Cochlear implants: Modeling electrophysiological responses

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CHAPTER 1

Introduction

1 Introduction

Cochlear implants are implantable hearing devices for individuals with severe to profound hearing loss. Since its introduction in the clinics in the 1980s many people have benefited from these devices and valuable adjustments to the design of the hardware and software have been implemented (Zeng et al., 2008). Over recent years however, in spite of considerable efforts, development of sound coding strategies has stagnated. The drawbacks and restrictions related to testing of new coding strategies in patients require innovative ways to evaluate sound coding developments. One such approach is the computational evaluation of sound coding in the implanted ear. The digital age, with its powerful computers and recent developments in information theory, provides all necessary means for the development of appropriate models and interpretation of their output. In this thesis, computational models of the implanted auditory periphery's response to sound are described. This introduction will explain the basic functioning of the auditory system, the working mechanism of cochlear implants and the state of the art of cochlear implant sound coding modeling.

1.1 The ear & hearing

In a healthy ear, sound travels through the outer ear (pinna and ear canal) and the middle ear (tympanic membrane and the middle ear ossicles) to the inner ear from where sound is transmitted to the auditory nerve. The purpose of the outer and middle ears is to focus the pressure of the sound wave on the oval window, a membrane that separates the middle ear from the cochlear endolymphatic fluid, figure 1.1A&B. The inner ear, or cochlea, is part of the vestibulocochlear organ depicted in figure 1.1A. Located in the scala media of the cochlea is the organ of Corti, shown in figure 1.1C. This is the actual hearing organ where hair cells located on the basilar membrane convert mechanical energy of the resonating membrane to an electric signal reaching the auditory nerve through synapses. The cochlea is a marvelous organ, it is tonotopically organized to fulfill its frequency-analyzing function. It contains active elements (outer hair cells) increasing its sensitivity and selectivity, and has nonlinearity in both inner and outer hair cell sensitivities to efficiently transduce relevant sounds. By virtue of these factors, the human ear is most sensitive to frequencies present in human speech and is optimized to analyze the dynamic range of speech. The auditory nerve is just as wonderous, it preserves the frequency-selectivity by both place- and time coding and sophistically encodes loudness by an associated spiking pattern in the auditory nerve. Because of spontaneous activity in both types of hair cells and in the auditory neurons, the auditory system is 'alert' and sensitive to sudden and soft sounds. Although the peripheral auditory system is very intriguing, the real magic happens higher up in the auditory system. Different relay stations, where information is sorted and processed, send the signal towards the brain. The most important relay stations are the cochlear nuclei, olivary nuclei located in the lateral lemniscus, the inferior colliculi and the medial geniculate bodies (the auditory portion of the thalamus).

After this, the signal reaches the auditory cortices. Information processing follows in a bottom-up approach (the afferent system), and is controlled and attuned by a top-down approach (efferent system). There are connections between the differently leveled and lateralized nuclei, which is a prerequisite for, amongst others purposes, our specific localization abilities. The further up in the system you go, the more complex the processing becomes. Attention, association, learning, memorizing and emotion, and other related connections with the limbic system are of essence to our perception of sound.

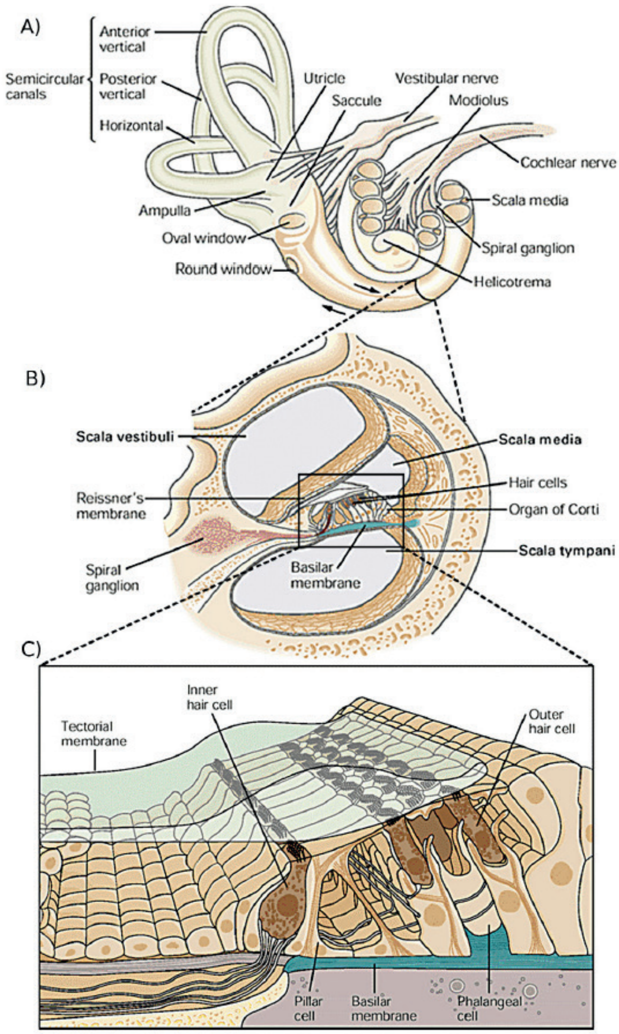

Figure 1.1 Anatomy of the inner ear. A) Vestibulocochlear organ; showing the semicircular canals, utricle and saccule of the vestibular organ and the spiraling cochlea; B) a cross-section of the cochlea showing the scala media; C) zoomed in at the organ of corti visualizing the inner and outer hair cells and the basilar membrane [Adopted from Kandel and Schwartz (2000), copyright McGraw-Hill Education]

1.2 Hearing loss and rehabilitation

Malfunctioning of (part of) the hearing system causes hearing loss. Conductive hearing loss is a consequence of damage to the outer or middle ear and can lead to a hearing loss of up to 60 dB. Damage to the inner ear, referred to as perceptive hearing loss, manifests as a hearing loss with a severity ranging from mild to profound. Auditory problems originating higher up in the auditory system, e.g. auditory neuropathy or auditory processing disorders, are much less common. Prevalence of disabling hearing loss is estimated by the WHO in 2018 at 6.1% of the world's population, when defined as a loss of more than 40 dB in the better hearing ear in adults and 30 dB in children (https://www.who.int/pbd/deafness/estimates/en/). Congenital hearing losses are hereditary, can be caused by infectious diseases, or due to prenatal complications. Acquired hearing losses can have hereditary or infectious causes but can also, and with increasing prevalence, be concomitant with age or manifest as a consequence of noise exposure.

The perception of sound is important for communication with others and for awareness of the world around us. Hearing rehabilitation is developed to disburden those suffering from hearing loss. It can come in the form of a hearing aid, a bone conduction device or a cochlear implant. A hearing aid amplifies sound before it enters the ear canal. A bone conduction device transfers the sound directly to the inner ear through mechanical vibration of the skull. In a cochlear implant (CI) the auditory nerve is directly activated through electrical stimulation by an electrode placed in the cochlea, see figure 1.2. Sign language provides a means of communication for those who cannot use, or are not sufficiently rehabilitated by a hearing device.

1.3 Cochlear Implants

The CI is the designated rehabilitation device for those with severe to profound hearing loss. As of 2016 an estimated 600 000 devices were implanted worldwide (The Ear Foundation, UK). Currently, in the Netherlands, people with rehabilitated speech perception scores, scored by phonemes correct, of lower than 70% for speech presented at a level of 65 dB_{HL} are considered eligible for implantation. The functional benefits brought about by CIs range from mere detection of environmental sounds to restoration of speech perception scores of over 90% in quiet surroundings. The prognosis for the functional outcome depends on the hearing loss history, etiology, age at implantation, cognitive abilities and electrode position (Holden et al., 2013), but the exact relation between patient characteristics and perceptual outcomes are not understood well enough to exactly predict outcomes. Due to this complexity, the question whether or not cochlear implantation is the optimal treatment for an individual patient should be carefully considered by a multidisciplinary team (involving an audiologist, speech therapist, ENT-surgeon, and social worker) in consultation with the patient.

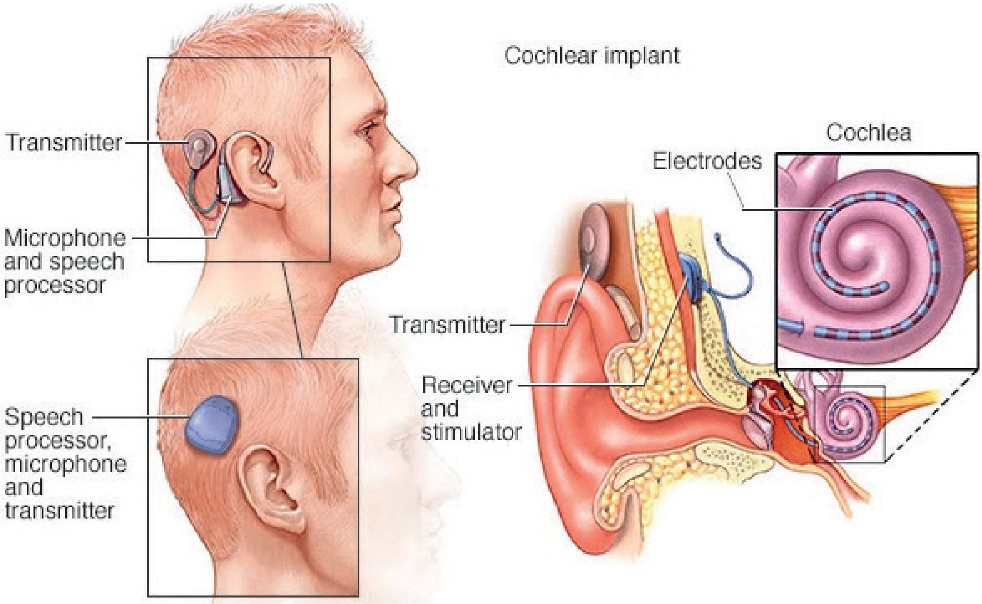

Figure 1.2. Configuration of the external (transmitter, microphone, speech processor) and internal parts (stimulator and electrodes) of the cochlear implant (Reprinted with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)

The first attempts to restore hearing with electrical stimulation were done in the late sixties and early seventies (Djourno and Eyries, 1957; Doyle et al., 1964; Simmons et al., 1964) but due to skepticism and safety issues it was not until 1984 that Food and Drug Administration (FDA) approval opened up the road for development of the CIs. The House 3M single-electrode device (House and Urban, 1973) was the first CI available on the market, and was followed in the years after by multichannel electrodes (Loeb, 1990). The CI consists of an external processor that detects and manipulates sound and a coil, connected via a magnet to the internal part, that sends the signal to the electrode placed in the inner ear (figure 1.2). Currently, CI electrodes contain between 12 and 24 electrode-contacts (depending on the manufacturer) located alongside one-another. Each electrode-contact stimulates a different part of the tonotopically organized auditory nerve, thereby making use of place-coding to provide frequency-specific information.

1.4 Sound coding in cochlear implants

The first cochlear implants used compressed analog techniques in which the electrical equivalent of the sound pressure was administered continuously to frequency-specific electrode-contacts. In 1991, the continuous interleaved sampling (CIS) technique was introduced, which employs consecutive stimulation of the different electrode-contacts. With this type of coding strategy, speech perception and safety improved and the clinical implementation of CIs gained momentum (Wilson et al., 1991). In CIs, the auditory nerve is excited by biphasic (charge-balanced) electrical stimulation from each electrode contact. Loudness is encoded by either increasing the width of the phases or the amplitude of the transferred current. Since the introduction of CIS, numerous researchers worked on further improvement of perception with and usability of CIs (Wouters et al., 2015). To save battery-life and to minimize electrode interactions, peak-picking strategies are combined with CIS, e.g. MP3000. To increase the number of stimulation contacts, 'virtual' electrodes are used in HiRes, in which, via current steering, the neural region in between physical electrode-contacts is stimulated. CIs are designed to encode speech in an optimized and efficient way, for this purpose they discard fine-structure to a large extent. In Fine-Structure Processing (FSP) strategies, the timing of stimulation is dependent on zero-crossings of the sound signal in a particular frequency band to maintain the fine structure of that band. However, even for such strategies, speech understanding in noise, tonal perception, voice recognition and music appreciation are often unsatisfactory. Despite all efforts, speech perception tests show that since the introduction of CIS, new strategies have not led to further improvement of speech scores, which have stagnated, on average, around 80% (Zeng, 2004).

Evaluation of new sound coding strategies is challenging for three reasons: it involves time- and energy consuming patient-testing, the study power is usually limited by group size, because only a restricted pool of patients is able to perform the tests and lastly a large patient-variability leads to negligible improvement on a group level, or may even cancel out opposing effects from different sub-groups. Alternatively, objective measurements, such as Evoked Compound Action Potential (eCAP) recordings, can also be used to test the performance of CIs. However, similarly to the difficulties of evaluating new coding strategies laid out above, the relationship between objective measures, individual fittings and performance are difficult to establish (de Vos et al., 2017; McKay et al., 2013). Parallel to the development of sound coding strategies, efforts to improve performance and subjective satisfaction with CIs were directed at electrode design (Dhanasingh and Jolly, 2017), musical therapy training (Fuller et al., 2014), bilateral implantation (van Schoonhoven et al., 2013), and electroacoustic stimulation (EAS) (Talbot and Hartley, 2008). EAS systems are designed for patients with residual hearing, so that they can benefit from the combination of acoustic and electrical hearing in the same ear.

1.5 Recording peripheral responses to sound segments

There are different objective measures that record the responses of the electrically stimulated peripheral auditory system to sound segments. Three such measures are introduced in this section. One example of an objective measure, in response to long duration electrical stimulation, is the single fiber action potential (SFAP). In the SFAP, responses to pulse trains in the electrically stimulated ear are recorded invasively from single neurons in animals. By doing so, exact spike timings of the neuron under test are recorded. From these spike times, average spike rates, or times between subsequent action potentials, can be calculated and plotted in a post-stimulus time histogram (PSTH) or inter-spike interval histograms (IH) respectively. When periodically amplitude modulated pulse trains are used, the spike times relative to the stimulus period yield the period histograms (PH), and modulation-following behavior can be calculated with the Vector Strength (VS). These responses all provide detailed information about how the neuron responds to stimulation. Due to its intrusiveness, the SFAP has only been recorded in animals. Animals' auditory nerve fibers are morphologically and physiologically somewhat different from human auditory nerve fibers, for instance in diameter and myelination (Liu et al., 2015; Paintal, 1966; Spoendlin and Schrott, 1989).

In contrast to the SFAP, which is recorded only from animals, the eCAP is the best available method to measure neural responses from human CI users. These recordings are therefore, very valuable to validate the simulated responses for the human situation. Moreover eCAP responses have been obtained in both humans and animals with different degrees of hearing loss. This provides the possibility to evaluate the effect of hearing loss on neural behavior. ECAPs in response to single or double pulses are studied extensively (Briaire and Frijns, 2005; Miller et al., 1999), but they can also be obtained in response to pulse trains (Wilson et al., 1997).

For the purpose of EAS, electrocochleography (ECochG), which goes way back as an objective tool in the diagnosis of hearing loss (Eggermont, 2017), recently found its place to objectively measure acoustic hearing during cochlear implant surgery and fitting (Koka et al., 2017). With this method responses of the implanted auditory periphery to acoustic sound segments can be recorded. In ECochG, electrical potentials generated by hair cell and neural activity in response to sound stimulation are recorded by an electrode, usually placed close to the round window. Nowadays, through the use of the reverse telemetry functionality of cochlear implants, ECochG could readily be recorded intracochlearly. In intracochlear EcochG recordings, cochlear potentials in response to acoustic stimulation are recorded by the cochlear implant electrode. This has recently been suggested as a tool to detect hair cell damage (Koka et. al., 2017b).

1.6 Modeling cochlear implant sound coding

To improve our understanding of objective measures, computational models can be used. Through the use of such models the effect of individual differences in the auditory system, perhaps related to hearing loss, can be investigated. Responses of the implanted auditory system can be modeled to gain more insight in interpatient-differences and to predict functional outcomes with different stimulation strategies. Such models can be built using either a biophysical or phenomenological approach.

In a biophysical model, expressions to describe behavior of physiological elements of the auditory neuron are based on voltage clamp recordings, usually made from laboratory animals. For an overview of existing models view O'Brien et al. (2016). Hodgkin and Huxley were the first to quantitatively describe nerve membrane behavior in response to an induced membrane current (Hodgkin and Huxley, 1952). Later, these differential equations were adjusted to describe myelinated and mammalian nerve fibers (Frankenhaeuser and

Huxley, 1964; Schwarz and Eikhof, 1987). To calculate responses to an external electrical stimulus, a cable model was required that calculates potentials at several nodes (McNeal, 1976), that was based on a realistic nerve morphology (Frijns et al., 1994; Frijns and ten Kate, 1994) and described the effects of the spatial distribution of currents outside the membrane (Reilly et al., 1985). It was shown that a multiple non-linear node model was required to accurately model stimulus repetition rates, as limits to these rates were caused by nerve fiber conduction properties rather than by single-node frequency-following behavior. In the later published generalized Schwarz-Eikhof-Frijns (GSEF) model, kinetics were based on mammalian fibers and generalized for different diameters. In the LUMC, a realistic 3D model of the intracochlear potentials and a multi-nodal active-cable model of the auditory nerve with GSEF characteristics has been developed and validated for evaluation of current spread and spread of excitation in response to single pulses (Dekker et al., 2014; Frijns et al., 2001, 1995; Kalkman et al., 2015, 2014). The model reproduced deterministic threshold characteristics and refractory behavior for different pulse shapes. Unfortunately, biophysical models often do not include stochasticity or long temporal effects, which are required for modeling long duration segments of stimulation. Inclusion of these factors while taking a biophysical approach would require a large number of parameters. Moreover, calculation of responses of a large number of nerve fibers to long duration segments would require tremendous computational power.

Phenomenological model types predict the neural response with a simplified description of neural behavior. The characteristics of phenomena are deduced from single fiber action potential (SFAP) recordings, gross potential recordings such as eCAPs or psychophysical measurements. For a review of phenomenological models of responses of the auditory periphery to electrical stimulation see Takanen et al. (2016). Phenomena related to electrical stimulation include refractoriness, adaptation after long duration of spiking, accommodation to prolonged stimulation (irrespective of the neural response), facilitation (increased firing in response to specific rates), latency, jitter and stochasticity in the neural responses. In most of these models, initial thresholds are determined with a statistical process (point-process) (Goldwyn et al., 2010, 2012), or with a simple electrical network such as the leaky integrate-and-fire (LIF) models (Bruce et al., 1999b, 1999a; Fredelake and Hohmann, 2012; Hamacher, 2004; Horne et al., 2016; Macherey et al., 2007). Both point process and LIF models can be extended with the spike-history and stochastic effects described here.

For both types of models, to calculate responses of the complete auditory nerve, a realistic distribution of current spread within the cochlea is required. So as to simulate responses to pulse trains, a 3D model should be combined with pulse-dependent thresholds, stochastic effects and long temporal components, all preferably minimizing the computational power, so that speech-relevant sections of sound can be modeled with reasonable amounts of computation.

2 Aims and method

The aim of the current research is to better understand how the implanted auditory periphery responds to sound, to

1. aid in the evaluation of sound coding

2. gain more understanding of inter-patient differences

To do this, models of responses to sound of the implanted auditory periphery were developed. Models of responses to sound in cochlear implant subjects can function as digital test-boards for sound coding strategies and recordings from the implant, thereby speeding up developments in CI design. Moreover, they can be used to relate interpatient differences from objective recordings to differences in behavior of the auditory peripheral system. Requirements for such models include accurate and fast simulations in response to a wide range of stimuli.

In this thesis, a model of responses to electrical stimulation was developed that combined a biophysical and phenomenological approach. Thresholds dependent on current distribution and different pulse shapes were pre-calculated with the detailed 3D cochlear model and the biophysical multi-nodal cable- neuron model and stored in a database. Parameters of neural behavior that required too much computational time, or with the biophysical model too many fitting parameters, were implemented using a phenomenological approach. Phenomena related to electrical stimulation include temporal and stochastic effects in the neural responses. The deterministic thresholds were adjusted according to phenomenological parameters to describe stochasticity, refractoriness, accommodation and adaptation. In this manner, a model that was fast enough to simulate responses to pulse trains, and detailed enough to simulate responses to all sorts of pulse shapes was developed.

A model of responses of the implanted auditory periphery to sound was also developed. This model had to include hair cell activation evoked by sound and was based on a previously developed model (Zilany et al., 2014). In addition, spatial spread of electrical currents evoked by hair cell activation had to be calculated. This was done with the 3D model describing electrical conductivities in the auditory periphery. By combining these, responses to acoustic stimulation could be modeled at the electrode locations for EAS-subjects.

The responses of both models were validated by comparison to objective recordings. Recorded inter-patient differences were explored by model parameter variations.

3 Outline of this thesis

Chapters 2 and 3 describe the neural model in detail and validate the models' responses to constant amplitude electric pulse trains and amplitude modulated electric pulse trains respectively. The work covers durations of several hundreds of milliseconds and with rates up to 5000 pps. **Chapter 4** shows that power-law adaptation is a required adjustment to the model when simulations with durations of seconds up to several minutes are required. In **chapter 5** the model is used to simulate eCAP responses to pulse trains. Previously published data of pulse-train recordings in humans are correctly replicated, indicating that the model is a reliable tool to evaluate human neural responses. Moreover, the pulse-train eCAP can be used as a tool to test inter-patient differences in their temporal responses. For the purpose of evaluating electroacoustic stimulation, and aid in the interpretation of ECochG recordings made intra- and post-operatively, **chapter 6** shows validation of a model that simulates recordings with the cochlear implant of hair cell responses to sound. An overall discussion of the outline, results, clinical relevance and future directions of the presented work is given in **chapter 7**.