# Chapter 1

# INTRODUCTION

## 1.1 PROBLEM STATEMENT

### 1.1.1 Context of the problem

Cochlear implants have been developed to help rehabilitate profoundly deaf persons by providing them with a measure of sound perception through electrical stimulation of auditory nerve fibres (ANFs). The cochlear implant injects electric currents directly into the cochlea by means of an electrode array to stimulate the ANFs directly. The challenge facing researchers is how to convey meaningful speech information to the brain via electrical stimulation. Modern implants are multiple-electrode implants, typically utilizing 16 to 22 electrodes, to take advantage of the tonotopic organization of the ANFs (Loizou, 1998).

However, while the average performance of cochlear implants has improved over the last three decades, large variability in speech performance across individual implant users is still a major problem (Shannon, Fu, Galvin III and Friesen, 2004). This can in part be ascribed to dissimilar neural excitation spread patterns, both intrasubject and intersubject, as a result of variability in factors such as implant type, degree of degeneration of the auditory nerve fibre population across human subjects, electrode geometry, intrascalar electrode location and stimulation strategy (Nadol Jr, 1990; Schuknecht, 1993; Zimmermann, Burgess and Nadol Jr, 1995; Nadol Jr, 1997; Arts, Jones

and Anderson, 2003; Cohen, Richardson, Saunders and Cowan, 2003; Abbas, Hughes, Brown, Miller and South, 2004; Abbas and Miller, 2004; Van Wieringen, Carlyon, Laneau and Wouters, 2005; Fayad and Linthicum Jr, 2006). Even though potential implantees undergo pre-operative auditory testing, the successful outcome of the implantation is not known until after the implant has been switched on (Niparko, 2004). Ideally the electrodes should be situated closest to the sites of surviving ANFs, since this leads to reduced power consumption in the implant, lower stimulation thresholds, narrower neural excitation spread patterns and an increased dynamic range (Townshend and White, 1987; Shepherd, Hatshushika and Clark, 1993; Rebscher, Snyder and Leake, 2001; Abbas and Miller, 2004; Leake and Rebscher, 2004; Glueckert, Pfaller, Kinnefors, Rask-Andersen and Schrott-Fischer, 2005a). A telemetric measuring system for cochlear implants, called Neural Response Telemetry (NRT) by Cochlear Limited, is available to measure the electrically evoked compound action potential (ECAP) of the ANFs (see for example Abbas, Brown, Shallop, Firszt, Hughes, Hong and Staller, 1999; Dillier, Lai, Almqvist, Frohne, Müller-Deile, Stecker and van Wallenberg, 2002). ECAP data can be used to obtain an objective estimate of the dynamic range, and thus the extent of neural survival, through measurement of the behavioural threshold and most comfort level (MCL) of implantees (see for example Abbas *et al.*, 1999; Franck and Norton, 2001; Dillier *et al.*, 2002). It is also used to examine the extent to which psychophysical measurements reflect the amount of neural excitation spread (Cohen *et al.*, 2003).

The primary means of modelling the electrically stimulated human auditory system is using mammalian research animals, especially cats and guinea-pigs (see for example Javel, Tong, Shepherd and Clark, 1987; Abbas and Miller, 2004). Since these animals' cochleae have larger dimensions than those of smaller rodents, multi-electrode arrays similar to those implanted in humans, can be used. Computational models are used in combination with animal studies to enhance understanding of the underlying physiology of electric hearing (Abbas and Miller, 2004). Several ANF models have been developed (Bruce, White, Irlicht, O'Leary, Dynes, Javel and Clark, 1999c; Frijns, Briaire and Schoonhoven, 2000; Matsuoka, Rubinstein, Abbas and Miller, 2001; Rattay, Lutter and Felix, 2001b; Briaire and Frijns, 2005; Macherey, Carlyon, van Wieringen and Wouters, 2007). The ANF models are frequently used in combination with volume-conduction models of the cochlea to predict neural excitation profiles (Frijns *et al.*, 2000; Hanekom, 2001b; Rattay, Leao and Felix, 2001a). An advantage of the computer models is that it is possible to isolate and manipulate critical model para-

meters, as well as modelling of the differences in cochlear anatomy and ANF physiology between species, which is not always feasible with animal studies (Morse and Evans, 2003). Most of these models are at least partially based on animal data. However, the differences in cochlear structures between animals and humans, differences in the number and percentage myelination of auditory nerve fibres and innervation patterns of both inner and outer hair cells across species, may be physiologically significant and care must be taken when extrapolating the animal results to predict results in human implantees (Nadol Jr, 1988; Frijns, Briaire and Grote, 2001). Computer models can only approximate a real neural system, owing to the complexity of the latter. The modeller therefore has to make certain simplification assumptions when abstracting the real system and this place some limitations on the model as to the realistic correctness and completeness of the physiology and anatomy represented (Morse and Evans, 2003).

### 1.1.2 Research gap

Human ANF models have been developed by Briaire and Frijns (2005; 2006) and Rattay *et al.* (2001b). These models are partially based on human morphometric[1] data, while the ionic current dynamics are still those of rat and squid respectively. However, the Briaire and Frijns (2005) model cannot fully account for the ECAP morphology[2] observed in humans, while Macherey *et al.* (2007) argue that the ion channels of the squid based model, on which the Rattay *et al.* (2001b) model is based, are not sufficient to account for non-monotonic excitation behaviour experimentally observed. Hence, a more comprehensive computer model is needed, based on human cochlear dimensions and peripheral ANF characteristics, incorporating simulation of temporal characteristics.

Even though the physical structure of human ANFs has been investigated (refer to

[1] In Murray, Simpson and Weiner (1989) morphometry is defined as: "The process of measuring the shape and dimensions of landforms, living organisms, or other objects; (also) the shape and dimensions of an object so measured."

[2] Morphology is defined in Murray *et al.* (1989) as: "**1.** *Biol.* The branch of biology that deals with the form of living organisms and their parts, and the relationships between their structures. Formerly: *spec.* the comparison of the forms of organisms and their parts in order to identify homologous structures (cf. quots. 1853, 1859, 1872). **2.** orig. and chiefly *Science.* Shape, form, external structure or arrangement, esp. as an object of study or classification. Also: a particular shape, form, or external structure, esp. of (a part of) an organism, landform, etc."

Section 2.2), the properties and types of ionic membrane currents of spiral ganglion cells have been characterised in murine (Mo, Adamson and Davis, 2002; Reid, Flores-Otero and Davis, 2004; Hossain, Antic, Yang, Rasband and Morest, 2005; Chen and Davis, 2006) and guinea-pig (Bakondi, Pór, Kovács, Szucs and Rusznák, 2008), but not in human. Since the human ANF is of the peripheral sensory type, the possibility exists that similar ionic membrane currents to those found in a peripheral sensory fibre might be present. Ionic membrane current data from single human myelinated peripheral nerve fibres have been recorded by Reid, Bostock and Schwarz (1993), Scholz, Reid, Vogel and Bostock (1993), Schwarz, Reid and Bostock (1995) and Reid, Scholz, Bostock and Vogel (1999), but only the Schwarz *et al.* (1995) data have been used to develop a human nerve fibre model. However, to date none of these data have been applied to simulate human ANFs (Section 2.1.1). The development of a general human peripheral sensory nerve fibre can hence serve as an intermediate step to develop a human ANF model, until ionic membrane current data from human ANFs become available.

## 1.2 RESEARCH OBJECTIVE AND QUESTIONS

The objective of this study is to determine whether parameters of the nerve fibre model by Rattay *et al.* (2001b), which assumes a propagating action potential driven by Hodgkin-Huxley (HH) dynamics (Hodgkin and Huxley, 1952), can be modified with human morphometric and physiological data to predict excitability behaviour of human ANFs more accurately, including temporal characteristics. When coupled to the volume-conduction cochlear model by Hanekom (2001b) simulation of the ECAP method is effected to facilitate comparison between simulated and measured psychophysical forward masking experimental results. These expansions on current ANF modelling capabilities could lead to a better understanding of neural excitation behaviour as measured in psychoacoustic experiments.

The following research questions can be formulated from this objective:

1. The original HH model is developed for the giant unmyelinated nerve fibre of squid. Is it possible to replace the squid morphometric and physiological properties by human morphometric and physiological properties to improve predicted

human ANF responses? What properties should be changed?

2. Different cochlear implant designs are available and their placements inside the cochlea differ. Does the new ANF model provide additional or improved estimates of the effects of these differences on nerve fibre excitation behaviour to those provided by existing ANF models?

3. Current nerve fibre models do not explicitly take temporal characteristics of the input signal into account. Will the adapted nerve fibre model be able to isolate the effects that these temporal characteristics have on measured data? How well will the model predict variations in temporal characteristics compared to the current models?

4. One way of comparing predicted results with measured psychophysical forward masking experimental results gained from human implantees is modelling the ECAP method used in NRT. A comprehensive model to predict ECAP data has been developed by Briaire and Frijns (2005). However, their results indicate that their nerve fibre model can not fully predict measured ECAP data. If the adapted nerve fibre model developed in this study is used in conjunction with their ECAP method, how well will the modelled ECAP results compare with results from literature? How well do these results predict nerve fibre excitation behaviour?

## 1.3 HYPOTHESIS AND APPROACH

The hypothesis is that a more accurate model of the electrically stimulated human Type I ANF will be able to predict excitation behaviour measurements better, for example ECAP profile widths and stimulus temporal characteristics (mean latency, threshold, threshold-distance and strength-duration relationships), compared to those predicted by current ANF models. Simulated results will be verified against experimental results from humans only. A bottom-up approach is followed, starting with the current Hodgkin-Huxley and Rattay *et al.* (2001b) models and ending with the revised ANF model. The revision is implemented in phases.

The solution to the main research questions can be broken down into five goals:

1. Expansion of the existing ANF model by Rattay *et al.* (2001b) to represent a more accurate model of the human ANF with regard to physiology and morphometry, both for damaged (degenerate) and non-damaged (non-degenerate) nerve fibres. Model development is broken down into three phases. Firstly, the HH model has to be 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). Secondly, a general human peripheral sensory nerve fibre cable model, based on a combination of the models by Rattay *et al.* (2001b) and Blight (1985), has to be constructed using human sensory nerve fibre morphometric data. Thirdly, a Type I human ANF model, based on the model by Rattay *et al.* (2001b), but with the axon replaced with the generalised human sensory nerve fibre model, has to be developed.

2. Development of a simple method to simulate the ECAP method and to estimate stimulus attenuation values by calculating the values that best fit the modelled excitation profile widths to the measured ECAP profile widths.

3. Comparison of predicted simulated ECAP profile widths with NRT results documented in literature to gain a better understanding of the effect neural excitation has on speech perception. Firstly the simulated data have to be compared with existing results (see for example Cohen *et al.*, 2003; Polak, Hodges, King and Balkany, 2004) to verify model outcomes. Then, using the same parameters used during the psycho-physical experiments, the simulated ECAP profile width results have to be compared with experimental results.

4. Evaluation of the temporal characteristics of the model. The model should be able to predict single-pulse and pulse-train responses as documented in literature.

5. Prediction of neural excitation threshold and excitation patterns (compare with Van Wieringen *et al.*, 2005; Macherey *et al.*, 2007) for different stimulation parameters (including pulse width, intensity, pulse rate, pulse shape, and stimulation mode).

## 1.4 RESEARCH CONTRIBUTION

The research contributions made by this study include the following:

1. The modification of the original HH model to predict the excitation behaviour of a generalised human peripheral sensory nerve fibre. This study was the first to show that the HH model equations could be modified successfully without using the Goldman-Hodgkin-Katz (GHK) equations. As far as is known, the proposed model is the most comprehensive available at present.

2. A more comprehensive establishment of temperature dependence of the model's physiological and electrical parameters compared to other existing models.

3. The development of a more realistic model of the human Type I ANF to predict excitation behaviour of the electrically stimulated human auditory system.

4. From the comparison between predicted and experimentally measured results of Type I ANF fibres, the existence of similar transient and persistent sodium as well as slow potassium ionic membrane currents to those present in general sensory nerve fibres can be deduced.

5. Confirmation that chronaxie, rheobase current, mean latency, threshold and relative refractory periods are dependent on the amount of degeneracy of the ANF.

6. Confirmation that electrode arrays located closer to the modiolus produce more focused neural excitation spread than more laterally located electrode arrays.

7. Evidence that the ANF model can account for threshold differences observed between different asymmetric waveforms.

8. Evidence that the combination of persistent sodium and slow potassium ionic membrane currents can in part predict non-monotonic excitation behaviour.

9. The simplified method to solve the inverse problem, i.e. to calculate the ECAP response as a result of neural excitation, contributes to the modelling approach to cochlear implant research in the following ways:

   (a) it provides a means to compare NRT experimental data with the results obtained from any model that predicts neural excitation profiles on the

neural level (including the detailed finite element volume-conduction neural model used in this study and purely analytical volume-conduction models where potential distribution is calculated in a homogeneous medium (Jolly, Spelman and Clopton, 1996; Hanekom, 2001a) coupled to a nerve fibre model) for verification of such models,

(b) it provides a computationally effective way to obtain an estimate of ECAP profile widths from the output of models that calculate the excitation profiles at the neural level, and

(c) it provides an indirect way to estimate stimulus attenuation by calculating the value of the parameter that produces the best fit to experimental data.

## 1.5 OVERVIEW OF THE STUDY

The development of a comprehensive model of the implanted human cochlea can be broken down into two parts, namely a volume-conduction model of the implanted cochlea and a model of the electrically stimulated ANF (Figure 1.1). As stated previously, the development of the human ANF model is covered in this study, as indicated by the black square blocks in the diagram in Figure 1.1. The ANF consists of dendritic, somal and axonal sections, as indicated by the dot-dashed block. The methods used to compare and verify simulated results against experimental data such as psychoacoustic phenomena and ECAP widths are grouped together in the grey dashed block in the figure.

Related issues not covered by the study include:

1. Modelling of ephaptic excitation between groups of nerve fibres (Jönsson, Hanekom and Hanekom, 2008).
2. An extension of the double cable model as suggested by Nygren and Halter (1999) to aid in the modelling of demyelisation of the long-term degenerate ANF (Schuknecht, 1993).
3. Modelling of stochastic nerve fibre membrane properties. ANF stochastic models have been described by Rubinstein (1995), Matsuoka *et al.* (2001) and Bruce (2007).

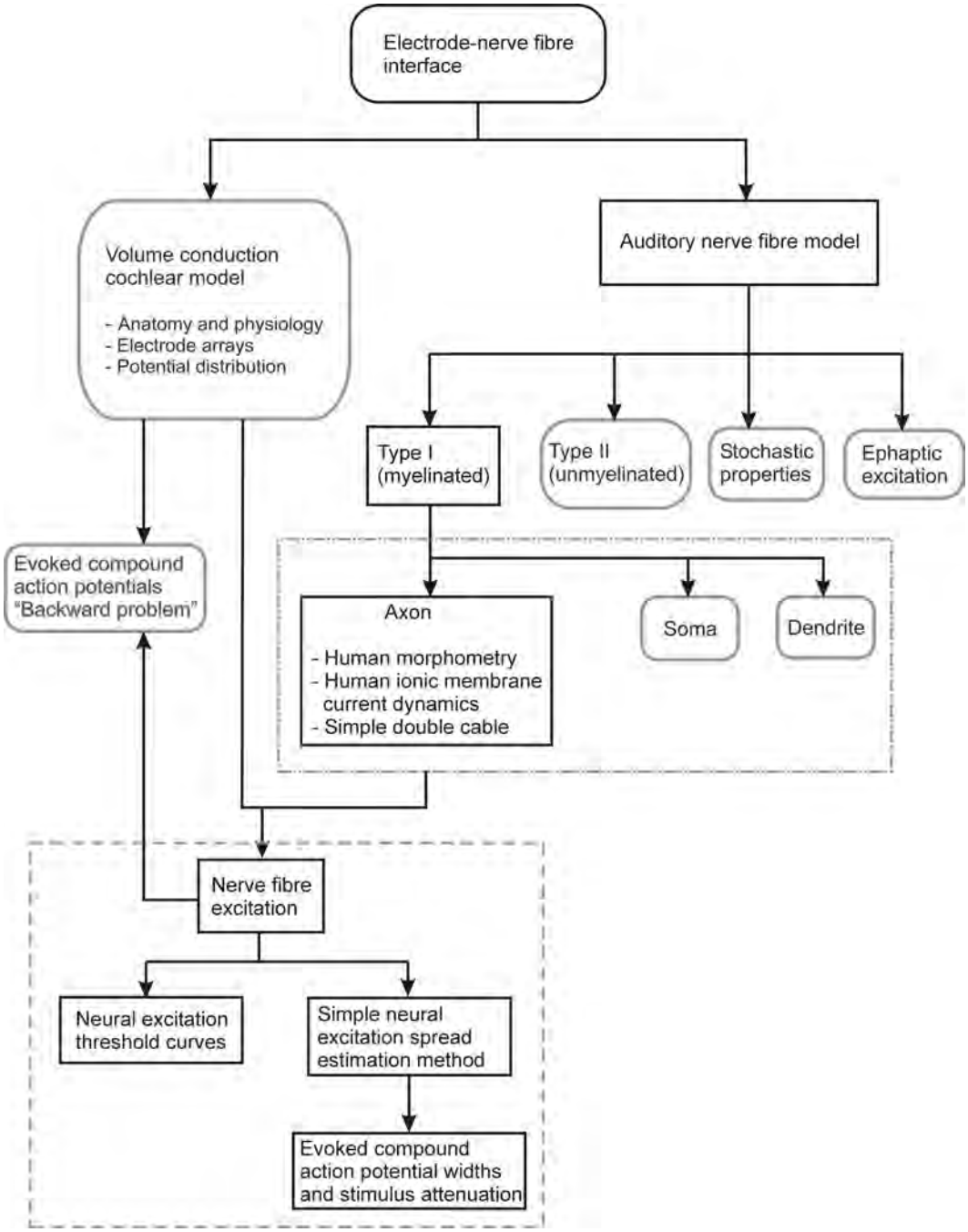


Figure 1.1: Diagram of the electrode-nerve fibre interface. Issues covered by this study are indicated by the black square blocks, while the grey rounded blocks represent related issues. Nerve fibre sections are included in the dot-dashed block. Simulation methods used to verify the model results are grouped together in the grey dashed block.

4. An expansion of the volume-conduction model to make provision for simulation of the full 2.75 turns, the tapering of the cochlear ducts and capacitances of the cochlear structures.

The thesis is divided into the following chapters:

**In Chapter 2** the background argument necessary to understand the research problem is presented.

**In Chapter 3** the development of the human Ranvier node model based on the modification of the HH model is described.

**In Chapter 4** the Ranvier node model is incorporated into a generalised human peripheral sensory nerve fibre model.

**In Chapter 5** the Type I ANF model of Rattay *et al.* (2001b) is modified by replacing the axon with the generalised sensory nerve fibre model.

**In Chapter 6** the development of a simple method to simulate ECAPs and subsequent calculation of neural excitation widths are discussed.

**In Chapter 7** the influence of the temporal characteristics of different waveforms on simulated behavioural threshold is investigated and compared to measured data.

**In Chapter 8** the thesis is concluded with a general discussion and conclusion of the study, as well as the provision of directives for future research.