Chapter 2

BACKGROUND REVIEW

Modern medicine increasingly uses electrical stimulation of nerve tissue to help patients regain lost functionality (Rattay, Resatz, Lutter, Minassian, Jilge and Dimitrijevic, 2003). Computational models aid in enhancing understanding of the behaviour of the electrically stimulated nerve fibre. In the cochlear implant research field much research is being done to unravel the secrets of the way the auditory system of a person with profound hearing loss translates an input sound signal presented through electrical stimuli into a perceptible sound (see for example Cohen *et al.*, 2003; Macherey, van Wieringen, Carlyon, Deeks and Wouters, 2006). Especially, a better understanding of the way the implanted auditory system decodes the temporal information carried in speech needs to be gained before improved implants can be developed.

Computational models of the ANF can be divided into physiologically based (Colombo and Parkins, 1987; Frijns, Mooij and ten Kate, 1994; Rubinstein, 1995; Matsuoka *et al.*, 2001; Rattay *et al.*, 2001b; Rubinstein, Miller, Mino and Abbas, 2001; Morse and Evans, 2003; Briaire and Frijns, 2005) and phenomenological ANF models (Shannon, 1989; Bruce, White, Irlicht, O'Leary and Clark, 1999b; Miller, Abbas and Rubinstein, 1999a; Zhang, Heinz, Bruce and Carney, 2001; Carlyon, van Wieringen, Deeks, Long, Lyzenga and Wouters, 2005; Macherey *et al.*, 2007). These models can be further subdivided into deterministic (for example Frijns *et al.*, 1994; Rattay *et al.*, 2001b; Briaire and Frijns, 2005) and stochastic models (for example Bruce *et al.*, 1999b; Rubinstein *et al.*, 2001; Macherey *et al.*, 2007).

The present study focuses on the development of a physiological, deterministic model based on the Rattay *et al.* (2001b) cable model, but with human morphometric and physiological data replacing the corresponding squid data. In this chapter a background argument is presented, which is necessary for developing such a model. Physiologically based deterministic models of both animal and human are presented, together with the temperature dependence of parameters. This is followed by an overview of the morphometric and physiological properties of the human peripheral Type I ANF.

The developed model will be verified against experimentally measured temporal characteristic data. Most of the earlier measurement studies centred on observations from single fibres in cats and guinea-pigs, while more recent studies increasingly made use of gross ensemble observations through ECAP measurements. The measurement of ECAPs can be used to examine the extent to which psychophysical measurements reflect the amount of neural excitation spread (Cohen *et al.*, 2003; Miller, Abbas, Nourski, Hu and Robinson, 2003). The development of a comprehensive model to simulate ECAPs falls outside the scope of this study. However, ECAP profile widths can be used to estimate stimulus attenuation and hence the extent of neural excitation spread inside the cochlea. Lastly an overview of the main temporal characteristics touched upon in this study is provided. Additional background information relevant to specific topics is provided in Chapters 3 to 7 when the respective topics are discussed.

2.1 PHYSIOLOGICALLY BASED MODELS

2.1.1 Animal-based models

Originally physiologically based models have been based on *in vitro* recorded experimental data from squid (Hodgkin and Huxley, 1952), toad (Frankenhaeuser and Huxley, 1964), rabbit (Chiu, Ritchie, Rogart and Stagg, 1979) and rat (Schwarz and Eikhof, 1987). These models consist of a cable model describing the way in which the action potential propagates along the nerve fibre. Fitting into this cable model is a membrane model, which describes the local action potential at the active nerve fibre sections (usually the nodes of Ranvier in myelinated nerve fibres). The main problem therefore is to decide upon the most applicable model.

Rubinstein (1993) developed a passive membrane cable model of a myelinated single ANF. Mammalian peripheral nerve fibre electrical parameter values and anatomical parameter values from cat Type I spiral ganglion ANFs at 37 °C were used in the model. Ranvier node kinetics were changed to a modified Frankenhaeuser-Huxley (1964) modelled fibre (Rubinstein, 1995). The axonal model consists of a deterministic representation of the internodes, a stochastic representation of the Ranvier nodes and no cell body representation (Rubinstein, Wilson, Finley and Abbas, 1999). Biophysical model parameters of the sodium channels, membrane capacitance and leakage current are chosen to best fit recorded single nerve fibre temporal properties in acutely deafened cats, while other anatomical parameters are the same as in the original passive membrane cable model.

Frijns and ten Kate (1994), Frijns, de Snoo and Schoonhoven (1995) and Frijns *et al.* (2000) developed a model based on the Schwarz-Eikhof nerve fibre model for rat (Schwarz and Eikhof, 1987), but modified with guinea-pig morphometry. Recently this Generalised Schwarz-Eikhof-Frijns (GSEF) model was modified for human ANF simulations by employing human morphometric data only (Briaire and Frijns, 2005; Briaire and Frijns, 2006). The ionic current dynamics of this model, however, are still those of rat. Even though similarities exist between the properties of ionic currents at the rat and human Ranvier node (Safronov, Kampe and Vogel, 1993; Röper and Schwarz, 1989), differences such as those in the activation and deactivation characteristics of voltage-gated potassium ion (K^+) channels can result in differences in nerve fibre conduction behaviour predictions (Reid *et al.*, 1999).

Moore, Joyner, Brill, Waxman and Najar-Joa (1978) simulated impulse conduction in myelinated nerve fibres, using the HH model, but with a tenfold increase in the ion channel density at the Ranvier nodes. Although the original HH model fails to conduct at temperatures higher than 30 °C, their high-density model can conduct impulses even at temperatures higher than 40 °C. A study comparing the applicability of the aforementioned animal models to predict human auditory nerve fibre excitation favours the HH model, provided the nodal ion channel kinetics are accelerated tenfold (Rattay, 1990; Rattay and Aberham, 1993). Replacement of the squid morphometric properties by human morphometric properties further improve predicted human auditory nerve fibre responses (Rattay *et al.*, 2001b). This modified HH model shows improved human auditory nerve fibre response predictions, as well as an improved prediction of chronaxie time of 340 μs versus 15 – 45 μs of the GSEF model (Frijns *et al.*, 1994), by

changing the cable morphometric properties to those of human (Rattay *et al.*, 2001b). Huxley (1959) also suggested that by accelerating the activation and inactivation of membrane sodium ion permeability of the HH model fourfold, firing behaviour at a myelinated amphibian Ranvier node can be represented.

Matsuoka, Abbas, Rubinstein and Miller (2000b) and Morse and Evans (2003) discussed the differences and similarities between animal and human data. In most animal studies, animals deafened acutely within a week before experiments are used. However, degeneration of the ANF morphology due to ototoxic effects can take several weeks and therefore a larger relatively intact neural population is expected, in contrast to the more degenerative neural population of the longer-term deafened animal or human (Morse and Evans, 2003). Acutely deafened animal models can thus only give a best case scenario for the electrical excitation of the human ANF (Abbas and Miller, 2004). In many of the animal experiments, a single electrode is placed inside the cochlea (Van den Honert and Stypulkowski, 1984), while in humans multiple-electrode arrays are used. The anatomy of the animal and human nerve fibres also differs (Rattay *et al.*, 2001b; Briaire and Frijns, 2005). Thus, nerve fibre models based on animal physiology at this stage can only roughly approximate human ANF behaviour.

2.1.2 Human-based models

Even though ionic membrane current data from single human myelinated peripheral nerve fibres have been recorded by Reid *et al.* (1993; 1999) and Scholz *et al.* (1993), no computational models have been developed employing these data. Schwarz *et al.* (1995) experimentally measured and computationally modelled the action potential and membrane currents at the human Ranvier node and compared the modelled results to a measured human Ranvier node action potential. Bostock and Rothwell (1997) used this model to explain differences in recorded latent addition results between motor and sensory human peripheral nerve fibres. Also, Wesselink, Holsheimer and Boom (1999) developed a fibre cable model partially based on the data and Ranvier node model by Schwarz *et al.* (1995) to predict human myelinated sensory nerve fibre responses to electrical stimulation of the spinal cord. However, to date none of these models has been applied to simulate human ANFs.

2.1.3 Temperature dependence of nerve fibre excitation behaviour

Nerve fibre excitation behaviour is affected by temperature changes (Burke, Mogyoros, Vagg and Kiernan, 1999; Moore *et al.*, 1978). Studies on human peripheral nerve fibres indicate an increase in action potential (AP) amplitude and duration, the absolute and relative refractory periods and chronaxie times when the temperature is decreased from 37 °C; while the rheobase current and conduction velocity decrease under the same temperature conditions (Kiernan, Cikurel and Bostock, 2001; Lowitzsch, Hopf and Galland, 1977; Buchthal and Rosenfalck, 1966). Temperature dependence of the sodium channel kinetics is included in computational models describing excitation behaviour in human nerve fibres; for example the models of Schwarz *et al.* (1995) and Wesselink *et al.* (1999), but not for the potassium channel and leakage kinetics, as well as other electrical parameters used. Similar to the HH model, temperature dependence of rate constants is effected using Q_{10} factors.

Temperature dependence of some of the parameters in ANF models has also been included. In the version of the HH model used by Rattay and co-workers, only the temperature dependence of the rate constants is considered (Rattay, 1990; Rattay and Aberham, 1993; Rattay *et al.*, 2001b). In the GSEF model the temperature dependence of the sodium and potassium membrane currents, rate constants, axoplasmic resistivity and external medium resistivity are included (Frijns *et al.*, 1994; Frijns *et al.*, 1995; Briaire and Frijns, 2005).

2.2 PERIPHERAL AUDITORY NERVE FIBRE

2.2.1 General overview and degeneration

The peripheral auditory pathway begins in the inner ear (or cochlea), where the ANFs innervate hair cells in the Organ of Corti which is housed inside the cochlea. From there the ANF bundle runs in a spiralled fashion inside a spongy bony canal, referred to as the modiolus, to the more central parts of the auditory system (Schuknecht, 1993). Detailed descriptions, together with transmission (TEM) and scanning (SEM) electron

microscopic studies of the auditory structures of the cochlea, are provided by Schuknecht (1993), Glueckert *et al.* (2005a), Glueckert, Pfaller, Kinnefors, Rask-Andersen and Schrott-Fischer (2005b) and Glueckert, Pfaller, Kinnefors, Schrott-Fischer and Rask-Andersen (2005c).

In normal hearing adult persons, the hair cells in the Organ of Corti are innervated by approximately 32,000 to 41,000 afferent myelinated ANFs (Schuknecht, 1993; Felder, Kanonier, Scholtz, Rask-Andersen and Schrott-Fischer, 1997; Nadol Jr, 1997). Innervation density varies from the cochlear base to the apex (Glueckert *et al.*, 2005a), with roughly 300 – 400 fibres per millimetre in the base and apex and about 1,400 fibres per millimetre in the lower second turn in a normal hearing person (Spoendlin and Schrott, 1989; Zimmermann *et al.*, 1995; Nadol Jr, 1997).

In mammals two distinct types of ANFs exist. The Type I ANF constitutes about 90% to 95% of the population, is bipolar, has a myelinated axon, thinly myelinated to unmyelinated somal perikaryon, and exclusively innervates the inner hair cells (Nadol Jr, 1988; Spoendlin and Schrott, 1989; Schuknecht, 1993; Rask-Andersen, Tylstedt, Kinnefors and Schrott-Fischer, 1997; Glueckert *et al.*, 2005a; Pamulova, Linder and Rask-Andersen, 2006). The Type II ANF has a smaller fibre diameter, is unmyelinated, pseudomonopolar, innervates the outer hair cells and constitutes about 5% to 10% of the population (Spoendlin and Schrott, 1989; Schuknecht, 1993; Glueckert *et al.*, 2005b; Pamulova *et al.*, 2006).

The degeneration and subsequent loss of ANFs resulting in hearing loss can be classified as primary or secondary. Primary neural degeneration is the normal age-related hearing loss a person experiences, while secondary (retrograde) neural degeneration is due to various factors including ototoxic substances, disease or trauma to the cochlear structures (Nadol Jr, 1990; Schuknecht, 1993). Retrograde neural degeneration, in which the dendrites retract but the somas and axons survive, occurs in persons with profound sensory hearing loss (Spoendlin and Schrott, 1989; Nadol Jr, 1990; Schuknecht, 1993). The surviving degenerate somas and axons are significantly smaller than in non-degenerate ANFs (Nadol Jr, 1990; Zimmermann *et al.*, 1995; Glueckert *et al.*, 2005a). The degree of retrograde neural degeneration depends on the severity of tissue alterations in the Organ of Corti during the original insult, as well as surgical trauma to cochlear structures due to electrode insertion, and concerns mostly Type I ANFs (Schuknecht, 1993; Fayad and Linthicum Jr, 2006). Even though retrograde

degeneration occurs at a slow pace, persons with long-term hearing loss have fewer surviving Type I ANFs than persons with shorter-term hearing loss (Linthicum Jr and Anderson, 1991; Nadol Jr and Xu, 1992; Schuknecht, 1993; Zimmermann *et al.*, 1995; Felder *et al.*, 1997; Fayad and Linthicum Jr, 2006). Type II ANFs are more resistant to retrograde degeneration and their relative percentage compared to Type I ANFs increases (Spoendlin and Schrott, 1989).

2.2.2 Type I auditory nerve fibre properties

In addition to the above-mentioned properties, the large Type I ANF can be subdivided into two subtypes based on morphological, morphometrical (somal, nuclear, dendritic and axonal diameters) and physiological data (Nadol Jr, Burgess and Reisser, 1990; Rosbe, Burgess, Glynn and Nadol Jr, 1996).

Dendritic lengths vary between 1.4 mm in the lower basal turn, 1.1 mm in the second turn and 0.8 – 1.0 mm in the apex (Spoendlin and Schrott, 1989; Glueckert *et al.*, 2005a; Glueckert *et al.*, 2005b). They are thinly myelinated having about 23 myelin layers, i.e. about 0.25 μm thick (Spoendlin and Schrott, 1989), with diameters between 1.2 and 1.4 μm (Nadol Jr *et al.*, 1990).

In general somal diameters vary between 24.6 and 32.4 μm (Spoendlin and Schrott, 1989; Nadol Jr *et al.*, 1990; Schuknecht, 1993; Rosbe *et al.*, 1996; Glueckert *et al.*, 2005a). Somal nucleae are almost spherical (Spoendlin and Schrott, 1989; Rosbe *et al.*, 1996), with diameters varying between 11.0 and 14.5 μm (Spoendlin and Schrott, 1989; Nadol Jr *et al.*, 1990; Rosbe *et al.*, 1996). Type I cells tend to cluster together in groups where they frequently share the same Schwann cell sheaths (Rask-Andersen *et al.*, 1997; Tylstedt and Rask-Andersen, 2001; Glueckert *et al.*, 2005a). Unmyelinated nerve fibres, possibly the dendrites of other Type I ANFs or nerve fibres belonging to the intra-ganglionic spiral bundle, form close associations with these cells (Rask-Andersen *et al.*, 1997; Tylstedt and Rask-Andersen, 2001; Glueckert *et al.*, 2005a). It is suggested that these neuronal interactions and cell clustering provide a trophic supply to the remaining cells and may in part explain the slow rate of the retrograde degenerative process and hence the longer survival of the somas and axons of ANFs compared to dendrites (Felder *et al.*, 1997; Tylstedt and Rask-Andersen, 2001; Glueckert *et al.*, 2005a; Pamulova *et al.*, 2006).

SEM photographs and measured data indicate that the largest fibre diameter in the basal turn is 4.3 μm and the smallest in the upper middle turn 3.2 μm, the average fibre diameter being about 3.75 μm (Rosbe *et al.*, 1996; Glueckert *et al.*, 2005a). Axonal diameters vary between 2.34 and 3.7 μm (Rosbe *et al.*, 1996; Glueckert *et al.*, 2005a). The number of myelin layers around the axons varies between 60 and 83, i.e. a myelin thickness between 0.7 and 1.0 μm and total axonal lengths vary between 30 and 40 mm (Spoendlin and Schrott, 1989).

2.3 SINGLE-FIBRE VERSUS GROSS ENSEMBLE AUDITORY NERVE FIBRE STUDIES

While computational models are used to explore separate physiological mechanisms of the ANFs and how these mechanisms influence temporal characteristic predictions, results from animal studies are used for validation. These animal studies are broadly divided into single-fibre and gross ensemble fibre studies (Abbas and Miller, 2004).

Most of the early work performed in determining the temporal characteristics of electrical stimulation were performed on single-fibre preparations of cats and guinea-pigs (Moxon, 1971; Kiang and Moxon, 1972; Hartmann, Topp and Klinke, 1982; Van den Honert and Stypulkowski, 1984; Javel *et al.*, 1987; Van den Honert and Stypulkowski, 1987a; Van den Honert and Stypulkowski, 1987b; Hartmann and Klinke, 1990; Javel, 1990; Dynes and Delgutte, 1992; Klinke and Hartmann, 1997; Shepherd and Javel, 1997; Shepherd and Javel, 1999; Javel and Shepherd, 2000). Although the results of these single-fibre studies aid in understanding and characterising single-fibre responses to electrical stimuli, gross ensemble potential studies are instead performed on humans where recent studies rely on the measurement of the electrically evoked compound action potential (ECAP) (Shannon, 1985; Brown, Abbas and Gantz, 1990; Abbas *et al.*, 1999; Miller, Abbas and Brown, 2000; Tykocinski, Cohen, Pyman, Roland, Treaba, Palamara, Dahm, Shepherd, Xu, Cowan, Cohen and Clark, 2000; Dillier *et al.*, 2002; Saunders, Cohen, Aschendorff, Shapiro, Knight, Stecker, Richter, Waltzman, Tykocinski, Roland, Laszig and Cowan, 2002; Cohen *et al.*, 2003; Abbas *et al.*, 2004; Cohen, Saunders and Richardson, 2004; Etler, Abbas, Hughes, Brown, Dunn, Zubrod and van Voorst, 2004; Cohen, Saunders, Knight and Cowan, 2006; Lai and Dillier, 2008). The ECAP requires the synchronous firing of the

ANFs to elicit a measurable potential, since it is in essence the summation of all the action potentials produced by the nerve fibre population (Abbas and Miller, 2004).

Miller *et al.* (1999a) used a phenomenological approach to develop an empirical model simulating ECAP responses, with the ECAP response assumed to be the summation of all the single-fibre responses. The model is based on their single-fibre cat data for cathodic responses from the Miller, Abbas, Robinson, Rubinstein and Matsuoka (1999b) study. Simulation results suggest that the ECAP amplitude is proportional to the number of actively responding nerve fibres. ECAP studies assume that the neural response to each individual stimulus is identical. Such assumptions depend on the level and rate of stimulus presentation, but can potentially be affected by the properties of the stimulated nerve fibres and their neuropathological state (Abbas and Miller, 2004).

Briaire and Frijns (2005) developed a model to calculate the ECAP response as measured via the NRT system. ECAP responses were simulated by solving what they termed the full "backward problem", i.e. calculating the ECAP responses at the electrode array level in the volume conduction cochlear part of the model from the single-fibre action potentials (SFAPs) calculated with the nerve fibre model discussed in Section 2.1.1. The superposition of these SFAPs then gives the ECAP response. The model is used to investigate the validity of the assumptions that the ECAP amplitude is proportional to the number of actively responding nerve fibres and that the neural response to each individual stimulus is identical, i.e. every nerve fibre contributes equally to the ECAP response. Results indicate that the nerve fibres from the centre of the excitation area make a different contribution to those around the edges. Electrodes placed closer to the outer wall are predicted to cause excitation in the peripheral part of the neurons, in contrast to electrodes placed closer to the modiolus. Their results also show that as the number of excited neurons increases, the ECAP response amplitude first increases up to a certain stimulus intensity, after which it decreases. However, the model cannot fully account for the ECAP morphology observed in humans and rather resembles the ECAP and AP shapes of the rat model by Schwarz and Eikhof (1987) on which the nodal kinetics of the GSEF model are based. They hence suggested the implementation of the human nodal kinetics model by Wesselink *et al.* (1999).

2.4 GROSS ENSEMBLE STUDIES: PREDICTING NEURAL EXCITATION SPREAD INSIDE THE COCHLEA

ECAP data are obtained by a forward masking paradigm and it is generally assumed that psychophysical forward masking profiles provide an indirect measure of neural excitation patterns (van der Heijden and Kohlrausch, 1994; Chatterjee and Shannon, 1998; Abbas *et al.*, 2004). In the case of ECAP data, the measure is more direct than in the case of psychophysical forward masking, since it is assumed that the central auditory processes do not contribute to the masking profile. Furthermore, the amplitude measurement of the ECAP gives an indication of the number of responding fibres (Miller *et al.*, 1999a). Cohen *et al.* (2003) reported that larger ECAP profile widths are measured for stimulation at higher most comfortable levels (MCLs) rather than for lower MCLs, indicating a wider spread of neural excitation in the former. The spread in excitation also increases with an increase in stimulus level (Abbas *et al.*, 2004). Miller *et al.* (2003) used the fact that the ECAP reflects the gross ensemble response of a neural population to investigate the effects of stimulation mode on neural excitation spread. The results indicate that monopolar stimulation produces wider ECAP profiles than bipolar stimulation, consistent with the observation that monopolar stimulation causes wider neural excitation (Van den Honert and Stypulkowski, 1987a). Townshend and White (1987) developed a paradigm based on the psychophysical thresholds measured for two human implantees to calculate the current spread patterns around the electrodes of a modelled electrode array. Their simulations confirmed wider neural excitation spread with monopolar compared to bipolar stimulation, as well as a reduction in excitation spread for an electrode array placed closer to the modiolus.

Stimulus attenuation directly relates to current distribution and thus the extent of neural excitation inside the cochlea. There have been only a few studies to determine the stimulus attenuation inside the cochlea. Black and Clark (1980) and Black, Clark, Tong and Patrick (1983) measured length constants of 8.0 – 16.0 mm (0.54 – 1.09 dB/mm) for monopolar stimulation in living cats. This compared well with the length constants of 4.0 – 13.0 mm (0.67 – 2.12 dB/mm) predicted with their lumped parameter model. Tank measurements by Kral, Hartmann, Mortazavi and Klinke

(1998) compared well with cadaver measurements from the basal part of cat cochleae. They found a length constant of 1.43 mm (6.07 dB/mm) for monopolar stimulation, which is a much larger attenuation value than those found in other studies.

2.5 TEMPORAL CHARACTERISTICS

Excitation behaviour in ANFs is described in terms of the temporal characteristics of pulses, whether these be single pulses or pulse trains. The most familiar of these are:

1. discharge rate
2. adaptation
3. alternation
4. absolute (ARP) and relative (RRP) refractory periods of the action potential
5. entrainment, also referred to as time-locking
6. phase-locking
7. synchronisation
8. mean latency and jitter
9. threshold
10. the threshold-distance relationship
11. strength-duration relationship

In the following subsections the main findings regarding the temporal characteristics investigated in this study are presented. These are refractory periods, mean latency, thresholds, threshold-distance relationships and strength-duration relationships. The review is, however, not exhaustive. The temporal characteristics not covered here are reviewed in Addendum A.

2.5.1 Absolute and relative refractory periods of the action potential

Stimulation in cochlear implants is typically in the form of pulse trains and, in the case of earlier implants, continuous stimulation. The refractory properties of the neural membrane play an important role in the choice of stimulation used and can limit ANFs' ability to encode the temporal characteristics of input stimuli (Miller, Abbas and Robinson, 2001a; Abbas and Miller, 2004) by

- placing a lower limit on the interphase / interpulse interval, hence raising the threshold stimulus intensity needed to elicit further responses during the RRP (see Section 2.5.3). Note that during the ARP, the fibre can elicit no further responses, even if the stimulus intensity is increased.
- placing an upper limit on the stimulus rate used. Most of the temporal phenomena discussed in the sections on entrainment, alternation, mean latency and jitter and discharge rate can possibly be attributed to the effects of neural refractoriness.

In studies on nerve fibre refractoriness, a two-pulse masker-probe paradigm is used (see for example Cartee, van den Honert, Finley and Miller, 2000; Miller *et al.*, 2001a). The masker probe interval (MPI) is varied and the amount of reduced excitability noted. In studies performed on cats, Hartmann, Topp and Klinke (1984) observed a reduction in fibre excitability for MPIs shorter than 5.0 ms. Bruce, Irlicht, White, O'Leary, Dynes, Javel and Clark (1999a) developed a phenomenological model of the ANF and estimated an ARP of 0.7 ms and a recovery time constant of 1.3 ms for pulse train stimulation. More recently, refractory observations in cat studies by Cartee *et al.* (2000) (monopolar, cathodic pseudomonophasic pulses) and Miller *et al.* (2001a) (monopolar, cathodic monophasic pulses) using a forward-masking paradigm, have shown a decrease in threshold intensity needed for the probe pulse as the interpulse interval (IPI) was increased. Cartee *et al.* (2000) suggested a mean ARP of 0.7 ms, while RRP values can be up to 5.0 ms (Cartee *et al.*, 2000; Abbas and Miller, 2004). ECAP responses measured in cats also suggest an ARP between 0.3 ms (Miller *et al.*, 2000) and 0.5 ms (Brown and Abbas, 1990). A mean ARP of about 330 μs and a mean recovery time constant of about 410 μs are estimated for cat auditory fibres by

Miller *et al.* (2001a). ECAP studies on humans suggest an ARP value larger than 0.5 ms and an RRP value around 5.0 ms (Brown *et al.*, 1990).

2.5.2 Mean latency and jitter

Spike latency is defined as the time latency between stimulus onset and maximum AP amplitude, while mean latency is the arithmetic mean of all the spike latencies measured for a specific stimulus intensity (Van den Honert and Stypulkowski, 1984; Rubinstein, 1995; Miller *et al.*, 1999b). Latency jitter, also just known as jitter, is defined as the standard deviation from the mean latency (Van den Honert and Stypulkowski, 1984; Rubinstein, 1995; Miller *et al.*, 1999b). Closely related is the concept of firing efficiency (FE), defined as the ratio of the number of observed spikes to the number of presented stimuli (Van den Honert and Stypulkowski, 1984; Rubinstein, 1995). Experimentally FE is computed as the percentage of stimuli that elicits an AP (Miller *et al.*, 2001a), and increases with an increase in stimulus intensity.

In single-fibre studies preformed on normal hearing cats, the mean latency shows a decrease with an increase in stimulus intensity, and hence with an increase in FE, reaching an asymptotic level at high stimulus intensities, while for laminectomated animals, in which the dendrites and somas are removed but the axons left intact, the mean latencies are much shorter and approximate the latency behaviour of normal fibres excited at high stimulus intensities (Van den Honert and Stypulkowski, 1984). Javel *et al.* (1987) used bipolar, biphasic stimuli on acutely deafened cats implanted with a multi-electrode array. They confirmed the findings of van den Honert and Stypulkowski by observing highly synchronised, short-latency responses with increased stimulus intensity. Responses have double peaks with latencies $\sim$ 0.3 and 0.6 ms and are considered to be a result of direct depolarisation of the neural membrane. These short latency responses are also maintained at higher discharge rates than is possible with acoustic stimulation.

Van den Honert and Stypulkowski's (1984) results indicate a decrease in jitter with increasing stimulus levels and hence FE, as well as a difference in jitter between normal and damaged fibres. Both the normal and damaged fibres show short latency jitter responses, while for longer latencies the high jitter responses are missing in the damaged fibres. Jitter in the damaged fibres is also greatly reduced. This is consistent

with the results of Kiang and Moxon (1972), showing shorter latencies and reduced jitter responses to electrical stimulation compared to normal neuronal responses, which reflect the characteristics of resonant systems.

At high stimulus intensities similarities in latency and jitter measurements are observed between normal and damaged fibres (Van den Honert and Stypulkowski, 1984). These authors suggest that the site of fibre excitation shifts more centrally towards the modiolus as the stimulus intensity is increased, since excitation in damaged fibres occurs in the axonal part of the fibre. In the double-peak response observed by Javel *et al.* (1987) the longer latency response is replaced by the shorter latency response as the stimulus intensity is increased. The authors argued that the former reflects peripheral dendritic excitation and that the shift in latency indicates a shift in excitation to a more centrally located site along the fibre, but they didn't rule out the possibility that the double-peak response is due to excitation by both phases.

Both latency and jitter are polarity-dependent and both phases of a biphasic stimulus pulse can elicit a discharge. The site of excitation shifts from peripheral dendritic excitation (longer latency and lower threshold) to a more centrally located site (shorter latency and higher threshold) for bipolar cathodic monophasic stimulation in the former compared to anodic stimulation in the latter (Van den Honert and Stypulkowski, 1987b). Miller *et al.* (1999b) recorded mean latencies and jitter in cats for monopolar, monophasic stimuli. Their results confirm results from previous studies that both latency and jitter are polarity-dependent, with longer latencies and greater jitter for cathodic stimuli compared to anodic stimuli. Latency and jitter are also higher for longer pulse durations, with a greater increase for cathodic stimuli compared to anodic stimuli. Both latency and jitter decrease with increasing FE, with the greatest decreases for cathodic stimuli. Some of the fibres tested have longer latencies than the average and the results indicate that these longer latency fibres have undergone greater reductions in latencies as FE increased. It is hypothesised that, given the position of the stimulating electrodes and the distribution of fibres through the cochlea, most fibres are excited centrally to the soma by both polarities, but that in a minority of the fibres excitation can occur both peripherally and centrally. There is thus a difference in the location of excitation between anodic and cathodic stimulation, consistent with observed trends in electrically stimulated neural tissue (Ranck Jr, 1975).

Bipolar, biphasic stimulation shows an order-dependent double-peak response (Van den

Honert and Stypulkowski, 1987b). Low stimulus intensity anodic first bipolar stimuli with an interphase gap show a long latency suprathreshold second peak response. With increased stimulus intensity, the response pattern becomes bimodal, with the first peak growing in intensity. For high stimulus intensities the second peak disappears and only the shorter latency first peak is elicited. It is concluded that the second peak is destroyed by the antidromic propagation of the first peak from a more central location to the peripheral dendritic sites, rendering the peripheral sites refractory during the times that the second peak should have been elicited. This same trend is also reported by Javel *et al.* (1987) using biphasic, no interphase gap stimuli. The bimodal response patterns have also only been observed during biphasic stimulation and not during monophasic stimulation. When the polarity is reversed, only a single-peak response is observed owing to the cathodic-first stimulation pulse, with no bimodal response pattern or observed shift in latency. The authors reasoned that the orthodromic propagation of the cathodic pulse response renders the more centrally located excitation site of the anodic pulse response refractory during its stimulus period.

A similar bimodal response pattern is also observed by Miller *et al.* (1999b). At low stimulus intensities only one long-latency response peak is observed, but at stimulus levels producing almost 100% FE, a discreet jump to a second shorter-latency response peak is observed. At high stimulus levels, only the shorter-latency peak is observed, consistent with the results from previous studies. Note, however, that in the previous studies (Javel *et al.*, 1987; Van den Honert and Stypulkowski, 1987b), bimodality is observed with biphasic stimuli in which each of the phases can elicit a response (Van den Honert and Stypulkowski, 1987b), whereas in the Miller *et al.* (1999b) study it is observed with monophasic stimuli only about 2% of tested fibres. Bimodality seems to be polarity-dependent, with some cats responding bimodally to anodic stimuli and others responding to cathodic stimuli. Since previous studies with monophasic stimuli (see for example Van den Honert and Stypulkowski, 1984) indicate no bimodality and the Miller *et al.* (1999b) study reports a very low incidence of bimodality, the authors caution against the conclusion of the influence the soma has on latency shifts observed with biphasic stimuli (see for example Shepherd and Javel, 1997). The discreet shift to shorter latencies is consistent with previous conclusions of a shift in excitation site from a more peripheral to a more central location across an unstimulable fibre segment such as the soma.

NRT measurements in human subjects implanted with the Nucleus 24 electrode arrays

also indicate the existence of similar response waveforms having either single positive or double positive peaks (see for example Lai and Dillier, 2000). The NRT waveform is characterised by a negative (*N1*) peak, followed by the positive peak(s) (*P1* and *P2*). For a single positive peak waveform, the *N1* peak occurred around 0.3 – 0.4 ms and the *P1* peak around 0.6 – 0.7 ms. In the double positive peak responses, the *N1* peak occurred at times too short to measure with the NRT system (< 0.11 ms), while the *P1* and *P2* peaks occurred around 0.4 – 0.5 ms and 0.6 – 0.7 ms respectively. Calculated latencies for the single-peak case are hence ~ 0.3 ms, while for the double-peak case it is ~ 0.4 ms and ~ 0.7 ms. Lai and Dillier (2000) concluded that the double-peak response indicates the existence of almost intact ANF fibres, while the single-peak response may be due to retrograde degeneration.

Miller *et al.* (1999a) used a phenomenological approach to develop an empirical model simulating ECAP responses. The model is based on their single-fibre cat data for cathodic responses from the Miller *et al.* (1999b) study. The model results confirm the decrease in both mean latency and jitter with an increase in stimulus intensity. The ECAP morphology is also polarity-dependent, with cathodic responses measured in guinea-pig and cat indicating longer latencies than measured for anodic responses (Miller, Abbas, Rubinstein, Robinson, Matsuoka and Woodworth, 1998; Miller *et al.*, 2001a; Miller, Robinson, Rubinstein, Abbas and Runge-Samuelson, 2001b). For cathodic stimuli, latencies in general also increase when the MPI is decreased (Miller *et al.*, 2001a), while longer latencies are also observed for monophasic stimuli compared to biphasic stimuli (Miller *et al.*, 2001b).

2.5.3 Threshold

Threshold indicates the stimulus level at which a firing response is elicited from a fibre. Miller *et al.* (1999b) used a slightly different definition of threshold, defining threshold to be at 50% FE.

Van den Honert and Stypulkowski (1984) reported lower thresholds for damaged fibres than for electrically stimulated normal fibres. Strength-duration curves also indicate lower thresholds at longer pulse durations for both normal and damaged fibres, with a significant reduction in threshold for damaged fibres compared to normal fibres for bipolar stimulation. Also no correlation is found between threshold and characteristic

frequency. The authors reasoned that the difference in threshold behaviour suggests a difference in site of spike initiation, with excitation of the peripheral dendrites the most likely place for low stimulus intensities with both monopolar and bipolar intracochlear electrodes for normal fibres. Also no significant difference in threshold is found between extracochlear monopolar and intracochlear bipolar stimulation in normal fibres (Van den Honert and Stypulkowski, 1987a). In contrast, Liang, Lusted and White (1999) demonstrated threshold changes of up to 10 dB/mm near monopolar stimulated electrodes and attributed the contrast with the Van den Honert and Stypulkowski (1987a) results to the more basal placement of the electrodes in the latter study.

Results from Moxon (1971) and Kiang and Moxon (1972) showed a frequency dependency of electrical threshold for sinusoidal stimulation, with a broad minimum threshold near 100 Hz for all fibres. A local minimum around 100 pps was also observed in humans for biphasic monopolar stimulation of pulse durations longer than 400 μs (Shannon, 1985). Dynes and Delgutte (1992) used electrical sinusoidal stimulation delivered to bipolar intracochlear electrodes in acutely deafened cats. Their results indicate a monotonical increase in threshold with increasing stimulus frequency. Although the growth of threshold with frequency is more than 3.0 dB/octave in some fibres, most resemble the 3.0 dB/octave growth found in previous studies (Kiang and Moxon, 1972; Hartmann and Klinke, 1990).

Single-fibre studies by Van den Honert and Stypulkowski (1987b) and ECAP studies by Miller *et al.* (1998; 1999b; 2001a) recorded lower thresholds for cathodic monopolar stimulation than for anodic stimulation in cats, indicating a threshold dependence on stimulus polarity. The difference may be due to the observation that cathodic stimuli excite fibres more distally than anodic stimuli do, although the influence the soma plays is unclear (Miller *et al.*, 1999b). However, in guinea-pigs the situation is reversed, with anodic stimuli yielding lower thresholds (Miller *et al.*, 1998). With bipolar stimulation no preference is observed between the stimulus polarities (Miller *et al.*, 2003). Thresholds are also lower for longer pulse durations (compare also Miller *et al.*, 2001b), with a greater decrease for anodic stimuli compared to cathodic stimuli. Javel *et al.* (1987) also reported lower thresholds for longer interpulse widths in biphasic stimuli, up to at least 300 μs/phase, and that the response behaviour of different fibres are the same, even though there is a difference in threshold among the fibres.

Thresholds are reported to be dependent on stimulus mode and electrode configuration. Monopolar stimulation in cats yielded thresholds 7.0 – 8.0 dB lower than bipolar stimulation (Black and Clark, 1980; Black *et al.*, 1983; Rebscher *et al.*, 2001), while in guinea-pigs monopolar thresholds are on average 5.7 dB lower (Miller, Woodruff and Pfingst, 1995). ECAP studies on cats confirmed earlier reports of lower thresholds for monopolar stimulation (Miller *et al.*, 2003). Lower thresholds are also recorded for monophasic stimuli compared to biphasic stimuli in single-fibre and ECAP studies performed by Miller *et al.* (1995; 1999b; 2001b) on cats and guinea-pigs. Increasing the duration of the second phase of the biphasic stimuli, i.e. stimulation with pseudomonophasic stimuli, leads to a relatively large reduction in threshold (Miller *et al.*, 2001b). Reversal of stimulus polarity results in larger observed threshold differences when monophasic stimulation is used (Miller *et al.*, 1999b), compared to the differences observed with biphasic stimuli (Shepherd and Javel, 1999). Van Wieringen *et al.* (2005), Van Wieringen, Carlyon, Macherey and Wouters (2006) and Macherey *et al.* (2006) investigated the effects of pulse shape, polarity and pulse rate of pulsatile waveforms on thresholds and MCLs in humans and reported threshold reductions of 3.0 – 6.0 dB when biphasic pulses are replaced with pseudomonophasic pulses, while the threshold is reduced by 5.0 – 8.0 dB in the case of alternating monophasic pulses.

2.5.4 The threshold-distance relationship

Electrode-to-axon distances play a significant role in the distribution of threshold responses to stimuli. For a monopolar electrode in an isotropic medium, the electric field strength varies with inverse proportionality to the square of the distance from the electrode, while the extracellular potential varies with inverse proportionality to the distance from the electrode. The further away from the electrode, the weaker both the electric and potential fields become, the former more quickly than the latter, with the result that larger threshold stimulus currents are necessary to excite the fibre as the electrode-to-axon distance increases.

Single-fibre studies by Ranck Jr (1975) and model results by, among others, Rattay (1990) indicate that the threshold current increases with the square of the distance from the electrode. This has the effect that as the fibre distance from the electrode increases, the excitation region around the electrode increases, since more Ranvier nodes will fall inside the depolarised region.

Javel *et al.* (1987) reported lower thresholds for fibres located closer to the stimulating electrodes. Fibres located further from the stimulating electrode could only be excited at higher stimulus intensities. Miller, Abbas and Brown (1993) and Shepherd *et al.* (1993) showed large threshold changes and growth rate of the fibre's ECAP response when the location of the intracochlear stimulus electrode was changed. Modelling data by Briaire and Frijns (2006) and Hanekom (2001b) also predicted a reduction in neural threshold as the stimulating electrodes were moved closer to the modiolus, with the greatest reduction for fibres lying closest to the electrodes.

2.5.5 Strength-duration relationship

The strength-duration function gives the relationship between the threshold stimulus current necessary to excite a fibre and the stimulus duration. The standard way of collecting data for such a function is to stimulate with a monopolar, monophasic block (square) pulse (Loeb, White and Jenkins, 1983). Since the neural membrane integrates the stimulus current, longer stimulus duration requires less threshold current than shorter durations. An increase in the stimulus duration leads to a monotonic decrease in threshold current, until it reaches an asymptotic value known as the rheobase current (Bostock, 1983).

The shape of the strength-duration curve gives an indication of the integration properties of the neural membrane. Curves can be represented by an exponential function (Lapicque, 1907), or by a hyperbolic function (Bostock, 1983; Colombo and Parkins, 1987). A perfect integrator will be represented by a hyperbolic and a leaky integrator by an exponential function respectively. Strength-duration curves measured by Van den Honert and Stypulkowski (1984) for both normal and damaged cat fibres follow an exponential curve. For the damaged fibres, thresholds at short pulse durations were lower than for the normal fibres, most probably due the fact that the damaged fibres were only excited in the axonal (central) part of the fibre, whereas in normal fibres excitation could occur either peripherally or centrally.

Chronaxie time, i.e. the stimulus duration of twice the rheobase current, is a convenient way of characterising the neural membrane integration properties. The steeper the slope of the strength-duration curve, i.e. the more the hyperbolic the curve becomes, the shorter the chronaxie time (Bostock, 1983; Colombo and Parkins, 1987).

Van den Honert and Stypulkowski (1984) reported significantly shorter (118 μs vs. 276 μs) chronaxies for laminectomated fibres (leaving only the axons intact) compared to normal functioning fibres, indicating axonal excitation in the former.

According to Abbas and Miller (2004) chronaxies depend on:

- the shape of the externally applied electric field, together with the membrane depolarisation profile (see also Bostock, 1983).
- the electrode-axon distance. A closer separation may lead to a decrease of the strength-duration time constant and thus shorter chronaxies.
- the stimulus waveform. Miller *et al.* (1995) reported longer chronaxies and less steeply sloped strength-duration functions for monophasic than for biphasic stimulation. Also, owing to the refractory properties of the neural membrane, the second phase of a biphasic pulse has a greater effect for short pulse durations, compared to longer pulse durations.