Chapter 8

GENERAL DISCUSSION AND CONCLUSION

8.1 RESEARCH OVERVIEW

In 1952 Hodgkin and Huxley published an empirical set of equations describing changes in the neural membrane potential of the squid giant axon during the application of depolarising or hyperpolarising stimuli. Since these equations were derived for an unmyelinated nerve fibre, reservations exist about their applicability to describe action potential propagation in myelinated mammalian nerve fibres adequately.

Huxley (1959) 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. The HH model is able to predict human ANF excitation, provided the nodal ion channel kinetics are accelerated tenfold (Rattay, 1990; Rattay and Aberham, 1993). This modified HH model shows improved human ANF response predictions by replacement of the squid morphometric properties by human morphometric properties, as well as changing the cable morphometric properties to those of human (Rattay *et al.*, 2001b).

The main endeavour of this study was to determine whether the HH model for unmyelinated nerve fibres could be modified more comprehensively to predict excitability

behaviour at Ranvier nodes of a human sensory nerve fibre, as applied specifically to the prediction of temporal characteristics of the human auditory system. The model was developed in three phases. Firstly, the HH-model was modified to describe action potential dynamics at Ranvier nodes using recorded ionic membrane current data from single human myelinated peripheral nerve fibres (Reid *et al.*, 1993; Scholz *et al.*, 1993; Schwarz *et al.*, 1995; Reid *et al.*, 1999) together with the temperature dependency of all parameters (Chapter 3). Secondly a nerve fibre cable model, based on a combination of the models by Rattay *et al.* (2001b) and Blight (1985), was constructed using human sensory nerve fibre morphometric data (Chapter 4). Lastly the morphological parameters of the nerve fibre model were changed to a Type I peripheral ANF and coupled to a volume conduction model of the cochlea (Chapter 5).

The Type I ANF model had to be verified against experimentally measured temporal characteristic data. Chapters 6 and 7 focussed on applications of the ANF model to verify the model and to determine its applicability as part of larger models to address questions pertaining to the cochlear implant research field.

8.2 RESULTS AND DISCUSSION

In Chapter 3 a model of a single Ranvier node was developed as part of a larger model to describe excitation behaviour in a generalised human peripheral sensory nerve fibre (Research objective 1). Parameter values describing the ionic and leakage conductances, corresponding equilibrium potentials, resting membrane potential and membrane capacitance of the original HH model were modified to reflect the corresponding parameter values for human, with the equations left unaltered. Parameter temperature dependence was included. The activation kinetics of the HH model's potassium current were slowed down to represent the activation and deactivation kinetics of a slow potassium current experimentally observed at mammalian Ranvier nodes (Taylor *et al.*, 1992; Devaux *et al.*, 2004; Schwarz *et al.*, 2006).

Action potential shape and amplitude were satisfactorily predicted at 20, 25 and 37 °C and were not influenced by this potassium current, in accordance with experimental observations. The chronaxie time constant of 65.5 μs compared favourably with the estimated value of 64.9 $\pm$ 8.3 μs at 37 °C for normal rat Ranvier nodes (Bostock *et*

al., 1983). No comparison could be made with human data owing to a lack of similar Ranvier node studies for humans. Temperature dependence simulations overestimated chronaxie times by almost a factor 2 for temperatures lower than body temperature.

Chapter 4 endeavoured to determine if the human Ranvier node model developed in Chapter 3 could predict the excitability behaviour in human peripheral sensory nerve fibres with diameters ranging from 5.0 – 15 μm (Research objective 1). The Ranvier node model was extended to include a persistent sodium current and was incorporated into a generalised simple double-cable nerve fibre model. Parameter temperature dependence was included. Simulated results suggested that the new nerve fibre cable model could satisfactorily predict excitability behaviour observed in human sensory nerve fibres at different temperatures and fibre diameters.

Similar to the results of the Ranvier node model the predicted AP characteristics compared favourably with experimental results. AP durations varied inversely with fibre diameter at temperatures higher than 27 °C, but at lower temperatures this relationship was valid only for fibres thicker than 12.5 μm. Conduction velocity values varied from 2.9 to 3.5 μs^{-1} for fibre diameters ranging from 5.0 – 15.0 μm at 37 °C, but values were underestimated for fibre diameters thinner than 12.5 μm. Conduction velocities also increased with a decrease in temperature, but at a slower rate compared to experimental data. ARP and RRP values decreased with an increase in temperature. Calculated RRP values overestimated and ARP values underestimated the experimental rates by 15% and 20% respectively. The strength-duration time constant ranged from 184.3 to 273.6 μs at 37 °C over the studied nerve fibre diameter range. However, just as in the case of the Ranvier node model, time constants were overestimated at temperatures lower than body temperature. Possible explanations included the fitting procedure employed to determine the chronaxie times, bias in measured parameter values due to the measuring methodologies used, as well as an assumption of linear parameter relationships to temperature variation.

The development of the Type I ANF model was undertaken in Chapter 5 (Research objectives 1 and 4). The general human sensory nerve fibre model was incorporated into the Rattay *et al.* (2001b) ANF model. The axonal morphological parameters were changed to a Type I peripheral ANF and the model coupled to a volume conduction model of the cochlea. The 3.75 μm diameter ANF fibre located in the basal cochlear turn was stimulated with a monopolar electrode configuration from either the contour

or straight electrode arrays at body temperature (37 °C).

ARPs and RRPs compared well and were similar to those of general sensory nerve fibres of the same calibre. RRPs decreased with progressive retrograde ANF degeneration. Chronaxie times deceased and rheobase current values increased when retrograde ANF fibre degeneration was simulated. Rheobase current values were also larger for straight array compared with contour array stimulation. Mean latencies decreased with progressive retrograde ANF degeneration and agreed well with NRT measurements (Lai and Dillier, 2000). They also decreased with an increase in stimulus intensity.

The objective of Chapter 6 was to develop a simple method to estimate stimulus attenuation values by calculating the values that best fitted the modelled neural excitation profile widths to the measured ECAP profile widths (Research objectives 2 and 3). Neural excitation profile widths at the neural level for monopolar stimulation with Nucleus straight and contour arrays respectively, were simulated using a combined volume conduction-neural model. Simulations were performed for the ANF and GSEF models respectively.

The simple model correctly predicted an increase in excitation spread with an increase in loudness level as well as wider ECAP profile widths for the straight array compared to the contour array. For both nerve fibre models, the simple model predicted realistic ECAP profile width ranges for the straight array while the lower limit for the width ranges predicted for the contour electrode was comparable to measured width ranges.

Results further indicated that the modelled excitation profile widths decreased with increasing stimulus attenuation. The predicted stimulus attenuation value that best fitted the experimental results was 3.5 dB/mm for the GSEF model compared to 5.5 dB/mm for the ANF model. Despite this difference it was suggested that the proposed simple model could provide an estimate of stimulus attenuation by calculating the value of the parameter that produces the best fit to experimental data in specific human subjects.

Fitting of modelled neural excitation profile widths to measured ECAP profile widths showed that different stimulus attenuation values were needed for different stimulation levels. This might be attributed to the impedance of the electrode-electrolyte interface, which is related to stimulus attenuation, and could be dependent on stimulus intensity

Whether this actually indicated a shortcoming in the model was not certain and it was suggested that the effects of stimulus intensity on the mechanisms of stimulus decay and on the electrode-electrolyte interface impedance require further investigation.

The ability of the ANF model to predict threshold differences for biphasic, pseudomonophasic and alternating monophasic waveforms was investigated in Chapter 7 (Research objectives 4 and 5). The effect of increases in the IPG, IPI, as well as pulse rate, on thresholds was also simulated. Simulations were performed for both anodic-first and cathodic-first stimuli.

Results indicated that the model correctly predicted threshold reductions for pseudomonophasic compared to biphasic waveforms, although reduction for alternating monophasic waveforms was underestimated. Threshold reductions were more pronounced for cathodic-first stimuli compared to anodic-first stimuli. Increases in IPG and IPI respectively also predicted threshold reductions. Reversal of the phases in pseudomonophasic stimuli suggested a threshold reduction for anodic-first stimuli, but a threshold increase in cathodic-first stimuli. The inclusion of the persistent sodium and slow potassium currents in the model resulted in a reasonably accurate prediction of the non-monotonic behaviour in thresholds for pulse rates higher than 1000 pps. However, thresholds were underestimated in biphasic waveforms at lower pulse rates. The model also did not correctly predict the threshold changes observed for low pulse rate alternating monophasic waveforms. It was suggested that these results could in part be explained by the difference in the refractory periods between real and simulated ANFs, but also the lack of representation of stochasticity observed in real ANFs.

8.3 CONCLUSION AND FUTURE RESEARCH DIRECTIVES

In this study evidence was presented that the temporal characteristics of the human auditory system might be better predicted by using a modified version of the original HH model. Since the ANF model contained both persistent sodium and slow potassium currents, it is suggested that the inclusion of these currents can in part simulate non-monotonic behaviour in ANFs. This finding is valuable to create more realistic neural

models of the electrically stimulated human auditory system.

However, the squid-based dynamics of the dendritic and somal model sections need to be replaced with human dynamics to account fully for experimentally observed ANF excitation behaviour. The general sensory nerve fibre model, on which the ANF model is based, was developed from measurement data on large diameter human peripheral sensory nerve fibres. The ion channel protein (KCNQ2) responsible for slow potassium current represented in this model co-locate with sodium channels at the Ranvier nodes of larger diameter fibres (Taylor *et al.*, 1992; Devaux *et al.*, 2004; Schwarz *et al.*, 2006). Although this protein is also found at Ranvier nodes in smaller diameter fibres, in smaller diameter fibres it co-locates with KCNQ3. The distribution and density of KCNQ3 is fibre diameter dependent, with a very low density of KCNQ3 found in large diameter fibres (Schwarz *et al.*, 2006). KCNQ2 is also not found in cell bodies (Devaux *et al.*, 2004). Hence, the general sensory nerve fibre model can most probably not be used to represent ionic membrane currents in the somas and dendrites of ANF fibres. Furthermore, the dendrite in die ANF model is assumed myelinated, while SEM and TEM studies indicate unmyelinated dendrites in Type I ANF fibres (Glueckert *et al.*, 2005a). Hence a remodelling of these components is advised. Furthermore, the properties and types of ionic membrane currents of spiral ganglion cells have been characterised in murine (Mo *et al.*, 2002; Reid *et al.*, 2004; Hossain *et al.*, 2005; Chen and Davis, 2006) and guinea-pig (Bakondi *et al.*, 2008), but not in human. Consideration to the existence of similar ionic current characteristics in human spiral ganglion cells is advised in further expansions of the ANF model.

The combination of persistent sodium and slow potassium currents alone cannot explain the non-monotonic trends observed in ANF excitation behaviour. A possible contributor to explain these trends may be the inclusion of a stochastic representation of the ion channels at the Ranvier nodes (Macherey *et al.*, 2007). Temporal characteristics such as jitter, FE and refractoriness are dependent on the stochasticity of the fibre and cannot be adequately investigated with a deterministic model (refer for example to Miller *et al.*, 1999b; White, Rubinstein and Kay, 2000; Matsuoka *et al.*, 2001). A stochastic representation of the ion membrane currents of the Ranvier nodes is thus advised.

In persons with longer-term sensory loss, surviving degenerate somas and axons are demyelinated and significantly smaller than in non-degenerate ANFs (Nadol Jr, 1990;

Schuknecht, 1993; Zimmermann *et al.*, 1995; Glueckert *et al.*, 2005a). In Chapter 7 mention was made of the dependency of threshold current on fibre diameter (McNeal, 1976; Deurloo *et al.*, 2001). Furthermore, evidence exists that demyelisation alters excitation behaviour in degenerate myelinated fibres (Dimitrov, 2005; Stephanova, Daskalova and Alexandrov, 2005; Stephanova and Daskalova, 2005a; Stephanova and Daskalova, 2005b). The inclusion of the double cable model as suggested by Nygren and Halter (1999) and Dimitrov (2005) to aid in the modelling of demyelisation of the long-term degenerated ANF is suggested.

Nerve fibre behaviour is also characterised in terms of afterpotentials, the super- and subnormality of the recovery cycle and threshold electrotonus (refer for example to the review by Burke *et al.*, 2001). Initially, after the nodal membrane has depolarised, the nodal and internodal discharges rapidly. This is followed by a slower discharge of the internodal axolemma creating the afterpotentials responsibly for the supernormal phase (Blight, 1985; Burke *et al.*, 2001). The extent of this supernormality is determined by the activation and inactivation of fast potassium ion channels under the myelin sheath in the paranodal region (Burke *et al.*, 2001; McIntyre *et al.*, 2002) as well as internodal sodium ion channels (Dimitrov, 2005). In the current model no internodal ion channels are modelled. The double cable model suggested in the previous paragraph does include representations of internodal ion channels. Inclusion of the double cable model will enable an investigation of the afterpotentials and recovery phase and is thus advised.