Phenomenological modelling of electrically stimulated auditory nerve fibers: A review

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Abstract

Auditory nerve fibers (ANFs) play a crucial role in hearing by encoding and transporting the synaptic input from inner hair cells into afferent spiking information for higher stages of the auditory system. If the inner hair cells are degenerated, cochlear implants may restore hearing by directly stimulating the ANFs. The response of an ANF is affected by several characteristics of the electrical stimulus and of the ANF, and neurophysiological measurements are needed to know how the ANF responds to a particular stimulus. However, recording from individual nerve fibers in humans is not feasible and obtaining compound neural or psychophysical responses is often time-consuming. This motivates the design and use of models to estimate the ANF response to the electrical stimulation. Phenomenological models reproduce the ANF response based on a simplified description of ANF functionality and on a limited parameter space by not directly describing detailed biophysical mechanisms. Here, we give an overview of phenomenological models published to date and demonstrate how different modeling approaches can account for the diverse phenomena affecting the ANF response. To highlight the success achieved in designing such models, we also describe a number of applications of phenomenological models to predict percepts of cochlear implant listeners.
1. Introduction

Cochlear implants (CIs) provide hearing for people suffering from deafness caused by sensorineural hearing loss of cochlear origin by electrically stimulating auditory nerve fibers (ANFs). Neurophysiological experiments on mammals (see, e.g. Moxon, 1971; Eddington et al., 1978; Hartmann and Klinke, 1990; Javel, 1990; Dynes, 1996; Bahmer et al., 2010; Miller et al., 2011; Boulet et al., 2016) have provided indispensable information about the phenomena related to electrical stimulation – these phenomena help to understand if and how auditory nerve fibers respond to the electrical signals delivered by the electrodes of the CI. Such information is essential for the development of CIs and their stimulation strategies because it is not possible to record responses of individual ANFs of human subjects. While compound nerve responses can be recorded, differentiating them into the contributions of individual nerve fibers to better understand the spatio-temporal response is difficult (Abbas et al., 2014; Cohen, 2009a,b,c,d; Undurraga et al., 2013). Likewise, the utility of psychophysical experiments to differentiate peripheral responses is also limited, even if issues of subject recruitment from a still-limited pool of CI users for time-consuming experiments can be handled (Bierer, 2007). Available subject time and response acuity also limit the use of psychophysical approaches to exhaustively optimize stimulation parameters across the multi-dimensional parameter space of stimulation strategies.

Computational auditory models offer an interesting additional approach to the direct use of human listeners in psychophysical experiments and neurophysiological measurements. Auditory models take a digitized signal as input and process it with signal processing algorithms that emulate the functional behavior and response of the nuclei in the auditory system. Considering the electrical stimulation of ANFs, computational models can be used to predict responses evoked by particular stimulating waveforms and the predictions can help to understand the functionality of ANFs (see, e.g. Kalkman et al., 2016). Computational simulations can also lead to hypotheses about the physiological functionality, which can be then tested in a neurophysiological experiment. Such models can also be used to efficiently test out new stimulation strategies employing novel pulse shapes and variable
pulse rates to encode, e.g., temporal information with high resolution for binaural hearing while considering inter-pulse and across-electrode interactions. In addition, models can be applied to explain psychophysical phenomena related to listening with CIs. For instance, hearing threshold and modulation sensitivity, as well as loudness and speech percepts, could be predicted instrumentally by inspecting the model outputs for specific stimuli. Recently, attention has been paid to predicting localization performance of CI users by combining models for peripheral electrical stimulation with those for binaural processing to predict the perceived direction of a sound event and performance in noisy and reverberant conditions for example (see the review by Dietz, 2016).

In general, models of the electrically stimulated ANF can be roughly divided into two categories based on the detail in which they account for the functionality and physiology of the neuron. Biophysical models (see the review by O'Brien and Rubinstein, 2016) mimic the biophysical mechanisms and functionality of the ANF in great detail using elements that have physiological counterparts in the actual neuron. They are ideal to investigate the contribution of each element to ANF function and can thus help to better understand physiological behavior. The great detail at which biophysical models can mimic the functionality of the ANF comes at the expense of a larger parameter space that needs to be fitted to neurophysiological data corresponding to the physiological model elements. The other model category consists of phenomenological models that describe the deterministic and stochastic input-output functionality of a single ANF without paying explicit attention to the actual physiological structure. Phenomenological models offer a greatly reduced parameter space and complexity compared to biophysical models, and parameters often reflect directly phenomenologically observable aspects like the neuron’s threshold, response latency and variance, or the time constant for its refractory behavior. This is beneficial for parameter fitting and for optimizing model performance, but it comes at the expense that parameters usually have no direct biophysical interpretation. In recent attempts, model parameters are inferred from compound or psychophysical responses such as thresholds and time-constants that can be measured with patients. The low parameter complexity is specifically useful for adjusting model parameters to individual CI patients, e.g. to explain their hearing percepts
in psychophysical experiments.

This article provides an overview of phenomenological models for electrically stimulated ANF and their capabilities to explain neurophysiological and psychophysical data from the literature. At first, the general modeling principles behind two main classes of phenomenological models, point-process and leaky integrate-and-fire models, are described in order to explain how each handles the ANF response to electrical stimulation. Thereafter, several aspects related to electrical stimulation are revisited to point out how phenomenological models have evolved to account for different response phenomena. The performance of phenomenological models is also reflected by the number of scenarios in which these models have been applied to predict results from psychophysical experiments. Some of those applications are also reviewed in this article, along with ideas for future developments.

2. Main modeling concepts

Phenomenological models reviewed in this article focus on predicting the number and/or timings of action potentials released by the ANF when it is being stimulated with a given pulsatile input signal. Both point-process and leaky integrate-and-fire models share this same goal, but they approach it from different angles: point-process models have their basis in mathematical formulations and statistics, while leaky integrate-and-fire models are based on elements from electrical circuits that are simplified from those used in detailed biophysical models.

Models following the point-process principle see the action potentials generated by the auditory nerve as events in realizations of a stochastic process that is characterized by the neuron’s firing rate (Perkel et al., 1967). Each spike train realization occurs over an observation time window and the interest in the models lies in the timings and/or the number of spike events occurring while the nerve is being stimulated within this time window. In essence, these models are generalizations of the Poisson-point process, as the fixed frequency of occurrence (i.e., spiking rate) is replaced with a time-varying one. However, typically, these models also restrict the general point-process principle by allowing only one event (i.e., action potential) to occur per each electrical pulse in the pulse train (e.g. Bruce et al., 1999a;
Goldwyn et al., 2010; Xu and Collins, 2003, 2004, 2005, 2007). Functionality of such a point-process model can be characterized with the help of three functions: the conditional-intensity function (CIF), the lifetime-distribution function, and the link function that determines the stochastic nature of the neuron’s threshold. The CIF describes the neuron’s probability of spiking as a function of time, the stimulus used to excite the neuron, and the neuron’s spiking history (Daley and Vere-Jones, 2003). The lifetime-distribution function is then derived from the CIF to describe the probability of observing at least one spike within a time interval \([t, t + T]\) (Snyder and Miller, 1991). Inclusion of the spiking history as one of the key parameters enables the point-process models to account for various temporal effects in pulse train stimulation, as demonstrated later in this article.

Leaky integrate-and-fire (LIF) models (Lapicque, 1907) use electrical circuit elements to simulate basic aspects of action-potential generation. Physiologically, the electrical stimulation changes the electrical field around an ANF resulting in charging up of the capacitive cell membrane, and consequently an increase or decrease in the neuron’s membrane potential (i.e., de- or hyperpolarization of the neuron) depending on the polarity of the electrical pulse. If the membrane potential reaches the neuron’s threshold value, voltage-gated channels are opened resulting in a sudden change in membrane potential that culminates in the generation of an action potential, which then starts to propagate along the auditory nerve. If the threshold value is not reached, the membrane potential recovers to the resting status within 1-2 ms due to leakage of ions through open ion channels. In an LIF model, the above-described process is simulated with a capacitor integrating the incoming electrical current while a parallel resistor simulates the membrane leakage resistance. This leaky integration is equivalent to a first-order low-pass filter having a specific time constant. The third element of a LIF model is a threshold-crossing detector that generates an ad hoc action potential if the membrane potential reaches the threshold value of the neuron. The whole process can be characterized with the help of just a few parameters: capacitance and resistance that describe the time constant, the resting potential (set at 0 V if the relative membrane potential is simulated) and the threshold value.
3. Modeling phenomena related to electrical stimulation

Next we want to discuss extensions to the basic point-process and LIF models and describe approaches to modeling important phenomena related to the electrical stimulation of auditory nerve fibers. Focus is placed on modeling pulsatile stimulation employed in modern CIs. Specifically, cochlear implants use charge-balanced pulses to avoid buildup of charge that could result in harmful electro-chemical effects at the electrode-electrolyte interface. Such pulses consist of two or more monophasic pulses with opposite polarities, possibly having a specific duration with zero amplitude between the pulses referred to as the inter-phase gap (IPG). In biphasic pulses, the leading (anodic or cathodic) and lagging (cathodic or anodic) phases have equal amplitude and duration. Pseudo-monophasic charge-balanced pulses consist of a short, high-amplitude stimulating phase followed by a longer secondary phase with lower amplitude. Such asymmetric pulse shapes could prove to be beneficial in the future since they lead to lower threshold currents and offer a more predictable response timing (Shepherd and Javel, 1999). Non-rectangularly shaped pulses are a further means explored to improve time and amplitude coding (see, e.g. Ballestero et al., 2015). In addition to charge-balanced pulses, we consider responses to monophasic pulses as several models were originally designed to predict physiological data for this kind of stimulation.

The modeling results presented in this section were derived using the original MATLAB (Mathworks) codes as implemented by the original authors. Code for the model by Hamacher (2003) was received through personal communication while codes for Bruce et al. (1999a), Fredelake and Hohmann (2012), and Goldwyn et al. (2012) were downloaded from URLs (1, 2, and 3). The code for Horne et al. (2016) model was implemented and is available at 4. The models were not optimized for the evaluated scenarios. Therefore, one should avoid comparing and ranking the models based on these evaluations that only aim to demonstrate what the different models are capable of.

Stochastic nature of the threshold

One of the intrinsic characteristics of all sensory neurons is the variability in the response due to limitations of sensory coding and internal noise (Adrian, 1932; Verveen, 1960;
Verveen and Derksen, 1968; Carney, 1993; Bruce et al., 1999c). Auditory nerve fibers also exhibit variability, e.g. in their spontaneous activity in the absence of any stimulating input. Although that spontaneous activity is greatly diminished in deaf cats (Shepherd and Javel, 1997), the ANF response to electrical stimulation remains probabilistic. One of the reasons behind the stochastic nature of the threshold lies in the probabilistic opening and closing of the voltage-gated ion channels, referred to as channel noise (White et al., 2000). These probabilistic processes result in fluctuation of the membrane potential and/or the threshold potential. Furthermore, the channel noise has been observed to resemble Gaussian noise having a $1/f$ shaped spectrum (Verveen and Derksen, 1968).

The probabilistic response to electrical stimulation was considered already in the point-process model by Bruce et al. (1999c). In their model, a cumulative distribution function (CDF) of a normal distribution was used to map the electrical current (or stimulus potential) of each stimulation pulse to a probability of spiking (Fig. 1a), building on the earlier work of White and colleagues (White, 1978; White et al., 1987). The mean value of the CDF is associated with the threshold, and the variance (i.e., through the relative spread, defined as the standard deviation of the CDF divided by its mean) of the normal distribution is linked with the channel noise. Similar mapping functions have been used in other point-process models (e.g. Bruce et al., 1999a, 2000; Xu and Collins, 2003, 2004, 2005, 2007; Cohen, 2009d; Goldwyn et al., 2010, 2012) as well as in LIF models (Hamacher, 2003; Cheng and Zhang, 2007; Macherey et al., 2007; Fredelake and Hohmann, 2012; Horne et al., 2016). Goldwyn et al. (2012) replaced the CDF of a normal distribution with the one of a Weibull distribution, finding only small differences between the two functions mainly at high and low stimulus levels where the CDF saturates.

Effect of pulse duration on required stimulation level

The functionality of CIs is based on the electrical signals charging the capacitive cell membrane to push the membrane potential above the neuron’s firing threshold. Due to the build-up of charge, pulse duration affects the stimulation current required to excite the
neuron. For very short pulse durations, there is an inverse relationship between the pulse duration and the required stimulation current. However, because of the leakiness of the integration, as captured by the LIF models, long pulses are not as effective in building up the charge as short pulses. In other words, increasing pulse duration lowers the stimulation current required to excite the neuron until the required current reaches an asymptotic value, denoted as the rheobase ($I_{\infty}^{\text{THR}}$; van den Honert and Stypulkowski, 1984). The pulse duration requiring a stimulation current twice the rheobase is known as the chronaxie. By measuring values for chronaxie and rheobase in electrically stimulated spiral ganglion neurons of cats, van den Honert and Stypulkowski (1984) derived the function

$$I_{\text{THR}} = \frac{I_{\infty}^{\text{THR}}}{1 - e^{-kd}}$$

that predicts the threshold level for the stimulation in amperes based on pulse duration ($d$) and chronaxie ($\ln(2)/k$).

The dependency of the threshold current on duration can be captured only by estimating the build-up of the charge – a procedure omitted from many models. To model the dependency without this estimation, Bruce et al. (1999c) formulated the threshold value of the CDF in their model as a function of the pulse duration, and similar formulations were used also in many other models (Bruce et al., 1999a, 2000; Goldwyn et al., 2010, 2012). As an example, Fig. 1(b) illustrates how pulse duration affects the threshold of the CDF employed in the model by Bruce et al. (1999c). Parameterizing the effects of pulse duration on threshold current was done not only to simplify the model structure but also to allow the parameterization of the effects of pulse duration on the relative spread (RS) of the CDF Bruce et al. (1999c). The build-up of the charge was simulated first in the LIF model by Hamacher (2003) where the charge delivered by a pulse was estimated based on the input arguments specifying the duration and current of the excitatory phase of the pulse, and the CDF was mapped based on the estimated membrane potential. In consequence, fixed threshold and variance values of the CDF can explain the effect across different pulse
durations. Effectively, the approaches used by Bruce et al. (1999c) and Hamacher (2003) yield a similar outcome for the spiking probability as a function of stimulation level (in dB). Figure 1(b) illustrates how the pulse duration affects both the threshold and the slope of the spiking probability curve in the model by Bruce et al. (1999c). To highlight how the response depends on the cumulative charge, Fig. 1(c) shows the spiking probability curves as a function of the charge delivered per pulse on a log scale. The range of the x-axis for panel C is set to be the same as that for panel B. It can be observed that when the input/output behavior is considered in terms of the cumulative charge rather than the current level, then the pulse duration has a much smaller effect. The remaining influence of the pulse duration when plotting spiking probability curves versus cumulative charge is due to the leaky nature of the neural membrane integration. The pulse-duration dependency of the model parameters requires pulse duration to be specified in the aforementioned models. To circumvent such a requirement, Macherey et al. (2007) presented a model that combines the outputs of parallel LIF and resonator \((f_{\text{res}} = 80\text{Hz})\) units having different time constants \((0.094\ \text{ms} \text{ and } 1.04\ \text{ms})\). The two units were considered to be independent, allowing each of them to spike whenever a corresponding threshold value was exceeded. The model was designed so that the integrator would account for the decrease in threshold until the phase duration is increased to about 0.5 ms, where the output of the integrator saturates, while the resonator would account for the effects for larger phase durations. More recently, Horne et al. (2016) demonstrated that a single LIF model is sufficient to reproduce the ANF data (Miller et al., 1999) on the dependency of stimulation current on phase duration when the time constant is set to a value of 248 \(\mu\text{s}\) (based on data by van den Honert and Stypulkowski, 1984).

**Latency and jitter of ANF**

In the real neuron, the action potential is generated shortly after the threshold value for the membrane potential has been reached and therefore there is always a delay between the onset of the electrical pulse and the time when the action potential occurs, and even a greater delay before the action potential is eventually observed by the recording electrode (Miller et al., 1999; Mino et al., 2004). The mean response delay to the recording site is
referred to as the latency of the neuron, and its standard deviation is called jitter (Miller et al., 1999).

While many, mostly earlier models (Bruce et al., 1999c,a, 2000; Cheng and Zhang, 2007; Macherey et al., 2007), were primarily interested in estimating the neuron’s firing rate for pulse train stimulation, latency and jitter came more recently into focus. Several models (Hamacher, 2003; Goldwyn et al., 2010; Fredelake and Hohmann, 2012; Goldwyn et al., 2012; Horne et al., 2016) simulate jitter and latency by introducing a random delay $\Delta t \sim N(\mu_{\text{latency}}, \sigma_{\text{jitter}}^2)$ to estimate the time of spiking from the point of threshold crossing based timing data collected from cat ANF by Miller et al. (1999). Latency and jitter also depend on the stimulation level – an increase in current level yields decreased values for both latency and jitter (Rubinstein, 1995; Mino et al., 2002). This aspect is simulated by Horne et al. (2016) by expressing jitter and latency as functions of the continously estimated probability of spiking after threshold crossing, requiring a few additional parameters (three for jitter and four for latency) to obtain accurate predictions of the neurophysiological data as illustrated in Fig. 2.

Effects related to biphasic and pseudo-monophasic pulses

Prediction of responses to charge-balanced symmetric and asymmetric biphasic pulses provides a specifically interesting application for computational models. One of the interesting features observed with symmetrical biphasic pulses is the ability of the lagging phase to cancel out the action potential that would have otherwise been evoked by the leading phase (see, e.g. van den Honert and Mortimer, 1979; Weitz et al., 2011). This feature is reflected also in the generally higher threshold level for biphasic pulses in comparison to equivalent monophasic pulses (Shepherd and Javel, 1999). However, the threshold level of a biphasic pulse depends on the IPG: for long IPGs of 100 - 200 $\mu$s it approaches that of the equivalent monophasic pulse (van den Honert and Mortimer, 1979; Weitz et al., 2011; Shepherd and Javel, 1999).
Since today’s clinical implants use only symmetrical, biphasic pulses with constant phase durations and IPG, most phenomenological models do not distinguish between biphasic, pseudo-monophasic or monophasic pulses (Bruce et al., 1999c,a, 2000; Hamacher, 2003; Cheng and Zhang, 2007; Macherey et al., 2007; Goldwyn et al., 2010; Fredelake and Hohmann, 2012). In fact, these models react to the leading phase similarly as they would react to an equivalent monophasic pulse. The distinction has been considered only in two recent models: the point-process model by Goldwyn et al. (2012) and the biphasic LIF (BLIF) model by Horne et al. (2016). Goldwyn et al. (2012) use two separate filters to integrate the charge delivered by the anodic and cathodic phases in a manner that each filter ignores the other polarity. Thereafter, a weighted-sum is computed from the filter outputs and mapped to the instantaneous spiking probability using the conditional intensity function (Goldwyn et al., 2012). The weights are optimized so that the model does predict a higher threshold for a biphasic pulse, although no quantitative comparison against neurophysiological data was presented. However, the IPG has no effect on the difference in threshold between biphasic and monophasic pulses and the potential abolishment of the action potential by the lagging phase is not considered. A different approach is exploited by (Horne et al., 2016). There, the action-potential process is divided into two events: an initiation process that starts immediately upon exceeding the threshold value, and the actual generation of the action potential following the completion of the initiation process. The initiation process needs to be completed within a critical period (Rubinstein et al., 2001), otherwise no action potential is generated. The critical period is defined by the time the lagging phase hyper-/depolarizes the neuron and is implemented by evaluating the time at which the cumulative charge (computed from the threshold crossing onwards) crosses zero. This means that charge of the stimulating pulse integrated after threshold crossing increases firing probability as does the IPG – the longer the time difference between threshold crossing and the start of the lagging phase which reduces cumulative charge, the higher the probability for the leading phase to evoke an action potential. The model by Horne et al. (2016) is able to characterize both the difference in the thresholds between biphasic, pseudo-monophasic and monophasic pulses as well as the effect of IPG on threshold, as illustrated in Fig. 3.
**Inter-pulse interactions**

All above described effects were limited to stimulation of auditory nerve fibers with single, temporally-isolated pulses and the models were used to predict whether and when a pulse evokes an action potential or not. While this is an important step for simulating electrical stimulation with CIs, several effects related to temporal inter-pulse interactions need also to be considered in order to accurately predict ANF responses to pulse trains employed in CIs. For instance, the ability of the ANF to phase lock to the stimulus is affected.

**Temporal coding**

In general, the response of an ANF is better synchronized to electrical pulses than what is achievable in acoustical stimulation (see, e.g. Moxon, 1971; Hartmann and Klinke, 1990). Consequently, temporal modulations in the input signal should be better transmittable by a population of synchronously firing electrically-stimulated ANFs (Wilson et al., 1997). However, due to diminished spontaneous activity of electrically-stimulated ANFs (Shepherd and Javel, 1997), the overall population of neurons is able to code temporal details accurately only at up to $\sim$800-1000 pps pulse rate (Hartmann and Klinke, 1990; Wilson et al., 1997), after which the refractoriness of the neurons prevents them from being excited by pulses that stimulate them after they have fired to a preceding pulse. In contrast, the less synchronous firing and the higher spontaneous activity of acoustically-stimulated ANFs ensures that some neurons are always ready to react to the input at rates below $\sim$4 kHz (Johnson, 1990). It has been suggested that the coding precision could be improved by adding a sustained high-rate pulse train to increase stochastic independence of ANFs – bringing the compound response of electrically-stimulated ANFs closer to that of acoustically-stimulated fibers (Rubinstein et al., 1999; Litvak et al., 2001).

Several instrumental metrics can be used to evaluate how accurately the spike train output reflects the temporal information in the stimulating pulse train sequence. For instance, vector strength is a numerical measure about the synchrony between two sequences (Goldberg and Brown, 1969). Here, vector-strength values were computed from the output of the
two models providing spike timing information (Hamacher, 2003; Goldwyn et al., 2012) when stimulated with biphasic pulse trains at different rates. The values were derived with the help of the MATLAB code by Kuebler and Thivierge (2014). Results are shown in Fig. 4 along with the neurophysiological data from cat ANF recordings for sinusoidal electrical stimulation (Hartmann and Klinke, 1990). Neurophysiological data from pulsatile electrical stimulation of cat (Miller et al., 2008) and monkey (Parkins, 1989) auditory nerve fibers are shown as well.

1. It should be noted that vector-strength depends on the number of spikes generated by the given model, the number which depends not only on pulse rate but also on stimulation level (as described in more detail later). This hinders comparisons between model predictions and neurophysiological data. That being said, the qualitative trend in the neurophysiological data from cats can be seen to be captured well by the model by Goldwyn et al. (2012), while the decrease in the synchrony at higher rates is overestimated by Hamacher’s 2003 model. The following subsections review important phenomena that contribute to the precision of temporal coding at different rates which, together with pulse rate, affect whether a given pulse in a pulse train evokes an action potential or not.

Refractory and recovery behavior

The most well-known phenomenon affecting responses to electrical stimulation at high pulse rates is the refractory and recovery behavior of the ANF. Like in any other neuron, generation of an action potential is followed by an absolute refractory period during which the neuron cannot be excited to generate another action potential, mainly because of inactivation of ion-channels. Afterwards, during the relative refractory period, the number of inactivated channels decreases gradually allowing the neuron to be excited again, but it takes time before all channels return to their resting states (Purves et al., 2001). Therefore, greater-than-normal membrane voltage is required to reach threshold while the neuron gradually recovers to the resting state.

1 Average vector-strength values were computed from the values reported in Fig. 8 of Miller et al. (2008) and in Figs. 6 and 10 in Parkins (1989).
Different studies have yielded estimates for the durations of the refractory periods with the values for the absolute refractory period ranging from 0.3 ms (Miller et al., 2001) to 0.7 ms (Dynes, 1996) and for the relative refractory period from 0.4 ms (Miller et al., 2001) to 5 ms (Imenov and Rubinstein, 2009). Commonly, the gradual change in threshold level during the relative refractory period is described by an exponential function.

The computational models that account for the refractory behavior share the same principle – the threshold level is set to an infinite value during the absolute refractory period and it is multiplied with an exponentially decaying function to simulate the relative refractory period (Bruce et al., 1999a, 2000; Hamacher, 2003; Cheng and Zhang, 2007; Goldwyn et al., 2010; Fredelake and Hohmann, 2012; Goldwyn et al., 2012). However, the exact formulations differ, resulting in differences in how significantly the threshold is affected during the relative refractory period (Fig. 5). Bruce et al. (1999a, 2000) as well as (Hamacher, 2003), followed by Fredelake and Hohmann (2012), formulated their exponential functions based on the neurophysiological data collected by Dynes (1996), which explains the good fit between the model predictions and the neurophysiological data in Fig. 5. Xu and Collins (2004) revised the model by Bruce et al. (1999a) and modeled the refractoriness mathematically using a multi-state Markov chain that was, however, tuned to yield the same effective performance as the threshold-adjustment in Bruce et al. (1999a). Cheng and Zhang (2007) did not fit their function to data, but increased the threshold only little during the relative refractory period – in fact, the maximum increase of 0.05 dB is not even visible in Fig. 5. The effective duration of the relative refractory period is also much shorter in the models by Goldwyn et al. (2010, 2012) than in the models by Bruce et al. (1999a, 2000) and Hamacher (2003). This difference originates from Goldwyn et al. (2010, 2012) formulating their function according to the coefficients estimated by Miller et al. (2001) and not fitting the function to the actual neurophysiological data (Miller et al., 2001). The shorter effective duration of the refractory period enables the model to respond more frequently to high-pulse-rate stimulation. The formulation defined by Miller et al. (2001) also formed the basis for the simulation of refractoriness in the point-process model by Cohen (2009d), implemented otherwise similarly to (Bruce et al., 1999a). However, Cohen adjusted the refractoriness formula depending on
the level of the masker in order to account also for facilitation.

[Figure Fig. 5 about here.]

In point-process models, the refractory and recovery behavior of ANF is likewise modeled by the conditional intensity function that uses the spiking history of the neuron as a parameter. In consequence, the time of last spiking affects the threshold, the relative spread and the scaling factor of the CIF function (Goldwyn et al., 2012). It should be noted that while the point-process models (Bruce et al., 1999a, 2000; Goldwyn et al., 2010, 2012) incorporate the time-course of the refractory recovery during the duration of a pulse, the exact time-course has limited accuracy because these models do not fully explain the latency and jitter for action potential generation, which will determine the true start time of the refractory period.

**Facilitation**

A pulse that does not itself evoke an action potential may facilitate another subsequent pulse to do so (Lucas, 1910). As described in Boulet et al. (2016), there are two components to facilitation: a passive component arising from residual charge on the neural membrane and an active component due to residual sodium channel activation (which can in turn produce an elongated depolarization also). If two sub-threshold pulses are presented with short inter-pulse interval (IPI), the neuron may still be slightly depolarized and/or its sodium channels activated when the second pulse is presented and, therefore, a smaller-than-normal charge is required from the second pulse to push the membrane potential to the threshold level. In electrically stimulated auditory nerve fibers, the largest effects have been observed with monophasic pulses with a threshold reduction ranging from 2 to 5 dB at IPIs smaller than 0.5 ms (Dynes, 1996). Slightly smaller effects of about 3 dB can be achieved with pseudo-monophasic pulses when the inter-pulse-interval is further reduced to 0.1 ms (Cartee et al., 2000). The secondary phase of biphasic pulses will tend to reduce the amount of residual change on the membrane compared to that of a monophasic pulse, but there is also supporting evidence for facilitation with biphasic pulses, measured as changes in probability for onset response in pulse-train stimulation (Heffer et al., 2010). These effects are
indeed substantial when one considers the limited perceptual dynamic range in electrical stimulation (of about 10 dB). Although facilitation has been observed only at very short inter-pulse-intervals, such IPIs correspond to realistic effective stimulation rates in modern CIs, particularly when one takes current spread between stimulation positions into account (see, e.g. Kral et al., 1998).

Only two point-process models (Cohen, 2009d; Goldwyn et al., 2012) contain elements that explicitly account for facilitation. As mentioned above, Cohen (2009d) achieves this by adjusting the refractoriness formula depending on the relative level of the preceding pulse to obtain a match for the electrically-evoked compound action potential (ECAP) data from CI users. Goldwyn et al. (2012) accounts for facilitation qualitatively by adjusting the filter coefficients of their two filters based on the time since the last spike using a specific summation time constant. The summation time constant is set on a per-stimulus-basis with the pulse rate and the nature of the pulses (i.e., monophasic, biphasic, or pseudo-monophasic) in the pulse train being considered following the data by Cartee et al. (2000, 2006). Effectively, the summation time constant affects how quickly the influence of the last non-spike-evoking pulse is forgotten and how much of the facilitatory effect there still exists to enable the current pulse to evoke a spike.

The leaky integrate-and-fire models for pulse train stimulation (Hamacher, 2003; Cheng and Zhang, 2007; Macherey et al., 2007; Fredelake and Hohmann, 2012; Horne et al., 2016) model the passive component of facilitation through their leaky integrative behavior, but they do not incorporate the active component of facilitation. However, LIF models could nicely explain the facilitation effect observed with monophasic pulses provided the time constant of the leaky integrator is selected accordingly: Figure 6(a) illustrates how the threshold level is reached by the second pulse because of the slow recovery of the integrator’s output after the first pulse. On the other hand, Fig. 6(b) depicts the problem of explaining the facilitation effects observed with charge-balanced pulses using a simple LIF model – the membrane potential remains more hyperpolarized by the second pulse because the integrator had not recovered from the effects imposed by the latter phase of the preceding pulse. Hence, a simple LIF model would predict the second pulse to require a larger-than-normal level to
excite the neuron.

[Figure Fig. 6 about here.]

**Accommodation**

The neurophysiological measurements by Dynes (1996) revealed that a sub-threshold pulse can also reduce the probability that the subsequent pulse evokes an action potential. This effect, known as accommodation, was found to occur when the inter-pulse-interval is increased to the range from 0.5 to 5 ms, i.e. beyond the effective range of facilitation. The neurophysiological basis for the increase in threshold during the accommodation period is still being debated, but biophysical models have provided a hypothesis that accommodation results from combined contributions of several ion-channels that can lead to reduced excitability (e.g., see Boulet et al., 2016). The accommodation phenomenon was included in a preliminary model by White (1978) and the model of Campbell et al. (2012), however in neither case was the model compared to the physiological data of Dynes (1996). The approach used to address accommodation in phenomenological models is to keep track of the pulse timings and to increase the threshold after non-spike evoking pulses.

**Spike-rate adaptation**

In general, sensory neurons adapt their response for continuous time-invariant stimuli in order to save energy and to avoid encoding redundant information. This phenomenon is exhibited also in the ANF’s response to the identical pulses in a pulse train, where the spike rate can progressively drop over the duration of a pulse train more than can be explained by refractoriness. The ANF response manifests an oscillatory pattern with alternating periods of higher spiking activity and lower spiking activity (Heffer et al., 2010). As a consequence, spikes are recorded at intervals that match with the integer multiples of the inter-pulse-interval (Miller et al., 2008). At higher pulse rates, the refractory, facilitation, and accommodation phenomena also interact with the spike-rate adaptation phenomenon: Pulses presented during the absolute refractory period of the neuron cannot evoke a spike and pulses falling within the relative refractory period are less likely to evoke a spike as well.
However, facilitation allows consecutive pulses to result in a spike even when the pulses are presented during the relative refractory period, i.e. when the threshold level of the neuron is elevated. In contrast, the accommodation phenomenon might be visible in the reduced spike rate after several consecutive pulses have failed to evoke a spike. Hence, it is difficult to disentangle spike-rate adaptation from the other above-described phenomena, as pointed out in Boulet et al. (2016). Nevertheless, spike-rate adaptation is evident also at high stimulation rates as variations of the spiking probability and spiking rate of the neuron over the course of the stimulus duration, the spiking rate being the highest at the onset of the pulse train and decaying then towards a stabilized lower spike rate (Zhang et al., 2007). Variation of the spiking probability along with its effect on latency and jitter are also visible in histograms of the inter-spike intervals, resembling a more continuous distribution at high pulse rates and reduced periodicity of the stimulating pulses (e.g., see Miller et al., 2008). However, spiking during the onset period of a high-pulse-rate sequence still exhibits some periodicity (Miller et al., 2008).

Phenomenological models have been used to simulate some of aspects of drops in spike-rate over the duration of a pulse train. Bruce et al. (1999a, 2000) accounted for drops in spike rate due to refractoriness when they used their point-process model to reproduce the dependency of spike rate on pulse rate and stimulation level as seen in the cat ANF data collected by Javel et al. (1987). Later, Hamacher (2003) and Fredelake and Hohmann (2012) used the same neurophysiological data to demonstrate the functionality of their LIF models. Figure 7 illustrates that both models (Bruce et al., 1999a; Hamacher, 2003) demonstrate the trend that an increase in stimulation level results in a more substantial increase of spiking efficiency (number of evoked spikes divided by the number of pulses) at low pulse rates than at high pulse rates – a pronounced effect being predicted by the model by Hamacher (2003). However, such effects are explained by the refractoriness limiting the spiking efficiency at higher rates, and spike-rate adaptation beyond refractoriness was not modeled. Therefore, inspecting the spike timings will help to see whether a model can truly account for spike-rate adaptation.
To that end, Goldwyn et al. (2012) compared qualitatively their model output to the neurophysiological data collected by Miller et al. (2008). Specifically, the comparisons were made based on inter-spike-interval histograms obtained for 300-ms-long pulse trains consisting of biphasic pulses presented at a rate of either 250, 1000 or 5000 pps. Figure 8 visualizes the spike-rate adaptation effect for the model by Goldwyn et al. (2012) through inter-pulse-interval histograms obtained for 250 and 5000 pps pulse trains over 100 repetitive runs. When spiking during the whole pulse-train sequence is inspected, the model output demonstrates the distribution of inter-spike intervals at multiples of the ISI for the 250 pps pulse rate and a stochastic distribution of inter-spike intervals for the 5000 pps pulse rate (Figs., 8(a) and 8(b), respectively). However, in Fig. 8(c), the 5000 pps pulse train can be seen to exhibit some periodicity during the onset part of the sequence, being in line with the neurophysiological data (Miller et al., 2008).

Nourski et al. (2006) used a specific formula to address spike-rate adaptation in their extension of the model by Bruce et al. (1999a). Specifically, the threshold level was affected not only by simulation of the refractoriness (Bruce et al., 1999a) but also by an activity-dependent component that reduced the responsiveness of the model for time scales larger than the refractory effects. Moreover, previous spiking activity was thought to have a cumulative effect on the threshold level while the contributions of refractoriness were determined solely by the last spike. The idea of long-term adaptation effects was exploited also by Campbell et al. (2012) whose model considered also stimulus-dependent aspects, allowing previous pulses to reduce the responsiveness of the model even when they did not evoke spiking activity (accommodation).

The electrical field generated by an electrode spreads along the length of the cochlea and therefore a given electrode may excite also other auditory nerve fibers besides the targeted ones closest to it. The extent of current spread depends on the stimulation method – bipolar
and tripolar stimulation methods generate more focused electrical fields around the emitting electrode than the monopolar one (Spelman et al., 1995). In addition, the current may also travel through the cochlear bone so that neurons even half or a complete cochlear turn apart may be excited (Mens et al., 1994; Holden et al., 2013). Consequently, a given auditory nerve fiber may be stimulated with a much higher effective stimulation rate than the pulse rate of the nearest implant electrode depending on the distances between the electrodes and the coding strategy.

Phenomenological models have also been extended to account for current spread in order to employ them in the evaluation of coding strategies and electrode placements in cochlear implant devices. In general, all of these models (Bruce et al., 1999a, 2000; Hamacher, 2003; Cheng and Zhang, 2007; Fredelake and Hohmann, 2012) account for spread of excitation based on three assumptions: (1) equal distribution of auditory nerve fibers along the length of the cochlea; (2) the electrodes in the implant are equally spaced along the cochlea; (3) excitation spreads only along the fluid in the cochlea and not through the bone. Cohen (2009b) used a more detailed approach based on ECAP measurements and finite element modeling (Cohen, 2009b), but the shapes of the current spread functions were not greatly different from the simpler models. Thus, even models with simplified descriptions of current have proven helpful to predict several perceptual aspects about hearing with CI, as discussed briefly below. More information about precise modeling of current spread with three-dimensional (3-D) models can be found in Hanekom and Hanekom (2016).

**Perceptual aspects**

Computational models that can predict hearing percepts evoked by the electrical stimulation are of great general interest in the field of cochlear implant research. Typically, some of the model parameters need to be tuned on a per-subject basis to obtain accurate predictions. Some of the phenomenological models reviewed in this article have been successfully applied in such tasks starting from the prediction of hearing thresholds based on the spiking probability of the model. For instance, Macherey et al. (2007) used their model to predict how detection threshold for a single biphasic pulse changes when the phase dura-
tion is varied from 0.1 to 8 ms (Shannon, 1987), and obtained thus supporting evidence for their above-mentioned integrator-resonator model. They also predicted hearing thresholds and most-comfortable-hearing levels of individual subjects (Macherey et al., 2006) for pulse trains consisting of either monophasic, biphasic or pseudo-monophasic pulses by individually tuning the thresholds and time-constants of the model. Bruce et al. (1999b) were also able to predict a number of different aspects of detection threshold, dynamic range and intensity discrimination as a function of pulse duration, number of pulses and mode of stimulation for low-rate pulse trains using their phenomenological model.

Generally, CIs deliver speech information by encoding the speech envelope in a form of amplitude-modulated electrical pulses (see, e.g. Wilson and Dorman, 2008). Such an encoding process is effective as long as the CI listeners are able to detect and utilize the modulation which is, for example, affected by the stimulation pulse rate (see, e.g. Shannon, 1992; Middlebrooks, 2004; Galvin and Fu, 2005; Won et al., 2011). Models can be used to evaluate whether the amplitude modulation is preserved in the spike train output of the model as well as to predict modulation detection thresholds. Cheng and Zhang (2007) processed amplitude-modulated pulse-train sequences with their model. By means of visual inspection they observed that their model output reflects the sound envelope better when the model is stimulated with 5000 pps than with 1000 pps. For more quantitative evaluation, they processed 5000-pps pulse trains with varying phase durations (30-50 µs) and argued 35 µs phase duration to be optimal based on correlation measures between the pulse train inputs and the model outputs. However, no comparisons were made against perceptual data to support their argument. Goldwyn et al. (2010, 2012) followed the idea further and used their model to predict modulation detection thresholds. In their approach, a modulated pulse train and a matching unmodulated pulse train are processed with the model and provided as input to an ideal observer that aims to identify which of the model’s responses corresponds to the modulated stimulus. Specifically, the observer makes the decision based on likelihoods of all response-stimulus pairings. By repeating the aforementioned process at different modulation depths, Goldwyn et al. (2010, 2012) obtained percentages for correct detections and defined the predicted modulation detection threshold as the modulation depth.
at which the observer made the correct decision 79.4% of the trials. They found that neither the pulse rate nor the modulation rate had a systematic effect on predicted modulation detection thresholds. These findings are not fully consistent with perceptual data (see, e.g. Shannon, 1992; Galvin and Fu, 2005). Xu and Collins (2007) determined modulation frequency detection thresholds from the change in the number of spikes outputted by their model (Xu and Collins, 2004). The modulation detection threshold was defined as the increment in modulation frequency \( \Delta f_{\text{mod}} \) required to yield a spike rate increase in 70.7% of the trials. Their predictions suggest that modulation frequency detection improves with higher pulse rate, being generally in line with the perceptual data collected by Chen and Zeng (1993).

The ideal-observer analysis can also be used to predict speech intelligibility scores and speech reception thresholds (SRTs) of CI listeners. Both Hamacher (2003) and Fredelake and Hohmann (2012) based their approaches on the comparisons of their model outputs for speech signals (single words from a limited vocabulary) presented in isolation and when accompanied by a masking noise. To that end, the coding strategy of a commercial cochlear implant device was emulated to transform the acoustical signal into pulsatile electrical stimuli. The spread of excitation was simulated as well. The predictions were obtained as follows. First, the noisy speech sample was processed with the model to obtain an internal presentation of it. Thereafter, a dynamic-time-warping algorithm (Sakoe and Chiba, 1978) was used to derive similarity measures between the obtained internal presentation and the stored presentations of the clean speech samples. Then, the word with the highest similarity was set to be the word identified by the model and the identification was classified either as correct or false. The proportion of correct identifications was used to predict the speech intelligibility and speech reception thresholds (SRTs) were obtained by varying the noise level to achieve 50% identification accuracy. By modifying the amount of internal noise in the model Hamacher (2003) and Fredelake and Hohmann (2012) were able to predict subject-dependent trends in perceptual data. Hamacher (2003) employed the model to predict the influence of SNR to SRT whereas Fredelake and Hohmann (2012) predicted the relationship between SRTs and slopes of the speech intelligibility function using the data.
by Hey et al. (2010). The approach appears promising, but the authors also stated that the simple modification of the amount of internal noise is not sufficient to obtain accurate predictions for individual listeners – more model parameters need to be tuned individually for each subject.

**Summary and Future Directions**

We have reviewed a range of computational models that aim to describe how an auditory nerve fiber responds to an electrical stimulation. The neural responses and the percepts evoked by electrical stimulation of auditory nerve fibers depend in a complex manner on several factors, which formed the outline of this review. Phenomenological models strive to emulate this complex dependency with signal processing algorithms that are controlled by a few parameter values. While phenomenological models were introduced to the CI research community some time ago by White (1978), more widespread interest in phenomenological modeling began only a little over 15 years ago. Nevertheless, even then models captured the stochastic nature of the threshold and effects of refractoriness Bruce et al. (1999c,a). Over the course of years, these models have evolved to account for a variety of findings from neurophysiological measurements and psychophysical experiments. Typically, improvements have required inclusion of additional elements into the model. For instance, a stochastic-delay element needed to be added to account for the latency and jitter of the action potential (Hamacher, 2003). Similarly, the principle of a critical period for action potential generation needed to be implemented in order to simulate how the second phase of a biphasic pulse may inhibit the generation of an action potential (Horne et al., 2016). Despite the additional features, phenomenological models continue to benefit from their low-complexity and limited number of parameters, which is extremely beneficial for tuning the models to individual subjects in order to predict and explain results from neurophysiological or psychophysical experiments with CI listeners.

Nowadays, phenomenological models can account for several phenomena of electrical stimulation found in neurophysiological recordings. Responses to single pulses are well reproduced by the models and do no longer require tuning of model parameters to the pulse.
shape used (Horne et al., 2016). Neurophysiological data for refractory and recovery behavior of the ANF are also accurately captured, allowing the models to predict responses to pulse train stimulation. However, some phenomena related to inter-pulse interactions still remain challenging. Present-day models are able to demonstrate some aspects of facilitation, accommodation and spike-rate adaptation phenomena, but quantitative comparisons to neurophysiological data are still to be made. That being said, phenomenological models have potential to account for these phenomena, and preliminary modeling attempts by several research groups have been presented at recent conferences. For instance, point-process models could follow the approach used by Goldwyn et al. (2012) to simulate facilitation effects and extend that approach to account also for accommodation. In leaky integrate-and-fire models, facilitation and accommodation phenomena could be simulated by keeping track of whether the pulses evoke spikes in order to adjust the threshold after failed initiations. However, it should be noted that more neurophysiological data about these phenomena needs to be gathered as well in order to obtain clearer goals for the models. For instance, various approaches have been employed to investigate spike-rate adaptation, which is also reflected in the diversity in the reported findings (Boulet et al., 2016).

Another intriguing topic for future work is to explain and predict results from psychophysical experiments from models, in general and for individual listeners. Some models have been applied to predict hearing and modulation detection thresholds of CI listeners as well as speech intelligibility scores in noisy conditions. In addition, Kelvasa and Dietz (2015) have recently used the model by Fredelake and Hohmann (2012) as a part of a binaural auditory model to predict localization performance of bilateral CI users (see also the review by Dietz, 2016). These are promising results demonstrating that phenomenological models can be used in various applications and that only a few model parameters need to be tuned to individual subjects. Several steps can be taken to improve the accuracy in the future. The most obvious one is to tune a few more model parameters individually to the subject. Important is to restrict individual adjustments since tuning of all parameters is likely to be neither relevant nor practical. Improvements could also be obtained by using other, more sophisticated metrics than correlation (Cheng and Zhang, 2007) or
Euclidian-distance (Hamacher, 2003; Goldwyn et al., 2010, 2012; Fredelake and Hohmann, 2012) in the ideal observer analysis for predicting modulation detection or speech reception thresholds. Additionally, more detailed and individualized simulation of the current spread, ANF position and nerve survival could generally improve modeling accuracy for percepts of CI users. To that end, one could use, e.g. the finite-element-analysis (FEA)-based model presented by Cohen (2009b) that was found to provide accurate predictions for the effective stimulation field derived from ECAP measurements with CI users. In fact, there are already a number of 3-D CI models available that account for the electro-and neurophysiological variations between CI users and different implant models (for a review, see Hanekom and Hanekom, 2016; Kalkman et al., 2016). The series of papers by Cohen (2009a,b,c,d,e) also demonstrated how ECAP data can be used to tune the model parameters to individual CI users.

The spatial hearing percepts are particularly interesting because of the challenges bilateral CI listeners continue to face in complex listening environments (e.g., Kerber and Seeber, 2012). Hence, device manufacturers and researchers are developing new coding strategies that could improve the ability of CI users to cope in such environments. To aid the development work, phenomenological models could be used to process various pulse trains and to provide inputs to neurophysiology-based models of lateral and medial superior olive (LSO and MSO, respectively). Those nuclei are responsible for the binaural cue decoding in the auditory system (Grothe et al., 2010). With such a modeling approach it would be possible to test, e.g., whether a given coding algorithm yields improved sensitivity to interaural time differences in complex listening scenarios. Taken together, the aspects discussed in this review show remarkable progress made in predicting responses and percepts evoked by electrical stimulation that open up new application scenarios for phenomenological models.

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Notes


Figure captions:

1. Relation between the stimulus current level (in dB) and the spiking probability of a single ANF in the point-process model by Bruce et al. (1999c). (A) The CDF of the model is defined in linear units of current and therefore, the spiking probability does not change symmetrically around the threshold when the current level of a monophasic pulse (phase duration of 40 µs) is changed around the threshold level. (B) A change in phase duration results in changes in both the threshold level and the slope of the spiking probability curve. (C) The spiking probability curves from panel B are replotted as a function of the charge delivered by each pulse.

2. Model (Horne et al., 2016) predictions and neurophysiological data (Miller et al., 1999) for (a) latency and (b) jitter of the action potential evoked by a 39-µs-long monophasic pulse at different stimulation levels (after Horne et al., 2016).

3. Model (Horne et al., 2016) prediction and neurophysiological data (Shepherd and Javel, 1999) of the difference in threshold between a monophasic pulse and biphasic pulses with varying inter-phase gap. Both mono- and biphasic pulses have phase durations of 100 µs.
Synchronization (measured as vector strength) between biphasic (phase duration 40 µs) pulse-train inputs and spike train outputs provided by the models (Hamacher, 2003; Goldwyn et al., 2012) at different pulse rates. The models were stimulated at the level for 90% spiking probability for a single pulse. For comparison, neurophysiological data from both sinusoidal (Hartmann and Klinke, 1990) and pulsatile electrical stimulation of cat auditory nerve fibers (Miller et al., 2008) as well as from pulsatile electrical stimulation of monkey auditory nerve fibers (Parkins, 1989) are shown.

Relative increase in threshold due to refractoriness in neurophysiological data (Dynes, 1996; Miller et al., 2001) and the exponential functions employed in the different models to account for refractoriness. Fredelake and Hohmann (2012) used the function specified by Hamacher (2003).

Figurative examples showing how a simple leaky integrate-and-fire (LIF) model (a) could explain facilitation with monophasic pulses, but (b) would not predict facilitation to occur with charge-balanced biphasic pulses.
Predictions obtained with the models by (a) Bruce et al. (1999a, 2000) and (b) Hamacher (2003) for the effect of pulse-rate on the spiking efficiency, and (c) neurophysiological data from similar stimulations (Javel, 1990). Both models reflect the trend in the neurophysiological data: a greater stimulation level is required at the higher pulse rates for all pulses in the sequence to evoke a spike. The predicted effect size differs between the models: Hamacher’s model predicts the highest pulse rate to be unable to achieve a spiking efficiency of one with the evaluated levels.

Modeling spike-rate adaptation with the model by Goldwyn et al. (2012). The inter-spike-interval histograms (bin size 10 µs) show that the model predicts (a) spikes to occur at the integer multiples of the inter-pulse interval at a low pulse rate of 250 pps and (b) a stochastic distribution of spiking intervals at a high pulse rate of 5000 pps. The levels for both pulse trains were adjusted separately to obtain an average spiking rate of \(\sim150\) spikes/s. However, in (c), spiking during the onset part (first 12 ms) of the 5000 pps pulse-train sequence is predicted to exhibit some periodicity corresponding to \(\sim1\) kHz spiking rate but not the 5 kHz pulse rate.
Figure 1:
Figure 2:
Figure 3:
Figure 4:
Figure 5:
Figure 6:
Figure 7:
Figure 8: