A NEURAL OSCILLATOR MODEL FOR TINNITUS AND ITS MANAGEMENT BY SOUND THERAPY

Hirofumi Nagashino, The University of Tokushima; Ken'ichi Fujimoto, The University of Tokushima; Yohsuke Kinouchi, The University of Tokushima; Ali A. Danesh, Florida Atlantic University; Abhijit S. Pandya, Florida Atlantic University

Abstract

Tinnitus is the perception of sound occurring without an external stimulus. Sound therapy is one of the most effective treatment techniques that have been employed by clinicians. To account for mechanisms of tinnitus generation and the clinical effects of sound therapy from the viewpoint of neural engineering, we have proposed a conceptual neural oscillator model with plasticity for the human auditory system. We found that this model has a bistable state, i.e., a stable oscillatory state and a stable equilibrium (non-oscillatory) state coexist at a certain parameter region. We also found that the oscillation can be inhibited by supplying sinusoidal or random stimuli, which is hypothesized as sound for treatment of tinnitus, in this model. Through numerical simulations we found that adequate noise stimulus can inhibit the oscillation. By hypothesizing that the oscillation and the equilibrium correspond to generation and inhibition of tinnitus, respectively, it can be stated that these phenomena could explain the fact that the human auditory system temporarily halts perception of tinnitus following sound therapy. This paper describes dynamical properties of the model and inhibition of the oscillation for sinusoidal stimulus and a kind of noise stimulus which corresponds to the sound in the treatment of tinnitus.

Introduction

Tinnitus is the perception of phantom sounds in the ears or in the head. It is believed that tinnitus is an auditory phantom phenomenon resulting from neuronal activity somewhere along the auditory pathway. This phantom perception is a common condition and it can originate from many sources. Tinnitus can be perceived due to the damages in a variety of the pathologies of the auditory system. It has been shown that auditory percept can be generated by exposure to loud noise or medications which have toxic effect on the inner ear. Additionally, tinnitus can be associated with a variety of diseases such as thyroid abnormalities, diabetes and hypertension. In some cases, tinnitus can be traced to an internally generated sound (e.g., spontaneous otoacoustic emissions). However, in the overwhelming majority of serious sufferes, there is no obvious sound source to account for the tinnitus percept [1-3].

Tinnitus is a chronic disease with a reported prevalence of 10–15% [4–8]. Globally speaking this corresponds to approximately 700 million people. The effect of tinnitus on quality of life in patients suffering from this disease should not be underestimated. It is noteworthy that an estimated 20% of patients indicate that their quality of life is significantly deteriorated. Many patients experience insomnia and depression, and in 1% of the population tinnitus seriously interferes with their life [7–9].

Attempts have been made to help those who suffer from tinnitus. The common types of tinnitus treatment include medication therapy, biofeedback, relaxation therapy, cognitive behavioral therapy and sound therapy. Although many therapies have been proposed and tried, there is no systematic and proven approach for treating tinnitus.

Despite numerous animal and human studies, the neural abnormalities underlying tinnitus are largely unknown despite numerous animal and human studies. In some patients tinnitus can be traced to an internally generated sound (such as vascular structures in pulsatile tinnitus), but in the vast majority no obvious sound source can be pinpointed. It has been proposed that tinnitus results from abnormal neuronal activity arising at some point along the auditory pathways which is interpreted as sound at a cortical level [10–12]. This abnormal neuronal activity is hypothesized to be the neural correlate of tinnitus, which is considered to be an auditory phantom phenomenon, similar to central neuropathic pain, due to neural plasticity in response to total or partial deafferentation somewhere along the auditory tract [10, 13–15]. Animal and human studies have provided some evidence for this theory [8, 12, 13, 16–22]. Functional MRI has been applied in a few studies, mainly case studies [23–25]. The purpose of these studies has been to visualize the entire central auditory pathway in patients with lateralized tinnitus and in patients with bilateral tinnitus to evaluate lateralization of fMRI signal change and activation clusters. The most important fMRI study shows an abnormally low percent signal change in the inferior colliculus (IC) contralateral to the side of the perceived tinnitus [26]. Structural brain changes in tinnitus have also been discovered using MRI [27].

The role of neural plasticity in the auditory system and tinnitus has been discussed in neurophysiologic studies, and thalamocortical correlates or dorsal cochlear nucleus activities with plasticity have been investigated [28-32]. Electrophysiological studies of the auditory system have demonstrated an evidence for thalamic plasticity via top-down modulation [29]. Computational modeling of thalamocorti-

cal correlates with plasticity from the perspective toward understanding of the tinnitus has been reported [33]. A tinnitus model based on the work by Jastreboff [11] combined with the adaptive resonance theory of cognitive sensory processing [34] has been proposed for identification of neural correlates of the tinnitus decompensation [35]. The effect of auditory selective attention on the tinnitus decompensation has also been investigated by modeling corticothalamic feedback dynamics [36, 37].

There are two typical sound therapy techniques, namely, TM (Tinnitus Masking) technique and TRT (Tinnitus Retraining Therapy) where those who suffer from tinnitus listen to these therapeutic sounds for several hours a day [38]. In these techniques white noise or spectrum modified white noise are introduced to tinnitus sufferers as therapeutic sound. These sounds are usually presented via a custom-made noise (sound) generator or a tinnitus masker. It has been reported that sound therapy has a clinical effect that in a great number of cases in this management method, tinnitus perception is temporarily halted after the removal of the noise (sound) generator. This cessation of tinnitus following the presentation of a masking stimulus is referred to 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 [39] while others consider it a habituation process [40].

The purpose of our study is to address mechanisms of tinnitus generation and the clinical effect of the sound therapies from the viewpoint of neural engineering. Accordingly, we have proposed a plastic neural network model for the human auditory system. We have previously reported [41] that a certain region of the parameter hyper space exists where an oscillatory state and an equilibrium (non-oscillatory) state coexist. It was shown that the oscillatory state is inhibited by supplying a sinusoidal stimulus resulting in a transition to an equilibrium state [42, 43]. By hypothesizing that the oscillation and the equilibrium correspond to generation and inhibition of tinnitus, respectively, we demonstrate that these phenomena could explain the fact that the human auditory system temporarily halts perception of tinnitus following sound therapy. This paper illustrates inhibition of the oscillation in the proposed model using band noise stimulus as therapeutic sound [44, 45]. In the tinnitus clinics across the globe, similar noise stimuli have been employed for treatment of tinnitus by TM.

Model Description

The human auditory system consists of two divisions, a peripheral portion and a central portion. The cochlear hair cells are located in the peripheral portion and transform acoustic vibrations received by the ear into neural signals. The central auditory pathway is composed of many portions. It receives the neural auditory messages that have travelled via the auditory nerves to the cochlear nucleus, the superior olivary complex, the inferior colliculus, the medical geniculate body, and the auditory cortex. Subsequently the brain perceives the neural signals as sound. In case of certain tinnitus patients it has been observed that cochlear dysfunction occurs, and abnormal neural signals from the cochlea cause abnormality in the central nervous system. Consequently, tinnitus can be triggered. In addition to ascending pathway, the cochlear nucleus complex receives descending efferent fiber bundles to control the function of cochlear outer hair cells [9].

We have proposed a conceptual neural network model to account for tinnitus generation and its inhibition from the neural engineering point of view [33]. Figure 1 shows the proposed neural oscillator model of the human auditory system.

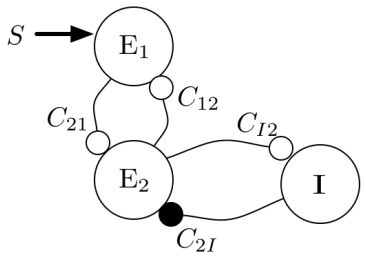

Figure 1. A Neural Oscillator Model.

The human auditory system in this case is represented as a neural oscillator which consists of two excitatory units denoted by "E_1" and "E_2", and an inhibitory unit denoted by "I". The unit represents the aggregate of a neural ensemble in our model. The excitatory units E_1 and E_2 form a positive feedback loop by mutual coupling, while the units E_2 and I form a negative feedback loop by mutual coupling. These two loops enable the model to oscillate. This configuration is the simplest in terms of neural arrangement that could demonstrate oscillatory behavior. The unit E_1 receives an incoming signal, S, which is associated with an external sound signal.

The neural coupling from the j-th unit to the i-th unit is expressed by the positive constant C_{ij} ($i, j \in \{1, 2, I\}$).

$$\frac{dx_1}{dt} = (-x_1 + C_{12}z_2 + S)/\tau_1 \tag{1}$$

$$\frac{dx_2}{dt} = (-x_2 + C_{21}z_1 - C_{2I}z_I)/\tau_2 \tag{2}$$

and

$$\frac{dx_I}{dt} = (-x_I + C_{I2} z_2)/\tau_I \tag{3}$$

where x_j and τ_j are the internal potential and time constant of the j-th unit, respectively. The output of the j-th unit is denoted by z_j, which is given by the equation

$$z_j = \frac{2}{\pi} \tan^{-1} x_j \tag{4}$$

We assume the coupling strength from the unit E_2 to the unit E_1, denoted by C_{12}, has plasticity in such a way that it changes according to the product of the outputs of the units E_1 and E_2. It means that the coupling strength C_{12} is one of the state variables in the model system. It is expressed as

$$\frac{dC_{12}}{dt} = (-C_{12} + b z_1 z_2 + C_0)/\tau_C. \tag{5}$$

The C_0, b, and τ_c are also positive constants which denote the equilibrium of C_{12} under $z_1 z_2 = 0$, the efficiency of strengthening the synaptic coupling based on Hebbian hypothesis [46], and the time constant of C_{12}, respectively.

At the present time we are not able to specify what regions in the brain correspond to each unit in the model. The model is hypothesized to represent tonotopic organization and depends on the perceived pitch and reported frequency of tinnitus. Based on the anatomical structure of the auditory system, the proposed model is likely to include the thalamus, at which a massive corticofugal projection ends. The thalamo-cortico-thalamic loop forms an ideal positive oscillatory loop, while the thalamic interneurons and thalamic reticular GABAergic neurons likely to play the role as inhibitory neurons.

The external auditory stimulus which is represented by S in Figure 1 is received as an input in unit E_1 and results in generation of aggregate neuronal activity of an ensemble in the proposed model. In the auditory system such processing occurs at the peripheral nervous system and the corresponding mechanism in terms of neural engineering is represented within unit E_1. Aggregate activity of thalamic interneurons and thalamic reticular GABAergic neurons are captured within the excitatory unit E_1 and inhibitory unit I. Aggregate neuronal mechanism represented within the cortex pertaining to perception of tinnitus is represented by the unit E_2. The thalamo-cortico-thalamic loop is represented by the excitatory links between the units E_1 and E_2 and the excitatory-inhibitory links between units E_2 and I.

Attractive Region of Non-Oscillation

The plastic system expressed by Eqs. (1) – (5) has two attractors. We can easily find an equilibrium point in the dynamical system: (x_1, x_2, x_I, C_{12})=(0, 0, 0, C_0). There is another attractor, an oscillatory orbit. Numerical analysis of the system unveiled that the equilibrium exists in the range of C_0, $0 \le C_0 \le 8.06$ and the oscillatory orbit in $C_0 \ge 2.65$ [40]. Consequently, the system is bistable in $2.65 \le C_0 \le 8.06$.

Also in the system with no plasticity, that is, where the coupling strength C_{12} is not expressed by Eq. (5), on the contrary given to a constant value, there are two attractors: an equilibrium point (x_1, x_2, x_I)=(0, 0, 0) and an oscillatory orbit. The system also has the similar bistable region of C_{12} to the region of C_0 in the plastic system. Which attractor the system converges to depends on the initial values of x_1, x_2 and x_I.

In Fig. 2 we show two examples of the region of the initial values of x_1 and x_2 with which the system is attracted to the non-oscillatory solution with different initial values of x_1 and x_2 are given when all coupling strength, namely $C_{12,}$ C_{21}, C_{2I} and C_{I2} values, are held constant. We fixed the parameters in Eqs. (1)–(3) such that τ_1=0.01 [sec], τ_2=0.01 [sec], τ_I=0.02 [sec], C_{21}=10, C_{2I}=10 and C_{I2}=20. The initial value of x_I was fixed at zero.

The dynamics of the system is governed by Eqs. (1) – (3). In the black region in Fig. 2, if the initial x_1, x_2 values are inside the black region other than (0, 0) then the system is attracted to the equilibrium point (0, 0, 0) and the oscillations subside. If the initial x_1, x_2 values are outside the black region, the oscillation occurs as the system is attracted to the oscillatory orbit.

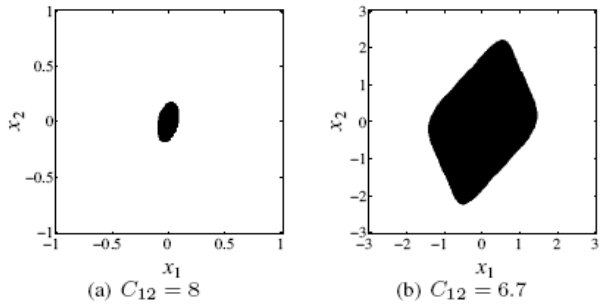

Figure 2. Regions of Attraction to the Equilibrium Point at All Constant Couplings, i.e., all C_{ij} are constant. The Initial Value of x_I Is Fixed to Zero.

Notice that these results show dynamical properties of the non-plastic neural oscillator model which is described by Eqs. (1) – (3). As the results, the model has the dynamical property that attractive region of the non-oscillatory solution is expanded by reducing the value of C_{12}. In addition, any oscillatory behavior in such region eventually settles down in non-oscillatory state without external stimulus according to the dynamical property of the model. Eventually, when

$C_{12} < 2.65$, any initial values gives non-oscillatory solution. Therefore, to inhibit the oscillation it is important that the states of (x_1, x_2, x_I, C_{12}) change into such an attractive region of non-oscillation by external stimulus.

Inhibition of Oscillation by External Stimuli

The inhibition of oscillation by various external stimuli was examined with the model incorporated the synaptic plasticity, which is the system described by Eqs. (1) - (5). In Eq. (5), the plasticity parameter values C_0=3, b=20, τ_c=0.5 [sec] were employed. These parameters of plasticity were arbitrarily determined so that the simulation is performed within appropriate time. The time scale would be much longer in the clinical situation as it is important to sufficiently expose the ears to sufficient duration of acoustic stimulation for better inhibition or habituation.

We demonstrate here some simulation results with sinusoidal wave and band noise as external stimulus. The stimuli were applied to the unit E_1 for the duration of $2 \le t \le 8$ [sec].

1) Sinusoidal stimulus

Auditory stimulations can be viewed as a composite of sinusoidal signals. Hence we first experimented by supplying an adequate sinusoidal stimulus [28]. Figure 3 shows an instance in which the oscillation is inhibited by sinusoidal stimulus defined as

$$S = 2\sqrt{2} \sin 20\pi t. \quad (6)$$

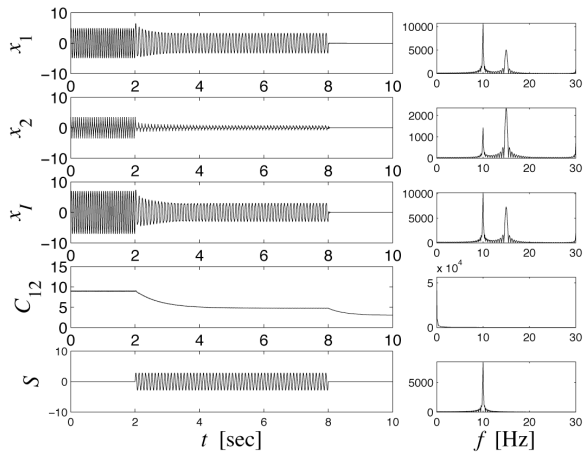

Figure 3. Inhibition of oscillation by sinusoidal stimulus.

The value of the amplitude was fixed so that the root mean squared value (RMS) of the stimulus is 2.0. The timing diagrams in the left column show the waveforms of x_1, x_2, x_I, C_{12} and S, respectively; and their corresponding power spectra are illustrated in the right column.

It can be seen that by applying stimulus, S, starting at 2 seconds the value of C_{12} gradually reduces, and consequently the oscillations are inhibited. Note that the oscillation does not reoccur even after the sinusoidal stimulus stops at 8 seconds. By hypothesizing that the damping of C_{12} oscillations corresponds to what is called residual inhibition in the human auditory system for tinnitus, the phenomenon could explain the fact that the human auditory system temporarily inhibits the perception of tinnitus after sound therapy. This is a promising observation and it can help in better management of tinnitus.

The reason why the coupling strength C_{12} decreases is explained as follows. The plasticity is formulated based on Hebbian hypothesis in Eq. (5). It works in such a way that the coupling strength C_{12} increases when the units E_1 and E_2 oscillate in in-phase, and decreases when the oscillations of the units E_1 and E_2 are anti-phase. Without stimulus, the oscillations of the units are in-phase, while they are out of phase with stimulus and close to anti-phase.

2) Band noise stimulus:

Band noise stimulus is typically used in treatment of tinnitus using TM approach [27]. In this approach the desired noise is a band of noise with a frequency emphasis that approximates the frequency of perceived tinnitus. The frequency (pitch match) of tinnitus can range from low frequencies to high frequencies in different individuals. Most of the tinnitus sufferers perceive tinnitus at high frequencies between 2–8 kHz.

In this experiment, we hypothesized that the fundamental frequencies of perceived tinnitus are 2, 4, 6, and 8 kHz. We subsequently employed a band noise which is generated from Gaussian white noise through a band pass filter which operates between each fundamental frequency with ± 5% margin. We also adjusted its RMS (Root Mean Square) to about 400.

Figures 4a-d show successful results for inhibition of the oscillations. The timing diagrams in the left column show the waveforms of x_1, x_2, x_I, C_{12} and S, in that order from the top to the bottom. Their corresponding power spectra are illustrated in the right column.

In Figures 4a and 4b, oscillation of x_2 and x_I stops immediately after the noise input is applied and it brings the rapid decrease of C_{12}. In Figure 4c, oscillation of x_2 and x_I is maintained for about 1sec, and n Figure 4d, oscillations of x_2 and x_I are maintained almost until t=8 [sec]. However, the value of C_{12} gradually decreases from the point of applying the

stimulus. Eventually, the oscillations of x_2 and x_I stop. This implies that plasticity in connectivity between various neuronal ensembles in the auditory system may play a role in the inhibition of tinnitus. Note that during the application of noise input unit E_1 is in an oscillating mode replicating perception of tinnitus. After removing the input, the oscillation of the unit is in the state of non-oscillation, which replicates the state where the tinnitus is not perceived. It was observed that the oscillation was inhibited with certainty in all the simulations when 100 trials were conducted with different random sequences.

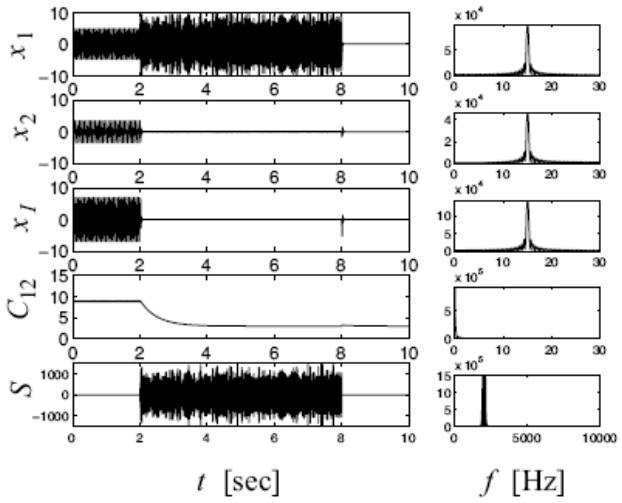

Figure 4a. Inhibition of oscillation by band noise stimulus with the band between 2kHz ± 5% margin and 400 RMS.

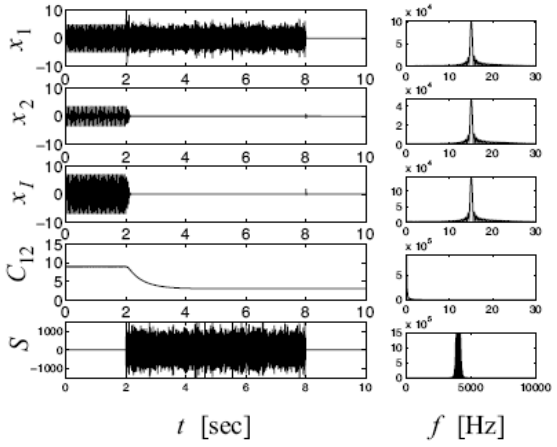

Figure 5b. Inhibition of oscillation by band noise stimulus with the band between 4kHz ± 5% margin and 400 RMS.

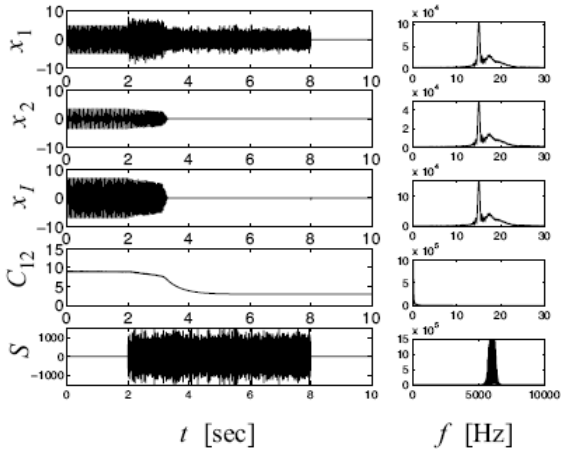

Figure 4c. Inhibition of oscillation by band noise stimulus with the band between 6kHz ± 5% margin and 400 RMS.

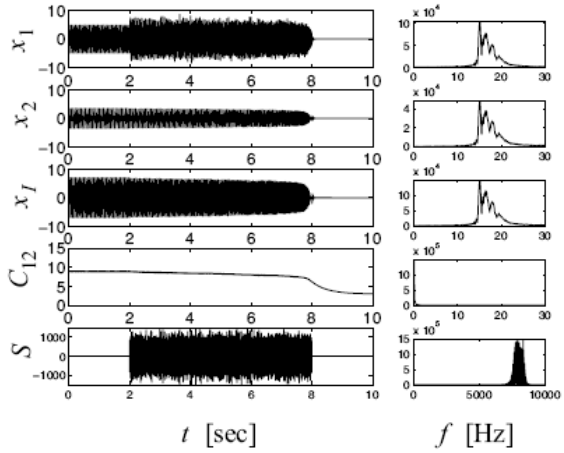

Figure 4d. Inhibition of oscillation by band noise stimulus with the band between 8kHz ± 5% margin and 400 RMS.

Figures 5a and 5b show the results for band pass filter with 4 kHz with ± 5% margin and RMS adjusted to about 200. Figures 5a shows a successful result as shown in Figure 4d. Oscillations of x_2 and x_I are maintained almost until t=8 [sec]. However, the value of C_{12} gradually decreases from the point of applying the stimulus. Eventually, the oscillations of x_2 and x_I stop. On the other hand, for the same conditions there were unsuccessful results in which the value of C_{12} is almost unchanged with 4 kHz filter, and consequently the oscillations continue through the entire simulation time, as seen in Figure 5b. It was observed that the oscillation was inhibited with the probability 74% when 100 different random trials were conducted.

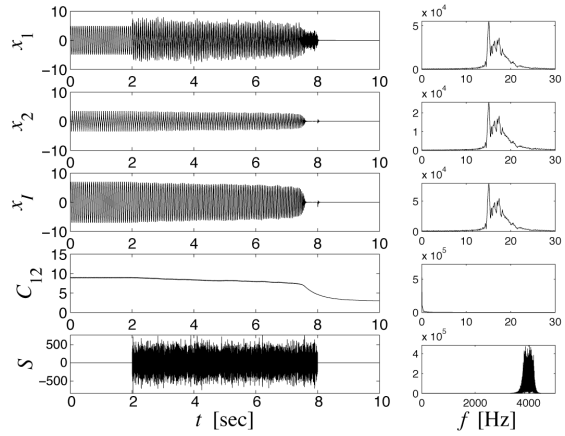

Figure 5a. A successful experiment for inhibition of oscillation by band noise stimulus with the band between 4kHz ± 5% margin and 200 RMS.

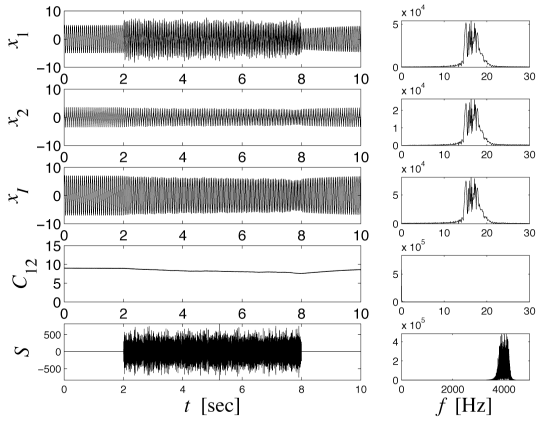

Figure 5b. An unsuccessful experiment for inhibition of oscillation by band noise stimulus with the band between 4kHz ± 5% margin and 200 RMS.

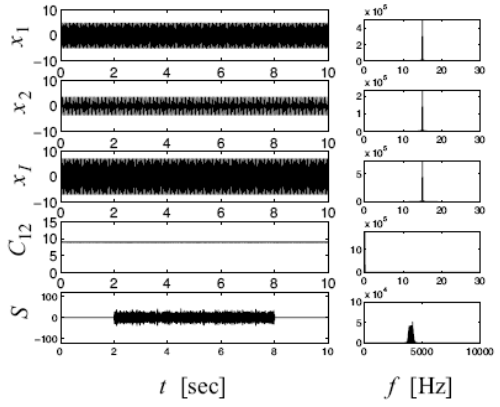

Figure 6. An unsuccessful experiment for inhibition of oscillation by band noise stimulus with the band between 4kHz ± 5% margin and 10 RMS.

As seen in Figure 6, for band noise with much lower power (RMS=10), it was observed that the value of C_{12} is almost unchanged and consequently the oscillations continue through the entire simulation time for all the simulations that we examined with 100 different random sequences.

Therefore, we can conclude that the inhibition of the oscillations by band noise stimulus requires an appropriately higher RMS value.

Discussion

Tinnitus is a debilitating condition and many researchers have attempted to establish treatment options for those who suffer from this condition. In the current paper a neural network model was proposed to address one of the most effective and noninvasive methods of tinnitus management referred to under the general term of sound therapy. Simulation results using sinusoidal and Gaussian white noise shown in Figures 3 and 4 demonstrate that introduction of external stimulus, S, results in reduction of the amplitude of oscillations in units E_1, E_2 and I. However, they continue to oscillate in synchronous fashion. This would correspond to the situations where tinnitus patients continue to perceive tinnitus in the presence of external auditory signal until inhibition occurs and all three units cease to oscillate.

On the contrary, simulations using band-pass noise seem to indicate that units E_2 and I cease to oscillate with the introduction of external stimulus, while unit E_1continues to oscillate. As seen in Figures 4a, b and c, band-pass noise is registered by unit E_1, which represents the peripheral nervous system, and the oscillatory activity is magnified (particularly in Figure 4a and c). This would seem to replicate the situations where tinnitus patients get habituated and do not perceive the effect of auditory activity in peripheral nervous system.

Simulation results in Figures 4d, 5 and 6 differ from these results and inhibitory behavior can be seen similar to the result in Figure 3.

For TM that uses band noise, higher amplitudes are used for the external sound in clinical practice so that the patients do not hear the sound of tinnitus [27]. It is not possible to compare precisely the RMS values of the noise in the simulation with the clinical data. However, the amplitude of the oscillation of x_1 is larger than the one that is seen before the noise is applied in Figures 4 and 5, and successful results were obtained. In Figure 6, the amplitude of the oscillation of x_1 is same as the one that is seen before the noise is applied and the result is unsuccessful. It corresponds to the situations when the noise is applied in clinic. Therefore, our results seem to be consistent with the practice.

Conclusions

In this study we demonstrated inhibition of the oscillation in the plastic neural oscillator model using various kinds of noise stimuli: including additive uniform noise, Gaussian white noise, and band noise. Through several numerical simulations we found that all of the noise stimuli can inhibit the oscillation. Therefore, the findings of this experiment could explain the fact that the human auditory system temporarily halts perception of tinnitus following sound therapy using a variety of noise stimuli.

The parameters of plasticity were arbitrarily determined so that the simulation is performed within appropriate time. The time scale would be much longer in the clinical situation. Further correspondence of the simulation data to clinical data needs to be examined.

It has been reported [27] that for TRT lower amplitudes are used for the stimulus so that the patients can hear the sound of tinnitus. We have been performing the simulations using Gaussian white noise. Our simulation results seem to be consistent with the practice [44].

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. The present model consists of the simplest arrangement of neuronal ensembles that can produce an oscillatory state which would resemble the perception of tinnitus. As discussed the arrangement represents the aggregate mechanisms in the thalamo-cortico-thalamic loop and future enhancements of the model will focus on adding excitatory and inhibitory connectivity between units E1 and I in order to capture intrathalamic interactions.

Acknowledgments

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Biographies

HIROFUMI NAGASHINO is currently Professor in Subdivision of Biomedical Information Science, Division of Health Sciences, Institute of Health Biosciences, The University of Tokushima. He received the Bachelor of Engineering and Master of Engineering degrees in Electrical Engineering from The University of Tokushima, Japan in 1972 and 1974, respectively. He received the Doctor of Engineering degree in 1982 from Osaka University, Japan. His research interest includes biocybernetics, neural networks and its application to biomedical engineering, particularly neural network models for oscillatory activities, signal source identification, pattern recognition, etc. Dr. Nagashino may be reached at nagasino@medsci.tokushima-u.ac.jp

KEN'ICHI FUJIMOTO is currently an Assistant Professor in Subdivision of Biomedical Information Science, Division of Health Sciences, Institute of Health Biosciences, The University of Tokushima. He received the Bachelor of Engineering degree in Information Science and Engineering from The University of Tokushima, Japan in 1995 and Master of Engineering degree in Information Science and Engineering from Tokyo Institute of Technology, Japan in 1997. He received the Doctor of Engineering degree from The University of Tokushima, Japan in 2000. His research interests include basic research on the dynamics of nonlinear dynamical systems and its applications to biomedical engineering, image processing, and image reconstruction in computed tomography. Dr. Fujimoto may be reached at fujimoto@medsci.tokushima-u.ac.jp

YOHSUKE KINOUCHI is currently a Professor Emeritus and Deputy Director, The University of Tokushima, Tokushima, Japan and is also a Guest Professor at Harbin Institute of Technology, Shenzhen Graduate School, Shenzhen, China. His current research interests include magnetic dentistry, biological effects of magnetic fields, bioimpedance, blood flow measurement, mobile telemedicine, medical applications of neural networks, physiological inverse problems and medical applications of LED. Dr. Kinouchi may be reached at kinouchi@ee.tokushima-u.ac.jp

ALI A. DANESH is currently associate professor in the Department of Communication Sciences and Disorders, Florida Atlantic University. He received Bachelor of Science degree in Audiology from College of Rehabilitation Sciences, Iran University of Medical Sciences, Tehran, Iran in 1987 and Master of Science in Audiology from Idaho State University, Pocatello, Idaho, USA in 1994. He completed his PhD in Audiology with an emphasis on Auditory Electrophysiology from the University of Memphis, Memphis, Tennessee, USA in 1998. His research interests include auditory electrophysiology, tinnitus, auditory processing and vestibular disorders. Dr. Danesh may be reached at danesh@fau.edu

ABHIJIT S. PANDYA is currently Professor in the Computer Science and Engineering Department at Florida Atlantic University, Boca Raton, Florida, USA. received his undergraduate education at the Indian Institute of Technology, Bombay and graduated with a M.Sc. in Physics (specialization in Electronics) in 1977. He earned his M.S. and Ph.D. in Computer Science from the Syracuse University, New York in 1985 and 1988 respectively. His areas of research include VLSI implementable algorithms, Applications of AI and Neural Networks, Image analysis in Medicine and Electronic Health Records. Dr. Pandya may be reached at pandya@fau.edu