Original Article

A Fast Approximate Method for Predicting the Behavior of Auditory Nerve Fibers and the Evoked Compound Action Potential (ECAP) Signal

Abstract

Background: The goal of the current research is to develop a model based on computer simulations which describes both the behavior of the auditory nerve fibers and the cochlear implant system as a rehabilitation device. **Methods:** The approximate method was proposed as a low error and fast tool for predicting the behavior of auditory nerve fibers as well as the evoked compound action potential (ECAP) signal. In accurate methods every fiber is simulated; whereas, in approximate method information related to the response of every fiber and its characteristics such as the activation threshold of cochlear fibers are saved and interpolated to predict the behavior of a set of nerve fibers. **Results:** The approximate model can predict and analyze different stimulation techniques. Although precision is reduced to <1.66% of the accurate method, the required execution time for simulation is reduced by more than 98%. **Conclusion:** The amplitudes of the ECAP signal and the growth function were investigated by changing the parameters of the approximate model including geometrical parameters, electrical, and temporal parameters. In practice, an audiologist can tune the stimulation parameters to reach an effective restoration of the acoustic signal.

Keywords: *Approximate method, auditory nerve fiber, cochlear implant, evoked compound action potential growth function, model*

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Introduction

Since the cochlear implant system is based on electrical stimulation, the quality and efficiency of the system can be improved through determining optimum stimulation methods and parameters of the signal processing algorithm. In this regard, it is necessary to find a criterion for evaluating the efficiency of the stimulation methods. The evaluation method of electrical stimulation may be carried out by conducting the audiometric assessment in which various patients with hearing impairments are examined.[1] Thus, this method is based on statistical evaluation and requires voluntary patients with different kinds of hearing disorders, which makes this process more complicated. A computational model is a useful tool for understanding the neural factors related to cochlear implant outcomes, such as cannot be accomplished by behavioral studies alone.[2] For example, electrode location in the implanted cochlea has been shown to effect on the various electrophysiological and psychophysical measures including evoked compound action potential (ECAP) thresholds, psychophysical detection thresholds, and ECAP amplitude-growth function linear slope.[3] In a recent computational study,[4] three multi-compartment cable models of the human auditory nerve fiber were investigated. While all three models presented similar values in certain single fiber properties to those obtained in experiments, none matched all experimental observations satisfactorily. In another study,[5] a stochastic and adaptive auditory nerve model was used to investigate neural behavior to amplitude-modulated electrical pulse trains. The model was validated by comparing with animal data.

In computer simulations, accurate methods simulate every individual fiber. Therefore, in contrast to approximate method, the main problem is the huge amount of computation required, due to the presence of 32000 to 35000 nerve fibers in the cochlea of a normal-hearing subject.[6] As a result, the simulation of individual fibers to consider

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the auditory nerve fibers' response is a time consuming process. Clinical tests are based on applying stimulus and recording the signals from a bundle of nerve fibers. Therefore, these tests represent statistical information about the performance results, not the structural features of fibers,[7] which are difficult to be practically applied in the accurate methods. In this paper, for reaching a better evaluation of the stimulation method and avoiding long and frustrating experiments on patients, a new approximate method has been proposed. This method is a quick tool with fewer errors to predict the electrically ECAP growth function[8] as well as the response of the auditory nerve fibers to various electrical stimulations.

Materials and Methods

Accurate simulation method

Methods, in which every nerve fiber is simulated, are capable of providing a high level of flexibility to the variation of fiber parameters. Since these methods use the complete model of the nerve fiber, they can consider the response of fibers to nonstandard tests and various electrical stimulation.[9,10] According to Figure 1, in simulating the response of a nerve fiber to an electrical pulse, the injected electrical current by the electrode should be considered. This current changes the electrical potential in the volume conductor. This is followed by a variation in the extracellular potential, which changes the behavior of the excitable membrane of the nerve fiber.

For modeling the electrical potential of the electrode current, an analytical model with a homogenous spherical volume conductor is used. Although this model is simple, it is able to predict the final results with acceptable accuracy. Compared to other models, the homogeneous spherical model has a high speed.[11,12] Since simulating the behavior of the nerve fibers requires a huge amount of computation therefore, fast models are preferred.

We used the Schwarz-Eikhof-Frijns model (SEF) model presented by Schwarz, Eikhof, and Frijns for investigating the dynamic behavior of the nodal membrane of the nerve fiber.[9,13] The idea of the current research has been taken from speech processing algorithms such as continuous interleaved sampling, which includes asynchronous stimulation pulses.[14] The attribute of these algorithms is that two electrodes are not stimulated simultaneously. Therefore, throughout all the simulations of the paper, the stimulation is applied through a single electrode. All the proposed formulas and methods are simulated and implemented by MATLAB (version 8.1.0.604 [R2016a]) using a computer with an Intel Core i7 processor.

Predicting neural behavior by the Approximate Method

In order to reach the approximate method for predicting the physiological behavior of nerve fibers along the length of the cochlea, the accurate method presented in "Accurate

Simulation Method" has been used. As a matter of fact, in this method by applying electrical stimulation to every fiber individually, we have saved useful information including activation threshold of fibers along the cochlea and the behavior of nerve fibers can be predicted using the spline interpolation method. By using the approximate method, the behavior of the cochlea and its' nerve fibers to different stimulation methods and under various parameters can be simulated and predicted.

Predicting evoked compound action potential signal by the approximate method

Here, we are trying to predict the ECAP growth function using the modified form of the model in which a reduced amount of computation is required. According to the all-or-none law, when a stimulus is applied to a nerve fiber, the current waveform and the membrane potential of each node can be determined as a delayed form of the previous node.[11] Hence, the current of the kth node belonging to the ith fiber can be calculated with the following equation:

$$I_{i,k}(t) = I_0(t - T_k) \qquad (1)$$

in which $I_0(t)$ is the standard waveform of the membrane current of the first stimulated node and T_k is the potential delay in the kth node. If L_k represents the distance between the kth node and the first excited node and V stands for the conduction velocity of the action potential, T_k can be easily calculated:

$$T_K = \frac{L_K}{V} \qquad (2)$$

Since an analytical model with a homogenous spherical volume conductor is used, the electrical potential around the stimulation electrode is a function of both the distance from stimulation electrode and electrical conductivity of the volume conductor. This electrical potential can be calculated with the following equation:

$$\psi_0 = \frac{I_0}{4\pi\sigma r} \qquad (3)$$

in which r is the distance from stimulation electrode, is the electrical conductivity coefficient of the volume conductor, I_0 is stimulation current, and Ψ_0 is distribution potential.

If we denote the number of fibers and the excitation status of each site by N_i and S_i, respectively, $S_i = 1$ specifies the activation mode and $S_i = 0$ specifies the nonactivation mode. Then, the ECAP signal can be calculated by the following formula:

$$V_{ECAP}(t) = \sum_{i=1}^{p}\sum_{k=1}^{m} N_i.S_i.f(r_{i,k},\sigma).I_0(t - \frac{L_k}{V}) \qquad (4)$$

where is the distance between the kth node of the ith fiber and the recording electrode, and $f(r_{i,k}, \sigma)$ is the function describing the relationship between the potential and electric current defined by Eq. 3 To reach the ECAP signal, the length of the stimulated region and the number

of excited fibers are determined based on the stimulus current amplitude using the approximate method presented in "Predicting neural behavior by the Approximate Method." Therefore, the ECAP signal is simulated using Eq. 4. Variations in the electrode-to-fiber distance does not have an influence on the propagation velocity of action potentials, so to use Eq. 4 does not make any problem for the spatial distribution of nerve fibers.

In the approximate method, the current waveform and the membrane potential are presumed to be constant for all the nerve fibers. This seems acceptable because the same membrane model is used for all the nerve fibers located in each region, and a similar membrane potential waveform is predicted by simulating various excitable membrane models.[10]

Results

Evaluation of the approximate method for predicting nerve fibers' behavior

In order to evaluate the reliability of the approximate method, the results from accurate and approximate methods have been compared using several interpolation methods. The percentage errors derived from this study by using three methods of interpolation, i.e., linear, cubic, and spline were equal to 0.592, 0.182, and 0.157, respectively. Accordingly, the percentage errors indicate the high reliability of the proposed approximate method as well as the least error obtained by spline interpolation method.
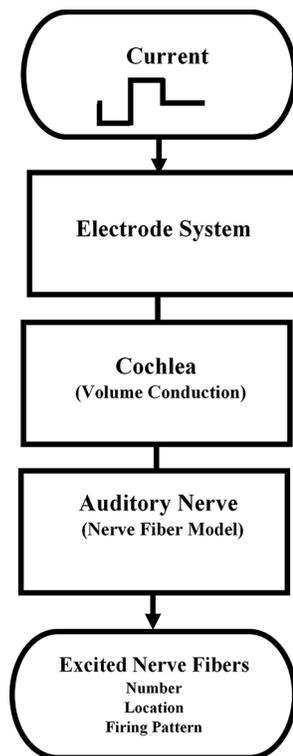
In addition, the operating time of behavioral simulation of auditory fibers' spatial distribution (222 nerve fibers) in the length unit of the cochlea is evaluated by using approximate and accurate methods. According to this experiment, simulation takes 1140 s by using the accurate method. However, in the case of approximate method, the operating time decreases by 99.91%, i.e., to just one second. As a result, it can be concluded that the approximate method is more practical in the simulations which require a large amount of computation.

Evaluation of the approximate method for predicting the growth function

The approximate method is able to predict the ECAP growth function and electrical behavior of fibers in the cochlea. To assess the reliability of this method, the growth function characteristics resulted from both accurate and approximate methods have been compared. The growth of the ECAP signal as a function of the stimulation current amplitude is calculated to simulate the ECAP growth function. The maximum current amplitude and intervals are presumed the same for both methods. The simulated growth functions are shown in Figure 2. The comparison gave an error of <1.66% [Figure 3], which proves the high level of reliability of the approximate method. Stimulation current is normalized to the threshold current in Figures 2 and 3.

Furthermore, the operating time required for simulating growth function by both methods was also computed. Simulation by the accurate method takes 3120 s. However, using the approximate method, the operating time decreases by 98.07%, i.e., to 60 s.

Hence, the approximate method can be used as a fast tool for predicting the ECAP growth function as well as the behavior of the auditory system.

Figure 1: Simulating the cochlea with the capability of tuning the model parameters
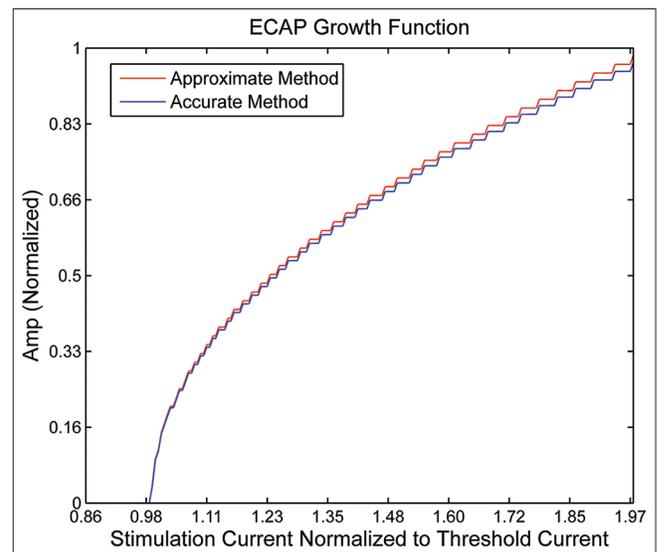
Figure 2: Comparing the growth functions acquired from approximate and accurate methods

The behavior of auditory fibers to electrical stimuli

The approximate method is able to predict the behavior of the excitable fibers along the cochlea quickly and precisely by applying stimuli with different current amplitudes. In addition, the response of auditory fibers to different stimulation methods under various parameters can be discussed. For instance, by choosing a spatial resolution of 0.2 mm (which means the distance between two adjacent fibers is 0.02 mm) and assuming a minimal and identical population distribution for excitable fibers in a certain length of the cochlea, the number of excited fibers per different stimulation current amplitudes is determined. The results of these considerations are shown in Figure 4. These results comply with clinical ones.[15,16]

Action potential follows the All-or-None principle. If the membrane potential is below the threshold limit or the inter-pulse interval is less than the refractory period, the action potential will not occur.[17,18] In order to study the effect of different parameters (including pulse amplitude, inter-pulse interval, and electrode-to-fiber distance) on the behavior of the nerve fibers, we simulated the response

of a nerve fiber to two sequential pulses. In the following paragraphs, the results are reported.

The effect of the amplitude of sequential pulses on the refractory period

Due to the important role of the refractory period in nerve fiber stimulation and the behavior of the cochlea, the response of a fiber to two sequential biphasic pulses has been simulated. In this simulation, different values were chosen for the first and second pulses; by changing the time interval between the two pulses, the occurrence of an action potential during the second pulse was selected as a basis for calculating the refractory period. The refractory period varies according to the amplitudes of the two pulses. As shown in Figure 5, it can be concluded that the refractory period is inversely proportional to the pulse amplitudes. In other words, an increase in the amplitudes of pulses leads to a decrease in the refractory period. It needs to be mentioned here, that increasing the amplitude of the second pulse is much more influential than the first one in decreasing the refractory period changes.

The effect of amplitude and inter-pulse interval on the activation threshold

Since the inter-pulse interval is an important parameter in electrical stimulation, the effect of this parameter on the activation threshold has been studied. According to the conducted investigations (in "The effect of the amplitude of sequential pulses on the refractory period"), the refractory period can be variable depending on the amplitudes of both pulses. Therefore, we studied the activation threshold of the second pulse with two intervals of 1.7 and 0.8 ms which are consistent with clinical results.[19]

As shown in Figure 6, by increasing the distance of the electrode from nerve fibers with a long interval equal to 1.7 ms, the threshold of the second pulse increases. Furthermore, an increase in the first pulse amplitude has an incremental impact on the threshold of the second pulse. However, this impact is not considerable. Assuming a short interval equal to 0.8 ms, the threshold of the second pulse increases by increasing both the electrode-to-fiber
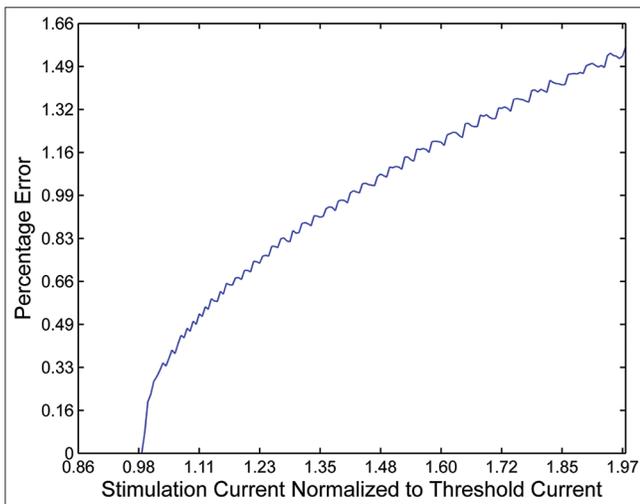
Figure 3: The simulation error of growth function resulted from the approximate method
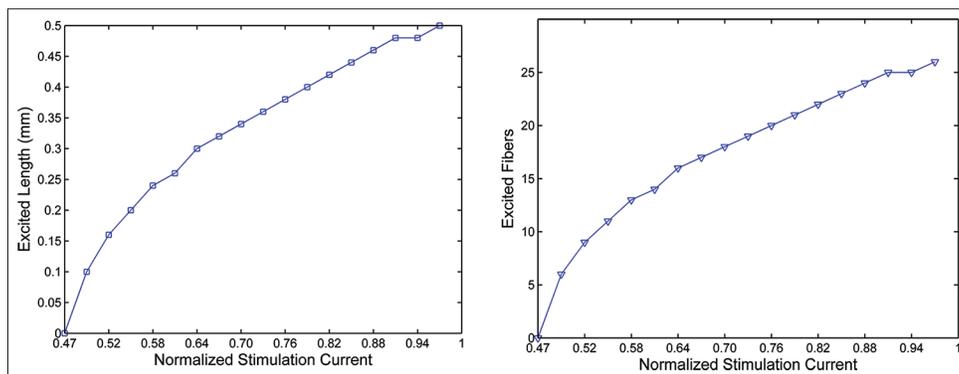
Figure 4: The length of the excited cochlear region and the number of excited fibers predicted by the Approximate Method
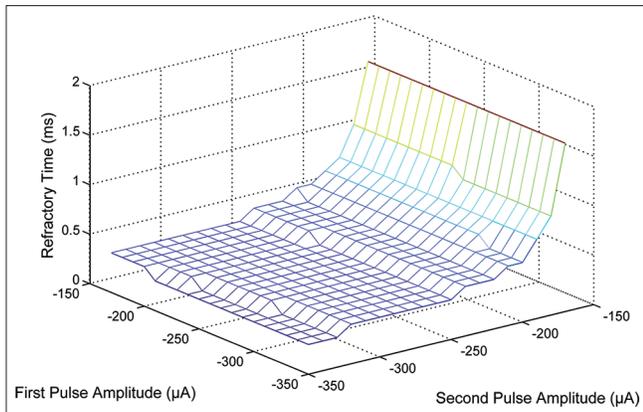
Figure 5: The refractory time changes of a nerve fiber's response to two sequential pulses

distance and the first pulse amplitude. Compared to the previous case (interval = 1.7 ms), the amplitude of the first pulse has more effect on the threshold. These results are consistent with clinical results.[17,20] In a recent study,[2] the effect electrode-to-fiber distance on spectral resolution in cochlear implant was also investigated by a computational model. It was observed that the spread of excitation increases with increasing electrode-to-fiber distance.

The effect of amplitude and inter-pulse interval on the excitability of nerve fibers

The number of excited fibers determines the hearing behavior of the cochlea. Therefore, in this section, we studied the effect of parameters such as the inter-pulse interval and the amplitude of the previous pulse on the excitability of the nerve fibers. We simulated the response of the spatially distributed fibers to two sequential pulses. The normalized amplitude of the first pulse was set to 0.29, 0.58, and 0.97. Then, we compared the number of excited fibers with respect to the amplitude of the second pulse with and without considering the effect of the first pulse amplitude. We performed this comparison with two intervals equal to 0.8 and 1.7 ms, which are consistent with clinical results.[19] The result of this consideration is shown in Figure 7. By choosing a relatively long interval equal to 1.7 ms as it does not have much effect on the result, the first pulse amplitude had a low impact on the number of excited fibers. Besides, for a short interval equal to 0.8 ms, the effect of the first pulse amplitude increased compared with the previous case. According to both cases, by increasing the first pulse amplitude, the number of excited fibers decreased (compared with the case that the effect of sequential stimuli is not considered). These results comply with clinical ones.[17,21]

The behavior of evoked compound action potential signal and the growth function

As shown in Figure 4, by increasing the stimulation current, the length of excited cochlear region increases. Therefore,
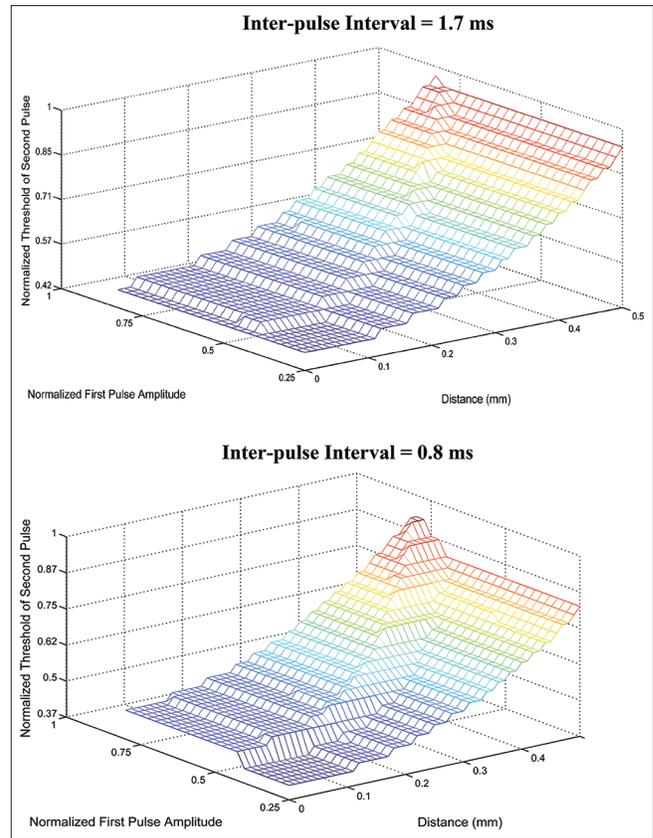
Figure 6: Characteristic of the second pulse threshold with respect to both electrode-to-fiber distance and the first pulse amplitude

the amplitude of the ECAP signal can be affected by density, the spatial resolution of fibers, and the rate of stimulation. Recording and investigating the ECAP signal are important from clinical and diagnosis aspects.[8] Therefore, we studied the impact of the mentioned parameters on the ECAP growth function.

Density distribution of excitable fibers

Figure 8 shows the ECAP growth function with different density distributions of the nerve fibers and similar spatial resolution. The stimulation current is normalized to the threshold value. Figure 8 shows the slope of the growth function increases with density of the excitable fibers, which is consistent with clinical results.[22,23]

The spatial resolution of nerve fiber bundles

Here, we studied the impact of different spatial resolutions of fibers on the growth function with the assumption of the same density in a unit length. Figure 9 shows the results obtained by approximate and accurate methods. The stimulation current is normalized to the threshold value. As observed, growth function increases stepwise and steps become larger by increasing the spatial distance of fibers or regions. In other words, if the distance between excitable regions is increased, a higher stimulus current is needed for stimulation of the next region. Since the density of fibers in
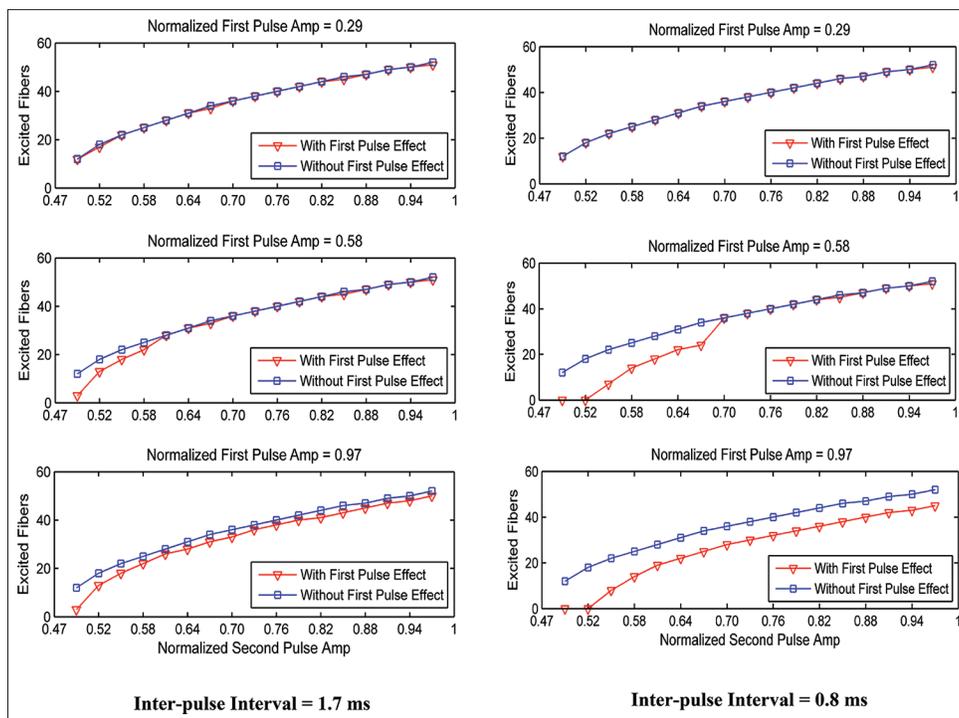
Figure 7: The number of excited fibers with respect to the second pulse amplitude. From top to bottom: the normalized amplitude of the first pulse is equal to 0.29, 0.58, and 0.97
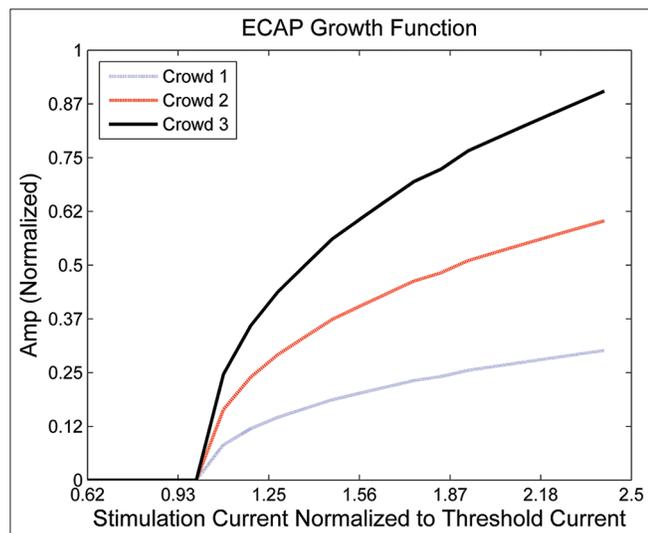
Figure 8: The normalized growth function with respect to different fiber density. It is assumed that Crowd represents the number of fibers and Crowd 3 > Crowd 2 > Crowd 1

a unit length is fixed, the slopes of the growth functions are the same. This figure shows the similarity of curves in the accurate and approximate methods, too.

The rate of sequential stimulation pulses

Since auditory fibers perform restoration of the acoustic signal and pulses are applied sequentially with different rates, we simulated the response of nerve fibers to a pulse train with different rates. Figure 10 shows the average amplitude of ECAP signal plotted as a function

of stimulation rate. The pulse train was composed of 10 biphasic pulses with equal amplitudes.

Discussion

Amplitude of the stimulation current required for creating the extracellular potential for activation increases by increasing the electrode to fiber distance. Therefore, to activate more fibers along the cochlea, the stimulation amplitude must be increased. An increase in the amplitude of the first pulse results in an increase in the activation threshold of the second pulse. This is verified by Figure 6 and also by the studies concerned with the response of fibers to two sequential pulses show. In "The effect of amplitude and inter-pulse interval on the excitability of nerve fibers," the effect of the first pulse on the excitability of the cochlear fibers was studied by applying two sequential pulses to the spatial distribution of nerve fibers. According to this investigation [Figure 7], an increase in the amplitude of the first pulse results in fewer excited fibers in response to the second pulse. The number of excited fibers decreases more by reducing the inter-pulse interval. In other words, it can be concluded that an increase in the first pulse amplitude raises the activation threshold of the second pulse. Therefore, it reduces the length of the excited cochlear region, and finally, it decreases the number of excited fibers. These results are consistent with Figure 6 which shows the validity of the performed simulation.

By using the approximate method, the ECAP growth function can be estimated with a precision of more than
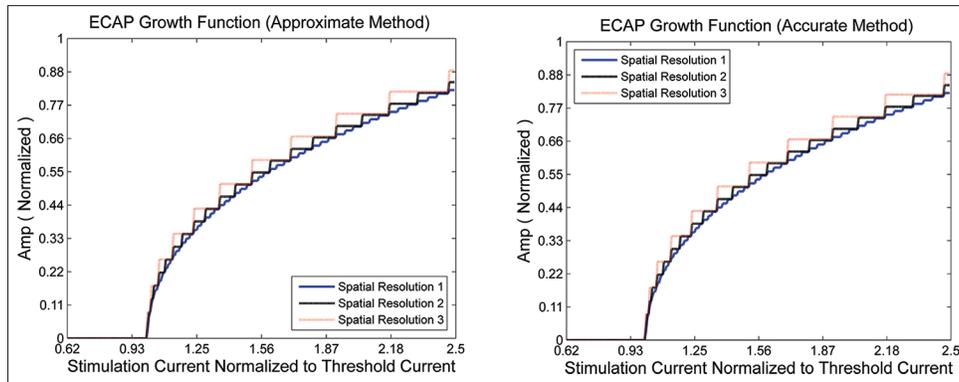
Figure 9: The normalized growth function obtained by the approximate and the accurate methods for different spatial resolutions and with the assumption of spatial resolution 1 > spatial resolution 2 > spatial resolution 3

98.34% and simulation time reduces by more than 98.07%. As shown in Figures 8 and 9, investigating the variations of growth function gives useful information about the number and spatial resolution of the cochlear nerve fibers. This information complies with clinical results.[22,23] The growth function characteristics have useful clinical applications, so that an audiologist can tune stimulation parameters to acquire an effective restoration of the acoustic signal. For example, if a low population of excitable fibers around a stimulation electrode is detected, the electrode can be deactivated and another electrode from an array which has more roles in hearing can be activated.

According to the response of nerve fibers to a stimulation pulse train with different rates [Figure 10], we can conclude that an increase in the stimulation rate increases the probability of a stimulation pulse occurring in the refractory period and consequently the lack of fiber excitation. Therefore, an increase in the stimulation rate reduces the recorded potential of activated fibers. Furthermore, reducing the stimulation rate increases the probability of a stimulation pulse occurring outside refractory period as well as the excitation of the nerve fiber. Therefore, by reducing the stimulation rate, activity of nerve fibers increases. If the rate decreases to an amount that the inter-pulse interval remains larger than the refractory period, the nerve fibers will become active by all stimulation pulses. Then, according to the characteristic of ECAP amplitude with respect to stimulation rate, the recorded potential of the nerve fibers will remain fixed at the maximum level. These results are consistent with clinical ones.[24]

Conclusions

In this research, we presented a model for the cochlea with the capability of tuning its parameters according to the physiological conditions of the patient. It can predict the behavior of the cochlea in response to variable geometrical (including electrode-to-fiber distance, density, and distribution of the cochlear fibers) and electrical parameters (including the inter-pulse interval, stimulation rate, and the stimulation pulse amplitude). In this regard,
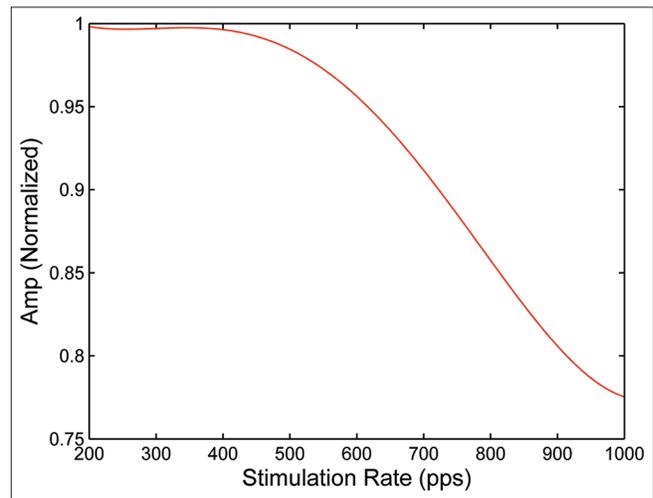
Figure 10: Normalized evoked compound action potential amplitudes averaged across pulses as a function of stimulation rate

the approximate method was presented as a fast and low error tool which predicts the nerve fiber response as well as the bioelectric behavior of the cochlea against electrical stimuli under different conditions. Furthermore, this method can predict the ECAP signal and its growth function. The precision of this method is within 1.66% of the accurate model. Also, the simulation time is reduced by more than 98.07%.

In this study, we also investigated the number of excited fibers along the cochlea as well as the variations in growth function and ECAP signal amplitude as tools for evaluating restoration of input stimulation. With the help of these tools, we can estimate the biological response of the cochlea. In other words, these characteristics alongside speech comprehension tests will help to tune the parameters of the speech processing algorithm. They can also be used as criteria for evaluating the efficiency of the chosen stimulation strategy.

Since refractory period has an important role in stimulating nerve fibers, its characteristic against the two sequential pulses was extracted. According to the obtained

characteristic, the refractory period in sequential stimuli is not fixed and has some variations. Therefore, future work is needed to simulate the behavior of auditory fibers by choosing random parameters and compliance with statistical results derived from clinical tests.

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Conflicts of interest

There are no conflicts of interest.

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