arm. A saline drip and propofol infusion pump were connected to the intravenous line.

The patient was informed that the AEP recording would resume and that they would then be anaesthetised. The AEP recording was restarted in continous recording mode (the averaging process was automatically restarted every 4000 sweeps) with data being streamed to disk for offline analysis. After one minute, anaesthesia was induced using 100 μg of fentanyl and a 2

mg per kg bolus of propofol. Propofol infusion was started at a rate of 2 mg per kg per hour. The patient rapidly lost consciousness (in around 10s).

The orthopaedic tourniquet was inflated to 300 mmHg and 0.1 mg of vecuronium (a muscle relaxant) was administered. The tourniquet prevents the muscle relaxant getting to the patient's arm, so the patient can still move the arm if he regains consciousness. However, after 20 minutes the cuff needs to be deflated for 2 minutes in order to allow blood to return to the arm, preventing any chance of ischaemic paralysis of the arm. After a period of 2 minutes the cuff could be re-inflated and the muscle relaxant re-administered.

The patient was ventilated with Oxygen via a facemask until the muscle relaxant had taken effect (approximately 3 minutes). Their trachea was then intubated and the patient was ventilated as the muscle relaxant prevents voluntary breathing. The patient was allowed to settle and the ventilation rate was adjusted to allow an end tidal CO_2 concentration of 5 kPa.

After approximately 5 minutes the propofol infusion was stopped to allow the patient to regain consciousness. Every minute the patient was asked to squeeze the hand of one of the researchers. When the patient started to respond to command, the propofol infusion was re-started at 6 mg per kg per hour and the patient returned to sleep. If time allowed this procedure was repeated. The entire length of the experiment was approximately one hour. After the experiment was completed, the AEP recording was stopped and the headphones and electrodes were removed from the patient. The patient continued to be anaesthetised and was moved to the theatre when it became available.

7.2.4 Problems with data acquisition

Finding suitable subjects who were willing to participate in the experiment, and who did not have medical contra-indications, was a slow process. On some occasions the operations of subjects who had consented to take part in the experiment were cancelled due to emergencies, so the experiment was not conducted.

There were a number of methodological problems with collecting data in the anaesthetics room at the hospital. This meant that although nine subjects participated in the experiment, good quality data were only obtained from four subjects.

Mains interference on recordings was much more of a problem in the anaesthetics room than in the sound proofed booths used for the previous experiments. Possible sources of

interference included strip lighting, overhead bar heaters, ECG and blood pressure monitoring equipment, the AEP recording equipment, the ventilator and the propofol infusion pump. Although mains interference can be excluded using notch filtering, this cannot be done if the amount of interference is so high that the ADC limits are exceeded and data are clipped.

The monitoring of interference relied on overload indicators on the Kemo Dual Variable filters and was not very accurate. In addition to this, the amount of interference varied during the experiment as the orientation of equipment and wires changed when different procedures were carried out on the patient (such as intubation). The data from three subjects had to be discarded due to mains interference exceeding the ADC limits. The problem was eventually overcome by reducing the amplifier gain from 30000 to 10000, trying to move interference sources away from the AEP recording equipment and finally by purchasing the additional battery powered pre-amplifier. This has a lower input impedance than the CED 1902 and has the advantage that it can be placed very near the patients head, so short electrode leads could be used, which reduces the area enclosed by the leads and hence the magnitude of electromagnetic interference.

Despite these measures, significant amounts of 50-Hz interference, and harmonics of 50 Hz, were present in the data. To exclude this, data were zero phase digitally filtered using a bank of notch filters at 50, 100, 150, 200 and 250 Hz. The filter order varied between 2^{nd} and 5^{th} order and was chosen using the 'Buttord' function in MATLAB to give at least 30 dB of attenuation in the stop band with a 4 dB bandwidth. As the filtering was done offline, it was not possible to monitor the quality of the AEP during data collection.

As mentioned above, none of the subjects were otologically normal and the average age was above 60. This will have an impact on the quality of any AEPs obtained. In general the amplitude of AEPs reduces and the latency of peaks increases with increasing age and hearing loss (Hall, 1992). This will result in reduced SNR compared to young subjects with normal hearing. The average hearing loss was in the mild to moderate hearing range.

The position of the reference electrode is an important consideration when recording the MLR. In Experiments 1 and 2 the reference electrode was placed on the nape of the neck, instead of the mastoid, to avoid interference from the post-auricular muscle. However, this was not thought to be a suitable position in the current experiment as the patients were lying on their backs. It was decided to use the sternum as an alternative non-encephalographic

position for the reference electrode. Unfortunately, examination of data revealed significant levels of ECG interference for some subjects (a low frequency feature occurring approximately once per second). This resulted in a reduced SNR. In one subject SNR was so poor that the data were highly variable and had to be discarded. (It is possible that an electrode contact had become poor during the experiment resulting in an increased noise level.) This problem might have been avoided if SNR had been displayed during the experiment. This would be a useful development for similar future experiments and would require the filtering of data in real-time to exclude mains interference.

Data from a further subject had to be discarded due to experimental error – the number of repeat recordings was set too low. As a consequence, the computer timed-out just before the patient started responding on the isolated forearm technique. Hence the critical segment of AEP data was lost.

7.2.5 Data analysis

Data collected during the experiment were streamed to disk for offline analysis. A bank of notch filters was used to exclude main interference from the data (see above), then artefact rejection was applied to the filtered data. Finally a moving average was used to extract the MLR as a function of experiment time.

For each 6 minute block of data, an artefact rejection level was found adaptively so that the 10% of epochs with the highest variance were excluded from the moving average. If data were to be analysed in real time during the experiment, the artefact rejection level would need to be fixed in advance. This would result in more data being excluded at the start of the experiment, when the subject was awake and active, than when the subject was anaesthetised. Using a variable rejection level allows parity of acquisition time for all blocks of data.

The number of averages used in the moving average window will affect SNR and the responsiveness of the average to changes in the MLR. If a small number of averages is used, changes in the MLR will be rapidly tracked, but SNR will be poor, so the data will show increased random fluctuations. If a large number of averages is used, SNR will be improved, but the moving average will only slowly track changes in the MLR. For the following analysis a moving average of 1000 epochs was used with 10% artefact rejection. With an epoch length of 90 ms, an average of 1000 epochs can be collected in 99 s (including 10% artefact rejection).

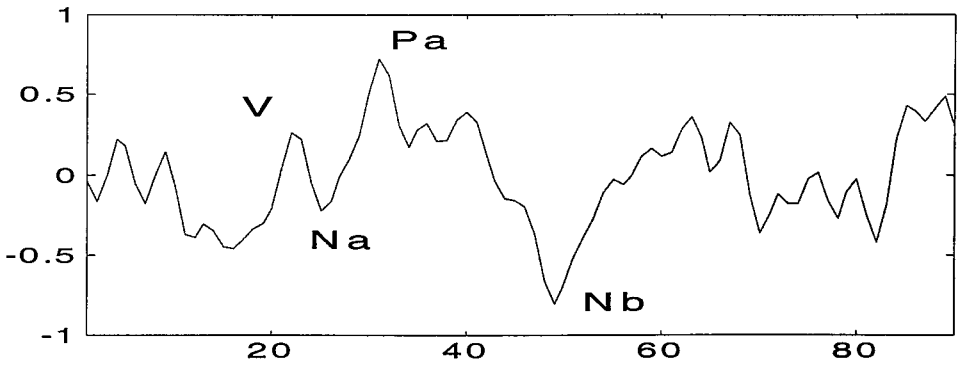
SNR was analysed using the F_{sp} technique (described in Chapter 2). The single point was chosen at 45 ms and the MLR variance measured between 20 and 70 ms. The variance of the MLR between 20 and 70 ms was used as a measure of response power and the single point variance was used as a measure of the noise power during the experiment.

7.3 Results

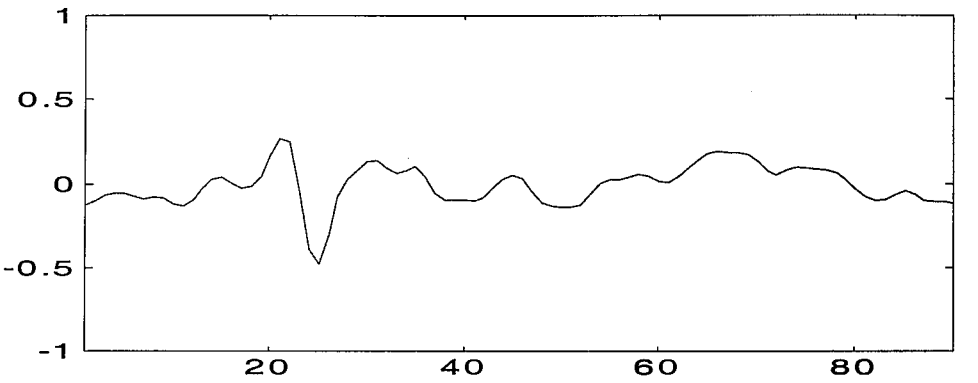
7.3.1 Change in the MLR morphology with awareness

It had been expected that a shift in N_b latency would be seen as a consequence of anaesthesia/sleep. For example, Thornton et al (1983) report an increase in the latency of the N_b wave with enflurane anaesthesia. However, examination of waveforms did not show an obvious shift in latency. Figure 7.3 shows example MLR waveforms from subject SM before anaesthesia, when anaesthetised, when responding on the isolated forearm technique and when re-anaesthetised. Whilst there is a definite change in the MLR between the different conditions, there is no obvious change in latency. The N_b wave is seen at approximately 48 ms in the pre-anaesthesia measurement. When SM was anaesthetised, there was no obvious shift in N_b latency, rather the P_a-N_b complex was reduced in amplitude (almost disappearing). When SM started to respond on the isolated forearm technique, the P_a-N_b complex increased in amplitude and then decreased when SM was re-anaesthetised. A similar pattern was seen for all subjects from whom good data were obtained (SM, JC, PB and DM). MLRs for subjects JC, PB and DM are shown in Appendix 3. In no subject was an obvious latency shift induced by anaesthesia. Rather the amplitude of the MLR appeared to change. It was therefore decided to investigate the variance of the MLR as a function of experiment time.

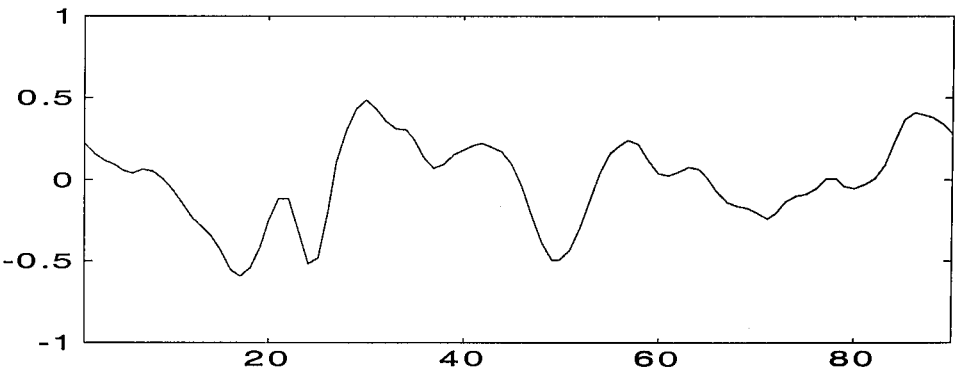
SM Pre Anaesthesia



SM anaesthetised



SM Responding



SM anaesthetised

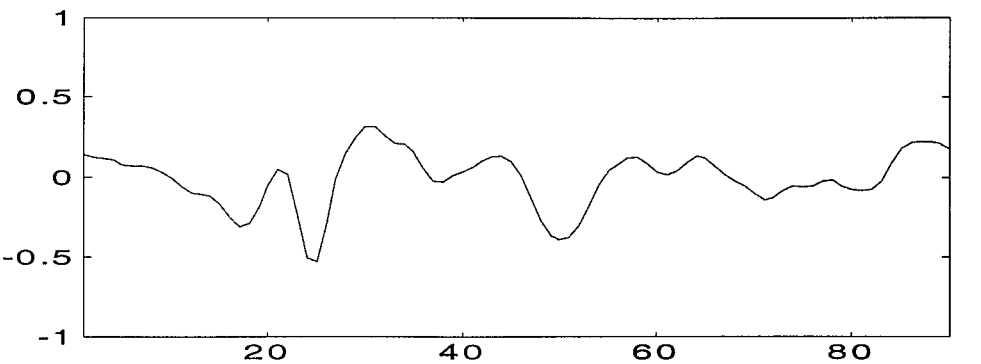


Figure 7.3 MLR Waveforms for SM. Before anaesthesia, during anaesthesia, when responding on the isolated forearm technique and re-anaesthetised. Vertical axis shows MLR amplitude in μV, horizontal axis shows time in ms.

7.3.2 Change in MLR variance with awareness

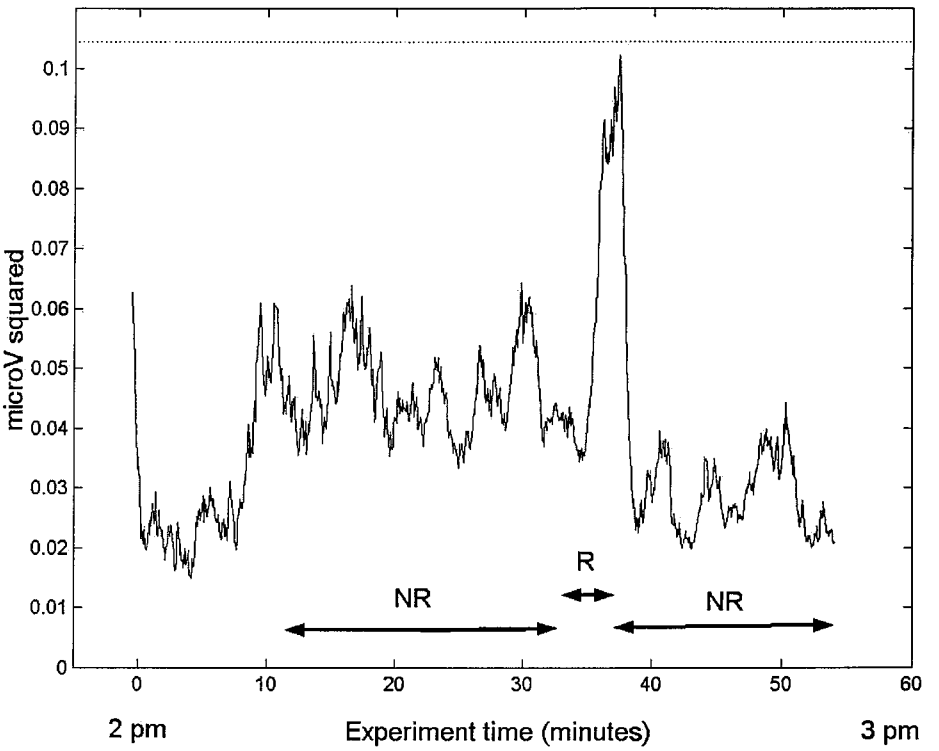
Figure 7.4 shows the MLR variance measured between 20 and 70 ms after the stimulus for the four subjects from whom good data were obtained. A moving average of 1000 epochs was used. The variance of the MLR recorded before anaesthesia is shown as a dotted line (a 'pre' measurement). The points when isolated forearm measurements were conducted are indicated by arrows, with R indicating a response to command and NR indicating no response (measurements were made every minute using the isolated forearm technique).

For all subjects, the variance of the MLR decreases as the subject is initially anaesthetised. For three subjects (SM, PB and JC), there is a categorical change in the response between non-responding and responding states as measured with the isolated forearm technique (indicating conscious awareness). Note that subject JC was allowed to regain consciousness twice during the experiment, so two categorical changes in variance are seen. There is a delay between subjects starting to respond to command and a change in the variance of the response, as it takes some time for the change in the MLR to be reflected by the average of 1000 epochs (i.e. there is a delay before changes in the MLR are reflected in the moving average). It takes 99 seconds to fully update the moving average (including artefact rejection).

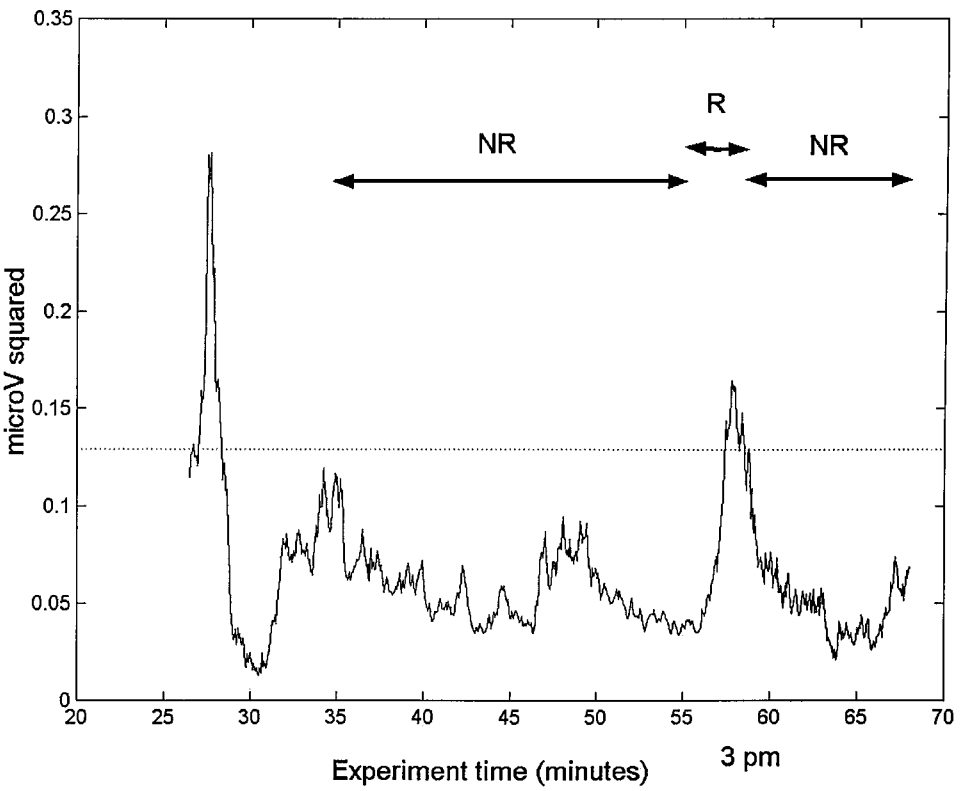
For subjects SM, PB and JC, there does not appear to be a graded change in the MLR variance, which might indicate anaesthetic concentration. When the anaesthetic is stopped, we might expect a half-life decay of anaesthetic in the blood stream with a corresponding graded change of the MLR response. Rather there appears to be a categorical difference in the MLR amplitude between responding and non-responding states. It would appear that, for these three subjects, the magnitude of the MLR reflects conscious awareness.

For subject DM, there is not an obvious change in the MLR variance between responding and non-responding states. The variance of the MLR is more variable than for the other three subjects from whom good data were obtained and it does not get higher than 50% of the 'pre' MLR variance. The variance of the 'pre' MLR from DM is approximately twice that of the other three subjects, although it is not known why. The variance of the MLR is highest before induction of anaesthesia and when responding to command on the isolated forearm technique, but the distinction between responding and non-responding states is not as clear as for the other three subjects.

SM


microV squared
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
R
NR
NR
0
10
20
30
40
50
60
2 pm
Experiment time (minutes)
3 pm

PB


microV squared
0.35
0.3
0.25
0.2
0.15
0.1
0.05
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R
NR
NR
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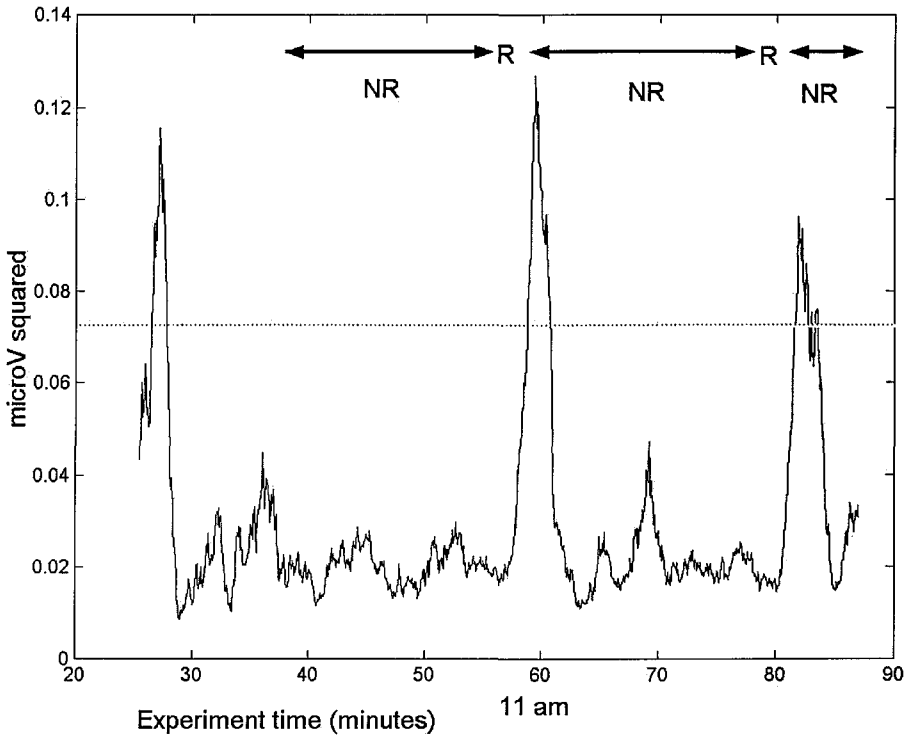
70
Experiment time (minutes)
3 pm

JC



DM

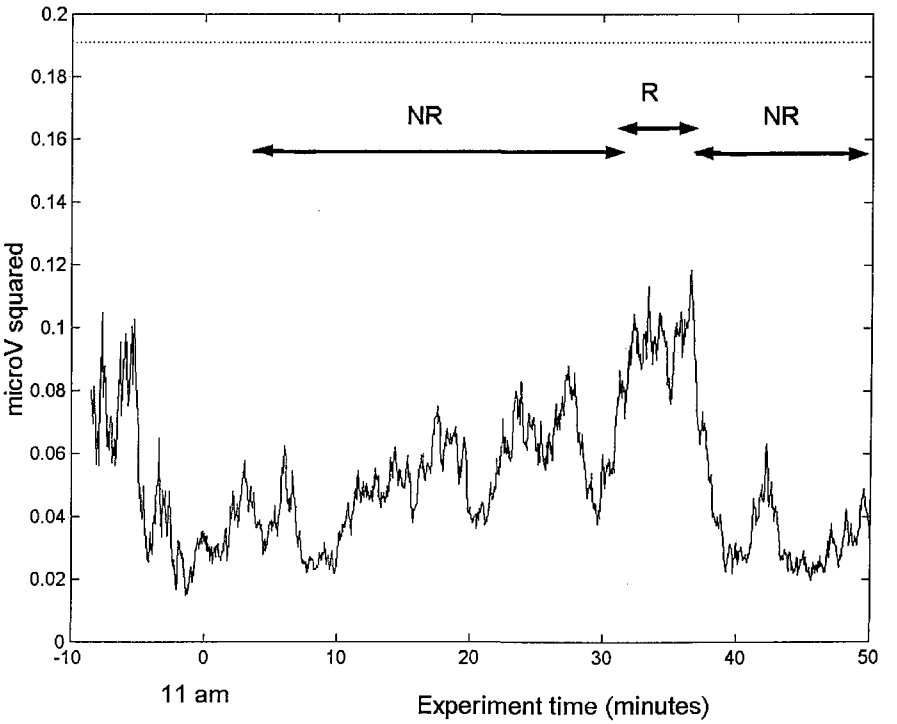


Figure 7.4 Variance of the MLR (20 to 70 ms post stimulus) for a moving average of 1000 epochs as a function of experiment time for four subjects. Response on the isolated forearm measurement is indicated with arrows where R = responding to command and NR = not responding. The variance of the 'pre' MLR before anaesthesia is shown as a dotted line.

7.3.3 The quality of recordings

The recordings from the current study were made in a challenging environment which was not sound proofed and had numerous sources of electrical interference. An important consideration was the quality of recordings. A moving average of 1000 epochs was used to extract the MLR from noise. The noise level was assessed as a function of experiment time using the variance of a single point 45 ms after stimulus onset calculated across the 1000 epochs of the moving average. Figure 7.5 below shows noise variance as a function of experiment time for subject SM. Most subjects are tense before an operation, so muscle tension and hence electrophysiological noise are likely to be high before anaesthesia, but the muscle tension will be abolished as the subject goes to sleep and muscle relaxant is administered. It can be seem that the noise level is initially high before SM is anaesthetised, but that the noise level rapidly drops over approximately 10 minutes as SM is anaesthetised and the muscle relaxant takes effect.

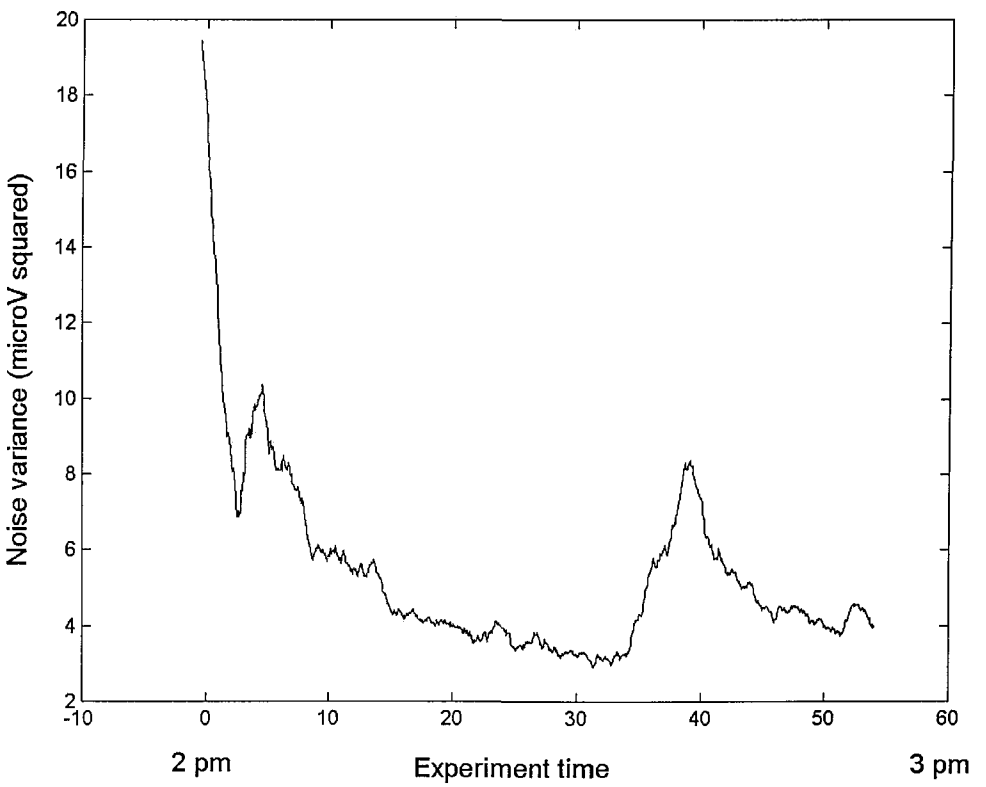


Figure 7.5 Noise variance as a function of experiment time for subject SM. Noise variance was calculated for a moving average of 1000 epochs with 10% artefact rejection.

SNR during the experiment was assessed using the F_{sp} technique (Elberling and Don, 1984). F_{sp} was assessed as a function of experiment time using the 1000 epochs in the moving

average. Figure 7.6 shows SNR as a function of experiment time for subject SM. SNR rises from 1 to 2.5 over the first 10 minutes of the experiment as SM is anaesthetised. This results from the noise level due to electrophysiological activity decreasing with the action of the anaesthetic and muscle relaxant (as seen in Figure 7.5). For the rest of the experiment, SNR is fairly stable at around 2.5, apart from a brief increase to 5 at around 38 minutes into the experiment. This increase in SNR occurred when SM started to respond to command on the isolated forearm technique. The variance of the MLR increases (as seen in Figure 7.3), hence SNR also increases (the noise level did not change significantly as SM had been given a muscle relaxant).

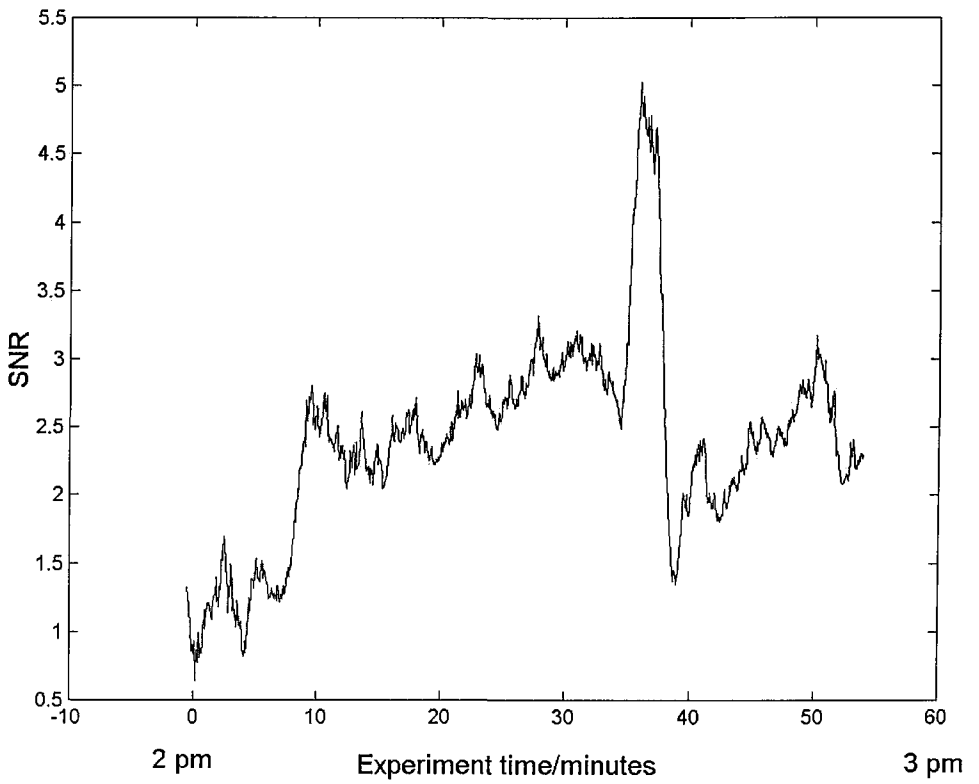


Figure 7.6. SNR as a function of experiment time for SM. SNR was calculated using the F_{sp} technique for a moving average of 1000 epochs with 10% artefact rejection.

The pattern of SNR change was similar for the other three subjects from whom good quality data were obtained, with SNR increasing during initial anaesthesia to reach a fairly steady state, apart from a brief increase in SNR when response occurred on the isolated forearm measurement. A summary of initial SNR, average SNR after anaesthesia and peak SNR is shown in Table 7.2. The rms SNR post-anaesthesia using a moving average of 1000 epochs is around 2. However, as a consequence of subject age and hearing loss, SNR is lower than it would be for otologically normal subjects (such as were used in Experiments 1 and 2). SNR

could be improved by increasing the number of epochs in the moving average, but it would result in the moving average being less responsive to rapid changes in the MLR. The SNR before induction of anaesthesia is lower than during anaesthesia, so the quality of the MLR recording improves with the action of the anaesthetic. The pre-anaesthesia noise level may make it hard to obtain a pre-anaesthesia MLR as a baseline for each subject.

	SM	PB	JC	DM
Initial SNR	1	1	1	0.5
SNR post-anaesthesia	2.5	2	1.5	1.5
Peak SNR	5	3.5	3	2.5

Table 7.2 Rms SNR at different points in the experiment for the four subjects from whom good data were obtained.

7.4 Discussion

Recording good MLR data in the anaesthetic room was harder than expected and, as a consequence, good data were only obtained from a small number of subjects. If the MLR is to be used routinely for monitoring in anaesthetics then the recording system needs to be robust. Part of the experiment involved a learning process of how to record good quality AEPs in the anaesthetics room, a process which has probably been overcome in the development of existing AEP recording equipment, such as the Northwick Park system (Jordan et al, 1995). Using a combination of a lower gain setting, a battery powered pre-amplifier and short electrode leads it was possible to record the MLR reliably in a room with strip lighting and numerous electrical equipment. However, it is not clear how the MLR recording process would be affected by monopolar or bipolar diathermy in the operating theatre.

A further drawback of the recording system was that it was not possible to monitor the quality of the AEP accurately in real time. This is because the filters used to exclude mains frequency interference had not been implemented in the MLS-MLR recording software (rather they were implemented offline in MATLAB). For future experiments it is desirable that the filters are implemented in real time together with a display of the MLR and SNR post-filtering. This would both avoid the problem of data loss due to mains frequency interference and it would help clinicians, who would not necessarily be experienced in AEP recording, to tell whether or not they were recording a good quality MLR. A traffic light system, such as that used in commercial otoacoustic emission recording software, might be

helpful to a clinician, with green indicating good SNR and red indicating unacceptable noise levels.

It was felt important to assess the hearing thresholds of subjects who took part in the study prior to an AEP being recorded. This demonstrated that no subjects who took place in the study had normal hearing, which is a consequence of the demographics of patients undergoing heart surgery. Whilst an AEP could be recorded from all the subjects (barring equipment problems) it is clear that the technique could not be used on all subjects. Lightfoot (1992) suggests that, in order to record the ABR, it must be possible to achieve a sensation level of at least 20 dB above threshold and it is likely that the same is true for the MLR. The technique is therefore probably not appropriate for patients with severe or profound hearing loss (around 2% of the population but rising to 4% in the age group 61-70 and 10% in the age group 71-80; Davis, 1995). For such subjects a monitoring technique that does not involve the auditory pathway, such as the bispectral index monitor, may be more appropriate. If the MLR were to be used routinely in anaesthetic monitoring, it would be critical to assess the hearing thresholds of the subjects prior to the technique being used and to be aware of surgical procedures that might affect hearing.

No shift in N_b wave latency was found in this study as a result of anaesthesia, rather a categorical change in response variance was found. It is unclear why other studies have found a latency shift (Thornton et al, 1983; Loveman et al, 2001). One possibility is that a moving average that takes a long time to update might result in smearing of the MLR response. A rapid amplitude change might appear as a slow latency shift due to the smearing or responses with different amplitude into one another. Alternatively, poor SNR might have resulted in variable MLR recordings. Another possibility is that placement of the reference electrode on the mastoid would have recorded the PAM. Abolition of the PAM response with anaesthesia might induce an apparent latency shift. Such an effect was found in the pilot experiment for Experiment 1, where PAM interference produced an apparent shift in N_b latency.

It is questionable whether we would expect a graded or a categorical change in the MLR with depth of anaesthesia. A graded change might be expected if the action of the anaesthetic was to disrupt the transmission of information along the auditory pathway. Increased concentration of anaesthetic might result in increased disruption of transmission and hence increased latency shift in the MLR. If this were the case, we might expect a half-life type decay of anaesthetic concentration once the anaesthetic is stopped and hence a graded change in wave latency. An alternative hypothesis is that the auditory centres which generate the

MLR are affected by the attentional state of the subject, so categorical changes in attention would produce corresponding categorical changes in the MLR. As anaesthetic concentration decreases, a point will be reached where a sudden change in arousal occurs (we wake up suddenly, not gradually). The thalamus is thought to regulate autonomic arousal in the brain. It is possible that as we pass from waking to sleeping, the thalamus would have an inhibitory effect on the MLR generator sites and hence would produce a categorical decrease in MLR amplitude. The data from three of the four subjects from whom good quality data were obtained would appear to support the latter hypothesis (i.e. there appears to be a categorical change in the variance of the MLR when subjects start to respond on the isolated forearm technique). The data from the other subject does not show a clear categorical change. It is not clear why.

Another possibility is that the categorical change seen in the data is a consequence of the high rates used with the MLS technique to elicit the MLR. As MLS uses higher stimulation rates than conventional stimulation, the auditory pathway is more stressed than it is with conventional stimulation. Responses obtained with high rate stimulation may therefore be more sensitive to disruption of the auditory pathway induced by anaesthesia than responses obtained with slower conventional stimulation rates. In order to address this question a study would need to compare the effects of anaesthetic on the conventional rate MLR and the MLS-chirp evoked MLR on a number of patients (which is beyond the scope of this thesis).

If the amplitude of the MLR reflects the state of arousal of a subject and changes categorically, not gradually, with anaesthesia, then it might best be referred to as a measure of conscious awareness. The term depth of anaesthesia might be misleading as it would imply that the MLR would show a graded change with anaesthetic concentration in the brain or blood stream. The data from this experiment suggest that the MLR is a measure of conscious awareness, not of depth of anaesthesia.

Although the findings of this study indicate that the MLR shows a categorical change with state of arousal, they should be treated with some caution. A clear pattern was seen in only three of the four good sets of data. The recording conditions in the study were far from ideal. Subjects were middle aged and did not have completely normal hearing. The anaesthetic rooms where the study was carried out were not sound proofed and had numerous sources of electrical interference. In order to confirm the findings, a more controlled study of the effects of anaesthesia on the MLR evoked with MLS-chirps would be needed. Ideally, otologically

normal volunteers who were not awaiting surgery would be used and recordings would be made in a sound proofed and electrically isolated room.

If the variance of the MLR were to be used as an indicator of conscious awareness during anaesthesia, a cut off level of variance which indicates conscious awareness would need to be found. It is likely that this would need to be subject specific as there may be significant intra-subject variation in MLR amplitude, for example as a consequence of subject age or hearing loss. In the current study, a MLR was obtained prior to anaesthesia. For three of the four subjects, MLR variance reaching 90% of the 'pre' value would appear to coincide with ability to respond to command on the isolated forearm technique. For the remaining subject, the 'pre' variance was very high and was not reached again. It is unclear if this is a consequence of measurement error, or a failure of the technique. In order to decide on a suitable cut off for conscious awareness, a similar experiment would need to be performed on a larger number of subjects and the sensitivity and specificity of different criterion to conscious awareness estimated.

A possible area for future research is to compare the amplitude of Wave V of the ABR with the N_b region of the MLR. It is thought that the MLR is affected by awareness, whereas the ABR is not. The ratio of MLR to ABR amplitude may be a reliable measure of awareness. Monitoring ABR amplitude may also be useful if anaesthetics are used which can affect hearing sensitivity. A reduction in ABR amplitude could indicate a reduction in hearing sensitivity, which would suggest that the use of the AEPs to indicate conscious awareness, in that instance, is suspect.

In a review of attempts to measure depth of anaesthesia, Kalkman and Drummond (2002) make the point that a suitable measure of depth of awareness would have to be highly reliable in order to be used in routine clinical practice to control anaesthesia. The number of patients who regain awareness during surgical procedures is estimated to be less than 1 in 500 (Sandin et al, 2000). If a measure of depth of anaesthesia were unreliable, there is a chance that it might incorrectly indicate that a patient was asleep when they were awake and so the patient might be under anaesthetised. This would result in an increase in the incidence of awareness during surgery due to an unreliable measure. A measure would have to be significantly more reliable than 1 in 500 false readings in order to improve anaesthetic practice. At present, it is not clear if the MLR can be measured reliably enough to be used as a suitable indicator of conscious awareness.

7.5 Conclusions

Obtaining good data for the experiment was problematic. No subjects had normal hearing thresholds. A combination of subject age, subject hearing loss and electrical interference resulted in only four good sets of data being obtained from the nine subjects who volunteered to participate in the study. The small sample size means that the findings should be treated with caution.

A change in the latency of the N_b wave with anaesthesia was not seen. Rather a change occurred in the amplitude of the MLR. In three of the four good sets of data obtained, the variance of the MLR showed a categorical increase in amplitude as subjects started to respond on the isolated forearm technique and then showed a categorical decrease when subjects stopped responding. A graded change in the MLR that might reflect depth of anaesthesia was not seen. Rather it would appear that a categorical change in the MLS-chirp evoked MLR reflects conscious awareness. In three of the four subjects from whom good data was obtained, the MLR variance reaching 90% of that of a baseline measure would appear to coincide with the subject responding on the isolated forearm technique. In one of the four subjects, a categorical change in the MLR was not seen. It is not clear whether this was due to difficulties in recording the MLR, or due to an underlying problem with the technique.

As subjects were anaesthetised, electrophysiological noise levels decreased. SNR correspondingly increased. A moving average of 1000 epochs was used to obtain the MLR with 10% artefact rejection. This took 100 seconds to fully update and resulted in rms SNR between 1.5 and 2.5 once subjects had been anaesthetised. Increasing the number of averages would improve SNR, but would make the moving average less responsive to rapid changes in the MLR.

In order to verify the findings of this study, there is need for a more controlled study using a larger number of otologically normal subjects in a better recording environment. Problems with data acquisition might be improved if notch filtering to exclude mains frequency interference and a display of SNR post filtering were implemented in the acquisition software in real time.

Before the MLR is used as an indicator of conscious awareness in clinical anaesthesia, further assessment needs to be done on the reliability of the technique. The technique would have to be highly reliable to reduce the incidence of awareness occurring in surgery, which is currently estimated at less than 1 in 500. The technique would not be suitable for patients with pronounced hearing loss. Hence hearing thresholds should be assessed before application of the technique. It the technique is not found to be sufficiently reliable for clinical application, it may still represent a useful tool for anaesthesia research.

CHAPTER 8

Summary/Conclusions and Further Research

8.1 Summary and Conclusions

The main goal of this work has been to improve acquisition of the auditory evoked potential (AEP) known as the MLR with a view to using the MLR to estimate depth of anaesthesia. The approach taken was primarily to improve the generation of the signal, rather than trying to better extract the MLR from background noise. Two stimulus generation methods have been recently developed in the field of AEPs: the Maximum Length Sequence (MLS) technique and the use of chirp stimuli designed to compensate for frequency dispertion on the basilar membrane. The use of these techniques to acquire the MLR has been investigated.

The conventional way to improve SNR for AEPs is to use synchronous averaging. The limit to the rate at which responses can be averaged is the reciprocal of the response duration (around 100 stimuli/s for the Auditory Brainstem Response (ABR) and 15 stimuli/s for the MLR). The MLS technique overcomes this limitation. MLS are a form of pseudorandom binary sequence. Auditory stimuli can be presented in an MLS sequence at higher rates than are used for conventional averaging. With stimulation rates faster than the reciprocal of the response duration, the responses overlap in time. However, the mathematical properties of MLS mean that the overlapping responses can be unravelled in order to retrieve the AEP. The MLS technique depends on linear superposition of the response. If an MLS were to be used to acquire an AEP at the same maximum rate as conventional stimulation, the SNR would be reduced as not all stimulation opportunities in an MLS are filled. However, the advantage of MLS is that higher rates of stimulation can be used than for conventional stimulation. This allows more rapid averaging and potentially a reduction in the time required to achieve a given SNR.

When using MLS stimulation to acquire AEPs, the stimulation rate cannot be increased indefinitely as the magnitude of the response starts to reduce with rate due to neural adaptation. There is a trade off between an increase in SNR due to more rapid averaging and a decrease due to response adaptation. Experiment 1 aimed to map the rate-adaptation function for the MLS evoked MLR to determine the optimum stimulation rate to achieve maximum SNR in a fixed time period. The rate adaptation curve for conventional stimulation rates was also mapped for comparison.

8.1.1 Experiment 1. Mapping rate adaptation of the MLR with conventional and MLS stimulation

Many studies of the MLR as a measure of anaesthetic depth have used conventional stimulation at 5 clicks/s. For a response duration of around 70 ms (which would allow correct identification of the N_b wave, which may be shifted in latency due to the action of anaesthetics), the maximum stimulation rate that does not result in overlapping of the response is around 15 clicks/s.

SNR was found to increase almost linearly with increasing conventional click rate, so a reduction in test time of 3 times can be expected by increasing the conventional click rate from 5 to 15 click/s. Further improvement in SNR was obtained using MLS. SNR was found to increase with MLS stimulation rate up to 167 opportunities/s, after which SNR reduced with rate. The test speed improvement that can be expected with MLS compared to

conventional stimulation at 5 clicks/s is 6.5 times, which is twice as much as can be achieved by simply increasing the conventional click rate.

In Experiment 1, MLR recordings could be reliably recorded using conventional stimulation rate clicks and high MLS stimulation rate clicks. The same time period of 185 s was used for all recordings. It was possible to record an N_b wave from all subjects at an MLS stimulation rate of 167 clicks opportunities/s.

Wave latency was not found to vary significantly with rate of presentation. P_a-N_b wave amplitude did not reduce significantly as conventional stimulation rate was increased, but did decrease for MLS stimulation rates above 167 opportunities/s. The pattern of rate adaptation found for the MLR was similar to that found for the ABR (Leung, 1998), where adaptation occurs at rates above 200 clicks/s. It is possible that this reflects an underlying property of the neurons in the auditory pathway.

Experiment 1 compared binaural and monaural presentation of stimuli. Binaural presentation increased the SNR of recordings compared to monaural presentation and resulted in an estimated reduction in test time by a factor of approximately 2.

A possible complication when recording the MLR is interference from the post-auricular muscle (PAM). In a pilot study, the amplitude of PAM interference was significantly reduced by moving the inverting electrode to a non-encephalographic position. It would appear that such an electrode configuration should be used in all studies of the MLR as presence of the PAM can produce an apparent shift in the latencies of the MLR waves. It is possible that several of the published studies of the MLR as an indicator of depth of anaesthesia, which have used a mastoid reference electrode, have recorded a combination of the PAM response and the MLR.

8.1.2 Experiment 2. A comparison of click and chirp stimuli to elicit the MLR

A further stimulation technique that may improve the acquisition of AEPs has been suggested by Dau et al (2000) and involves the use of chirp stimuli to compensate for temporal dispersion occurring in the response of the basilar membrane for stimuli at different frequencies. Click stimuli are commonly used to elicit AEPs as they have a wide band frequency spectrum and so stimulate a large portion of the cochlea. However, a click will take time to travel along the basilar membrane, so low frequency regions at the apex of the cochlea will be stimulated up to 10 ms later than high frequency regions at the base of the

cochlea. The response of the auditory nerve to a click will therefore be spread out in time. Dau et al (2000) generated chirps that compensate for the place-frequency mapping of the cochlea, sweeping from low to high frequency within 10 ms. They demonstrated that ABR elicited using such chirps have a larger amplitude than ABR elicited using clicks. However, no published study has investigated whether such chirps might improve the acquisition of other AEPs, such as the MLR.

The aim of Experiment 2 was to investigate whether the amplitude of the MLR might be increased by using such chirp stimulation for the optimal stimulation rates found in Experiment 1. An increase in amplitude would correspond to an increase in SNR. This should in turn further reduce the acquisition time for the MLR. Experiment 2 compared the MLR elicited using chirps and clicks at conventional rates of 5 and 15 stimuli/s and MLS rates of 143 and 167 stimulus opportunities/s. All recordings were made in the same time period of 185 s and the SNR of recordings was compared using the F_{sp} technique.

The best SNR was obtained using MLS chirps at 167 stimulus opportunities/s. The improvement in SNR compared to conventional stimulation at 5 clicks/s corresponds to a test time improvement of 14.9 times. This is a greater improvement in test speed than can be obtained using the MLS technique alone and may represent a significant reduction in test time if the MLR is to be used as a measure of anaesthetic depth.

The average increase in wave latency using chirps instead of clicks was 8.9 ms, which is slightly less than the length of the chirp. The discrepancy may imply that the true frequency-vs-delay characteristics of the cochlea at 60 dB SL are not exactly those predicted from the linear cochlea model of de Boer on which the approximate chirp stimulus was based.

Although an improvement in N_b amplitude was produced by using chirps instead of clicks at MLS recordings rates, a similar amplitude increase was not seen at conventional recording rates. Indeed, the SNR obtaining using 15 chirps/s is significantly worse than that for 15 clicks/s. This finding requires further investigation. A supplementary study carried out in addition to Experiment 2 appeared to demonstrate that the click evoked MLR adapts more rapidly with rate than the chirp evoked MLR. The supplementary study was only carried out on three subjects, so a larger study would be needed to confirm the result. However it would explain why an increase in MLR amplitude was seen in Experiment 2 for chirp stimulation at MLS, but not at conventional stimulation rates. The effect may be a consequence of the chirp stimulating a wider bandwidth of the auditory pathway than the click.

8.1.3 Experiment 3. The use of band-limited chirp stimuli to obtain the ABR

Experiment 3 investigated the possibility of generating a band-limited stimulus with frequency-delay characteristics that compensate for delay of the travelling wave on the basilar membrane. In order to generate such a stimulus, segments of the 'approximate chirp' of Dau et al (2000) were extracted using Hanning windows. Hanning windows were used to reduce frequency "splatter" (although, in a recent paper, Wegner and Dau, 2002, used a similar approach with rectangular windows). Objective estimation of hearing threshold at specific frequencies has been a goal of audiological research for some years. The AEP recorded was the ABR, not the MLR, as the ABR is more commonly used in clinical practice for objective estimation of hearing thresholds. The ABR is not affected by sleep in the same way as the MLR so it can be used on sleeping patients who are unable, or unwilling, to co-operate with hearing testing.

Using tone burst stimuli to record the ABR, good estimates of hearing threshold can be obtained at high, but not low frequencies (Gorga et al, 1988). At low frequencies, the objective threshold is approximately 35 dB above the behavioural threshold. The use of low frequency chirp stimuli in Experiment 3 resulted in objective thresholds closer to behavioural thresholds than are reported using tone burst stimuli. However, the spectral spread of the stimuli was pronounced as the length of the stimuli has to be very short in order to have the rapid frequency-delay sweep characteristics of the approximate chirp over a limited frequency range. Whilst the frequency-delay characteristics of the stimuli may produce a better synchronised response at low frequencies than tone bursts, spectral spread of the stimuli means that they may stimulate unwanted frequency regions of the cochlea. They may therefore not give frequency specific estimates of hearing threshold and may not have widespread clinical application.

Steady state auditory evoked potentials (SSAEPs), which utilise amplitude (and sometimes frequency) modulated tones, are probably the best approach to obtain objective estimates of hearing threshold in clinical practice. Although the objective thresholds obtained are no closer to behavioural thresholds than can be obtained using tone burst ABR, the advantage of SSAEPs is that several frequencies and both ears can be tested at once (rather than one frequency at a time in one ear as for tone-burst ABR). The time required to obtain an objective audiogram is therefore greatly reduced.

8.1.4 Properties of the EEG and quality estimators for AEPs

Chapter 6 used simulations and recorded signals to investigate properties of the EEG, quality estimators for AEPs and the use of two signal processing techniques to improve acquisition of the MLR. When recording AEPs, EEG activity is a major source of noise and will be present even if electromagnetic sources of interference are eliminated and myogenic activity is minimised. The EEG contains most energy at low frequencies. When recording AEPs a high-pass filter is used to reduce low frequency noise. Late latency AEPs (such as the MLR or SVR) are thought to contain more low frequency energy than short latency AEPs (such as the ABR or electrocochleogram). The high-pass filter setting is therefore reduced when recording long latency AEPs, so more low frequency EEG energy is present in the raw data.

The issue of signal quality is an important consideration when recording AEPs and one which has not been addressed in many papers which investigate the use of the MLR as a measure of anaesthetic depth. In Chapter 6 the ± difference and F_{sp} quality estimators were compared and it was seen that the ± difference technique results in a progressively more variable estimate of SNR as the high-pass filter setting is reduced. When recording the ABR, low frequency noise is not a significant problem, particularly if a high-pass filter setting of 100 Hz is used, so the two estimators will produce similar results. However, the F_{sp} estimator should be used to avoid bias when recording the MLR (which has a high-pass filter setting of around 15 Hz).

8.1.5 The use of Bayesian averaging to acquire the MLR

A signal processing technique that was investigated in Chapter 6 was the use of weighted (Bayesian) averaging. Investigation of EEG from a relaxed subject in Experiment 1 showed the EEG variance was fairly constant, but has obvious non-stationarities arising from muscle artefacts. The standard way to deal with artefacts in AEP recording is to define an artefact rejection level for the peak-to-peak amplitude in a given epoch. If the amplitude exceeds defined limits then the epoch is not included in the average. An alternative to such a binary approach is to weight each epoch according to the variance in the epoch. Elberling and Wahlgeen (1985) investigated the use of weighted averaging to obtain the ABR. In their approach blocks of several epochs were weighted according to the reciprocal of the variance of the blocks. As the SNR for an epoch is very low, the variance of an epoch will be an estimate of the noise power in the epoch, so epochs with high variance can be considered 'noisy'. The reciprocal of the variance is therefore a measure of precision. Such an approach where data is weighted according to its precision is referred to as a Bayesian approach.

Elberling and Wahlgeen (1985) suggested that the duration of a single epoch of the ABR (around 10 ms) is too short to obtain an accurate measure of EEG variance. They therefore divided the ABR data into blocks of 250 epochs. However, the duration of an MLR epoch is around 70 ms, so a better estimate of variance can be obtained from a single epoch. Indeed, when the variance of blocks of 200 sweeps are investigated, there is little variation between sweeps, so little advantage is seen from weighting blocks of data. If the variance is investigated on a sweep-by-sweep basis, more variation is seen between epochs, suggesting the approach would be best applied to single epochs.

In Chapter 6, the data from Experiment 2 were re-analysed using Bayesian averaging on a sweep-by-sweep basis. This produced a small increase in SNR for all recordings in Experiment 2. However the magnitude of the improvement was small and a lot less than the difference in SNR between chirp and click stimulation at MLS rates found in Experiment 2. In Experiment 2, subjects were relaxed in a comfortable chair, so the amount of myogenic interference was small. A Bayesian approach might have more success when data is more non-stationary, for example when applied to data from subjects who were restless during data acquistition.

Applying the Bayesian technique to the data from subjects having general anaesthesia may be complicated by the action of the anaesthetic and muscle relaxants, which will change the variance of EEG and myogenic noise. The problem may occur at the transition from consciousness to unconsciousness. A Bayesian approach might reduce AEPs recorded when subjects were awake and noise levels were high and increase the AEP when subjects were anaesthetised and noise levels were low. The change in the AEP seen at the transition from awake to anaesthetised may therefore be less pronounced when Bayesian averaging is used (although data collected when the subject is in a steady state of anaesthesia should not be affected). Brief changes in the AEP between the awake and anaesthetised states might therefore be hidden if Bayesian averaging was applied to the data.

8.1.6 The use of ARX modelling to acquire the MLR

Several papers have described impressive results for the technique of ARX modelling to acquire the MLR (Elkfafi et al., 1997; Jensen et al., 1998). In the technique, a reference MLR (such as the average of 1000 epochs) is filtered by an ARMA filter which is calculated to produce the least squares estimate with the next recorded MLR sweep (buried in EEG noise). The filtered reference is taken as an estimate of the MLR. Somewhat surprising claims have

been made for ARX modelling such that the technique can extract the MLR on a sweep by sweep basis, rather than needing to average thousands of epochs. An assumption implicit in the technique is that an MLR filtered by a low order ARMA filter will match the MLR better than the unwanted EEG noise. The assumption has not been formally justified.

In Chapter 6 the use of ARX modelling to obtain the MLR was investigated. The ARX approach was used to extract an MLR from noise for different SNRs. The MATLAB signal processing toolbox was used to generate an ARX model. The ARX model consisted of an ARMA filter with a variable delay. A reference MLR was filtered by the ARX model to best match a noisy MLR. The noisy MLR was obtained by adding different amounts of EEG noise to a shifted version of the reference signal. The number of filter parameters and the delay was variable and the signal processing toolbox calculated the optimal filter for a number of different orders and delays. The optimal order and delay could be selected which produced the least mean squared error between the filtered reference signal and the noisy MLR. The optimally filtered reference signal was taken as an ARX estimate of the MLR. The ARX estimate corresponded well with the shifted MLR when SNR was favourable (variance SNR of 1 or 2). The delay in the MLR was therefore correctly identified. However as SNR decreased, the match between the ARX estimate and the shifted MLR became progressively worse. At variance SNR 0.1, the match between ARX estimate and the target MLR was poor.

From these results, it appears that the ability of ARX modelling to extract a MLR from a noisy signal have been exaggerated in some papers. The approach works for favourable SNR, but when SNR is poor, the ARX model simply matches the noise which the MLR is embedded in. A possible explanation for the claims that have been made for ARX modelling is that the AEP recorded by the researchers was the post-auricular muscle (PAM) response and not the MLR. The PAM is much larger in amplitude than the MLR (tens of μV instead of 1 μV) and hence SNR is better than for the MLR. As found in a pilot study for Experiment 1, PAM activity can be increased by poor reference electrode placement (e.g. using a mastoid reference instead of a non-encephalographic reference). The figures shown in the paper by Jensen et al (1997) appear to show similar waveforms to PAM recordings from the Experiment 1 pilot. PAM recording would result in a good SNR being obtained in a small number of sweeps and hence the ARX model would be able to estimate the response quickly. However the response estimated would not be the MLR.

8.1.7 A clinical investigation of the effect of anaesthesia on the MLR evoked with MLS-chirps

Experiment 4 was a clinical investigation of the effect of anaesthesia on the MLR obtained using MLS-chirp stimulation at 167 chirps/s (the optimal stimulation paradigm from Experiment 2). It was hoped that the improved SNR obtained by using such a stimulation technique would reduce the time required to obtain the MLR and/or make changes in the MLR more obvious. Previous studies have suggested that the effect of anaesthesia on the MLR is to induce a latency shift.

It was problematic to obtain good AEP data in the environment of the anaesthetic room. Mains frequency interference from electrical equipment, lighting and heating in the rooms was of such large amplitude that data from some subjects was clipped and could not be used. The interference problem was eventually solved by using a battery powered preamplifier with short electrode leads and by reducing the amplifier gain. In addition to the interference problem, one set of data was lost due to software problems and another set of data had very poor SNR due to high levels of ECG interference (a problem with placing the reference electrode on the sternum). Although nine subjects consented to take part in the study, only four good sets of data were obtained. Audiometry demonstrated that no subjects had normal hearing, and the MLR recordings were reduced in amplitude compared to the data from otologically normal subjects in Experiments 1 and 2. Furthermore, the average subject age was around 60 and AEP amplitude reduces with age.

As subjects were anaesthetised, electrophysiological noise levels decreased. SNR correspondingly increased. A moving average of 1000 epochs was used to obtain the MLR with 10% artefact rejection. This took 100 s to fully update and resulted in a rms SNR between 1.5 and 2.5 once subjects had been anaesthetised. Increasing the number of averages would improve SNR, but would make the moving average less responsive to rapid changes in the MLR.

A change in the latency of the N_b wave with anaesthesia, such as has been reported by Thornton et al (1993), was not seen. Rather a change occurred in the amplitude of the MLR. In three of the four good sets of data obtained, the MLR showed a categorical increase in amplitude as subjects started to respond on the isolated forearm technique and then showed a categorical decrease when subjects stopped responding. A graded change in the MLR that might reflect depth of anaesthesia was not seen. Rather it would appear that a categorical change in the MLS-chirp evoked MLR reflects conscious awareness. In three of the four subjects from whom good data were obtained, the MLR variance reaching 90% of that of a baseline measure would appear to coincide with the subject responding on the isolated forearm technique. In one of the four subjects, a categorical change in the MLR was not seen,

although it is not clear whether this was due to difficulties in recording the MLR, or due to an underlying problem with the technique.

Due to the data acquisition difficulties in the study, the results should be treated with caution. In order to verify the findings of this study, there is need for a more controlled study using a larger number of otologically normal subjects in a better recording environment. Problems with data acquisition might be improved if notch filtering to exclude mains frequency interference and a display of SNR post filtering were implemented in the acquisition software in real time.

The data from the study appear to indicate that the MLR obtained with MLS chirps shows a categorical change with state of arousal. It would appear to have potential as an indicator of conscious awareness during surgery, but would not be suitable as an indicator of anaesthetic depth. (i.e. it would not reflect the concentration of anaesthetic in the brain). Further research in a more controlled environment is necessary to confirm this finding. A possibility is that the categorical change found in this study was a consequence of using high MLS stimulation rates to obtain the MLR, in combination with the chirp stimulus, which has a longer duration than the click. It would therefore be useful to compare the effects of anaesthetic on the MLR evoked using MLS-chirp stimulation to that evoked using conventional click stimulation.

8.2 Further Research

A number of areas for further research have been identified.

The chirp stimulus used was the 'approximate' chirp of Dau et al (2000). This chirp was designed using de Boer's linear model of the cochlea. However, it is know that the cochlea is not linear, particularly at low sound intensities where the active mechanism of the cochlea affects the propagation of the travelling wave. Whilst the 'approximate' chirp increases ABR magnitude compared to a click stimulus at levels of 60 dB SL, less benefit is seen at lower levels. The chirp may not be optimised for lower levels. With further research it might be possible to optimise the chirp stimulus for different sound intensities, for example by using non-linear cochlear models. It might also be possible to compare the frequency-delay characteristics of the chirp with OAE data, such as tone burst OAEs, in order to optimise the frequency-delay characteristics. The frequency spectrum of the 'approximate' chirp is weighted to low frequencies. Dau compensated for this weighting by generating a 'flat spectrum' chirp with equal acoustic energy across the frequency range. However, the action of the chirp might be improved by compensating for the hearing sensitivity of the ear. For

example an A-weighted chirp might better stimulate the entire cochlea than the 'approximate' or 'flat spectrum' chirps.

It was problematic to generate band-limited chirp stimuli with the same frequency-delay characteristics as the chirp used by Dau et al (2000) as spectral splatter meant that the stimuli could not be made frequency specific. An alternative way to obtain a frequency-specific ABR with a chirp stimulus would be to present the chirp in the presence of notched noise (broad-band noise with a notch between two frequencies removed). Wegner and Dau (2002) investigated the effect of a chirp in notched noise at high stimulus levels, but they did not address the question of whether a chirp in notched noise can give a better threshold estimate than can be obtained using tone-burst stimulation. This is an area for further study. Steady state AEPs offer an alternative method of choice to obtain an objective audiogram in clinical practice.

In Experiment 2 the chirp stimulus was found to produce greater MLR amplitude than the click stimulus at high MLS rates, but not at conventional stimulation rates. (An increase in amplitude for the ABR with the chirp was seen at all rates.) The most likely explanation for this finding is that rate adaptation is different for chirp than click stimuli. A pilot study showed results consistent with such an effect. However a larger study is needed to confirm a different rate adaptation function for chirps than for clicks.

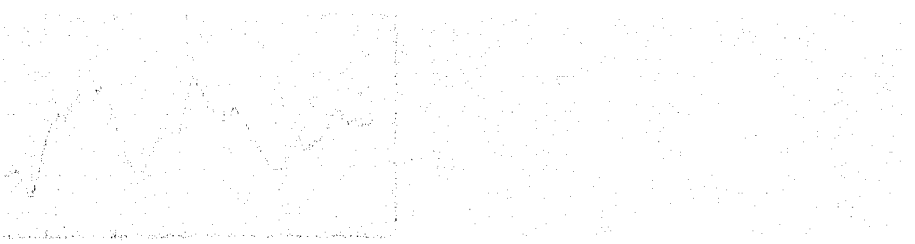
As the 'approximate' chirp is designed to stimulate a wider frequency region of the cochlea than a click stimulus, AEPs obtained with a chirp stimulus may be more robust to hearing loss than click evoked AEPs. This might be an important consideration if AEPs are to be obtained from subjects with some degree of hearing loss for clinical monitoring (for example, using the MLR to estimate depth of anaesthesia. In Experiment 4, none of the subjects who took part in the study had normal hearing). The sensitivity of the chirp evoked AEP to hearing loss is therefore an area for further investigation.

The results from Experiment 4 indicate that there is a categorical change in the MLS-chirp evoked MLR with anaesthesia. The MLR might be a suitable indicator of conscious awareness during anaesthesia. However, obtaining good quality data in the anaesthetic room and with the target population was problematic. Further work is necessary to confirm the findings of Experiment 4. A study performed on otologically normal subjects in controlled recording conditions is necessary to confirm the finding of a categorical change in the response with anaesthesia.

There is a possibility that the categorical change in the MLR found in Experiment 4 was a consequence of the high MLS rates used to elicit the MLR and that such a change would not be seen for conventional click stimulation. This question would best be answered by a normative experiment comparing the effects of anaesthetic on the MLR evoked with MLS-chirps to that evoked with conventional click stimulation.

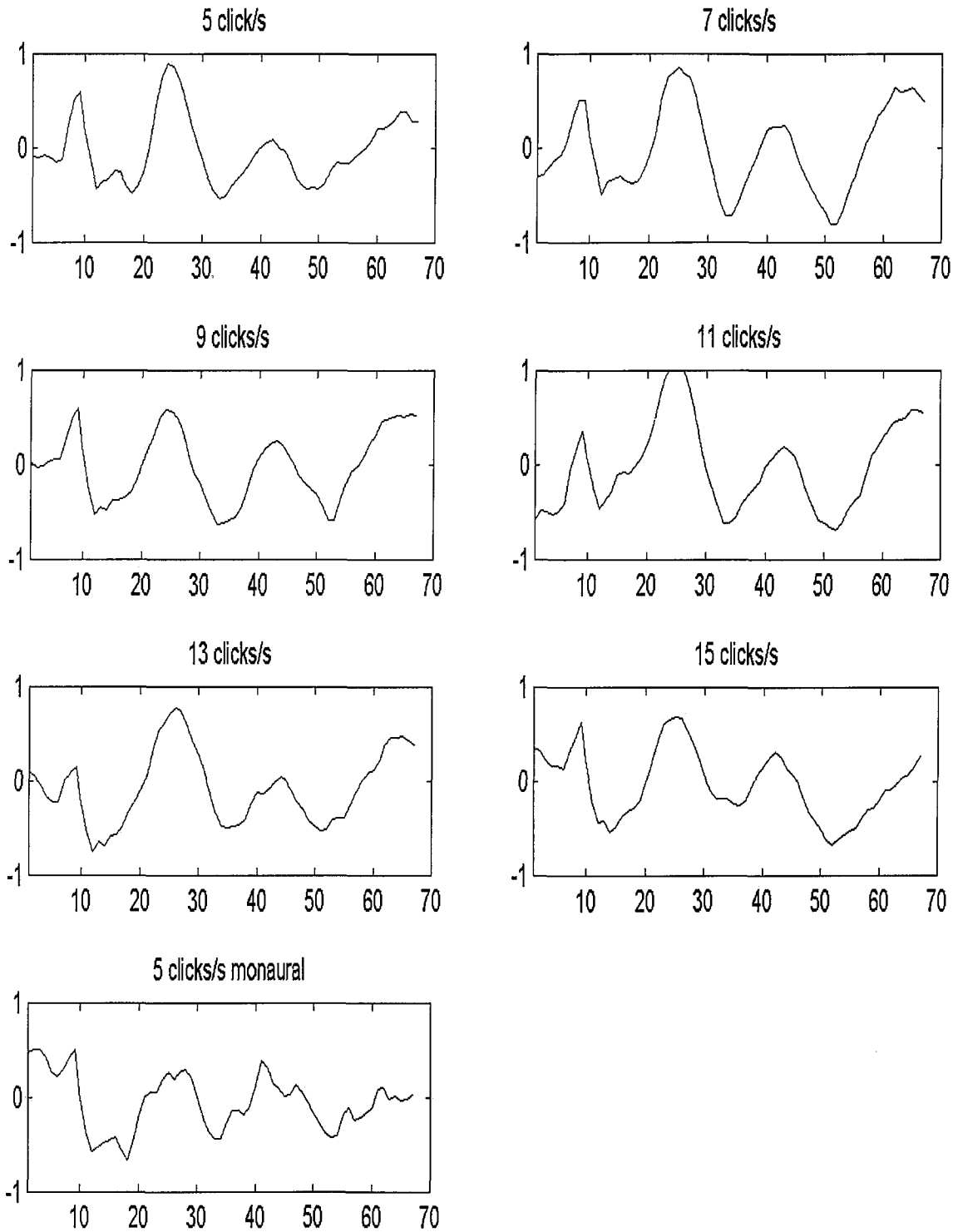
In Experiment 4 it was found that the variance of the MLR, not the latency of the N_b wave, appeared to change significantly with conscious awareness. However, the variance of the response may not be the parameter most sensitive to awareness; for example, higher order statistics may be more sensitive and further research should be undertaken to identify the best parameter. Also the effects of different anaesthetics on the MLS-chirp evoked MLR should be investigated.

The size of the population for which the MLR can be used as an indicator of conscious awareness needs to be better identified. The technique might well have limited application to children or patients with significant hearing loss. If the finding of a categorical change in the response with anaesthesia is confirmed, a large clinical study would be needed to assess the effects further of hearing loss or age on the MLS-chirp evoked MLR. In addition to this, the use of other techniques to indicate conscious awareness (or depth of anaesthesia), such as the Bispectral Index, could be compared with the MLR evoked with MLS-chirps.

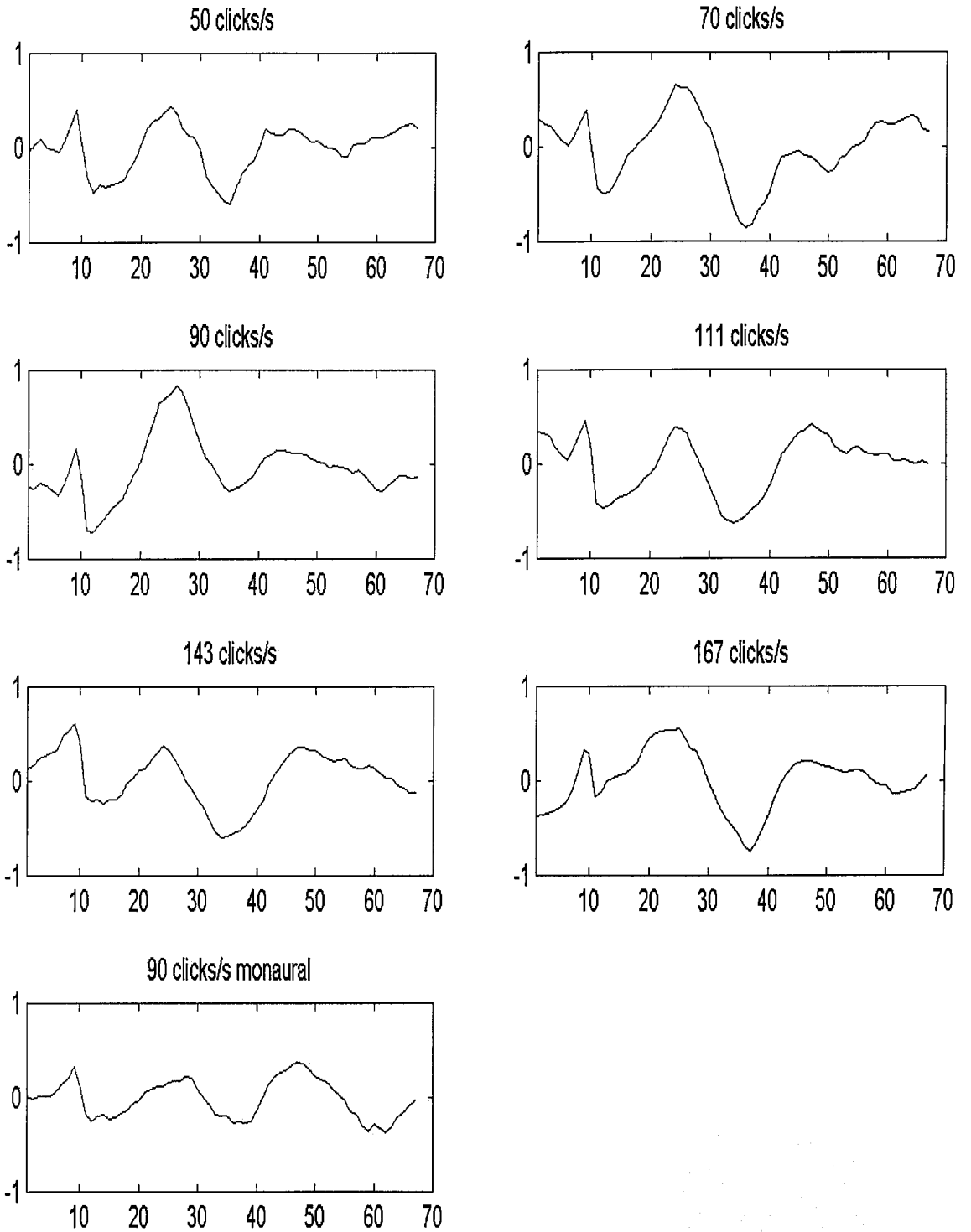


Appendix 1

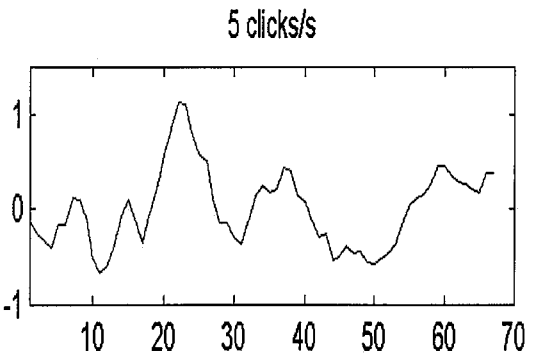
Average MLR responses from Group 1 of Experiment 1 for conventional stimulation rates. 14 subjects. Horizontal axis : time in ms, vertical axis : amplitude in μV

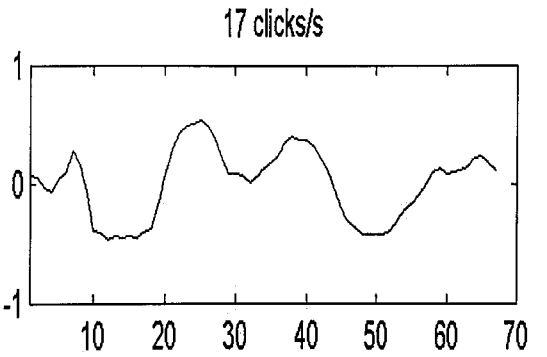


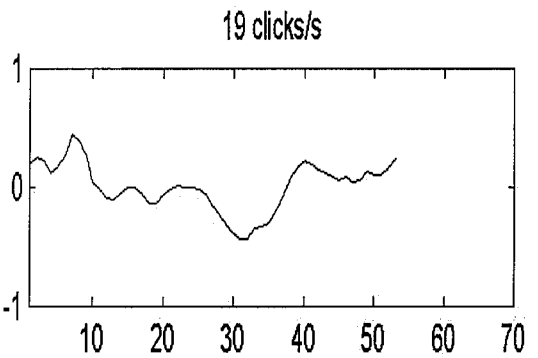
Average MLR responses from Group 1 of Experiment 1 for MLS stimulation rates. 14 subjects. Horizontal axis : time in ms, vertical axis : amplitude in μV



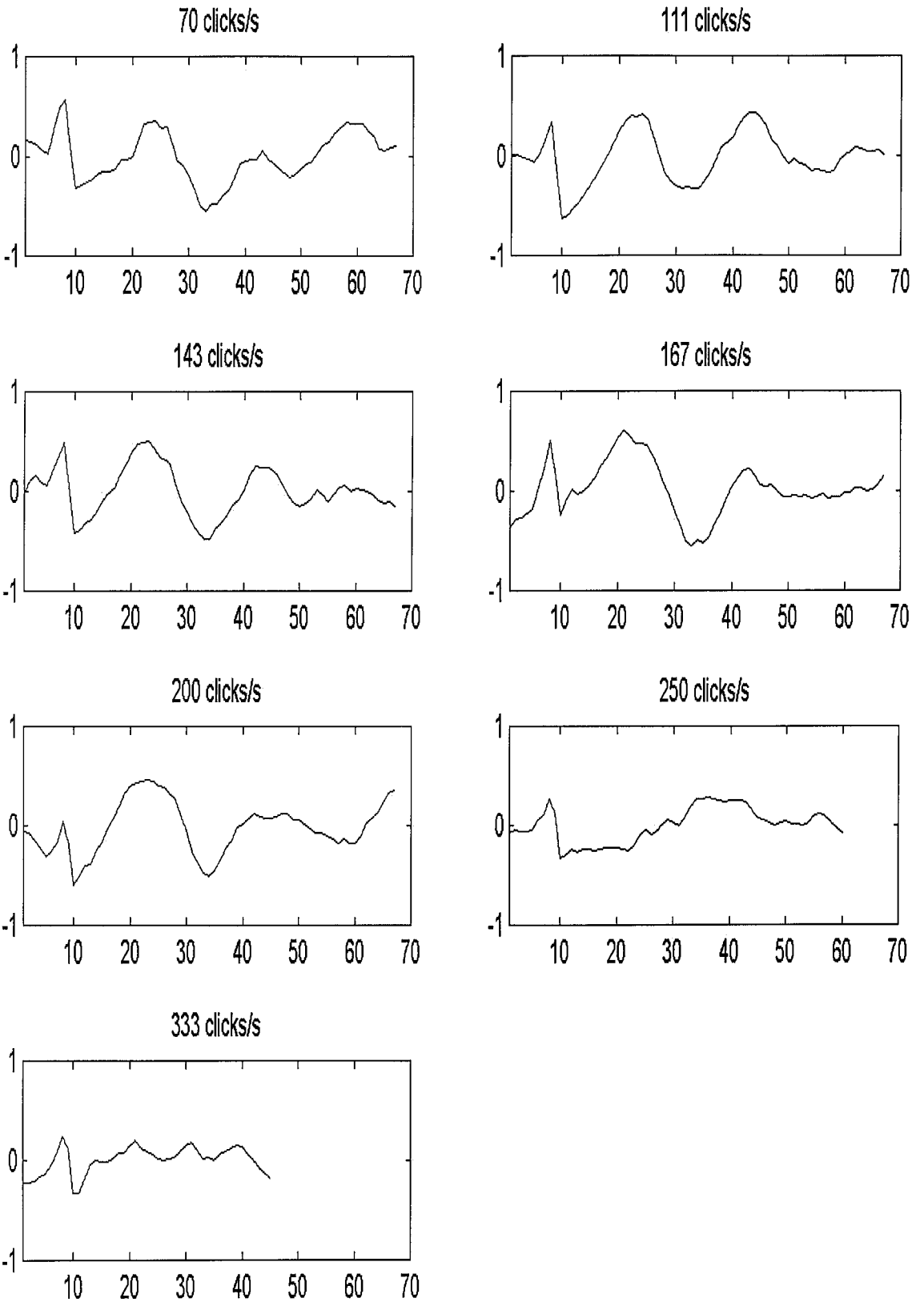
Average MLR responses from Group 2 of Experiment 1 for conventional stimulation rates. 11 subjects. Horizontal axis : time in ms, vertical axis : amplitude in μV





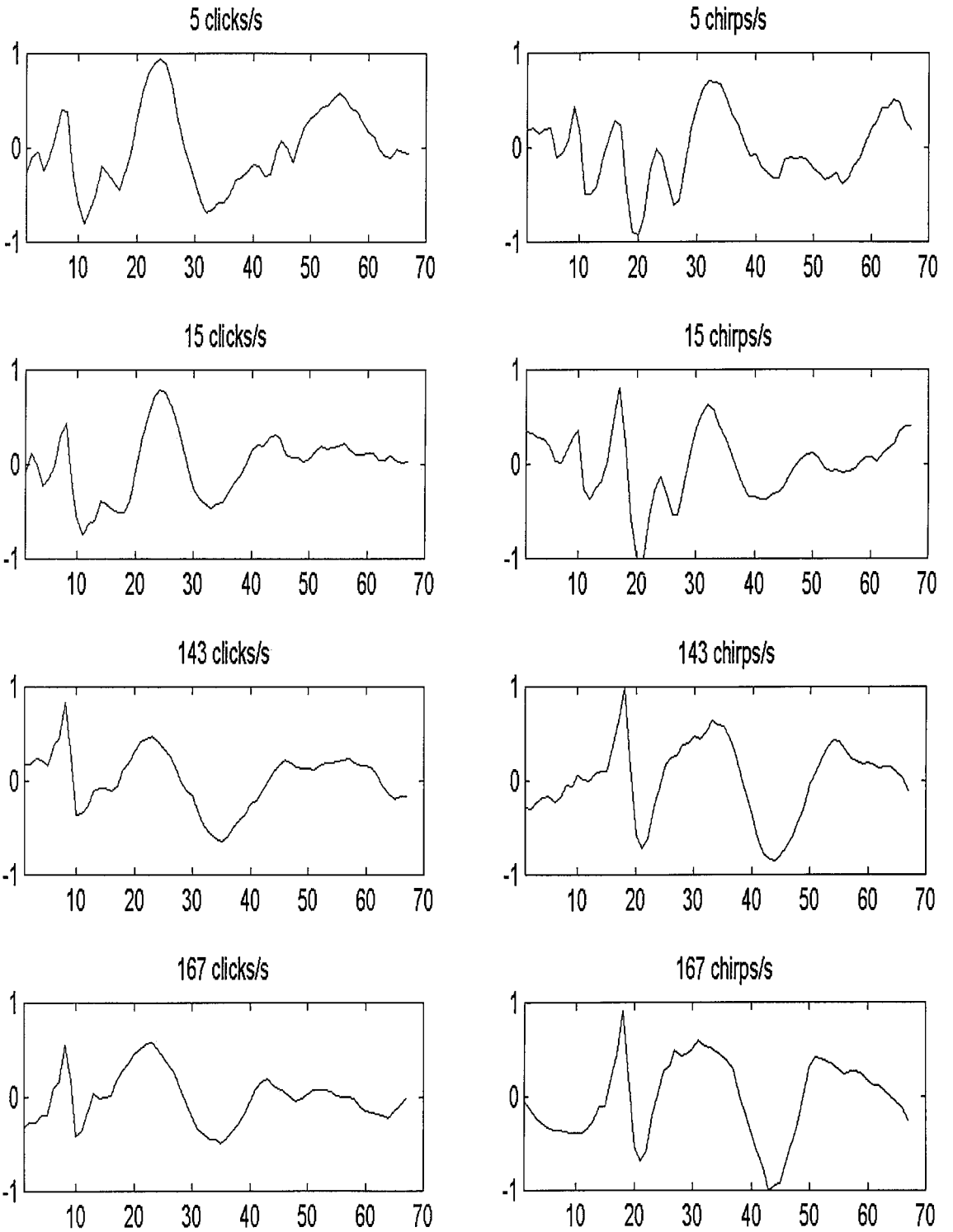


Average MLR responses from Group 2 of Experiment 1 for MLS stimulation rates. 11 subjects. Horizontal axis : time in ms, vertical axis : amplitude in μV



Appendix 2

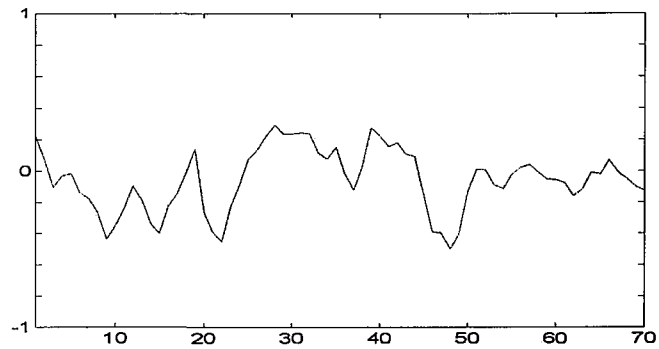
Average MLR responses from Experiment 2. 10 subjects. Horizontal axis : time in ms, vertical axis : amplitude in μV



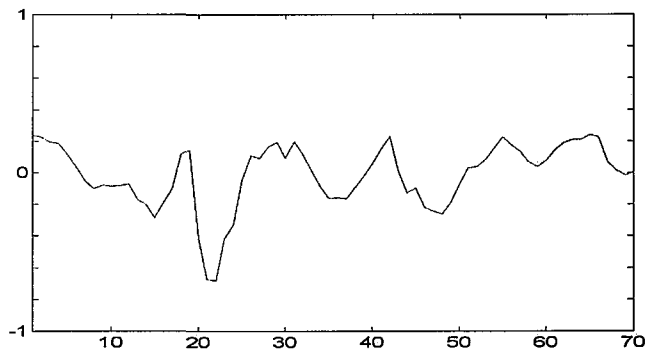
Appendix 3

MLR waveforms from Experiment 4 for PB, JC and DM. Horizontal axis : time in ms, vertical axis : amplitude in μV. All recordings made with 167 chirp stimuli/s.

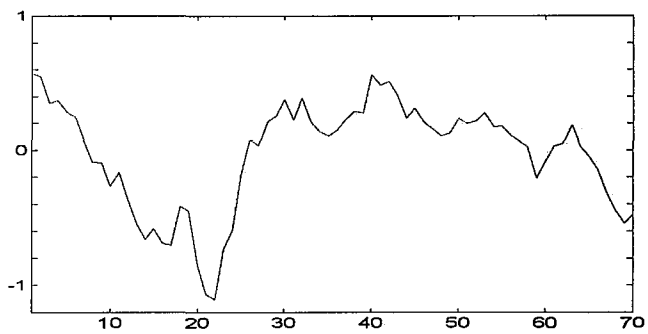
PB PRE ANAESTHESIA



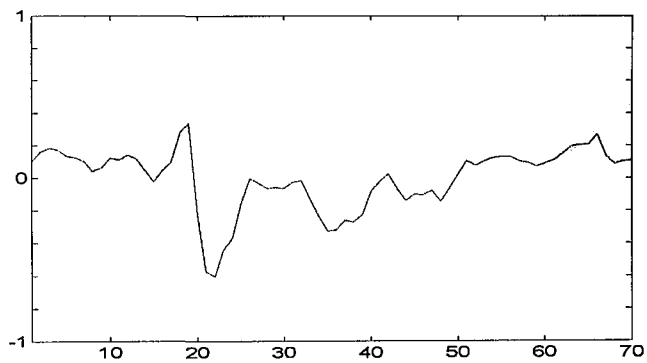
PB ANAESTHETISED



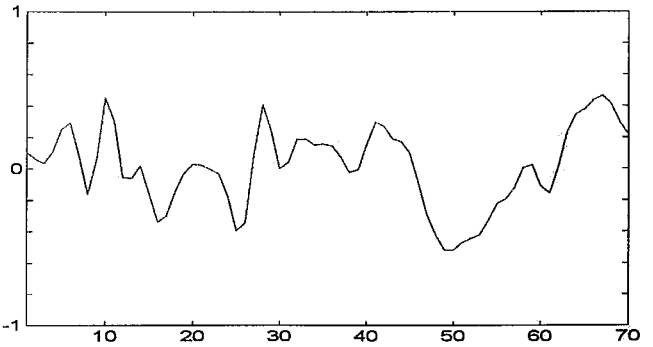
PB AWAKE



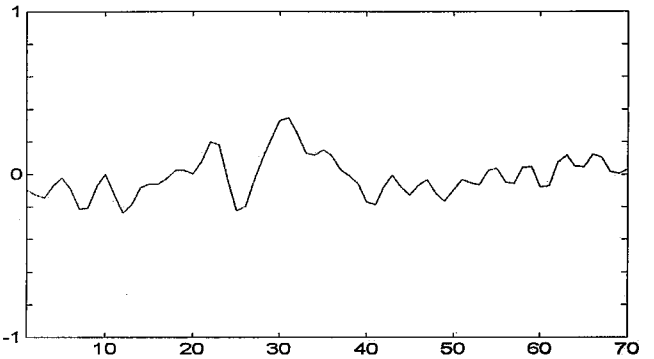
PB ANAESTHETISED 2



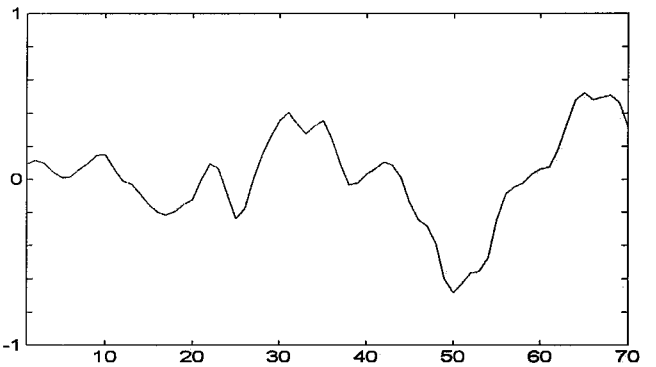
JC PRE ANAESTHESIA



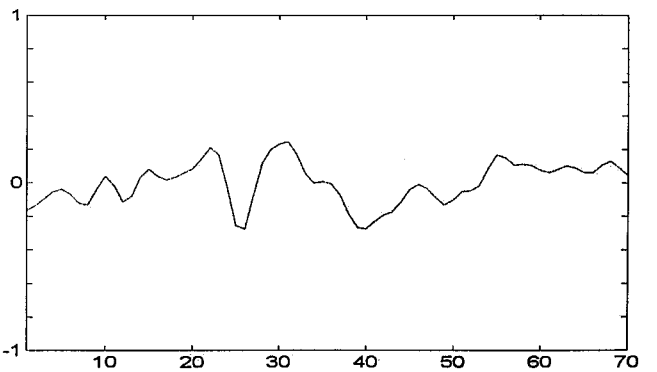
JC ANAESTHETISED



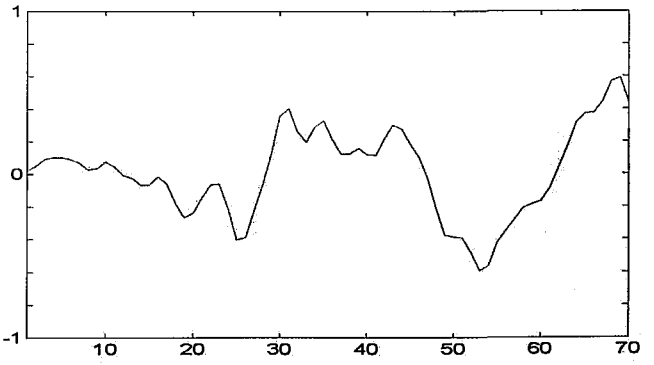
JC AWAKE (1)



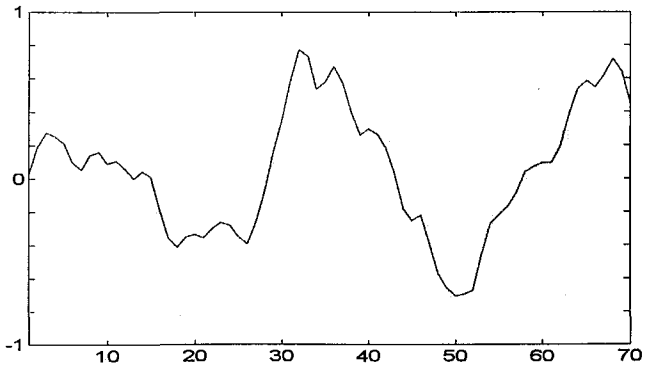
JC ANAESTHETISED (2)



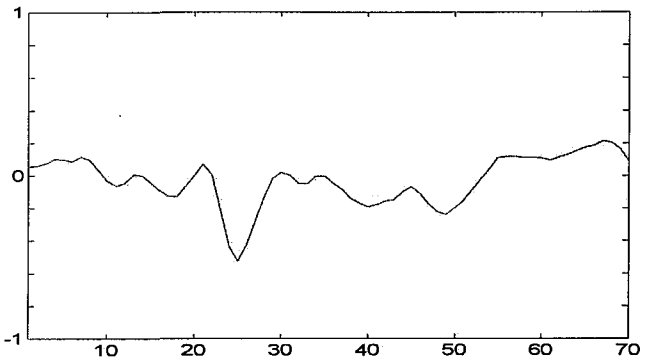
JC AWAKE (2)



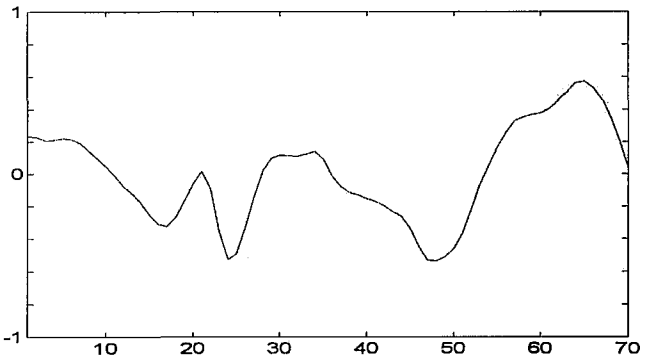
DM PRE ANAESTHESIA



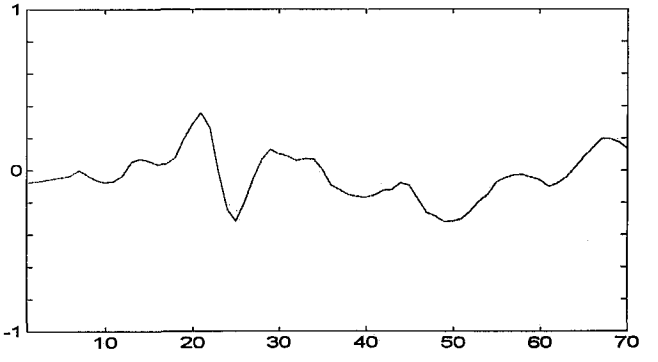
DM ANAES



DM AWAKE



DM ANAESTHETISED (2)



Appendix 4

Screening questions used for Experiments 1,2 and 3

Do you think that your hearing is normal?

Have you ever had any persistent problems with your ears or hearing, for example discharging ears or earache?

Do you suffer from troublesome tinnitus?

Have you been exposed to loud noises, for example at work, gunfire or explosives?

Are you suffering from or recently had a cold?

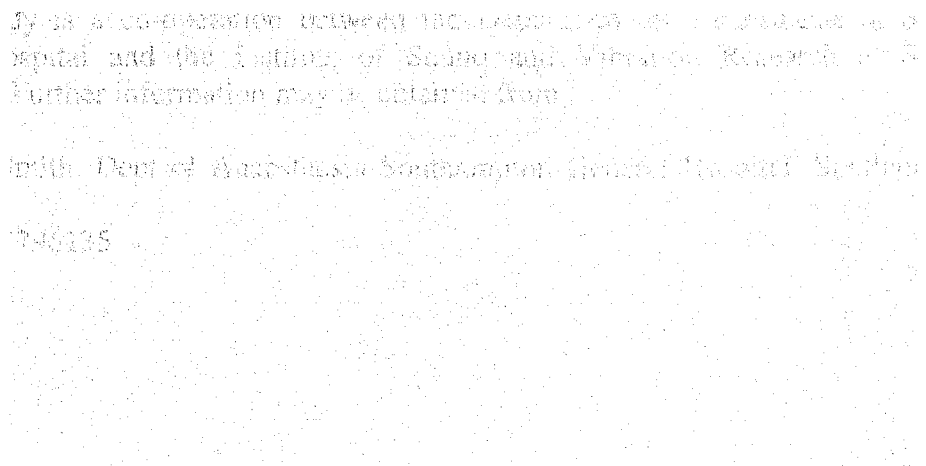
Have you ever had attacks of dizziness or loss of balance related to vestibular (balance) disorder (if known)?

Have you ever suffered from high or low blood pressure?

Have you ever had an epileptic attack with convulsions or loss of consciousness?

Have you ever suffered with heart trouble?

Are you receiving any medical treatment or medication that may affect your hearing?



Appendix 5

Patient information sheet for Experiment 4

Study title : Evaluation of maximum length sequence stimulation patterns for derivation of the auditory evoked response.

The aim of this research is to validate the use of the auditory evoked response (AER) as a measure of the 'depth' of anaesthesia. During your operation your anaesthetist ensures that you do not experience any pain and that you are not aware of what is happening around you. However, in rare cases it is possible that a patient may hear sound during their operation which they are able to remember afterwards, because we cannot, at present, measure how deeply anaesthetised our patients are. We have been working to develop a method of measuring depth of anaesthesia using the auditory evoked response.

The technique involves measuring brain activity under anaesthesia by fixing three small electrodes to your scalp before you go to sleep. The electrical response of the brain to a series of clicks played into the ears through small earpieces forms the basis of the AER. During this study we will measure your AER as you are anaesthetised, enabling us to determine criteria within the AER which indicate adequate anaesthesia. For the purpose of the study the depth of anaesthesia will be varied as you are anaesthetised to look for corresponding changes in the AER. We will also perform a hearing test before you are anaesthetised.

The AER technique does not involve any additional risk to you. Your treatment will be the same as for all other patients for comparable operations, but your anaesthetic will be administered one hour earlier in order that we can complete the study before your surgery starts.

Participation in this study is entirely voluntary, and you may withdraw your consent to participate at any time, even after you have agreed to take part.

This is study is a co-operation between the Department of Anaesthesia at Southampton General Hospital and the Institute of Sound and Vibration Research at Southampton University. Further information may be obtained from :

Dr David Smith, Dept of Anaesthesia Southampton General Hospital, Southampton SO16 6YD
Tel : 02380 796135

Appendix 6

MATLAB 'm' files used in the experiments

1) 'avr.m'

Averages data and performs artefact rejection.
Data is placed into an array 'A1'
An artefact level is calculated to give 10% rejection ± 2%

```
% inputs : fs=sample rate, t=time of average in s, d=input signal
%          reject=artefact rejection level in 1401 scale units

L=length(d);
N=L/(t*fs)  % no.of sweeps
sweep=t*fs; % length in ms of a sweep
accept=0;

for j=1:N
% artefact rejection, accept = num of good sweeps
      current=d((((j-1)*sweep)+1):(j*sweep))';
      if max(current)<reject
            if min(current)>-reject
                  accept=accept+1;
            end
      end
end

% include adjustment of reject to make sweep rejection 10% +/- 2%
paccept=accept/N
if paccept>0.92
      clear sweep accept
      reject=reject-250
      avr
end

if paccept<0.88
      clear sweep accept
      reject=reject+250
      avr
end

% averaging loop
accept=0;
for j=1:N;
% include artefact rejection, accept = num of good sweeps
% j = num of current sweep
current=d((((j-1)*sweep)+1):(j*sweep))';
if max(current)<reject
      if min(current)>-reject
            accept=accept+1;
            A1(accept,:)=current;
      end
end
end
average=(mean(A1));
```

2) 'Deconv.m'

Deconvolve an MLS order 4 array of sweeps 'A1' with artefacts rejected i.e.the output of 'avr.m'

```
% A1 is A with artefacts rejected i.e. only good sweeps
% t = time of sweep (ms), fs=sample rate
% N = number of averages in avr, accept = number of good sweeps
order = 4;
array=zeros(accept,(t*fs));
length = (2^order)-1
segment=(((t*fs)))/length
sequence=[1 1 1 1 0 1 0 1 1 0 0 1 0 0 0]
s=[1 1 1 1 -1 1 -1 1 1 -1 -1 1 -1 -1 -1]
for i = 1:length
      mat=A1(:,(((i-1)*segment)+1):(length*segment));
      mat1=A1(:,1:((i-1)*segment));
      mat2=[mat mat1];
      mat2=mat2*s(i);
      array=array+mat2;
      clear mat mat1 mat2
end
array=array/8;
```

3) 'fspcalc.m'

Calculates the Fsp statistic (rms) using either the array of good sweeps 'A1' from avr.m, or the deconvolved 'array' from 'deconv.m' if MLS was used (flag 'mls'=1). Note the position of the single point and the window of the average used depends on whether a chirp or click stimulus was used. For clicks, s.p.=35ms, window=25-45ms, for chirps, s.p.=45ms, window = 35-55ms.

```
% A1 is the array of good sweeps
% array is the good sweeps deconvolved
% mls on or off, chirp on or off

if mls==0
   if chirp==0
   % point contains raw data of a point at 35ms after stimulus
   point=A1(:,35);
   % sweep is average between 25 and 45,s after the stimulus
   average=mean(A1);
   sweep(1:21)=average(25:45);
end
end

if mls==1
   if chirp==0
   point=array(:,35);
   average=mean(array);
   sweep(1:21)=average(25:45);
end
end

if mls==0
   if chirp==1
   point=A1(:,45);
   average=mean(A1);
   sweep(1:21)=average(35:55); % CHIRP
end
end

if mls==1
   if chirp==1
   point=array(:,45);
   average=mean(array);
   sweep(1:21)=average(35:55);
end
```

```
end

fsp=((std(sweep)^2)*accept)/(std(point)^2);
% square rooted to give amplitude SNR
fsp=fsp^0.5
```

4) 'plusmin.m'

Calculates the ± difference statistic for an array of good sweeps 'A1' (note this is just the statistic, not a direct measure of SNR

```
% calculate +/- difference for array of good sweeps
for i=1:(size(A1,1)/2)
   sumarr(i,:)=A1(i*2,:)+A1(((i*2)-1),:); % add alternate sweeps
   diffarr(i,:)=A1(i*2,:)-A1(((i*2)-1),:); % subtract alternate sweeps
      plusmin(i)=std(mean(sumarr))/(std(mean(diffarr))
end
```

5) 'bmchirp.m'

Kindly supplied by Torsten Dau. This calculates a chirp which compensated for dispertion on the basilar membrane based on the linear cochlear model of DeBoer. Either the 'approximate chirp' with constant amplitude, or a flat spectrum chirp is generated.

```
function sig = bmchirp(f1,f2,fs,len,flat)
%  BMCHIRP generates optimized Chirp described in Dau et al. (2000)
%
%  sig = bmchirp(f1,f2,fs,len,flat)
%  generates the ``approximated'' optimized chirp developed by Dau et al.
%  (2000). This chirp compensates for travel-time differences along the
%  cochlear partition. The equations were derived on the basis of a linear
%  cochlea model (de Boer, 1980).
%
%  A vector sig is returned. The vector is filled with zeros to match the
%  length of len. If len equals zero the minimum length for the chirp will
%  be calculated.
%
%  f1   : lower (start) frequency of the chirp (in Hz)
%  f2   : upper (stop) frequncy of the chirp (in Hz)
%  fs   : sampling frequency in Hz (standard: 25000 Hz)
%  len  : length of the chirp in s (standard: 0 s)
%  flat: flat spectrum (1) or not (0) (standard: 0)
%  sig  : the resulting chirp (output)
%
%  This script is based upon the article by
%  T. Dau, O. Wegner, V. Mellert and B. Kollmeier (2000): "Auditory
%  brainstem response with optimized chirp signals compensating
%  basilar-membrane dispersion." J Acoust Soc Am 107(3): 1530-1540.
%
%  Derivation of traveling wave velocity:
%  E de Boer (1980): "Auditory physics. Physical principles in hearing
%  theory I", Phys Rep (62), 87-274.
%
%  Cochlear frequency-position function:
%  DD Greenwood (1990): "A cochlear frequency-position function for
%  several species -- 29 years later", J Acoust Soc Am (87), 2592-2605.
%
% (c) O. Wegner, T. Dau 09/96
% $Revision: 1.7 $  $Date: 2001/02/19 08:18:15 $

% All numbered equations refer to the corresponding equations in the
% JASA article by Dau et al. (2000).
```

```
% check for f1 and f2
if ( nargin < 2 )
  help bmchirp
  return
end

if (f1 > f2)
  error('f1 > f2: not allowed');
end

% standard values:
len_std = 0.0;        % standard value for len (means minimum length)
flat_std = 0;         % standard value for flat-spectrum switch
fs_std = 25000.0;     % standard value for fs

% check for flat
if (exist('flat') ~= 1)
  flat = flat_std;
elseif isempty(flat)
  flat = flat_std;
end

% check for len
if (exist('len') ~= 1)
  len = len_std;
elseif isempty(len)
  len = len_std;
end

% check for fs
if (exist('fs') ~= 1)
  fs = fs_std;
elseif isempty(fs)
  fs = fs_std;
end

len = ceil(len*fs);      % len in samples (rounded towards next integer)
t0 = bmtime(0);          % time for 0 Hz (reference)
t1 = t0 - bmtime(f1);       % time for f1
t2 = t0 - bmtime(f2);       % time for f2
samples = ceil((t2 - t1) * fs);   % samples needed (rounded towards next
integer)
if (len == 0) len = samples; end % len = 0 => optimal fill
if (samples > len)       % is len long enough?
  error(sprintf('at least %f s are needed',samples/fs));
end
t = t1 : 1/fs : t2;      % time-axis
sig = amplitude(t,flat) .* sin(instphas(t)-instphas(t1));   % generate
chirp
sig = [sig zeros(1,len-length(t))];          % fill up with zeros

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%
function time = bmtime(f)
%BMTIME   traveling time on the basilar membrane
%
%  time = bmtime(f)
%  returns the time (in s) a pulse needs to get to the
%  position on the basilar membrane which represents the
%  frequency f (in Hz).
%
% (c) O. Wegner, T. Dau 09/96

% Constants:
% from de Boer (1980):
```

```
C0 = 10^9;           % 10^9 g s^(-2) cm^(-2) == 10^4 N cm^(-3)
h = 0.1;          % cm
rho = 1.0;           % g cm^(-3)
alpha = 3.0;            % 1/cm
% from Greenwood (1990):
a = 0.006046;           % 1/Hz
c = 1.67/log(10);       % cm
L = 3.485;           % cm

beta = 2/alpha*sqrt(2*rho/(h*C0));  % s

time = beta*((a*f+1).^-(alpha*c/2)*exp(L*alpha/2)-1); % rf. eq. (13)

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%
function phi = instphas(t)
%INSTPHAS instantaneous phase
%
%  phi = instphas(t)
%  calculates the instantaneous phase at a given time t
%  (in s) for a stimulus that should compensate the
%  spatial dispersion on the basilar membrane. It is used
%  by the function bmchirp.
%
% (c) O. Wegner, T. Dau 09/96

% Constants:
%from de Boer (1980):
C0 = 10^9;     % 10^4 N cm^(-3)
h = 0.1;    % cm
rho = 1.0;     % g cm^(-3)
alpha = 3.0;      % 1/cm
% from Greenwood (1990):
a = 0.006046;           % 1/Hz
c = 1.67/log(10);       % cm
L = 3.485;           % cm
%
t0 = bmtime(0);            % time for 0 Hz (reference)
beta = 2/alpha*sqrt(2*rho/(h*C0));
gamma = -2/(alpha*c);
tau0 = t0+beta;

phi = -2*pi/a * (t+ ( (tau0-t).^(gamma+1) - tau0^(gamma+1) ) / ...
                    ((beta*exp(alpha*L/2))^gamma * (gamma+1)) );


%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%
function amp = amplitude(t,o_flat)
% AMMPLITUD calculates the amplitude factors
%
%  amp = amplitude(o_flat)
%  calculates the tiem dependent amplitude factors for the normal chirp
%  (o_flat = 0) or the flat-spectrum chirp (o_flat=1).
%
%  t  time axis
%  o_flat   flat-spectrum (1) or not (0)
%
% (c) O. Wegner 11/00

% Constants:
%from de Boer (1980):
C0 = 10^9;     % 10^4 N cm^(-3)
h = 0.1;    % cm
rho = 1.0;     % g cm^(-3)
alpha = 3.0;      % 1/cm
```

```
% from Greenwood (1990):
a = 0.006046;           % 1/Hz
c = 1.67/log(10);       % cm
L = 3.485;          % cm
%
t0 = bmtime(0);             % time for 0 Hz (reference)
beta = 2/alpha*sqrt(2*rho/(h*C0));
gamma = -2/(alpha*c);

if o_flat,
  amp = sqrt(1/a*( -gamma*exp(-L*alpha/2)/beta* (exp(-L*alpha/2)*(1+(t0-
t)/beta)).^(gamma-1) -1));
  amp = amp / max(amp);
else
  amp = 1;
end
```

6) 'Bayes.m'

Weights each sweep according to the variance of each sweep to generate the array 'B1'. The resulting array is then scaled by the sum of the reciprocal variances.

```
% A1 is the array of good sweeps
for n=1:size(A1,1);
   varsweep=var(A1(n,1:(fs*t)));
   B1(n,1:(fs*t))=A1(n,1:(fs*t))/varsweep; % divide sweep by var sweep
   b(n)=1/varsweep; % sum of reiprocal variances
end
B1=B1*size(A1,1)/sum(b); % normalise - * num sweeps / sum reciprocal vars
average=mean(B1);
```

7) 'mls.m'

Generates an mls sequence using a shift register with 2 taps. Output is 'mls'. The user is asked to choose the length of the sequence and the position of the 2nd tap (the first tap is fixed at the end of the register).

```
% length L, tap b (integer)

L=input('What length is the shift register?');
a=L;
b=input('where is the tap? (distance from end)');

% start with all 1's in register
for i=1:L
   register(i)=1;
end

% loop for length of sequence
% shift the register and use xor on taps to generate new first bit
for i=1:((2^L)-1)
   mls(i)= register (L);
   for j=1:(L-1)
      temp(j+1)= register (j);
   end
   temp(1)=xor(x(a),x(b));
   register =y;
end
```

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