A neuronal network model for tinnitus and its management by sound therapy

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

***Abstract*—**Tinnitus is a state in which one hears sounds in the ear or head without any external source. Sound therapy is one of the most effective techniques for tinnitus treatment that have been proposed. In order to investigate mechanisms of tinnitus generation and the clinical effects of sound therapy from neural engineering point of view, we have proposed computational models with plasticity and inhibitory feedback using a neural oscillator or a neuronal network model described by simplified Hodgkin-Huxley equations. In the present paper, the simulation results of the neuronal network model are described. The model is able to replicate the clinical results that human auditory system temporarily halts perception of tinnitus following sound therapy.

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

I. Introduction

TINNITUS is a state in which one hears sounds in the ear or head without any external sound [1, 2]. Contribution of neural plasticity has been discussed by many in order to understand the neural correlates of tinnitus [3-5]. Tinnitus has many subclasses and attempts have been made to categorize tinnitus based on its characteristics that in turn can facilitate the selection of treatment methods [6]. 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 [7]. This cessation of tinnitus following the use of sound therapy has been termed as "residual inhibition." The mechanisms of tinnitus and its management by sound therapy, however, are not clear. Some attribute the success with sound therapy to brain plasticity [8] while others consider it a habituation process [9].

Neurophysiological models have been proposed to understand the mechanism of the tinnitus [10, 11]. Structural brain changes in tinnitus have been discovered using MRI [12].

Computational modeling of thalamocortical correlates with plasticity from the perspective toward understanding of the tinnitus has been reported [13].

A tinnitus model based on the model by Jastreboff [2] combined with the adaptive resonance theory of cognitive sensory processing [14] has been proposed for identification of neural correlates of the tinnitus decompensation [15]. The effect of auditory selective attention on the tinnitus decompensation has also been investigated by modeling corticothalamic feedback dynamics [16, 17].

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 [18]. 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.

In the present paper, we propose a different model composed of model neurons described by simplified Hodgkin-Huxley equations [19]. This model (model 1) 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 can show that inhibition of the oscillation which the synaptic plasticity causes can be observed in this model as well by constant input [20]. However, on several occasions during simulations it was observed that even after the neurons stopped firing, postsynaptic output pulses continued for a few cycles. Note that the model still replicates the effect of sound therapy in subjects, since the neuronal firing stops due to the external stimuli.

We modified the model 1 by setting the threshold for determining the output of the neurons a higher value in order to

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remove the inappropriate output pulses observed in model 1 [21]. We also modified the model 1 by incorporating a bias current to the neuron. In the absence of such a bias current it was observed that the neuronal firing completely ceased when the threshold was substantially raised.

The results of computer simulation of the modified model (model 2) show that the unnecessary output pulses observed in model 1 are nearly absent and the inhibition of oscillation can also be reproduced, which replicates the effect of sound therapy.

II. Tinnitus and its Treatment

A. Tinnitus

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.

B. Tinnitus evaluation procedures

Following audiological evaluation and completion of appropriate tinnitus-related questionnaires (e.g., Tinnitus Handicap Inventory [22] and Tinnitus Reaction Questionnaire [23]) tinnitus subjects undergo tinnitus evaluation which includes a variety of psychoacoustic assessments. These include Tinnitus Frequency (pitch) Match (TFM), Tinnitus Intensity (loudness) Match (TIM) and measurement of Minimal Masking Level (MML). The psychoacoustic assessment of tinnitus combined with proper implementation of the audiologic data will enable clinicians in the proper management of tinnitus [24].

A retrospective review of the data from 21 individuals with tinnitus seen at out tinnitus clinic revealed that the TFM ranged from 750Hz to 8000Hz with the majority of them around 3-4kHz. The TIM (i.e., loudness match) revealed that most of the individuals had less than 10dB SL (sensation level) loudness match with a great part of them perceiving their tinnitus at 5dB or less above their hearing threshold at the frequency of their tinnitus. In many cases their perceived tinnitus was completely masked by the use of white noise or a narrow band noise centered at the frequency of their TFM.

C. Tinnitus treatments.

Many approaches for tinnitus management and treatment have been proposed by clinicians and scientists. These include use of medications, supplemental vitamins and micronutrients; employment of surgical procedures; psychotherapy and biofeedback; electrical stimulation [25]; 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. 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 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 [6, 26]. 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.

III. 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 [27]. 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) [28-30]. We employed it instead of HH to save the time of simulation by reduction of the number of state variables for each neuron from four to two.

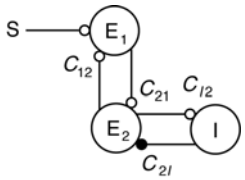


Fig. 1. Basic structure of the present model.

A. *Formulation of model 1 without plasticity*

We describe the basic dynamics of model 1 as

$$\frac{dv_1}{dt} = \frac{G(v_1, m_1, n_1, h_1) + C_{12}z_2 + S}{C_m}, \tag{1}$$

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

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

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

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

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

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

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

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

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

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

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

The parameters of the neuron model were fixed as C_m=1[μF/cm^2], $\bar{g}_{Na} = 120$[mS/cm^2], $\bar{g}_K = 36$[mS/cm^2], $\bar{g}_l = 0.3$[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

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

B. *Model 2 by slight modification of model 1 without plasticity*

In case of model 1, it was occasionally observed that output of the neuron z_j registered a high value (1) and output pulses were emitted even when the neurons involved were not firing. This could be due to the fact that z_j in Eq. (14) purely relies on the vj value which could be greater than unity due to external input or residual voltages even though the neuron is not firing. In order to remove such cases, model 2 is formulated by modifying the threshold value of the membrane potential v_j as

$$z_j = \begin{cases} 1(v_j \geq 5) \\ 0(v_j < 5) \end{cases}. \tag{15}$$

Moreover, a bias term D is introduced in the equation of the membrane potential v_1 of the neuron E_1, Eq. (1) in order to compensate for the decrease of output pulses due to the larger threshold as

$$\frac{dv_1}{dt} = \frac{G(v_1, m^\infty(v_1), n_1, h_1) + C_{12}z_2 + D + S}{C_m}. \tag{16}$$

The bias may also be introduced in the equations of v_2 and v_I, Eqs. (3) and (5). Here it is given only to Eq. (1) to minimize the change from the previous model.

C. Formulation of plasticity

We assume that the coupling strength from the neuron E_1 to the neuron E_2, C_{12}, has plasticity in such a way that it increases when the neurons E_1 and E_2 fire simultaneously, and decreases when the firing of the neurons E_1 and E_2 are not synchronized. This assumption is based on Hebbian hypothesis regarding synaptic plasticity [31]. We describe the dynamics of C_{12} as

$$\frac{dC_{12}}{dt} = \frac{-C_{12} + p(z_1,\ z_2) + C_0}{\tau} \tag{17}$$

where

$$p(z_1, z_2) = \begin{cases} 0 & (z_1 = z_2 = 0) \\ b(z_1 - 0.5)(z_2 - 0.5) & (otherwise) \end{cases}, \tag{18}$$

In Eq. (17) C_0, b and τ are positive constants. The constant C_0 is associated with the equilibrium of C_{12}. The constants b and τ denote the efficacy of synaptic plasticity and the time constant of C_{12}, respectively.

IV. Results

We demonstrate the results of computer simulation of the model. Throughout the simulation the parameter values $D = 11$, $C_{21} = 10$, $C_{2I} = 10$, $C_{I2} = 20$ 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. Examples of the time series of the solutions obtained by simulations of model 2 are shown in Fig. 2. Those in model 1 are similar.

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 $1.5 < C_{12} \le 8.9$ in model 1, and when $C_{12} \ge 1.9$ in model 2. 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 1 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 value $b = 40$ and $\tau = 50$ [ms] were employed.

The value of τ is much smaller than the clinical process. It was given the value so that the simulation is completed in a reasonable time. Simulations were performed where the parameter C_0=2, 2.5, 3, 3.5 and 4. For each trial the amplitude I of the input was increased one by one [μA/cm^2] in the range $0 < I \le 30$ [μA/cm^2].

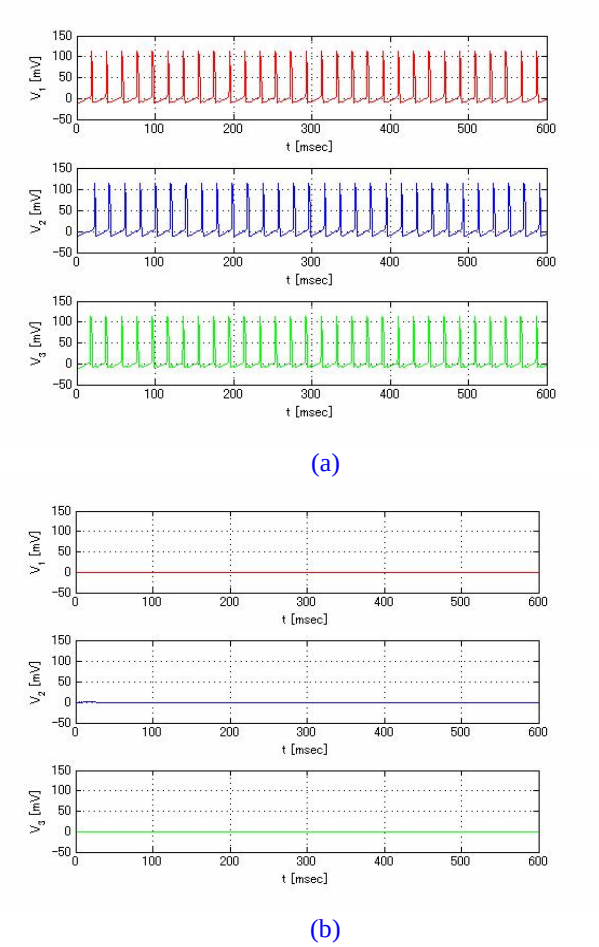
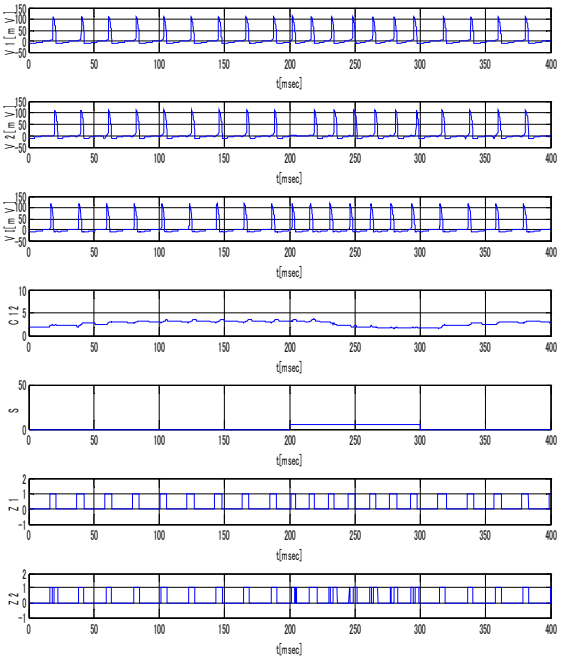


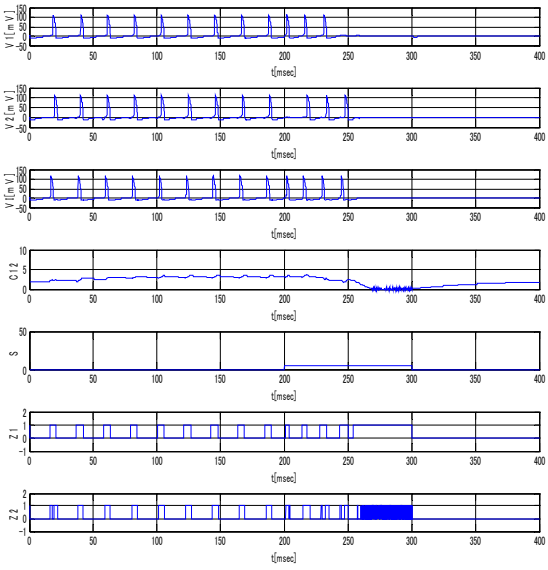
Fig. 2. Two solutions in the modified model, (a) oscillatory state, (b) non-oscillatory state.

Figs. 3 and 4 show the examples of simulation results when $C_0 = 2$ and $C_0 = 3$, respectively. As shown in Fig. 3, when $C_0 = 2$, the input with I=5 [μA/cm^2] for 100ms makes the network stop the oscillation after the input is removed, while the input with I=4 [μA/cm^2] fails to stop the oscillation. For $C_0 = 2$ and $C_0 = 2.5$, the amplitude I not less than 5 [μA/cm^2] was required for inhibition of oscillation. As shown in Fig. 4, when $C_0 = 3$, the input with I=6 [μA/cm^2] for 100ms makes the network stop the oscillation after the input is removed, while the input with I=5 [μA/cm^2] fails to stop the oscillation. For $C_0 = 3$ the amplitude I not less than 6 [μA/cm^2] was required for inhibition of oscillation. For $C_0 = 3.5$ and $C_0 = 4$ the amplitude I not less than 6 [μA/cm^2] was required for inhibition of oscillation.

The reason why a larger value of I is necessary to inhibit the oscillation in cases where C_0 value is larger is speculated as follows. A larger C_0 results in a larger stationary value in C_{12}. Moreover, it causes a larger basin of the oscillatory solution in

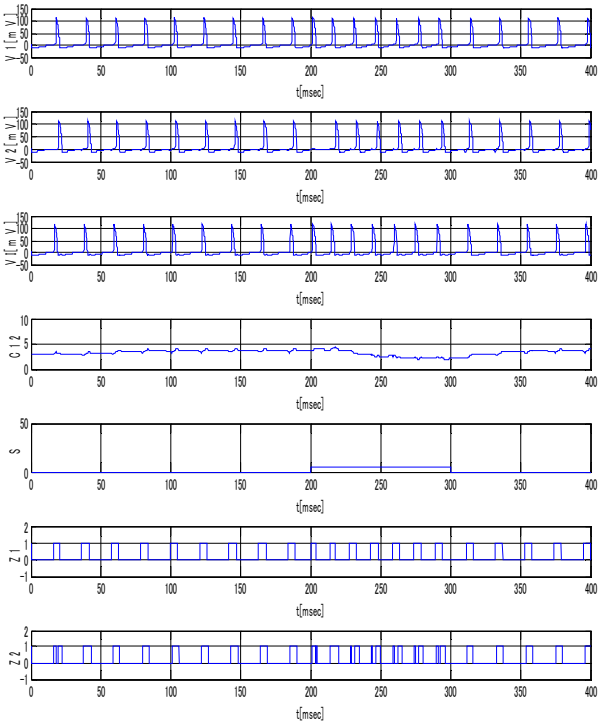


(a)



(b)

Fig. 3. Simulation results in the model 1 with $C_0 = 2$, (a) an unsuccessful result, $I = 4\,[\mu\text{A/cm}^2]$, (b) a successful result, $I = 5\,[\mu\text{A/cm}^2]$.



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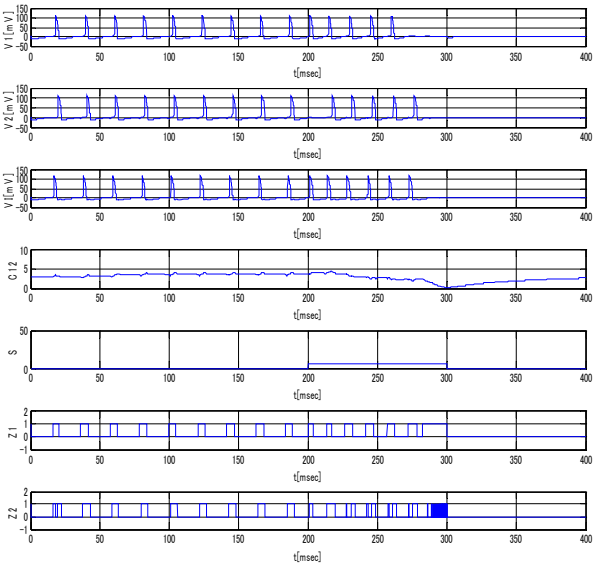
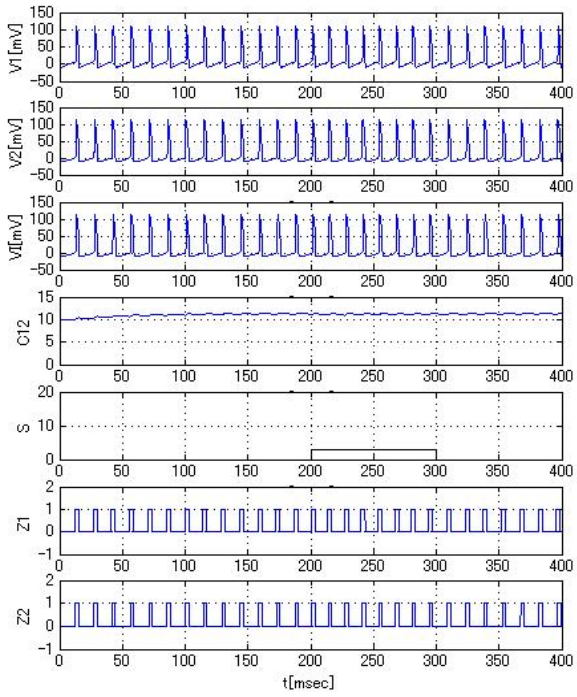
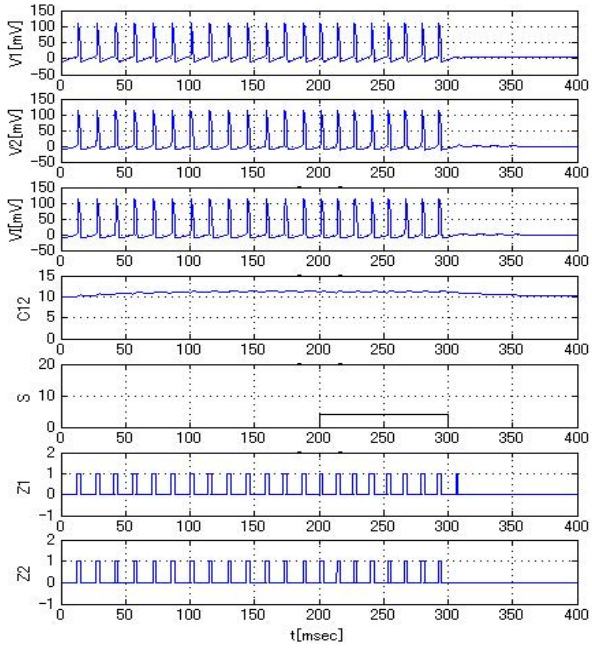


(b)

Fig. 4. Simulation results in the model 1 with $C_0 = 3$, (a) an unsuccessful result, $I = 5\,[\mu\text{A/cm}^2]$, (b) a successful result, $I = 6\,[\mu\text{A/cm}^2]$.

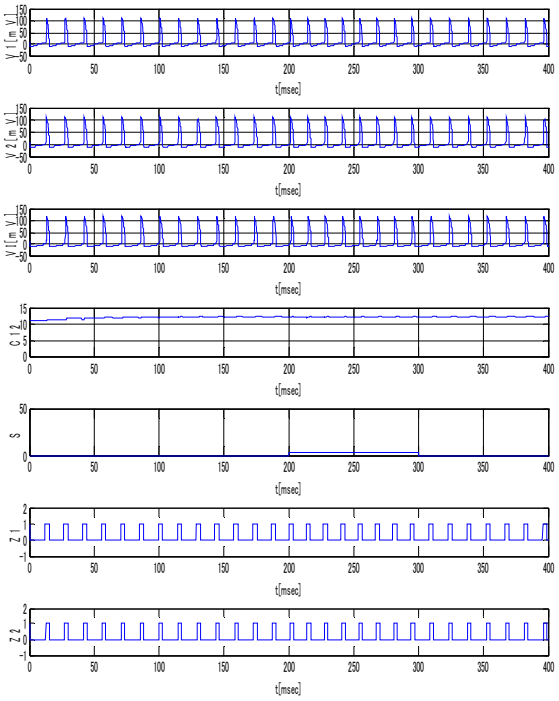


(a)

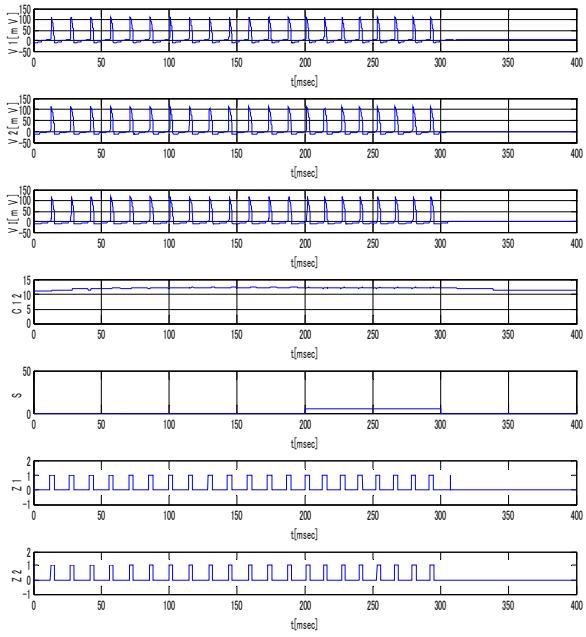


(b)

Fig. 5. Simulation results in the modified model with $C_0 = 10$, (a) an unsuccessful result, $I = 3\,[\mu\text{A/cm}^2]$, (b) a successful result, $I = 4\,[\mu\text{A/cm}^2]$.



(a)



(b)

Fig. 6. Simulation results in the modified model with $C_0 = 11$, (a) an unsuccessful result, $I = 3\,[\mu\text{A/cm}^2]$, (b) a successful result, $I = 4\,[\mu\text{A/cm}^2]$.

the state space of the model equations. In order to reduce the value of C_{12} a stronger stimulation is required.

The performance of the model 1 is not satisfactory since the output of the neurons E_1 and E_2, z_1 and z_2 occasionally becomes 1 and the output pulses are emitted in spite that the neuron does not fire.

In summary, it was observed that model 1 succeeds in demonstrating the effect of plasticity, when the coupling coefficient C_{12} diminishes with the introduction of the external stimulus S. This leads to termination of firing of the neurons. However, z_1 and z_2 provide zero as seen in Fig. 3 (b) and 4 (b). In order to address this deficiency changes are proposed in model 2, which include raising the threshold value for output.

C. Analysis of model 2 with input and plasticity

For model 2, the parameter C_0 was changed one by one in the range $2 < C_0 \le 20$. The amplitude I of the input was increased one by one $[\mu\text{A/cm}^2]$ in the range $0 < I \le 30\,[\mu\text{A/cm}^2]$. Figs. 5 and 6 show the examples of simulation results of model 2. An unsuccessful result (a) and a successful result (b) are shown when $C_0 = 10$ in Fig. 5 and when $C_0 = 11$ in Fig. 6.

As shown in Figs. 5 and 6, the constant input with I=3 $[\mu\text{A/cm}^2]$ fails to inhibit the oscillation of the network, while the input with I=4 $[\mu\text{A/cm}^2]$ for 100ms makes the network stop the oscillation after the input is removed. For all the values of C_0, the amplitude I not less than $4\,[\mu\text{A/cm}^2]$ was required for inhibition of oscillation. Longer application of the input did not seem to bring different results.

The model was modified by the change of the threshold for output of the neurons and introduction of bias term D to the neuron E_1. We examined different values of the threshold for output of the neurons. Higher values than a certain value remove unnecessary output. With too high values, however, the network does not oscillate without input. The value five was chosen in order to remove unnecessary output keeping the firings without input for the first 200ms in simulation.

By this modification the outputs to postsynaptic neurons without firing almost disappeared as shown in Figs. 4-5. However, an output pulse of the neuron E_1 is still observed without firing after the stimulation ends. Besides, the coupling coefficient does not decrease during the stimulation, which occurred in model 1. Consequently, we cannot state in model 2 that the inhibition of oscillation is reproduced as the result of synaptic plasticity. 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 by synaptic plasticity.

V. Conclusion

In this study a conceptual and computational neuronal network model with plasticity 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 were shown for the model that was first constructed and the one that was modified so that the unnecessary output pulses to the postsynaptic neurons are almost removed. Through analysis of this model, it is shown that, similarly to the previous neural oscillator model, oscillation can be inhibited.

The present model only replicates the inhibition of tinnitus by external sound stimulation. Modeling the habituation would much larger network configuration.

In the modified model, the inhibition of the oscillation is not due to the change of coupling strength between neurons but some change of the state condition of the model by supplying constant input to the model. In order to demonstrate in the modeling that the synaptic plasticity brings the inhibition of oscillation is realized, more investigation is necessary.

Our future work will 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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