A plastic neuronal network model with STDP for tinnitus management by sound therapy

Hirofumi Nagashino, Yohsuke Kinouchi, Ali A. Danesh, and Abhijit S. Pandya

***Abstract*—**Tinnitus is a perception of sound in the ears or in the head without external source. There are many therapeutic approaches for tinnitus. Sound therapy is one of the effective techniques for its treatment. We have proposed computational models with plasticity by Hebbian hypothesis using a neural oscillator or coupled model neurons described by simplified Hodgkin-Huxley equations in order to investigate mechanisms of tinnitus generation and the clinical effects of sound therapy from the neural engineering point of view. In the present paper, a neuronal network model with synaptic plasticity by STDP (spike-timing-dependent plasticity) hypothesis is proposed for replication of the clinical results that human auditory system temporarily halts perception of tinnitus following sound therapy.

***Keywords*—**neuronal network model, tinnitus, sound therapy, STDP hypothesis, oscillation, inhibition

I. Introduction

TINNITUS, a perception of sound in the ears or head with no external source, is considered as one of the most debilitating disabilities for human beings [1]. A variety of environmental and pathological conditions can result in the tinnitus generation. The environmental etiologies include exposure to loud levels of noise and exposure to chemical agents such as ototoxic medications. Both of these elements can potentially harm cochlear hair cells which can result in tinnitus and hearing loss. Pathological etiologies which result in tinnitus include a variety of diseases from the external ear to the brain. Abnormalities of the middle and inner ears and pathologies of the ascending auditory pathway from the hearing nerve to the auditory cortical regions of the temporal lobe can result in tinnitus. Additionally, metabolic and organic disorders such as thyroid dysfunction, diabetes and heart problems can be associated with tinnitus perception. Tinnitus and hearing loss may coexist or be present independent from each other. In other words, many of individuals with tinnitus have clinically normal hearing sensitivity and not all of those with hearing loss report tinnitus.

Neurophysiological models have been proposed to understand the mechanism of the tinnitus [2, 3]. A computational tinnitus model based on one of the neurophysiological models [2] combined with the adaptive resonance theory of cognitive sensory processing [4] has been proposed for identification of neural correlates of the tinnitus decompensation [5]. The effect of auditory selective attention on the tinnitus decompensation has also been investigated by modeling corticothalamic feedback dynamics [6, 7]. Structural brain changes in tinnitus have been discovered using MRI [8].

Contribution of neural plasticity to tinnitus has been discussed by many in order to understand the neural correlates of tinnitus [9-13]. Computational modeling of thalamocortical correlates with plasticity from the perspective toward understanding of the tinnitus has been reported [14]. It has been suggested that the damage of the peripheral system decreases auditory nerve activity and this change leads to plastic adjustments, a shift in the balance of excitation and inhibition, and increase of spontaneous firings in the central auditory system [12, 13].

For management and treatment of tinnitus, a number of approaches have been proposed by clinicians and scientists. Tinnitus can be classified in many subclasses and attempts have been made to categorize tinnitus based on its characteristics that in turn can facilitate the selection of treatment methods [15]. These include use of medications, supplemental vitamins and micronutrients; employment of surgical procedures; psychotherapy and biofeedback; electrical stimulation [16]; laser therapy; and the noninvasive methods of sound therapy or acoustic therapy. There are also a variety of miscellaneous approaches that anecdotally have been shown to be effective in some cases.

Many clinicians and scientists agree that sound or acoustic therapy is one of the most effective methods in tinnitus management among a number of therapies. Sound therapy techniques for tinnitus treatment have the clinical effect that tinnitus disappears or reduces in its loudness after the sound presentation [17]. Sound therapy employs a variety of stimuli such as music, white noise, narrow band noise and environmental sounds to facilitate the habituation process to tinnitus. The therapeutic sounds can be introduced to the users' ears via ear level devices or can be downloaded to their personal music players. For those individuals with hearing loss associated with tinnitus, sound therapy techniques may

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employ hearing aids or custom-made music files based on the users' hearing thresholds. When combined with appropriate rehabilitation and counseling sessions, sound therapy enables the tinnitus suffering individuals to perceive tinnitus in a more manageable level and enables them to reduce the negative impact of tinnitus in their daily life and activities [15, 18, 19]. Many tinnitus sufferers habituate to their tinnitus and need not to use sound generating devices after a while. In some successful cases tinnitus may be inhibited for a limited time following the presentation of an acoustic stimulus. This inhibition is referred to as Residual Inhibition (RI) and the underlying reasons for this phenomenon are not clear as of now.

The mechanisms of tinnitus management by sound therapy, however, are not clear. Some attribute the success with sound therapy to brain plasticity [20] while others consider it a habituation process [21]. It has been reported that paring of electric vagus nerve stimulation with tones reverses neural activity of noise-induced tinnitus in an animal study [22].

To account for the mechanisms of tinnitus and its management by sound therapy from the neural engineering point of view, previously we proposed a computational model using a neural oscillator [23, 24]. We demonstrated that the model conceptually reproduces tinnitus generation and its inhibition using sound stimuli. It was detected that by providing the model with sinusoidal or noise stimulus that is hypothesized as sound for treatment of tinnitus, we can inhibit the oscillations. This was accomplished by incorporating neural plasticity through parameters such that their values can be modified. By hypothesizing that the oscillation and the equilibrium correspond to generation and inhibition of tinnitus, respectively, we reported that these phenomena could explain the fact that the habituated human auditory system temporarily halts perception of tinnitus following sound therapy. However, that model relied on a somewhat conservative simplification of the central auditory pathways and associated central nervous system areas that are relevant to tinnitus.

Next we proposed a different model [25, 26] composed of model neurons described by simplified Hodgkin-Huxley equations [27-29]. This model is still conceptual since it consists of only three neurons with positive and negative feedbacks, but more realistic than the previous one because it shows time series corresponding to the firings of neurons. We showed that inhibition of the oscillation can be observed in this model as well by constant or pulse train stimuli.

In those models, the synaptic plasticity was modeled applying Hebbian hypothesis [30] to one of the couplings of the components in the model. Hebbian hypothesis has been adopted in a number of neural network models for many years. As a newer and biologically plausible hypothesis, "spike-timing-dependent plasticity (STDP)", was proposed for the mechanism of synaptic plasticity [31, 32]. It does not replace the idea of Hebbian hypothesis, but describes Hebbian synaptic plasticity more specifically. This hypothesis has been adopted in a number of computational models of neuronal networks [33].

In the present paper, we propose a neuronal network model with a plastic coupling of neurons expressed by STDP equations [34]. The structure and equations for the membrane potentials of the neurons are the same as those in the former model. We demonstrate the results of computer simulation of this model. The results show that the inhibition of oscillation can be replicated with appropriate input and model parameters, similarly to the previous models, which explains the effect of sound therapy. What is different from the former models is that the inhibition of oscillation takes place with the increase of the plastic synaptic strength.

II. A Neuronal Network Model

In a sound proof chamber, the vast majority of healthy subjects suffer from tinnitus-like symptoms when deprived of any auditory stimuli [35]. These symptoms become weaker with time and vanish when the subjects are once again reexposed to a normal acoustic environment. This could imply that auditory sensations during the absence of an external sound source could be caused by underlying physiological mechanisms.

We propose a neuronal network model shown in Fig. 1 in which firing sequences in the nervous system are simulated. The present model only replicates the inhibition of tinnitus by external sound stimulation. Modeling the habituation would much larger network configuration. The present model is a conceptually simplified system of a tinnitus generation network. However, we believe that the neural mechanism proposed here could form components of models involving large-scale neural correlates for providing a neurophysiological framework such as the Jastreboff's tinnitus model [2].

It is composed of two excitatory neurons and one inhibitory neuron as shown in Fig. 1. This model includes a positive feedback loop of the excitatory neurons E_1 and E_2 mutually coupled, and a negative feedback loop with the excitatory neuron E_2 and the inhibitory neuron I that are also mutually coupled. The negative feedback loop controls the firing rate. The model can be bistable with a sustained firing state and a non-firing state.

The coupling strength between neurons is denoted by C_{ij} ($i, j \in \{1, 2, I\}$). The neuron E_1 receives external stimuli S that is afferent signal due to the acoustic stimuli that are employed in sound therapy.

We express the dynamics of the model by a simplified version of Hodgkin-Huxley equations (HH) [28, 29]. We employed it instead of HH [27] to save the time of simulation by reduction of the number of state variables for each neuron from four to two.

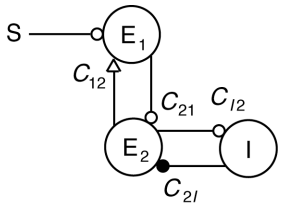


Fig. 1. Basic structure of the present model.

A. Formulation of the model without plasticity

We describe the basic dynamics of model 1 as

$$\frac{dv_1}{dt} = \frac{G(v_1, m^{\infty}(v_1), n_1, h_1) + C_{12}z_2 + D + S}{C_m}, \tag{1}$$

$$\frac{dh_1}{dt} = \alpha_h(v_1)(1-h_1) + \beta_h(v_1)h_1, \tag{2}$$

$$\frac{dv_2}{dt} = \frac{G(v_2, m_2, n_2, h_2) + C_{21}z_1 - C_{2I}z_I}{C_m}, \tag{3}$$

$$\frac{dh_2}{dt} = \alpha_h(v_2)(1-h_2) + \beta_h(v_2)h_2, \tag{4}$$

$$\frac{dv_I}{dt} = \frac{G(v_I, m_I, n_I, h_I) + C_{I2}z_2}{C_m}, \tag{5}$$

and

$$\frac{dh_I}{dt} = \alpha_h(v_I)(1-h_I) + \beta_h(v_I)h_I. \tag{6}$$

where v is the membrane potential, m, n and h are the variables associated with activation of sodium ion channel, inactivation of sodium ion channel and activation of potassium ion channel in the neuron E_1, E_2 or I. The functions $G(v,m,n,h)$, m and n are expressed as

$$G(v,m,n,h) = \overline{g}_{Na}m^3h(V_{Na}-v) + \overline{g}_K n^4(V_K - v) + \overline{g}_l(V_l - v) \tag{7}$$

$$m = \alpha_m(v)/\{\alpha_m(v) + \beta_m(v)\} \tag{8}$$

and

$$n = 0.8(1-h) \tag{9}$$

respectively. In HH m and n are expressed by differential equations. In the simplified version that we employ in the present study, m is expressed by the function of the membrane potential v, as Eq. (8), and n is expressed by the function of the variable h, as Eq. (9), since the change of m and n rapidly converges compared with v and h. The functions $\alpha_m(v)$ and $\beta_m(v)$ in Eq. (8) are expressed respectively as

$$\alpha_m(v) = 0.1(25-v)\Big/\left\{e^{(25-v)/10} - 1\right\} \tag{10}$$

and

$$\beta_m(v) = 4\,e^{-v/18} \tag{11}$$

Functions $\alpha_h(v)$ and $\beta_h(v)$ in Eq. (2), (4), (6) are expressed respectively as

$$\alpha_h(v) = 0.07\,e^{-v/20} \tag{12}$$

and

$$\beta_h(v) = 1\Big/\left\{e^{(30-v)/10} + 1\right\}. \tag{13}$$

The parameters of the neuron model were fixed as C_m=1[μF/cm^2], $\overline{g}_{Na} = 120[\mathrm{mS/cm^2}]$, $\overline{g}_K = 36[\mathrm{mS/cm^2}]$, $\overline{g}_l = 0.3[\mathrm{mS/cm^2}]$, V_{Na}=115[mV], $V_K = -12$ [mV], V_l=10.6 [mV], based on the values in Hodgkin-Huxley model.

The output of the neuron j to its postsynaptic neurons is denoted by z_j and expressed as function of the membrane potential v_j as

$$z_j = \begin{cases} 1 & (v_j \geq 6) \\ 0 & (v_j < 6) \end{cases}. \tag{14}$$

In Eq. (14) the threshold value is given six in order to remove the cases where the output value 1 arises when the neurons do not fire.

The bias term D is introduced in the equation of the membrane v_1 of the neuron E_1, Eq. (1) in order to compensate for the decrease of output pulses due to the larger threshold of output function. The bias may also be introduced in the equations of v_3 and v_I, Eqs. (3) and (5). Here it is given only to Eq. (1) to minimize the change from the previous model [26].

B. Formulation of plasticity

To replicate the effect of sound therapy, we assume that the coupling strength from the neuron E_1 to the neuron E_2, C_{12}, has plasticity. In the present model the plasticity based on STDP hypothesis [31, 32] is introduced. The key idea of this hypothesis is that when the presynaptic neuron fires before the postsynaptic neuron, the synaptic strength becomes stronger (long term potentiation), and when the postsynaptic neuron fires before the presynaptic neuron fires, the synaptic strength becomes weaker (long term depression). This mechanism is simply modeled in the present study as follows.

The time difference between firings of neuron E_2 and neuron E_1, t_{21}, is defined as

$$t_{21} = t_2 - t_1 \tag{15}$$

where t_1 and t_2 are the latest firing times of E_1 and E_2, respectively as shown in Fig. 2. The value of coupling strength with plasticity C_{12} at time $t + \Delta t$, $C_{12}(t + \Delta t)$, is given by addition of the value at time t, $C_{12}(t)$, and the change of C_{12}, ΔC_{12},

$$C_{12}(t + \Delta t) = C_{12}(t) + \Delta C_{12}, \tag{16}$$

where Δt is the time step of calculation, and ΔC_{12} is given as

$$\Delta C_{12} = \frac{dC_{12MIN}}{T_1}t_{21} - dC_{12MIN}, \tag{17}$$

when $0 < t_{21} < T_1$,

$$\Delta C_{12} = \frac{dC_{12MAX}}{T_2}t_{21} + dC_{12MAX}, \tag{18}$$

when $-T_2 < t_{21} \leq 0$, and

$$\Delta C_{12} = 0 \tag{18}$$

when $t_{21} \le -T_2$ or $t_{21} \ge T_1$, which is illustrated in Fig. 3.

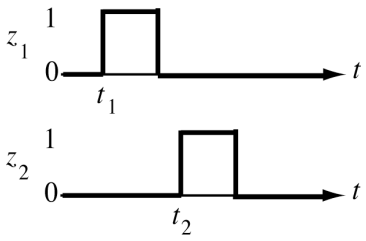


Fig. 2. Definition of firing time.

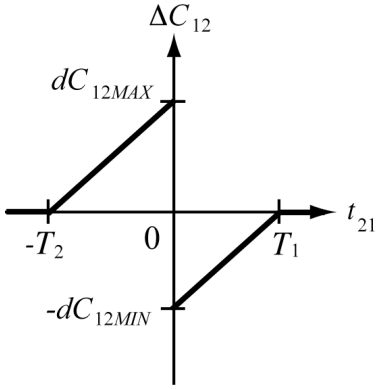


Fig. 3. Modeling of STDP hypothesis.

III. Results

We demonstrate the results of computer simulation of the model. Throughout the simulation the parameter values $D = 11$, $C_{21} = 10$, $C_{2I} = 10$, $C_{12} = 20$ were employed.

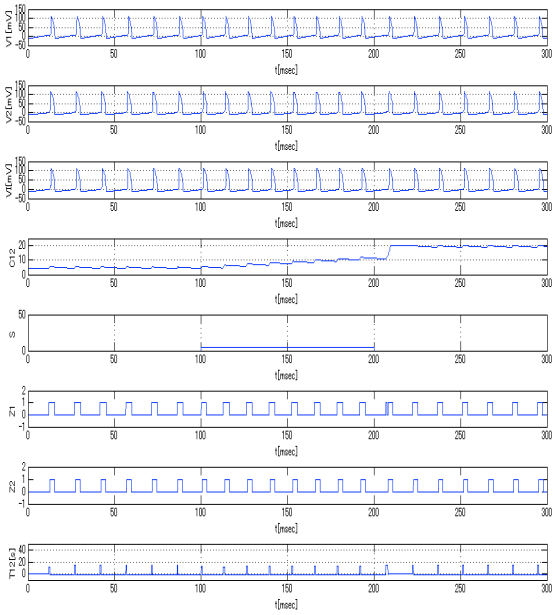
A. Analysis of the model without input or plasticity

Without stimulation or plasticity, the model has two stable solutions, an oscillatory state by sustained firings and a non-firing state. They are bistable for a parameter region. We performed the simulation changing the value of the coupling coefficient C_{12} by 0.1 in the range $0 < C_{12} \le 30$.

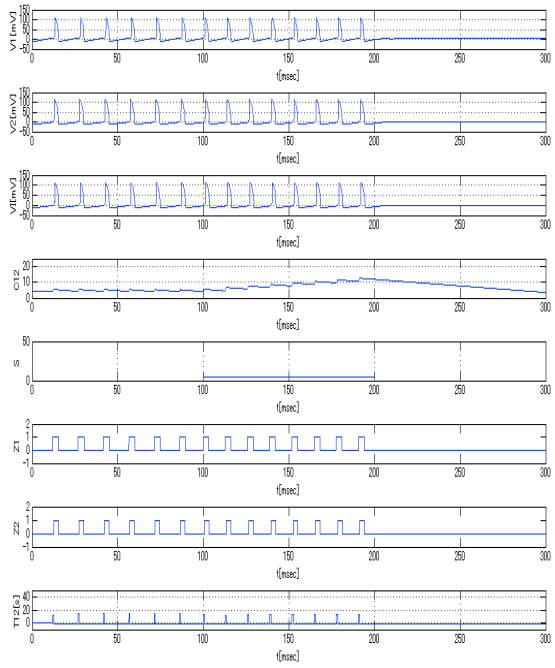
The non-firing state exists for any value of C_{12} in the range. On the other hand, the oscillatory state exists when $C_{12} \ge 1.9$. That is, the two states coexist when $C_{12} \ge 1.9$. The larger C_{12} brings the larger basin of the oscillatory solution in the state space of the model in the region. It corresponds to the clinical fact that a number of patients of tinnitus claim that they do not always hear sound when there is no external sound.

B. Analysis of the model with input and plasticity

The inhibition of oscillation by constant input with amplitude I as stimulus S to neuron E_1 was examined with plasticity. The constant input I was applied for 100ms from 200ms to 300ms to the network that is oscillating in the simulation. The parameter values $dC_{12MAX} = 0.048$,

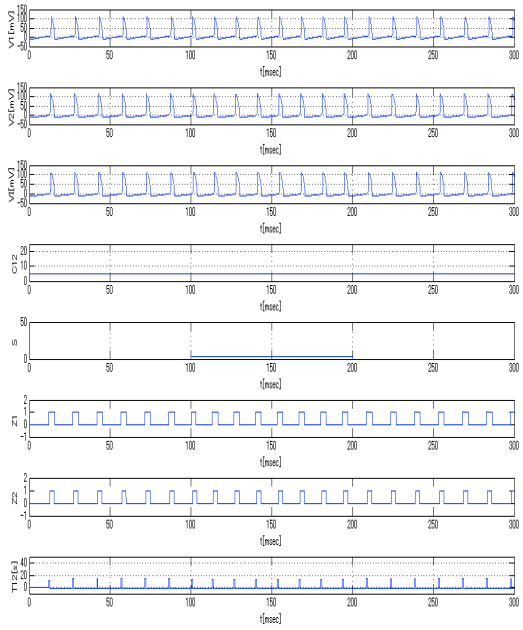


(a)



(b)

Fig. 4. Simulation results in the model with $C_0 = 4$, (a) an unsuccessful result, $I = 4$ [μA/cm^2], (b) a successful result, $I = 4.5$ [μA/cm^2].



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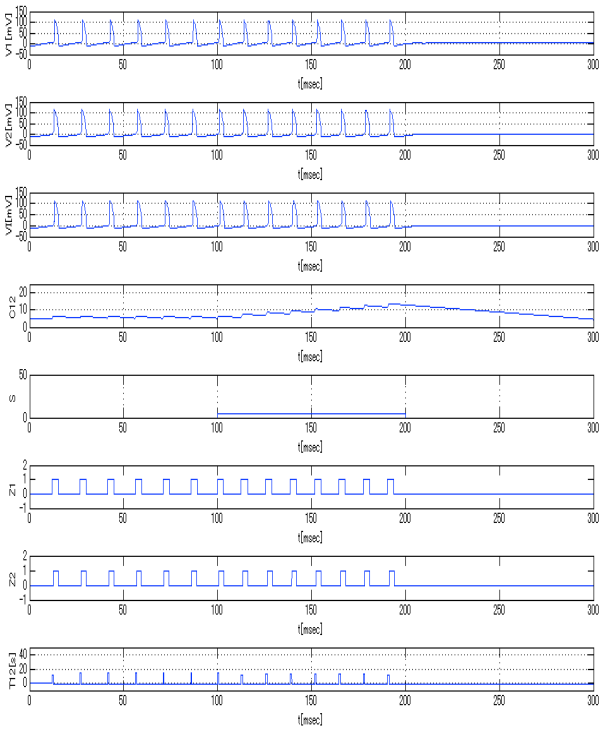
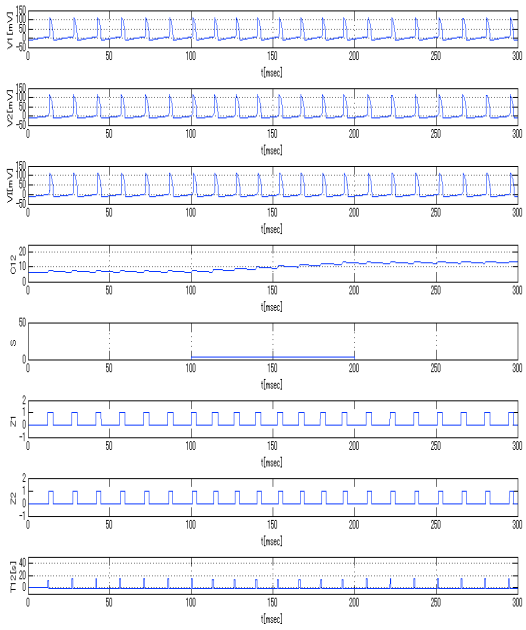


(b)

Fig. 5. Simulation results in the model with $C_0 = 5$, (a) an unsuccessful result, $I = 3.5$ [μA/cm^2], (b) a successful result, $I = 4.5$ [μA/cm^2].



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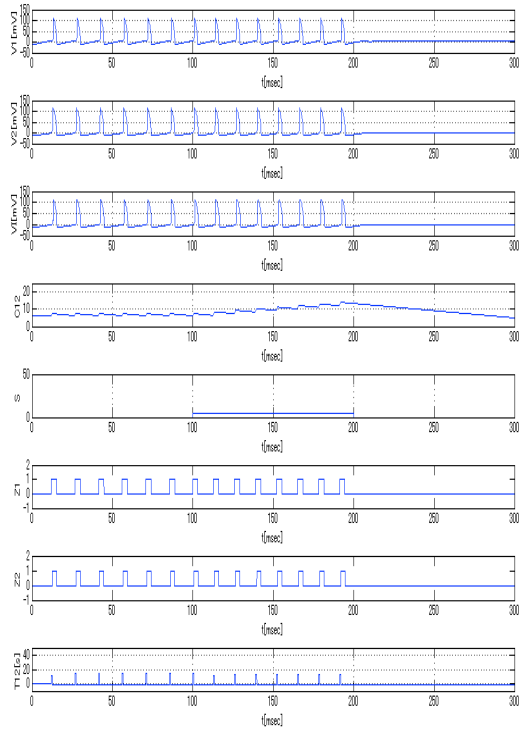

(b)

Fig. 6. Simulation results in the model with $C_0 = 6$, (a) an unsuccessful result, $I = 3.5$ [μA/cm^2], (b) a successful result, $I = 4$ [μA/cm^2].

$dC_{12MIN} = 0.001$, $T_1 = 25[\text{ms}]$, $T_2 = 5[\text{ms}]$ and $\Delta t = 0.01[\text{ms}]$ were employed for plasticity. The time scale of the change of the synaptic strength is much smaller than the clinical process. It was arranged so that the simulation is completed in a reasonable time. The initial value of the coupling strength C_{12} is denoted by C_0. Simulations were performed for several values of C_0. The amplitude I of the input was changed by 0.1 [μA/cm^2] in the range of $0 < I \le 10$ [μA/cm^2].

Some of simulation results are shown in Figs. 4, 5 and 6. In the figure, the rows illustrate the membrane potentials v_1, v_2, v_I, the coupling strength C_{12}, input S, output of the neurons z_1, z_2, z_I, respectively from the top.

Fig. 4(a) shows an unsuccessful result and Fig. 4(b) shows a successful result when $C_0 = 4$. As shown in Fig. 4, the constant input with I=4 [μA/cm^2] fails to inhibit the oscillation of the network, while the input with I=4.5 [μA/cm^2] for 100ms makes the network stop the oscillation after the input is removed. With values of I smaller than 4.2 [μA/cm^2] of I, the oscillation was sustained, and with values of I equal to or larger than 4.2 [μA/cm^2], the oscillation was inhibited after the input was removed.

This threshold of the input value I for the inhibition of the oscillation was larger with the smaller value of the initial value of the coupling strength C_{12}, C_0. .

Fig. 5(a) shows an unsuccessful result and Fig. 5(b) shows a successful result when $C_0 = 5$. As shown in Fig. 5, the constant input with I=3.5 [μA/cm^2] fails to inhibit the oscillation of the network, while the input with I=4.5 [μA/cm^2] for 100ms makes the network stop the oscillation after the input is removed. With values of I smaller than 3.5 [μA/cm^2] of I, the oscillation was sustained, and with values of I equal to or larger than 4.1 [μA/cm^2], the oscillation was inhibited after the input was removed. Fig. 6(a) shows an unsuccessful result and Fig. 6(b) shows a successful result when $C_0 = 6$. As shown in Fig. 6, the constant input with I=3.5 [μA/cm^2] fails to inhibit the oscillation of the network, while the input with I=4 [μA/cm^2] for 100ms makes the network stop the oscillation after the input is removed. With values of I smaller than 4.0 [μA/cm^2] of I, the oscillation was sustained, and with values of I equal to or larger than 4.0 [μA/cm^2], the oscillation was inhibited after the input was removed. After the oscillation is inhibited, the plastic coupling strength C_{12} decreases for all the cases.

For each value of C_0, there is a threshold of the value of the input amplitude I for the inhibition of oscillation. In order to inhibit the oscillation the amplitude I larger than the threshold is required. The minimal value of I for each C_0 is shown in Table 1.

In the present model the inhibition of oscillation is reproduced not only by synaptic plasticity but also by the bistability of solutions. The oscillation stops in the present model due to the change of the state of the model by the input. Hence, further investigation of modeling is necessary in order to reproduce the inhibition of oscillation only by synaptic plasticity.

A larger value of I is necessary to inhibit the oscillation with smaller C_0 value. The reason of this result is speculated as follows. By application of input I, the value of C_{12} increases gradually. The inhibition takes place when the input is removed after the value of C_{12} reaches some higher value. With a smaller C_0 it takes a longer period to reach some high value of C_{12} or the value of C_{12} does not reach that value. With much smaller I, the value of C_{12} does not change as in the case where I=3.5 [μA/cm^2] and C_0=5 (Fig. 5 (a)).

Table 1 the value of the constant input I required for inhibition of oscillation with different values of the initial value C_0 of the synaptic strength C_{12}.

C_0	The minimal value of I for inhibition of oscillation
3.3	4.5
3.5	4.5
4	4.2
4.5	4.2
5	4.1
5.5	4.0
6	4.0
6.5	3.9
7	3.9

IV. Conclusion

In this study a conceptual and computational neuronal network model with synaptic plasticity by STDP hypothesis in the human auditory system is proposed to explain the mechanisms of tinnitus and its management by sound therapy using simplified Hodgkin and Huxley equations. Simulation results of this model show that oscillation of the model can be inhibited with appropriate input and model parameters, similarly to the previous neural oscillator model and the neuronal network model with conventional Hebbian hypothesis for plasticity. It means that the effect of acoustic stimuli in the sound therapy of tinnitus is replicated. The present model, however, is different from the former ones in that the inhibition of oscillation takes place with the increase of the plastic synaptic strength

The cause of the inhibition of oscillation is not only the change of the plastic coupling strength between neurons in the model but also some change of the state condition of the model by supplying constant input to the model. In order to demonstrate that only the synaptic plasticity brings the inhibition of oscillation, further investigation of the modeling is necessary.

It has been pointed out that homeostatic plasticity is necessary for stability of the activities in the nervous system and it is observed in a number of systems [36]. A computational model for tinnitus-related hyperactivity through homeostatic plasticity has been proposed, and the prediction of appropriate acoustic stimulation that can reverse such

hyperactivity has been presented [37]. That model is not a dynamical system. We need to develop a dynamical model incorporating not only the Hebbian plasticity but also homeostatic plasticity.

Our future work will also expand this model so that it can more effectively relate to the underlying physiology of tinnitus, and explore better stimulation for its inhibition. This in turn will result in improvement in designing better and more effective sound therapy techniques and stimuli.

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