Universiteit Leiden
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Cochlear implants: Modeling electrophysiological responses

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Citation

Gendt, M. J. van. (2021, March 25). *Cochlear implants: Modeling electrophysiological responses*. Retrieved from https://hdl.handle.net/1887/3149359

Version: Publisher's Version
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Title: Cochlear implants: Modeling electrophysiological responses
Issue date: 2021-03-25

CHAPTER 7

Discussion

Two models that can simulate acoustic responses of the implanted peripheral auditory system were presented in this thesis. One model describes responses of the auditory nerve to electrical stimulation, the other describes how responses to acoustic stimulation are recorded in a cochlear implant. In the first section of this discussion, both model designs are discussed. In the following section, the different outcome measures are discussed: single fiber action potential (SFAP), evoked compound action potential (ECAP). The SFAPs and ECAPs were calculated with the neural model, ECochG recordings were calculated with the cochlear model. In the section thereafter, the most important model parameters, and how they affect outcomes of objective measures are discussed. Limitations and suggestions for improved model design are discussed in the next section. The concluding sections describe alternative model applications and future research directions.

Model design

Neural response to electrical stimulation

With the first model responses of the auditory nerve to electrical pulse trains were simulated. It was built on an existing model of the cochlea and auditory nerve that simulates deterministic initial fiber thresholds in response to single pulses (Kalkman et al., 2015, 2014). The model was extended so that responses to pulse trains can be simulated. In the previous model, the initial thresholds were calculated with a realistic 3D geometric model of the cochlea and a biophysical active multi-nodal cable-neuron model of 32,000 nerve fibers (Frijns et al., 1994; Frijns and ten Kate, 1994; Kalkman et al., 2015). Thresholds could be calculated in response to predefined electrode configurations, pulse shapes, sizes and amplitudes, irrespective of spiking and stimulation history. In the current model, these initial thresholds were pre-calculated and stored in a database. To calculate responses to pulse trains, stochasticity and temporal components have to be described in a computationally efficient manner and with a limited parameter space. To achieve this, the pre-calculated thresholds were adjusted temporally and stochastically using a phenomenological approach. To accurately simulate temporal behavior in response to long duration pulse trains, long-term-adaptation components were introduced in the new model. it was shown that both a spiking-dependent adaptation and a stimulus-dependent adaptation (or accommodation) are required to correctly predict spike patterns. The resulting model is the first of its kind to include a combination of adaptation and accommodation. Stochasticity was implemented in the model as a relative spread (RS) on the threshold, by stochastic distributions of parameters over the fibers and by stochastic variation of the parameters in time. In a further refined version of the model, latency and jitter were implemented in the phenomenological part of the model. By having combined a biophysical approach with a phenomenological approach, this model can deal with both spatial and temporal effects in a computationally efficient manner. Because of this, single fiber action potentials (SFAPs) can be simulated for all nerve fibers in response to pulse trains. All single fiber responses together yield the pulse-train evoked compound action potentials (ECAPs). To simulate these, the spike patterns were convolved with their contributions to the potentials recorded at each electrode contact.

Cochlear implant recordings of hair cell activity

The second model simulates how the implanted electrode records hair cell activity in response to sound, the intracochlear electrocochleography (ECochG). This model is a combination of two existing models; a model of hair cell activation (Zilany et al., 2014) and a 3D electrical conduction model (Kalkman et al., 2015) of the cochlea. Intracellular hair cell voltages were calculated with the hair cell activation model. The thus calculated intracellular voltages were similar to recordings from animal studies. Extracellular currents are calculated based on hair cell membrane resistances and capacitive low-pass filtering properties of the membrane. The 3D volume conduction model is used to calculate electrical impedances between hair cell dipoles at 3200 spatially different locations along the basilar membrane and each electrode contact. For the implanted electrode array two different designs and cochlear morphologies were used. Combining the extracellular hair cell currents with the impedances yielded simulations of the intracochlearly recorded ECochG.

Model outcomes

Responses of the peripheral auditory system either to acoustic or electrical stimulation can be recorded objectively with SFAP, ECAP and eCochG recordings, as elaborated in the introduction. Here, the ability of the models to simulate such recordings is evaluated. Single Fiber Action Potential (SFAP) recordings are made from individual neurons and can therefore be directly compared to simulated spike timings. The model of neural responses accurately simulated discharge rate I/O curves, post-stimulus time histograms (PSTH), period histograms (PH), and inter-spike interval histograms (IH), and their variances obtained from SFAP recordings (Bruce et al., 1999a; Javel et al., 1987; Litvak et al., 2001; Miller et al., 2008; Zhang et al., 2007; chapters 2 and 4) and in the case of amplitude modulated (AM) pulse trains also vector strengths (VS) and fundamental frequency (F0) amplitudes (Hu et al., 2010; Litvak et al., 2003b, 2003a; chapter 3). The simulated responses were in good agreement with animal data for continuous and amplitude modulated long-duration, pulse trains over a wide range of stimulus rates and amplitudes. The modulation detection thresholds, as interpreted by an ideal observer, inferred from the VS, yield realistic upper bounds when compared to data from human experiments (Shannon, 1992; chapter 3).

Simulated pulse-train-ECAP responses, to both short and long duration stimuli (chapter 5), replicated studies in both animals and humans (Carlyon and Deeks, 2015; Hughes et al., 2012; Jeng et al., 2009; Ramekers et al., 2015; chapter 5). Pulse train ECAP recordings show an alternation, which is replicated by the model. Modeled pulse train ECAPs showed that with the standard parameter settings, or with longer refractory periods when combined with a larger stochasticity, describe the human data very well. Interpatient differences can now be explored with the model by investigating how parameters affect the pulse train ECAP response.

In chapter 6, intracochlear ECochG simulations were compared to recordings from two different subjects. The model replicated characteristics seen in intracochlear ECochG recordings in the temporal, spectral and spatial domains. Impedance calculations with the 3D volume conduction simulations demonstrate that the intracochlear ECochG is a local measure of activation, although possibly sensitive to neighboring cochlear turns. In response to high stimulus levels, double peaks may occur which can either be contributed to cross-turn sensitivity, or to broad hair cell activation within the cochlea. Simulations of the hair cell response showed that increasing stimulus frequency results in a basal shift of the peak cochlear microphonic (CM) amplitude. The exact location on the array of the peak CM amplitude depended on cochlear geometry and electrode array type. Simulations of phase recordings showed that the recorded pattern becomes unreliable when the special sampling is too low.

Model parameters

As discussed in the previous section, the models and their average parameters are well equipped to replicate the different objective recordings of the auditory periphery to acoustic or electrical excitation. This section describes how recordings are affected by specific model parameters and how the parameters, and thus differences in recordings, might be related to hearing loss.

Neural adaptation and accommodation

Chapters 2 to 5 showed that adaptation must be implemented to correctly model auditory neuron spike rates in response to pulse trains. Adaptation decreased the discharge rate over time, and improved modulation following behavior. Only a few models of auditory nerve responses to electrical stimulation include adaptation (Negm and Bruce, 2008; Woo et al., 2009). Those models take a biophysical approach, where adaptation behavior is implemented in specific ion channels. Such models are important to provide further understanding of the origin of adaptation, but are too slow to be used to simulate spike trains in response to sound segments in a complete auditory nerve. Implementing adaptation using a phenomenological approach enabled fast simulations of neural responses to pulse trains. Spike-adaptation alone did not describe the long-term behavior; stimulus-dependent adaptation, sometimes referred to as accommodation, or sub-threshold adaptation, also had to be implemented. The time constant was assumed similar for both accommodation and adaptation. Biophysical studies have shown that there are at least a few different ion channel-types in spiral ganglion cells; fast voltage-gated sodium (Na_v) and delayed rectifier potassium (Kv) channels (Hodgkin and Huxley, 1952), but also low-threshold potassium (KLT) channels and hyperpolarization-activated cation (HCN) channels (Negm and Bruce, 2008). These different channels invoke different currents flowing over the neural membrane which all may result in different forms of adaptation with different time scales. Because biologically it might very well be that different mechanisms underlie accommodation and spike-adaptation, different time constants for both processes could perhaps be physiologically more viable. Adaptation over different time scales can be modeled by a power-law. Power-law adaptation is suggested in general neuroscience (Fairhall et al., 2001) and is implemented in models of acoustic stimulation of the auditory periphery (Zilany et al., 2009; Zilany and Carney, 2010), but not in models of electrical stimulation. Chapter 4 shows that the adaptation is best described by a power-law, especially for long duration data. As suggested in literature, this power-law adaptation can be approximated with multiple exponentials, and the number of exponentials required to fit the data depended on the duration of stimulation to simulate. Chapter 5 shows that decreasing the magnitude of adaptation in the model produced increases in alternation of ECAP amplitude and response amplitude, as seen in deafened guinea pigs (Ramekers et al., 2015). In their study, Ramekers et al see an increased alternation depth of pulse-train ECAP in chronically deafened animals that is hypothesized to be related to altered refractoriness or jitter in hearing impaired animals. In chapter 5 this hypothesis was tested and it was shown that instead, decreasing the adaptation amplitude better reproduced recordings from the deafened animals. Thus, measurement of the pulse-train ECAP's alternation can provide a measure of adaptation, which might be related to hearing loss. Generally, explanations for the relation between hearing loss and neural behavior can be sought in axonal shrinkage, demyelination and progressive retraction of the peripheral axon (Leake and Hradek, 1988). To date, however, there is no exact biophysical explanation for any relation between hearing loss and decreased adaptation.

Refractoriness

Refractoriness has, by the use of two-pulse paradigms, been much more extensively studied than adaptation. Simulations in chapters 2 and 3 show that for longer duration stimulation, effects of refractoriness interplay with effects of accommodation and adaptation. Effects of refractoriness were mostly visible at short time scales, such as SFAP onset rates and initial rate decrements. Larger refractory parameters in the model lead to larger inter-spike intervals in the SFAP interval histograms. ECAP simulations showed that refractoriness affects the frequency at which alternation is maximal, alternation depth and, for short duration simulations, also the final response amplitude. Several previous studies show that refractory periods are longer in animals with hearing loss than in control animals (Rubinstein, 1995; Shepherd et al., 2004; Shepherd and Javel, 1997; Sly et al., 2007; Walton et al., 1995). Prolonged refractory time-constants are observed in demyelinated neurons (Waxman and Ritchie, 1993), of which the chronically deafened auditory nerve is an example (Leake and Hradek, 1988). Demyelinated nerve fibers have fewer potassium channels than myelinated fibers, which might result in a leakage of internodal potassium currents into the nodal regions and thus cause a prolongation of refractory time constants.

Stochasticity

Stochasticity was implemented in various parts of the neural model by using: a stochastic distribution of thresholds over all nerve fibers, a threshold variability, an internal variability of the refractoriness and a distribution of model parameters over the fibers. The relative stochasticity (RS) and the internal variability of the refractoriness were essential model attributes to obtain I/O curves similar to animal data in response to electrical pulse trains. Variation of RS affected the width of the peaks in the interval histograms obtained from simulated SFAPs. A lower RS resulted in slightly improved modulation following behavior and stronger phase-locking over time in response to low stimulus amplitudes. This can be explained by a more deterministic fiber more strongly relying on the exact stimulus amplitude to determine whether it fires or not. The model presented here shows that decreased stochasticity (i.e., reduced RS), or increased refractoriness of the nerve, may lead to increased alternation depths in the temporal ECAP, independent of stimulus rate. A psychophysical study by Carlyon and Deeks (2015) shows that patients with larger alternation depths in their ECAP responses perform worse on rate discrimination tasks. The simulations presented in chapter 5 suggest that CI wearers with better rate discrimination have auditory neurons with short refractory periods and strong stochastic behavior. Biophysically this can be understood as that stochasticity, or the RS of the threshold, depends on the myelination of the nerve, with demyelination reducing RS (Resnick et al., 2018).

Latency and jitter

For the SFAP simulations, latency and jitter were not implemented. This resulted in slightly later spike timings in the animal experiments than in the model simulations, visible in the post-stimulus time histograms. In the ECAP simulations latency and jitter were included. An increased latency induced a small delay in the ECAP responses. Jitter did not affect any of the output measures. Latency and jitter are important parameters when exact spike timing is of interest, such as in a model of ITD differences. Spike timing is, however, also affected by adaptation (Prescott and Sejnowski, 2008), and the exact location of the auditory neuron relative to the stimulus (Mino et al., 2004).

3D model

Both the neural model's responses to electrical stimulation and the hair cell model's responses to acoustic stimulation include a 3D model of the cochlea. It is demonstrated in chapter 2 that spike rate adaptation depends on the spatial location of the nerve fiber relative to the current source. Relative rate decreases, and thus the amount of adaptation, was largest at the borders of the stimulated area. The deterministic single pulse threshold distribution thus has a large effect on final firing patterns. The local sensitivity of the intracochlear ECochG, as obtained with the 3D volume conduction model, was in line with a previous modeling study using a finite element approach (Teal and Ni, 2016) and with measurements made close to the hair cells (Dong and Olson, 2013; Fridberger et al., 2004), but contradicting other beliefs of wider fall-offs (Ayat et al., 2015; Charaziak et al., 2017; Davis et al., 1958; Tasaki and Fernández, 1952; v. Békésy, 1952, 1951; Whitfield and Ross, 1965). This local sensitivity implies that the intracochlearly located electrode contact is most sensitive to a small region of hair cells, located in closest proximity to the recording location. As a result of this local sensitivity of the intracochlear ECochG, it is possible to measure acoustic tuning in the cochlea. For both types of models, it is thus of the utmost importance to include an accurate and realistic 3D volume conduction model.

Hair cell degeneration

In the intracochlear ECochG simulations of chapter 6, different forms of hearing loss were modeled by implementing different degrees and types of hair cell degeneration. CM phase changes, as recorded with the intracochlear ECochG, are suggested to indicate hair cell damage (Giardina et al., 2019; Koka et al., 2018), and most, but not all, data seems consistent with this theory (Tejani et al., 2019). Simulations with hair cell degeneration resulted in ECochG responses that better resembled the recordings from subjects in terms of CM onset responses, higher harmonics, and the width of the tuning curve. Changes in the ECochG recording in the temporal, spectral, and spatial domains were thus related to the degree and type of hair cell degeneration. Hence, it is concluded that the intracochlear ECochG recording has the potential to elucidate on the type and degree of hair cell degeneration. Simulations show that OHCs are the main contributor to the intracochlear ECochG response, in line with previous recordings from animal studies (Dallos, 1986, 1985, 1983; Dallos et al., 1972; Dallos and Cheatham, 1976; Davis et al., 1958; Russell et al., 1986). Animal studies correlating post-mortem histological counting of the hair cells to audiometric thresholds show that hair cell degeneration generally starts in the base and then proceeds to the apex. Laterally positioned hair cells are more vulnerable than those medially positioned. Hence, degeneration progresses from base to apex, and affects lateral OHCs first and the medially positioned IHCs last (Dallos et al., 1972; Eric Lupo et al., 2011; Stebbins et al., 1979; Van Ruijven et al., 2005, 2004). Despite this, the exact relation between audiogram and hair cell degeneration, especially in humans, remains unknown. Synaptic or retro-cochlear pathologies might cause hearing loss regardless of the status of hair cells in the cochlea (Hill et al., 2016). To verify the relationship between intracochlear ECochG responses and hearing loss, further studies relating hair cell degeneration in humans to degree and etiologies of hearing loss are necessary.

Model design suggestions

Neural model parameters

Temporal and stochastic parameters are known to depend on fiber diameter and pulse shape (Liberman and Oliver, 1984; Miller et al., 1999a; Resnick et al., 2018; Verveen, 1962; Woo et al., 2010; Zhang et al., 2007). These factors have not yet been included in the parameters of the phenomenological model, but could be included in a further refinement of this model. The RS was assumed to be independent of the time since a spike occurred, whereas some data suggest that RS depends on time since spike (Imennov and Rubinstein, 2009; Matsuoka et al., 2001). In response to some stimulation rates, SFAP recordings may exhibit an increased sustained firing rate (Zhang et al., 2007), which can be hypothesized to be a result of integration effects, also referred to as summation or facilitation. In some ECAP recordings, increased amplitudes over the stimulus duration were observed (He et al., 2015), probably also related to integration. Such temporal integration was not implemented in the current model, because its exact dependency on pulse train characteristics such as rate and amplitude level needs to be investigated more thoroughly.

Hair cell model parameters

A challenge in modeling hair cell membrane behavior is the relatively sparse animal data available. Pujol et al. show that the outer hair cell length is correlated to the characteristic frequency in different species (Pujol et al., 1992). In the present study the dependency of conductance parameters on the characteristic frequency was determined from relatively sparse data (Johnson et al., 2011). A wider range of data recording how the hair cell conductance depends on characteristic frequency would be desirable. A limitation of the hair-cell model for the current application is the non-physiologically large IHC responses to stimulus levels above 80 dB SPL. From the auditory peripheral model, only responses to hair cells with a characteristic frequency larger than 125 Hz can be obtained, although hair cells with characteristic frequencies below 125 Hz might also influence the ECochG response.

ECAP and the Unitary response

The exact unitary response, or contributions from each individual nerve fiber to the ECAP is unknown, especially for humans. Simulations in this thesis were done with a unitary response based on cat data (Miller et al., 1999b). Differences in fiber kinetics, neuron myelination, size and morphology between the cochleae of different species influence the contribution of each action potential. An important species-dependent factor is, for instance, that in humans the soma is unmyelinated, which effectively adds a large capacitance to the human auditory nerve: leading to altered spike propagation times along the nerve. For simulation of the human ECAP, a unitary response derived especially for the human situation would be desirable (Dong et al., 2018). To test sensitivity to the shape of the unitary response, simulations were repeated with an alternative unitary response (Versnel et al., 1992). With this different unitary response, the simulated normalized pulse-train ECAP responses were similar, thus such differences in shape of the unitary response would not influence the results reported in chapter 5.

Model applications

Recording adaptation in humans

The pulse train ECAP can be used as a measure of adaptation based on findings in chapter 5, as a decrease in adaptation magnitude produces an increased alternation and response amplitude in long duration simulations. First, the average refractory period of the auditory nerve should be estimated based on a two-pulse paradigm ECAP recording, or by identification of the stimulus rate at which the ECAP alternation is maximal. After adjusting the model parameters of refractoriness accordingly, the adaptation amplitude can be altered so that recorded responses are best replicated. This will yield an indication of the adaptation amplitude. From such recordings, data on adaptation levels in patients can easily be obtained. This can be used to investigate the relationship between neural adaptation and outcomes on functional tests. Ultimately, information about the level of neural adaptation in an individual can be used to optimize settings in sound coding strategies.

Simulating other ECochG responses

The model of the eCochG responses presented in chapter 6 mainly investigated CM responses, but it can also be used to simulate intracochlear SP. With such simulations the eligibility of the SP as a diagnostic measure can be established and the origin of the SP response can be further elucidated on (Dallos and Cheatham, 1976; Davis et al., 1958; Durrant et al., 1998). In a similar approach to the ECAP simulations discussed above, after implementing neural responses, this eCochG model could also simulate compound action potential (CAP) and auditory nerve neurophonic (ANN) responses. This can be useful to evaluate how stimulus shape affects the intracochlear CAP response and ANN. The ANN is often believed to be reflected in the AC potentials in the summed response. Contrasting with this, the simulations presented in chapter 6 with only hair cells and no neurons simulated, also show an AC potential in the summed response. As another future application, the ECochG model developed here can be used to simulate the much more common extracochlear, round window, recordings. Responses to different stimulation patterns, such as chirps, clicks or tone bursts (Schoonhoven et al., 1995), or masked noises (Chertoff et al., 2012) could be modeled to better understand how these responses potentially differentiate between different types and degrees of hair cell degeneration. By combining simulations of the auditory periphery with simulations of the neural model, while incorporating electro-acoustic interactions, responses to an EAS system could also be simulated in future.

Towards model-based evaluation of sound coding strategies

Owing to the efficient implementation of spatial and temporal components, the model of responses to electrical pulse trains can be used to evaluate whole nerve responses to long duration sound segments. Simulated spike patterns in response to different stimuli, coded with different stimulation strategies, or from both ears in binaural stimulation, can now be compared. From these simulated neural responses, CI users' performance on tests as used in perceptual patient testing, such as minimal detection and identification tests, could be inferred with an interpretation model. Such simulations, whether with a basic interpretation, or a more complex perceptual interpretation model, can evaluate responses to different stimulation patterns, or sound coding strategies. Moreover, the simulations could be used to investigate how inter-subject differences in auditory nerve characteristics will affect interpretation. These patient specific neural parameters, and related performance expectations, could yield patient specific recommendations for sound coding strategies. Whether used for optimizing sound coding strategies in general, or for personalization, the simulated spike trains have to be interpreted. In other words, spike trains have to be decoded to give information about the underlying stimuli. There are different approaches to evaluation of the information in, or to decode, these simulated spike trains.

One way to interpret spike trains would be to define a metric that can be calculated directly from the spike train, that quantifies embedded information. This outcome can be related to a stimulus. For example, a simple measure of modulation following behavior is the vector strength, which can be used to simulate modulation detection thresholds (Goldwyn et al., 2010; O'Brien et al., 2016; Xu and Collins, 2007; chapter 3). Another example of a metric that can be used to compare spike trains is cross-correlation, or coincidence counting (Heinz et al., 2001; Heinz and Swaminathan, 2009). Such measures can be very well used to compare binaural coincidence neurons for their interaural differences (Dietz, 2016). The cross-correlation metric does however, not take into account spatial effects, since only two neurons are compared. In modeling speech perception this will generally not suffice, because the whole nerve contains information about the stimulus. Also, for modeling localization in cochlear implant users, these metrics will probably not suffice. Due to differences in electrode placement and neural survival binaurally, the binaural coincidence neuron will receive unequal information. The cochlear implant recipient might use other cues for localization. Another example of a metric based on the spike pattern is using averaging in the spatial and temporal domains. For this, first an internal representation of a stimulus over time is defined from the spike patterns by a spatial averaging over all neurons and temporal windowing (Fredelake and Hohmann, 2012; Hamacher, 2004; Hines and Harte, 2012). Hereafter, this internal representation over time is compared to a reference representation by calculating the shortest Euclidean distance from the signal to the reference stimulus (Chiba and Sakoe, 1978). The temporal integration can be done by calculating average discharge rates over a steady or moving rectangular or asymmetric window, e.g. a running exponential integration window (McKay and McDermott, 1998). Instead of using time warping averaged spatially over all neurons, similarity can be assessed of the 2D representation. Here, the spatiotemporally averaged spike pattern is treated as an image, with the structural similarity index (Wang et al., 2004). In both metrics, representation with the smallest difference with the representation of the reference stimulus has the largest chance to be perceived as similar to the reference stimulus. All the metrics described here define a specific attribute of the spike train that should be evaluated. Its ability to predict psychophysical outcomes is largely dependent on the stimulus.

An alternative approach to interpreting spike patterns is the use of a neural network (Kell and Mcdermott, 2019). Neural network models have already been found useful in speech recognition (Graves and Jaitly, 2014). For auditory sciences, neural networks often use spatiotemporally averaged spectrograms as inputs. From these, image classification features are extracted and used as inputs to the neural network. In a neural network, there are weights and layers connecting different aspects of the input to each other and to the output. In supervised learning, the weights of the different units that relate the output to the inputs are adjusted to minimize the error on a training set. This training set relates spectrograms to specific outputs. With this set, for example, the neural network can be trained to distinguish between two different sounds. Because in the training stage the desired output is known, this is referred to as a supervised learning deep neural network. Performance of deep learning neural networks is increasingly enhanced by introducing different levels of complexity such as multiple layers, pooling of input and optimized filtering operations. A specific class of neural networks, the spiking neural network, includes a temporal component and can be trained directly on spike trains simulated at the level of the auditory nerve (Paugam-Moisy and Bohte, 2012). Even though this is more directly applicable to the spike trains simulated in this thesis, its implementation is not straightforward because a more complex learning algorithm is required. So, it can be seen that there is a vast and growing variety of neural network designs, and there are many factors to consider when designing one for the current purpose.

Future perspectives

With an interpretation model, simulated spike trains can be compared for evaluating the effect of neural health, sound coding strategies, or binaural implants on the perceptual outcomes for cochlear implant users. This model can be used to test new sound coding strategies and to evaluate its performance in general. Sound coding strategies can be optimized for their expected performance on speech discrimination tasks, minimal just noticeable difference and detection tasks and optimal directional hearing. Moreover, patient specific performance, due to inter-individual differences in cochlear morphology and neural health, can also be modeled. Settings of the cochlear implant, its design, and its sound coding, can then be adjusted to realize an optimal performance for each individual. With this kind of modeling, the development of sound coding can be boosted, so that CI wearers will benefit more from their implants in the future.