Spike-Time-Dependent Plasticity of Excitation and Inhibition in a Neuronal Network Model for Tinnitus Relief with Sound Therapy

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

***Abstract*—**Perceiving sound in the ear(s) or head without any external source is referred to as tinnitus. Over the years we have learned that tinnitus is a central nervous system activity that may or may not be associated with hearing loss. Many approaches have been proposed for tinnitus treatment and management. Sound therapy is considered as one of the most effective and noninvasive methods for tinnitus management. Computational models have been proposed to investigate mechanisms of tinnitus generation and assessment of the effectiveness of sound therapy. These computational models employ a dynamic neuronal oscillator network with plasticity. The current paper proposes a new neuronal network model with a novel neuronal connection. In this model plasticity is spike-time-dependent and it is independently modeled for excitatory and inhibitory couplings**.** The simulation data of these models show that oscillation, which represents tinnitus in the central auditory system, is inhibited following the presentation of external input, which represents sound therapy stimulation in the clinical situation.

***Keywords*—**neuronal network model, tinnitus, sound therapy, spike-time-dependent plasticity, oscillation, inhibition

I. Introduction

As early as first days of civilization, many people have complained about tinnitus. This annoying auditory phenomenon has been attributed to many factors such as noise or chemical exposure and aging. Tinnitus is not a real sound [1]. It can be perceived in one ear, both ears or in the head. For many years, tinnitus has been considered as a difficult-to-manage clinical condition. Throughout the history many scientists and clinicians have attempted to find ways to help those who suffer from this condition. Tinnitus generation is still a mystery. There are many proposed theories that have attempted to explain its generation. Some of these theories relate the percept of tinnitus to hyperactivity of the auditory cortex and some attribute the changes in inhibitory and excitatory neurotransmitters of the auditory system. The most favored tinnitus generation theory describes tinnitus as a product of brain reorganization as a consequence of hearing loss [2]. Based on the tonotopic organization maps of the auditory cortex, it has been shown that those cortical areas that represent the corresponding frequency region of hearing loss are "invaded" by adjacent frequencies. This reorganization and neuroplasticity has been credited in generating tinnitus.

Additionally, the mechanisms of tinnitus generation have been proposed based on neurophysiological models [3, 4]. The contribution of neural plasticity to explain the neural correlates of tinnitus has also been reported [5]-[12]. The thalamic plasticity via top down modulation has been addressed with the utilization of auditory electrophysiological recordings [5]. It has been suggested that cochlear damage 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 [9], [10]. Structural brain changes in tinnitus also have been discovered using MRI [13].

Computational modeling has been applied for better understanding of tinnitus [14]-[17]. There are many areas in the brain that contribute to tinnitus generation; however, it has been shown that the thalamo-cortical network is important for generation of tinnitus [13], [18]. A neural network modeling of thalamocortical correlates with plasticity toward understanding of the tinnitus has been reported [14]. A tinnitus model based on the neurophysiological model of Jastreboff [3], combined with the adaptive resonance theory of cognitive sensory processing [19] has been proposed for identification of neural correlates of tinnitus [20]. Using models of corticothalamic feedback dynamics, the effect of auditory selective attention on the tinnitus decompensation has also been investigated [20, 21]. The current paper proposes a computational and dynamical model for tinnitus generation by spike-time-dependent plasticity of the thalamo-cortical network.

A variety of therapeutic approaches for tinnitus has been used for the management of tinnitus [22]-[24]. These include use of medications, supplemental vitamins and micronutrients, psychotherapy and biofeedback, electrical

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stimulation, transcranial magnetic stimulation, and more importantly and least invasively sound therapy or acoustic therapy. Tinnitus has many types and subcategories depending what caused it. Attempts have been made to categorize tinnitus based on its characteristics which in turn can facilitate the selection of management methods [25].

The process of sound therapy is one of the most effective methods. The tinnitus patients who have gone under sound therapy protocol report diminished annoyance from it [26]. Potentially, patients may perceive a reduction in tinnitus loudness following acoustical stimulation through sound therapy. This cessation of tinnitus following the use of sound therapy has been termed as "residual inhibition". 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 mechanisms of tinnitus management by sound therapy, however, have not been thoroughly clarified. Some attribute the success with sound therapy to brain plasticity [27] while others consider it a habituation process [28].

Our previous computational and dynamical models have employed a neural oscillator [19], [30], [31] or a neuronal network [32]-[34] to replicate tinnitus generation and its management by sound therapy. We have demonstrated that those models conceptually imitate tinnitus perception and exhibit tinnitus inhibition with sound. This inhibition is provided by implementing theoretical models of stimuli such as constant, sinusoidal or noise that is hypothesized as an acoustic stimulation for treatment of tinnitus. By employing this model we could inhibit the oscillations (i.e., tinnitus). This was accomplished by incorporating neural plasticity through parameters in a way that their values can be modified. By hypothesizing that the oscillation and the equilibrium in the model 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.

In the present paper, we propose a different model composed of the same model neurons described by simplified Hodgkin-Huxley equations [20] as we reported in the previous studies [32]-[34]. The major difference is a new variation in connection of neurons. This model structure is adopted based on the recent physiological observations related to tinnitus [13], [18].

In our previous models, synaptic plasticity was modeled with Hebbian hypothesis [35] or spike-time-dependent plasticity (STDP) [36]. STDP can be viewed as a biologically plausible hypothesis which can provide a more specific mechanism for the Hebbian hypothesis. STDP focuses on the causality between input and output spike trains as an underlying mechanism for memory. This hypothesis has been adopted in a number of computational models of neuronal networks including recurrent networks [37]. The plastic coupling between the components in our previous models was excitatory similar to most of the physiological studies on synaptic plasticity which have focused on excitatory synapses. However, scientific investigations of plasticity in inhibitory synapses in the auditory brainstem are increasing. STDP along with long-term depression and potentiation is known to influence the synaptic strength in auditory brainstem and midbrain. Differential forms of synaptic plasticity involving inhibitory and excitatory neurons within a circuit could form the basis for the underlying mechanism for persistent neuronal activity in patients with tinnitus [38]. Moreover, recent physiological observations on tinnitus generation suggest the importance of change in inhibitory activities [18]. In the current paper, a theoretical framework of plasticity of excitatory or inhibitory coupling between neurons is proposed. In this framework STDP was formulated as a synaptic plasticity.

Here we demonstrate inhibition of oscillation as a result of computer simulations. This is accomplished by providing the model with appropriate input and parameters for the plasticity of both excitatory and inhibitory couplings. Similar to the previous models the effects of sound therapy are replicated.

II. A Neuronal Network Model

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 [3].

It is composed of two excitatory neurons and one inhibitory neuron as shown in Fig. 1. This mechanism 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_1 and the inhibitory neuron I that are also mutually coupled. The negative feedback loop controls the firing rate. The mechanism can be bistable with a sustained firing state and a non-firing state.

The coupling strength between neurons is denoted by C_{ij} ($i, j \in \{1, 2, 3\}$). 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) [39-41]. We employed it instead of HH to reduce the computational complexity and the related simulation time by reducing the number of state variables for each neuron from four to two.

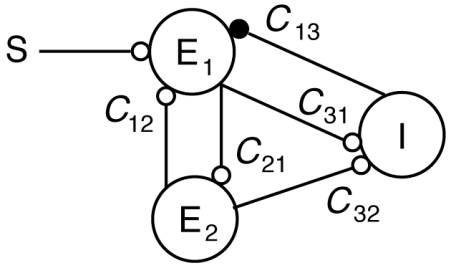


Fig. 1 A neuronal network model.

A. Formulation of the model without plasticity

We describe the basic dynamics of the model as

$$\frac{dv_1}{dt} = \frac{G(v_1,\, m_1,\, n_1,\, h_1) + C_{12}z_2 - C_{13}z_3 + D + S}{C_m}, \tag{1}$$

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

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

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

$$\frac{dv_3}{dt} = \frac{G(v_3,\, m_3,\, n_3,\, h_3) + C_{31}z_1 + C_{32}z_2}{C_m}, \tag{5}$$

and

$$\frac{dh_3}{dt} = \alpha_h(v_3)(1-h_3) + \beta_h(v_3)h_3. \tag{6}$$

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 the original HH model [41] 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 the original HH model [41].

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

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

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 enable the neurons to elicit sustained firings keeping z_j at 0 when the neurons are not firing.

B. Introduction of plasticity

We assume that one of the couplings between neurons has plasticity. In the present model the plasticity based on STDP hypothesis [36] is introduced. The key idea of this hypothesis on excitatory synapses 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). The hypothesis of STDP has been adopted in a number of computational models of neuronal networks [14]. This mechanism is simply modeled in the present study as follows.

C. Formulation of plasticity of excitatory coupling

First we postulate that one of the excitatory couplings, 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 E_1 fires after E_2 fires, and decreases when E_2 fires after E_1 fires. The time difference between firings of neuron E_2 and neuron E_1, t_{12}, 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

$$\Delta C_{12} = 0, \tag{19}$$

when $t_{21} \leq -T_2$ or $t_{21} \geq T_1$, where T_1 and T_2 are parameters that give the time span in which the plastic change of the synaptic coefficient occurs.

D. Formulation of plasticity of inhibitory coupling

Secondly we postulate that the inhibitory coupling, the coupling strength from the neuron I to the neuron E_1, C_{13}, has plasticity in such a way that it increases when E_1 fires after E_2 fires, and decreases when E_2 fires after E_1 fires. The time difference between firings of neuron E_2 and neuron E_1,

t_{12}, is defined as

$$t_{31} = t_3 - t_1 \tag{20}$$

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_{13} at time $t + \Delta t$, $C_{13}(t + \Delta t)$, is given by addition of the value at time t, $C_{13}(t)$, and the change of C_{13}, ΔC_{13},

$$C_{13}(t + \Delta t) = C_{13}(t) + \Delta C_{13}\ , \tag{21}$$

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

$$\Delta C_{13} = -\frac{dC_{13MAX}}{T_1} t_{31} + dC_{13MAX} \tag{22}$$

when $0 < t_{31} < T_1$,

$$\Delta C_{13} = -\frac{dC_{13MIN}}{T_2} t_{31} - dC_{13MIN} \tag{23}$$

when $-T_2 < t_{31} \le 0$, and

$$\Delta C_{13} = 0, \tag{24}$$

when $t_{31} \le -T_2$ or $t_{31} \ge T_1$.

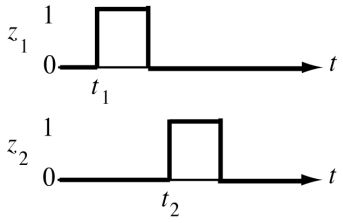


Fig. 2 Definition of firing time in plasticity 1.

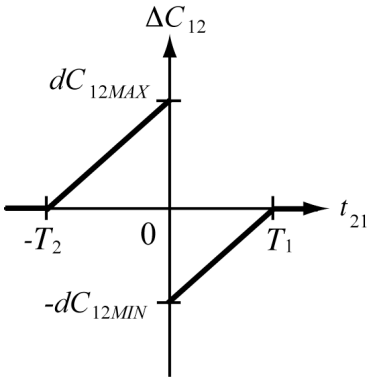


Fig. 3 Modeling of STDP in excitatory coupling strength C_{12}.

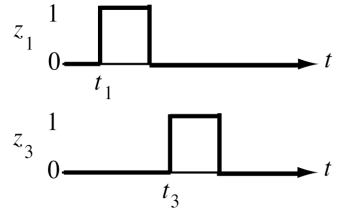


Fig. 4 Definition of firing time in plasticity 2.

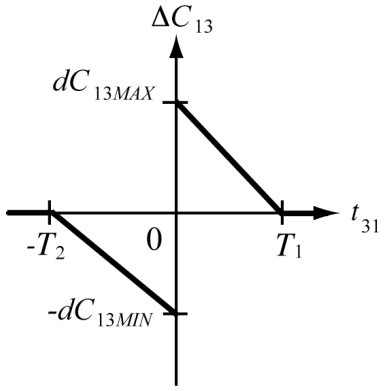


Fig. 5 Modeling of STDP in inhibitory coupling strength C_{13}.

The sign of slopes in the Eqs. (22) and (23) is opposite to the one for the excitatory coupling strength. Because the effect of the inhibitory coupling on firing of the postsynaptic neuron is opposite to that of the excitatory coupling.

III. Results

We demonstrate the results of computer simulation of the model. Throughout the simulation the parameter values $D = 18$ [μA/cm^2] , $C_{21} = 10$, $C_{31} = 10$, $C_{32} = 20$ were employed.

A. Analysis of the model without input or plasticity

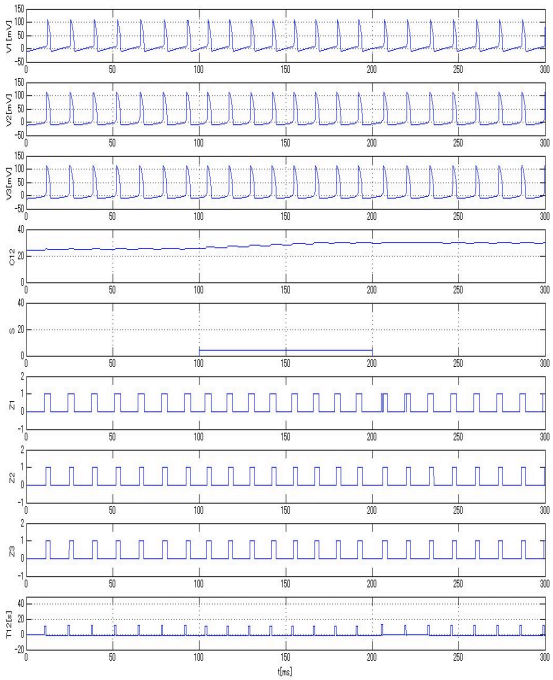
Without stimulation or plasticity, the model has two stable solutions, an oscillatory state by sustained firings and a non-firing state. They are bistable for a parameter region.

First, we performed the simulation changing the value of the coupling coefficient C_{12} by one in the range $0 < C_{12} \le 30$ with the value C_{13}=10. The non-firing state exists for any value of C_{12} in the range. On the other hand, the oscillatory state exists when $C_{12} \ge 23$. That is, the two solutions coexist when $C_{12} \ge 23$. 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. The larger C_{12} brings the larger basin of the oscillatory solution in the state space of the model in the region.

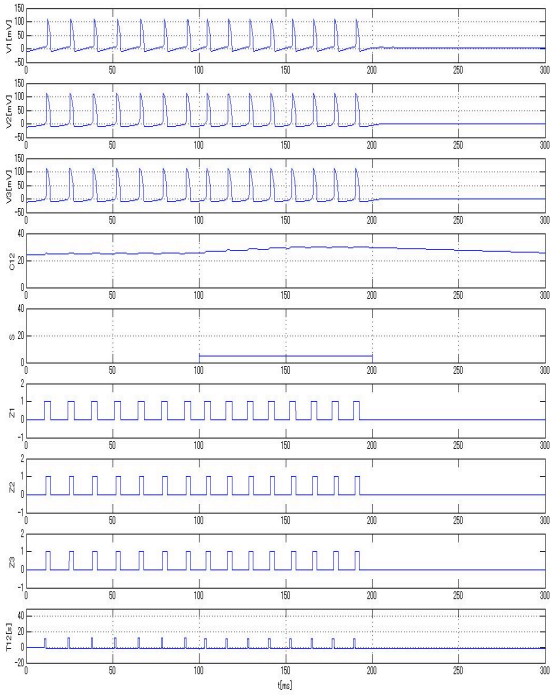
Secondly, we performed the simulation changing the value of the coupling coefficient C_{13} by one in the range $0 < C_{13} \le 30$ with the value C_{12}=25. The non-firing state exists for any value of C_{12} in the range. On the other hand, the oscillatory state exists when $0 \le C_{13} \le 22$ and $27 \le C_{13} \le 30$. Also in this case the two solutions coexist when $0 \le C_{13} \le 22$ and $27 \le C_{13} \le 30$.

B. Analysis of the model with input and plasticity of an excitatory coupling

Temporarily constant input with amplitude I as stimulus S was supplied to neuron E_1 in the model with plasticity of an excitatory coupling strength C_{12}, and inhibition of oscillation was examined. The constant input I was applied for 100ms

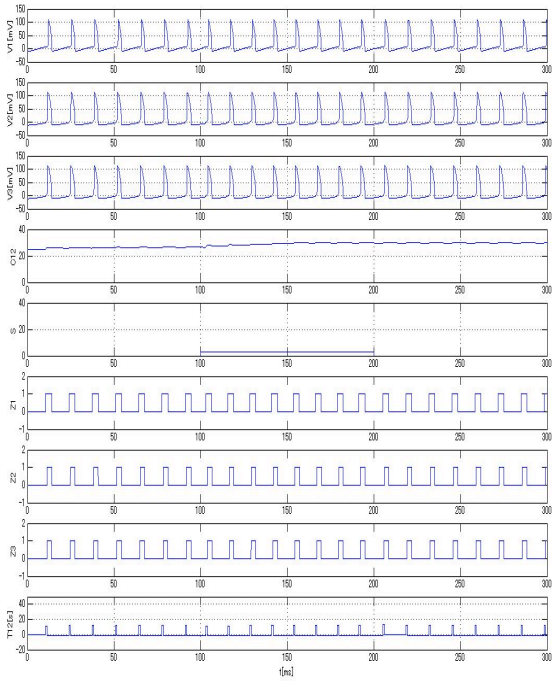


(a)

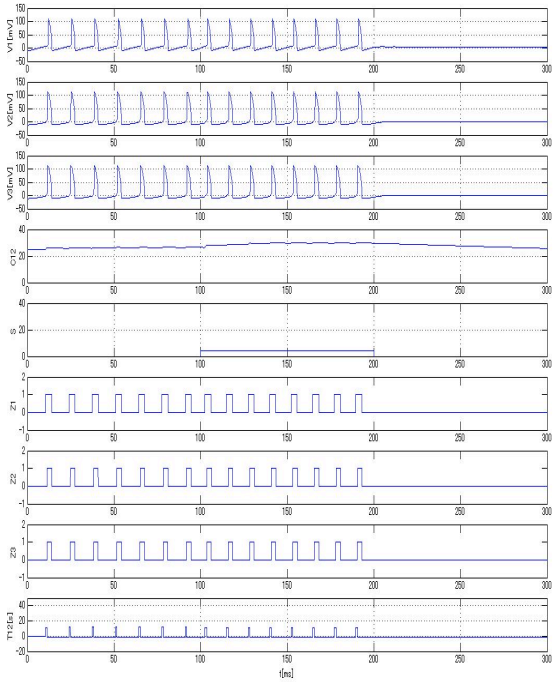


(b)

Fig. 6 Simulation results in the model with plasticity of excitatory coupling, $C_0 = 24$, (a) an unsuccessful result, $I = 4$ [μA/cm^2], (b) a successful result, $I = 5$ [μA/cm^2].

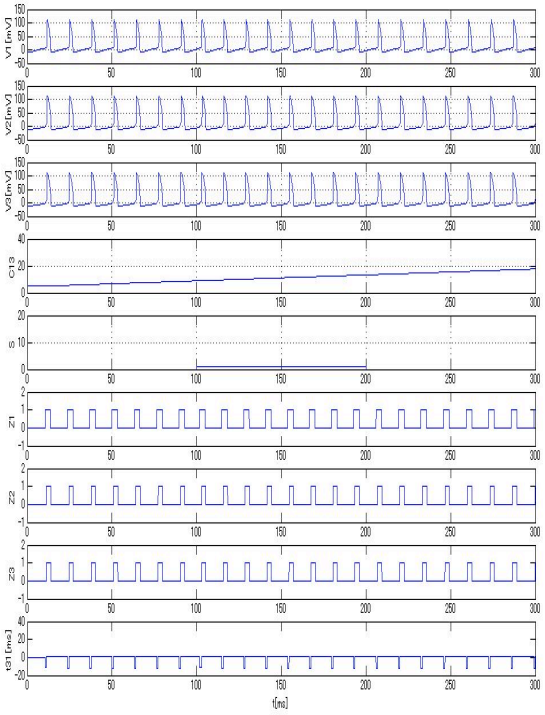


(a)

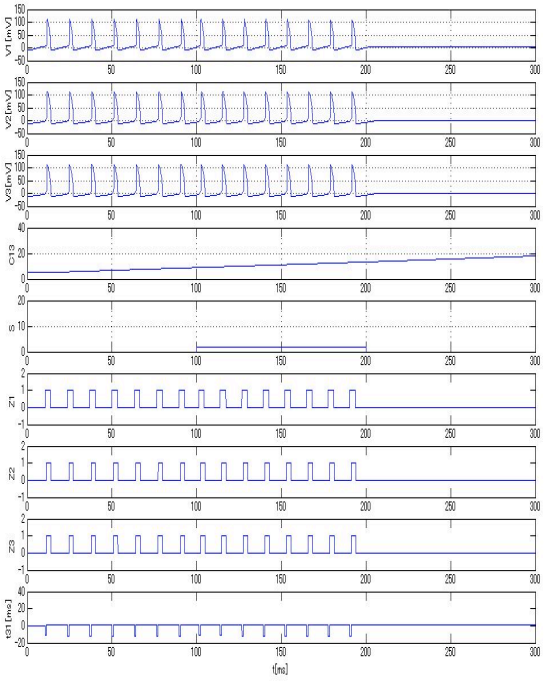


(b)

Fig. 7 Simulation results in the model with plasticity of excitatory coupling, $C_0 = 25$, (a) an unsuccessful result, $I = 3$ [μA/cm^2], (b) a successful result, $I = 4$ [μA/cm^2].

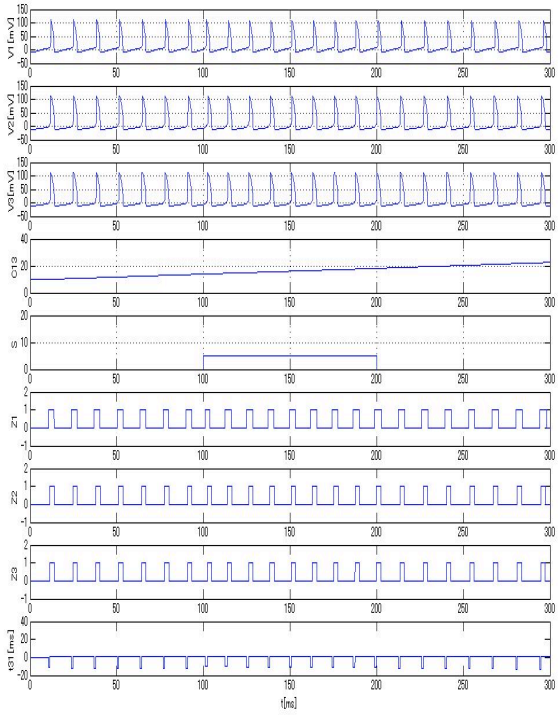


(a)

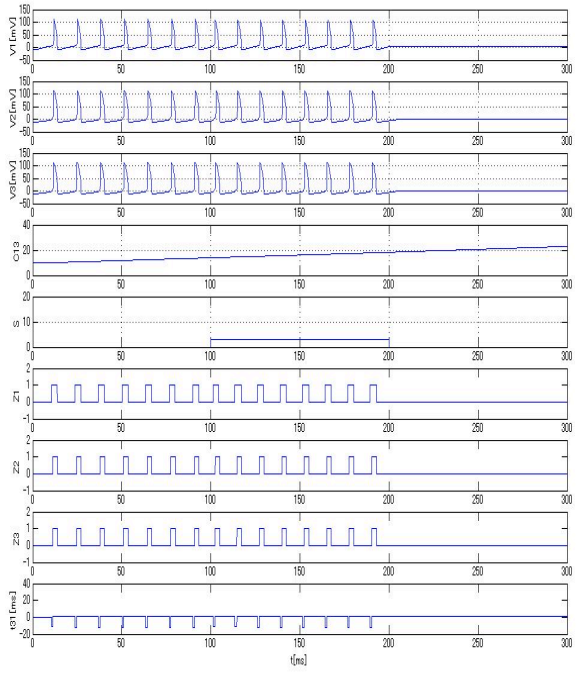


(b)

Fig. 8 Simulation results in the model with plasticity of inhibitory coupling, $C_0 = 5$, (a) an unsuccessful result, $I = 1$ [μA/cm^2], (b) a successful result, $I = 2$ [μA/cm^2].



(a)



(b)

Fig. 9 Simulation results in the model with plasticity of inhibitory coupling, $C_0 = 10$, (a) an unsuccessful result, $I = 5$ [μA/cm^2], (b) a successful result, $I = 3$ [μA/cm^2].

from 200ms to 300ms to the network that is oscillating in the simulation. The parameter values $C_{13} = 10$, $dC_{12MAX} = 0.048$, $dC_{12MIN} = 0.0005$, $T_1 = 15[\text{ms}]$, $T_2 = 5[\text{ms}]$ and $\Delta t = 0.01[\text{ms}]$ were employed. 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 where the parameter C_0=23, 24 and 25. The amplitude I of the input was changed by 1 μA/cm^2 in the range of $0 < I \le 10$ [μA/cm^2].Figs. 6 and 7 show the examples of simulation results when $C_0 = 24$ and $C_0 = 25$, respectively. 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 and z_2, and time difference between firings of neuron E_2 and neuron E_1, t_{12}, respectively from the top. As shown in Fig. 6, when $C_0 = 24$,

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. Fig. 7 shows that when $C_0 = 25$, the input with I=4 [μA/cm^2] for 100ms makes the network stop the oscillation after the input is removed, while the input with I=3 [μA/cm^2] fails to stop the oscillation. When $C_0 = 23$, the input with I=5, 6,7[μA/cm^2] for 100ms was required to make the network stop the oscillation after the input is removed. For $C_0 = 24$, the amplitude I=5, 6[μA/cm^2] brought the inhibition of oscillation. For $C_0 = 25$, the amplitude I=4, 5 or 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
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.

C. Analysis of the model with input and plasticity of inhibitory coupling

In order to examine the effect of plasticity of inhibitory coupling on the oscillation in the model, temporarily constant input with amplitude I as stimulus S was supplied to neuron E_1 in the model with plasticity of the inhibitory coupling strength C_{13}. Similarly to the above, the constant input I was applied for 100ms from 200ms to 300ms to the network that is oscillating in the simulation. The parameter values $C_{12} = 25$, $dC_{12MAX} = 0.0005$, $dC_{12MIN} = 0.0005$, $T_1 = 15[\text{ms}]$, $T_2 = 5[\text{ms}]$ and $\Delta t = 0.01[\text{ms}]$ were employed. Simulations were performed where the parameter C_0=5 and 10. The amplitude I of the input was changed by 1 μA/cm^2 in the range of $0 < I \le 10$ [μA/cm^2]. Figs. 8 and 9 show the examples of simulation results. An unsuccessful result (a) and a successful result (b) are shown when $C_0 = 5$ in Fig. 8 and when $C_0 = 10$ in Fig. 9.

As shown in Fig. 8, when $C_0 = 5$, the constant input with I=2 [μA/cm^2] for 100ms makes the network stop the oscillation after the input is removed, while the input with I=1 [μA/cm^2] fails to inhibit the oscillation of the network. For $C_0 = 5$, the amplitude I=2, 3 or 4 [μA/cm^2] was required for inhibition of oscillation. For $C_0 = 10$, the amplitude I=2 or 3 [μA/cm^2] was required for inhibition of oscillation. Longer application of the input did not seem to bring different results.

D. Discussion

In summary, it was observed that the model succeeds in demonstrating the effect of the introduction of the external stimulus S for the plasticity of both excitatory and inhibitory couplings. This leads to termination of firing of the neurons. However, the coupling coefficients do not change to the value in which the firing solution does not exist during the stimulation, which occurred in previous models. The oscillation stops in the present model due to the change of the state of the model as well as the change of the coupling coefficient by the input. Hence, further investigation of modeling is necessary in order to reproduce the inhibition of oscillation by synaptic plasticity only.

IV. Conclusion

A dynamic computational neuronal network model with plasticity for tinnitus generation and its management by sound therapy was proposed in this paper. The model structure is constructed based on recent physiological studies for tinnitus generation. Dynamics of the neurons are described with simplified Hodgkin and Huxley equations. STDP hypothesis is employed for plasticity of excitatory and inhibitory couplings independently.

Through computer simulations of this model, it is shown that oscillation can be inhibited by application of external input. The present model replicates the inhibition of tinnitus by external sound stimulation as it is employed in clinical situations.

In the present model, the inhibition of the oscillation was realized by both the change of the plastic coupling strength and the change of the state of the model by supplying the input. More investigation for improvement of the model is required in order to demonstrate that only the synaptic plasticity brings the inhibition of oscillation and the model is more robust in the input amplitude for inhibition of oscillation.

Our future work will expand this model so that it can more effectively explain underlying physiology of tinnitus, and explore better stimulation for its inhibition through sound therapy techniques.

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