

Simulation of the Physiological Characteristics of Pillar and Modiolar Fibers of the Auditory Nerve

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Abstract— The study of the physiological characteristics of the auditory nerve fibers is fundamental to understand their capability to encode sounds. These characteristics include their spontaneous firing rate, their threshold, and their dynamic range. Although it is possible to perform *in vitro* recordings of these characteristics in different cell models, it is complicated to obtain *in vivo* measurements of them directly from the cochlea. For example, the apex of the cochlea since it is an unreachable region which is vulnerable to surgical trauma that could result in altered recordings. In this paper, the behavior of Pillar and Modiolar fibers of the auditory nerve were simulated in response to tone bursts of different frequencies and intensities. The proposed model allowed us to associate the basal firing rates with the physiological characteristics of the different auditory nerve fibers. This is especially important since some noise-associated hearing losses, such as acoustic trauma, have been explained as selective fiber damages.

Clinical Relevance— Models that describe the properties of auditory nerve fibers are important to study specific aspects of maturation as well as the causes of sensorineural hearing loss in humans.

I. INTRODUCTION

Inner Hair Cells (IHC) located in the cochlea, and the afferent nerve fibers of the auditory nerve conform the first synapse in the auditory pathway of mammals. The human cochlea has about 3000 IHCs connected to 30000 - 90000 nerve fibers (about 10 to 30 per IHC). Afferent fibers generate action potentials (spikes trains) in response to the glutamate secretion released by the IHC when an acoustic stimulus appears. These action potentials trains encode the sound characteristics, such as its frequency and intensity, to ensure the correct transmission of sound information [1].

It has been reported that fibers present a basal (spontaneous) rate (SR) of action potentials even in the absence of acoustic stimulation. A pioneer work performed in cats classified fibers in two classes: those exhibiting high rates of electrical discharges or spikes ($>18 \text{ s}^{-1}$) and those having low rates ($<18 \text{ s}^{-1}$) [2]. On the other hand, SR value has been related to the sensitivity to sound intensity, since high SR fibers (HSR) have the lowest intensity thresholds, and low SR fibers (LSR) have the highest intensity thresholds, existing an intermediate one named medium SR fibers (MSR) [3]. Anatomical studies show that for the same IHC, LSR fibers have thin axons and few mitochondria, and together with MSR fibers, they make contact with just one side

of the IHC named the Modiolar side (Fig. 1). In contrast, HSR fibers have thicker axons and more mitochondria, and they make contact with the opposite side of the cell, named the Pillar side [2]. Moreover, the active zones where glutamate secretion occurs in the IHC have different sizes that match the contact area of the nerve fiber. This complex spatial organization shows that IHC-fiber synapses are highly specific and sensitive systems [1].

Spontaneous rates and threshold sensitivity impact the dynamic range of the fiber, allowing it to discriminate between more than five orders of magnitude for both sound intensity and sound frequency. This ability is lost if there is an IHC-fiber synapse dysfunction (called auditory synaptopathy), which affects the auditory nerve encoding of sounds. Auditory synaptopathy has three principal origins: 1) Genetic, which includes alterations in glutamate loading of synaptic vesicles, in Ca^{2+} influx, or in vesicle refilling. 2) Age-related hearing loss, and 3) Noise-induced hearing loss (also called acoustic trauma). Indeed, acoustic trauma causes permanent hearing loss and involves hard damage to IHCs, producing a reduction of spontaneous firing rates of their LSR fibers [3]. Despite its clinical importance, synaptopathies are not easy to classify and treat, then a computational tool that helps to find the origin of the disease is highly relevant.

In this paper we simulate the firing rates of Modiolar (LSR and MSR) and Pillar (HSR) fibers for sounds of different intensities and frequencies. We analyze the rate- intensity functions, the dynamic ranges, and the sound threshold values towards the understanding of the abilities of these fibers to discriminate sounds. Our final goal is to link clinical measurements such as dynamic ranges and thresholds to the dynamics of subcellular mechanisms of IHCs and nerve fibers.

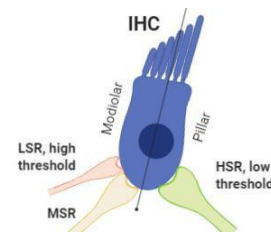


Figure 1. An Inner Hair Cell (IHC) of the cochlea has three different types of synapses with low (LSR), medium (MSR), and high (HSR) spontaneous rate fibers. LSR and MSR fibers are located preferentially in the Modiolar side of the IHC, in spatial opposition to HSR fibers which are located on the Pillar side.

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II. METHODS

A. IHC-fiber synapse

In [4], Meddis proposed a probabilistic model of auditory-neural transduction at the IHC. This model has two stages: the first one includes functions coupling acoustic stimulation to Glutamate secretion from the IHC, and the second one corresponds to the auditory nerve fiber response due to this Glutamate secretion. We have used only the output of the first stage of this model as the input to our nerve fiber model described in the next section (see section B. Fiber response model) since the former model is not able to simulate a LSR fiber, as explained below, and it cannot take into account the spatial organization of the postsynaptic area. As mentioned in the previous section, these two features are necessary to study the specific damages that cause sensorineural hearing losses.

The initially published set of Meddis' model parameters in [4] corresponds to a Pillar HSR. In a later work, the authors changed these parameters to explain the differences between HSR and MSR fibers in terms of the permeability of the IHC membrane [5]. They mentioned that a low permeability of the IHC causes a low spontaneous rate, a less strong response to stimulus onset, and a slower reduction of available Glutamate. Three parameters govern the permeability of the innervation: A , B , and g . Readers interested in knowing the description of other parameters (y , l , r , and x) should review [6]. For the present work, we used the parameter values shown in Table I to simulate HSR and MSR corresponding to Pillar and Modiolar active zones of secretion, respectively. Fig. 2 shows an example of the glutamate secretion, using the parameter values of Table I, of Pillar and Modiolar active zones contacting high and medium/low SR fibers. Notice the non-linear growth of secretion as intensity increases.

B. Fiber response model

The firing rate of action potentials generated by the nerve fibers in response to the IHC secretion was simulated considering that the postsynaptic area contacting the active zone of the IHC is a circular area of 0.1 microns radius with a height of 10 nanometers, where 100 glutamate receptors (AMPA receptors), are uniformly distributed. This geometry is used for the HSR and the MSR fibers, but for the LSR fiber, the radius was decreased by two, as discussed later.

TABLE I. Values of parameters used in Meddis' model to simulate Pillar and Modiolar rates of secretion. *

Parameter	Pillar (HSR)	Modiolar (LSR/MSR)
A	5	10
B	300	3000
g (release)	2000	1000
y (replenish)	5.05	5.05
l (loss)	2580	2580
r (recovery)	6580	6580
x (reprocessing)	66.31	66.31

* Fixed parameters were $M=1$, $h=50000$, and $dt=0.00005s$.

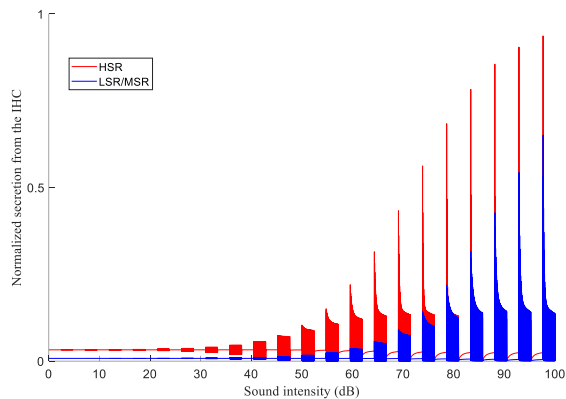


Figure 2. Example of the simulated glutamate output used as the input to our fiber model. In this example, a tone burst of 1000 Hz was used with intensities ranging from 0 to 100 dB in 10 dB steps. Two different active zones were simulated, Pillar corresponding to HSR fibers (red) and Modiolar corresponding to LSR/MSR fibers (blue). Notice silences between sounds to separate the responses to different intensities.

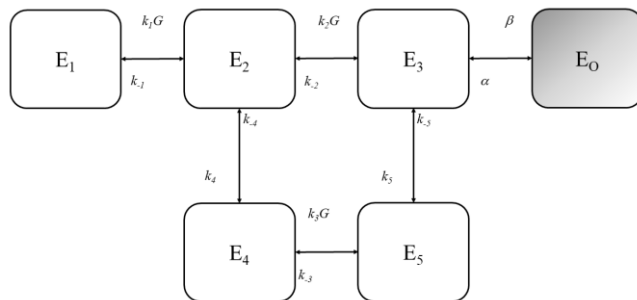


Figure 3. State-model of the glutamate receptors located in the postsynaptic area of the fibers. The model has six states where E_0 (marked in gray) is the Open state that leads to action potentials. Values for rates k_i are given in [7].

The instantaneous firing rate is assumed to be proportional to the number of receptors in state E_0 (Fig. 3). The model of Fig. 3 was solved using the ODE45 solver of Matlab to calculate the number of open receptors over time. Since these receptors are rapidly activated and deactivated for auditory protection, the maximal firing rate or *Onset Rate* is obtained in the first milliseconds after the beginning of the acoustic stimulation (as marked with arrows in Fig.4). This rate is relevant to study the properties of the fibers, as we discussed previously [7]. In the present work, we used this onset rate for the analysis of the physiological characteristics of the Pillar and Modiolar fibers.

III. RESULTS

A. Rate- Intensity function

Fig. 4 shows the dynamics of the instantaneous firing rate (FR) for the Pillar and Modiolar nerve fibers in response to a 1000-Hz pure tone lasting 50ms with 50 dB intensity. For each fiber, the maximal FR (*Onset rate*) is indicated with arrows in the figure. Modiolar (MSR/LSR) fibers exhibit a lower maximal rate than Pillar (HSR) fibers, as reported in other works [2], [8].

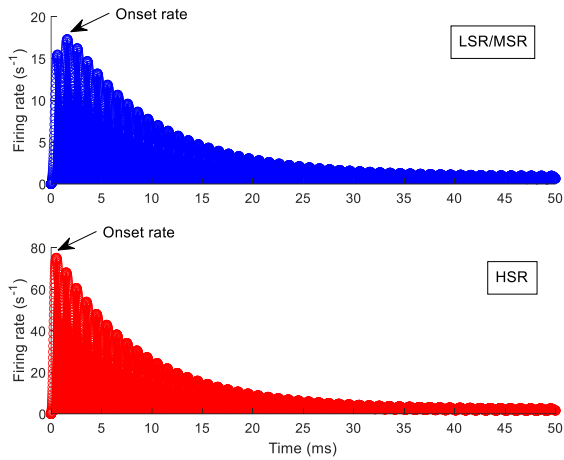


Figure 4. Dynamics of the instantaneous Firing rate (FR) for the Modiolar (MSR/LSR) fiber (in blue) and the HSR fiber (in red). Responses due to a tone burst of 1000 Hz lasting 50 ms with 50 dB intensity. Arrows indicate the maximal firing rate (*Onset rate*), which has a higher value in the HSR fiber than in the LSR/MSR fibers.

Fig. 5 and 6 show the rate-intensity functions for the Pillar (HSR) and Modiolar fibers (LSR/MSR), respectively; notice that functions have a horizontal shift in as much as frequency changes. This behavior means that the threshold to initiate electrical firing increases with frequency, and in the same line, MSR fibers have a higher intensity threshold while HSR fibers present a lower intensity threshold for sounds of the same frequency. In both figures, the Spontaneous Rate is indicated, and corresponding to their classification, in our simulations LSR / MSR fibers have low spontaneous rates (11 s^{-1}), whereas HSR fibers present a higher spontaneous rate (50 s^{-1}). These rates and the shifts in thresholds are perfectly in agreement with previous experimental observations in cats [6] and mice [9].

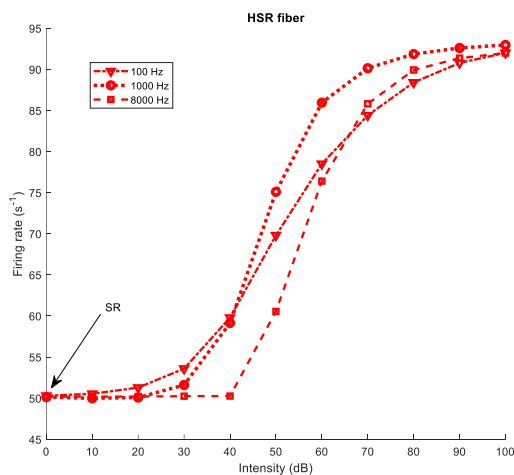


Figure 5. Rate-intensity functions for the HSR (Pillar) fiber for sounds of 3 frequencies: apical (100Hz), middle (1000Hz), and basal (8000Hz); intensity ranges from 0 to 100 dB in 10 dB steps. Spontaneous Rate (11 s^{-1}) is indicated with an arrow.

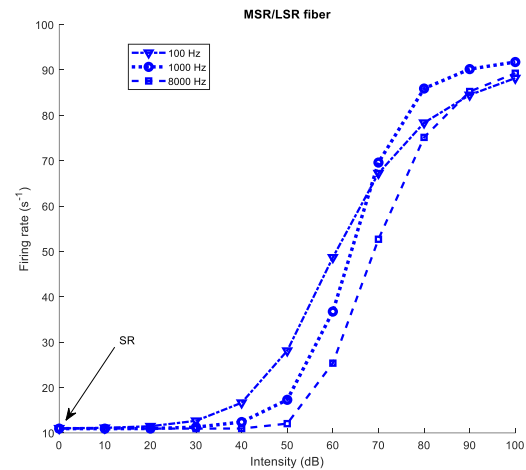


Figure 6. Rate-intensity functions for the MSR/LSR (Modiolar) fiber for sounds of 3 frequencies: apical (100Hz), middle (1000Hz), and basal (8000Hz); intensity ranges from 0 to 100 dB in 10 dB steps. Spontaneous rate (50 s^{-1}) is indicated with an arrow.

Fig. 7 shows the comparison between the dynamic ranges of the rate-intensity functions for HSR and LSR/MSR fibers. The dynamic range was calculated as proposed in [9]: the range that covers the 10 to 90% between maximal and minimal rates. It is possible to observe the clear reduction of the dynamic range of the HSR fiber (20dB) compared to the MSR/LSR fiber (45dB). The difference in the dynamic range between fibers is an important feature of the nerve since its function may extend the global dynamic range of the sound transmission [1]. As shown in the previous results, with our IHC-fiber model, we are able to simulate Pillar and Modiolar rates of secretion. However, it was not possible to distinguish between MSR and LSR fiber types (see Fig. 7); both make contact with the Modiolar part of IHC. In order to differentiate between LSR and MSR fibers, micro and nanodomain coupling of the postsynaptic area were considered. Those terms are used to distinguish tight and loose coupling regimes of subcellular components [10].

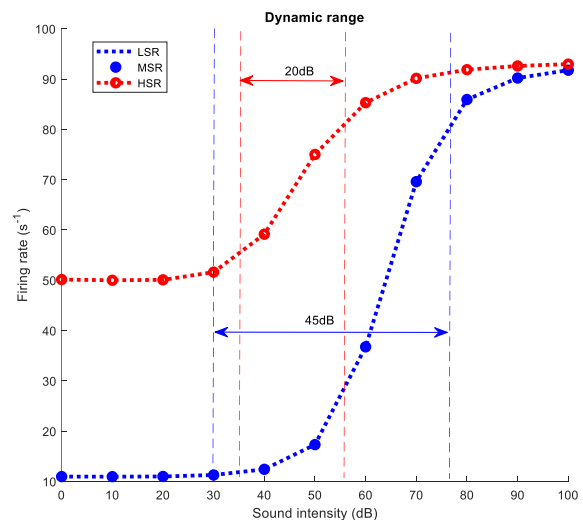


Figure 7. Comparison between the dynamic ranges of Pillar (red trace) and Modiolar (blue trace) fibers.

In our case, we implemented this idea by considering that postsynaptic AMPA receptors are spread over a smaller region in the fiber, as a simple approximation to a nanodomain. In particular, we use a LSR postsynaptic area of half the size of the areas of HSR and MSR fibers. This consideration is in accordance with the observations of Liberman et al. [11], who observed that the contact regions of AMPAs in LSR fibers of cats are smaller than in HSR fibers. Using the spatial consideration detailed before, we also simulated the firing rates for a LSR fiber. Fig. 8 shows the three rate-intensity functions for HSR, MSR, and LSR fibers for a middle sound of 1000Hz. Now, it is possible to observe the fundamental differences in thresholds and dynamic ranges between fibers (low threshold and reduced dynamic range for HSR versus high threshold and wider dynamic range (about the double) for LSR and MSR fibers), but we also observe a steeper rate-intensity function for the LSR fiber. Notice that the sound threshold for this fiber is higher than the one for the MSR fiber, but once this threshold is surpassed, LSR fibers rapidly reach their maximal firing rates. These differences make fibers useful for expanding sound sensitivity, but at the same time, make fibers more prone to damage. Indeed, there are experimental studies in different animal species that explain how the threshold behavior of these fibers can be affected in different hearing losses [12]. For example, Furman et al. reported that noise-induced hearing loss is selective to LSR, and that hearing loss due to aging is characterized by a loss of HSR fibers [13].

IV. CONCLUSION

In this paper, three physiological characteristics of the auditory nerve fibers were analyzed: 1) the rate-intensity function, 2) the dynamic range, and 3) the threshold behavior. These characteristics were obtained in the three types of fibers making contact with each IHC in the cochlea: Pillar HSR and Modiolar MSR and LSR fibers.

The characteristic low threshold of fibers with HSR was observed in our simulations. It is reported in the literature that this could explain the ability of the auditory system to detect sound in a quiet environment. On the other hand, the characteristic high threshold of fibers with LSR was also observed. Because of this characteristic, these fibers could have particular importance to extend the dynamic range of hearing and contribute to hearing in noisy environments.

Additionally, it was possible to distinguish between LSR and MSR fibers by reducing the postsynaptic contact area in the fiber by assuming that AMPA receptors are distributed in a smaller region, increasing their coupling. Our results open the possibility to study, for example: 1) micro and nanodomain couplings which have an impact on the speed and efficiency of the synaptic transmission and are related to the maturation of the auditory system; 2) noise-induced neuropathy which is selective for LSR fibers; and 3) the damage of HRS fibers related to the normal aging process which contribute to the problem of hearing in noisy environments, called "the cocktail party problem".

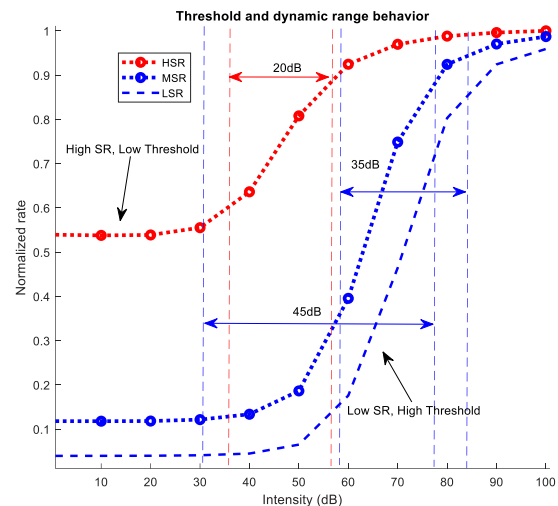


Figure 8. Rate-intensity functions for LSR, MSR and HSR fibers. Firing rates are normalized to the maximal rate of the HSR fiber to enhance differences in thresholds and dynamic ranges.

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