Modeling the primary auditory cortex using dynamic synapses: Can synaptic plasticity explain the temporal tuning?

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Abstract

The molecular mechanisms underlying the temporal plasticity (temporal tuning) of cortical cells remain controversial. Experimental observations indicate that the neuronal responses at the primary auditory cortex are affected by behavioral learning. In this paper, we present a minimal feed-forward model of the primary auditory cortex, based on the dynamic synapse and the leaky integrate-and-fire neuron models, in order to search for the origin of the observed plasticity. We demonstrate that the frequency response of the model is markedly modified by regulating the contribution of synaptic facilitation to the short-term dynamics of synapses \((U_1)\). Consequently, we propose that the variation of this parameter may be responsible for primary auditory cortex enhancement achieved by behavioral training. Based on our model, we assume that the contribution of facilitation arises from the amount of Ca\textsuperscript{2+} influx each time an action potential arrives at the nerve terminal. Regardless of what really leads to the long-term variation of Ca\textsuperscript{2+} influx, we suggest that this process is responsible for the temporal tuning of responses observed in experimental studies. We believe that measurement of the long-term variation of Ca\textsuperscript{2+} influx at the pre-synaptic area of the cortical cells in auditory learning trials would be the first step to validate our hypothesis.

Keywords: Primary auditory cortex; Synaptic plasticity; Modeling; Cortical temporal plasticity

1. Introduction

The primary auditory cortex (A1) has always been the focus of neurophysiologists’ attention for its fundamental role in auditory signal processing. Recent findings suggest that it might serve as a general-purpose hub of the auditory pathway, forming a basis for the representation of the features of auditory signals (Griffiths et al., 2004). One of the most interesting functions observed in A1 is the temporal tuning (plasticity) of neural responses, which means that the characteristics of responses change with learning. For instance, Kilgard et al. (2001) have observed that auditory learning in adult rats leads to changes in the firing rate of cortical neurons in response to different frequencies of sound. As another example, an experiment on the primary auditory cortex of rats being trained in a “sound maze” indicates that behavioral learning can affect the response magnitude of cortical neurons, without remarkably changing the latency (Bao et al., 2004). A more rapid plasticity in A1 cell responses has also been reported for domestic ferrets under behavioral training (Fritz et al., 2003).

Several phenomena are assumed to underlie the plasticity of cortical cell responses in A1, but there is no global agreement on the issue (Kilgard et al., 2001, 2002; Wehr and Zador, 2005). Kilgard and Merzenich (1998) have proposed that the alteration of synaptic time constants, intrinsic temporal characteristics or network structural transformation may account for the observed plasticity. Krukowski and Miller (2001) have suggested that the plasticity may arise from the variation of NMDA receptor conductances in cortical inhibitory-excitatory circuitry. In their model, the variation of conductances modifies the
ration of excitation and inhibition in the entire circuitry, and provides a way to tune the frequency response of cells. Finally, Kilgard et al. (2002) have definitely enumerated three possible causes, including lowering or raising of spike thresholds, increased or decreased synaptic strength, and added or reduced number of neural connections; however, they have not evaluated their hypotheses experimentally.

Inspired by the efforts of Denham (2001) and Loebel and Tsodyks (2002) in using depressing synapses to model some aspects of the auditory cortical cells, we propose a minimal feed-forward model of the primary auditory cortex, comprised of excitatory dynamic synapses (Markram et al., 1998) and leaky integrate-and-fire (LIF) neurons (Izhikevich, 2005), in search for the origin of temporal plasticity in auditory cortical cells. More specifically, we exploit three LIF neurons at three layers: one to represent a pre-thalamic sensory neuron, the second to represent a thalamic neuron, and the third to stand for a cortical neuron at the thalamus. Thus, two excitatory dynamic synapses are utilized: one to represent a pre-thalamic sensory afferent, and the other to stand for a thalamocortical connection. The assumption of feed-forward (Suder et al., 2002; Reyes, 2003) and excitatory (Hu et al., 1994) structure for the modeled region of the auditory pathway seems biologically plausible.

We will show that the presented model is able to imitate the response properties of the A1 cells, obtained by Bao et al. (2004) in an experimental study. To this end, we will initially use the genetic algorithm in order to optimize some of the model parameters. We are obligated to apply this method since the real biological values of some parameters are not accessible. Afterwards, we will study if the plasticity of synaptic parameters (synaptic plasticity) could be responsible for the observed (Bao et al., 2004) temporal tuning in the model. This will be investigated over various aspects of the responses, including repetition rate transfer function (RRTF), response latency and single burst response magnitude. Based on the proposed model and the results, we will go for the possible biological origin(s) of temporal plasticity in the auditory cortex.

2. Methods

2.1. The stimulus

The stimulus signals consist of repetitive noise bursts, in accordance with Bao et al. (2004). Each noise burst is comprised by an ensemble of white Gaussian noise modulated by a pulse signal with 25 ms duration and 5 ms rise (fall) time. The power of the white noise is set to one, and the repetition rate of the bursts ranges from 2 to 20 pulses per second (pps).

We apply the generated stimulus signals to the first layer neuron of the model, as an excitatory post-synaptic current.

2.2. The model

The proposed model is comprised of a three-layer feed-forward network of neurons. Each layer contains one neuron in our attempt to simplify the model as much as possible. The neurons are connected to each other via dynamic synapses, as depicted in Fig. 1. The biological interpretation of the model structure is as follows: the first neuron represents a pre-thalamic sensory cell, the second one represents a thalamic neuron, and the third one stands for a cortical layer 4 cell. The “layer 4” neuron serves as the output of our model since the data captured by Bao et al. (2004) are mostly from this layer.

The input of the model is the post-synaptic current stimulating the first neuron, while the output is the sequence of action potentials generated by the third neuron.

2.2.1. The neuron model

The LIF model is utilized for simulating a neuron having ohmic leakage current, in which the membrane potential is obtained as the leaky integral of the post-synaptic currents due to the release of neurotransmitter vesicles. The statement can be formulated as (Izhikevich, 2005)

\[
\frac{dV(t)}{dt} = I(t) - g_{\text{leak}}(V(t) - E_{\text{leak}}),
\]

where \(V\) is the membrane potential, \(I\) is the ionic current caused by neurotransmitter release, \(C\) is the mean membrane capacitance, \(g_{\text{leak}}\) is the mean conductance due to leakage, and \(E_{\text{leak}}\) is the minimum mean membrane potential at which the outward leakage current starts. When the membrane potential \(V\) reaches a threshold value, the neuron fires an action potential (spike) and \(V\) is reset to potassium equilibrium potential, \(E_K\), which is typically less than \(E_{\text{leak}}\). Right after the action potential, the neuron is in its refractory period, during which it is less excitable (Izhikevich, 2005). We have modeled this behavior by including a constant refractory period value for all neurons, during which they do not fire any action potentials.

2.2.2. The dynamic synapse model

The deterministic model of dynamic synapse, which encompasses short-term synaptic mechanisms, has been introduced and comprehensively discussed by Tsodyks et al. (1998). The model encompasses a variety of short-term mechanisms that regulate the synaptic strength. However, some simpler models have been proposed based on this model (Markram et al., 1998; Fuhrmann et al., 2002) in which there are two distinct short-term synaptic mechanisms, depression and facilitation, each of which is modeled by a first-order differential equation. In this study, we utilize the model introduced by Markram et al. (1998).

The depression phenomenon takes place since the readily releasable neurotransmitter pool declines following each
action potential. Assuming an action potential at time \( t_{sp} \), this phenomenon can be expressed by the following equation:

\[
\frac{dR(t)}{dt} = \frac{1 - R(t)}{\tau_{rec}} - U(t) \cdot R(t) \cdot \delta(t - t_{sp}),
\]

in which \( R \) is the fraction of neurotransmitter pool available for transmission, \( U \) is the fraction of \( R \) to be utilized due to each spike, and \( \tau_{rec} \) is the pool recovery time constant.

The facilitation mechanism, on the other hand, is caused by an increase in the synaptic utilization at each presynaptic spike and can be formulated through the following equation:

\[
\frac{dU(t)}{dt} = -\frac{U(t)}{\tau_{facil}} + U_1 (1 - U(t)) \cdot \delta(t - t_{sp}),
\]

where \( U_1 \) is a constant determining the step increase in \( U \) and \( \tau_{facil} \) is the relaxation time constant. \( U_1 \) is supposed to be bounded to \([0, 1]\).

The ionic current (synaptic response) generated by an action potential at \( t_{sp} \) is obtained by

\[
I(t) = A \cdot R(t) \cdot U(t) \cdot \delta(t - t_{sp}),
\]

in which \( A \) is a constant value representing the absolute synaptic efficacy. It corresponds to the maximal synaptic response obtained if all synaptic resources are released at once. The product \( A \cdot R(t) \cdot U(t) \) is generally referred to as the synaptic efficacy.

2.3. Model optimization by genetic algorithm

The genetic algorithm (GA) is an appropriate tool for the optimization problems where no definite analytical method is available. The GA is based on the theories of genetics and natural selection, by means of searching for the optimal solution in a large population. It utilizes a fixed length vector, called chromosome, in order to represent a possible solution for a given problem domain (Goldberg, 1989). In our study, chromosomes are made up of real numbers, called genes, each one representing one of the model parameters. More specifically, each chromosome consists of all synaptic parameters, i.e. \((U_{1,1}, \tau_{facil,1}, \tau_{rec,1}, A_1)\) and \((U_{1,2}, \tau_{facil,2}, \tau_{rec,2}, A_2)\), regarding the two synapses, respectively.

The GA consists of a population of chromosomes—from which possible solutions are chosen—and two operations: (1) parent selection, and (2) mutation. The initial population is comprised of several randomly chosen real-valued vectors (chromosomes). The fitness (a measure of appropriateness of the solution) of each chromosome is evaluated by a fitness function. In this study, the fitness
function is defined as the reciprocal of the Euclidean distance between the desired response (i.e. RRTF, to be defined in analysis methods) and the response (RRTF) obtained if the values of the chromosome’s genes are substituted for their corresponding model parameters. The parent selection operator selects chromosomes from the population based on their fitness. A chromosome with higher level of fitness has more chance to be chosen.

After parent selection, each selected chromosome (parent) is mutated using some deterministic and stochastic calculations, called mutation, in order to create a child. In this study, we use the method presented in Yao (1999) in order to perform the mutation process. In this way, a variance \( \eta(j) \) is attributed to each gene \( x_i(j) \) of the chromosome \( x_i \), where \( i \) and \( j \) stand for the \( i \)th chromosome in the population and the \( j \)th component (gene) of that chromosome, respectively. The mutation process is formulated as below:

\[
\eta_i^{\text{new}}(j) = \eta(j) \exp(\tau N(0,1) + \tau' N_j(0,1)), \tag{5}
\]

\[
x_i^{\text{new}}(j) = x_i(j) + \eta_i^{\text{new}}(j) N_j(0,1), \tag{6}
\]

where \( x_i^{\text{new}} \) and \( \eta_i^{\text{new}} \) indicate the child chromosome and its corresponding variance, generated by the parent chromosome \( x_i \) and its corresponding variance \( \eta_i \), respectively. \( N(0,1) \) denotes a normally distributed one-dimensional random number with mean zero and variance one. \( N_j(0,1) \) indicates that the random number is generated anew for each value of \( j \). The parameters \( \tau \) and \( \tau' \) are commonly calculated as below (Yao, 1999):

\[
\tau = \left( \sqrt{2 \sqrt{n}} \right)^{-1}, \tag{7}
\]

\[
\tau' = \left( \sqrt{2n} \right)^{-1}. \tag{8}
\]

As a consequence of the mutation process, a population of parents and children emerges. The parent selection operator is applied again to the new population, and the mutation process is performed on the selected parents. This procedure continues cyclically until the stop criterion is reached, i.e. when the difference between the best fitness values of two successive generations is less than a predefined threshold.

2.4. Analysis methods

The comparison between the experimental data (Bao et al., 2004) and our proposed model response is accomplished by introducing some mathematical concepts, including response latency, response magnitude, normalized response magnitude, RRTF, and the single burst response. The response latency is defined as the time from the stimulus onset to the earliest response. The response magnitude is the average number of spikes activated by each stimulus burst, and the normalized response magnitude at each repetition rate is calculated as the average response magnitude to the last five bursts divided by the response magnitude to the first burst. The RRTF is the variation of normalized response magnitude over different repetition rates. Finally, the single burst response is defined as the magnitude of response to the first burst, i.e. the magnitude of response to a single burst when the system is at rest.

3. Results

3.1. Model optimization

The genetic algorithm was executed in the way mentioned in Methods. The total number of chromosomes in each generation and the number of eligible chromosomes (parents) being selected for the next generation were set to 50 and 15, respectively. The desired RRTF response was the response obtained by Bao et al. (2004), which is demonstrated in Fig. 2 by dotted line. All synaptic parameters were regulated by GA; while other model parameters were fixed during the optimization stage. These parameters were set regarding their corresponding values in real neural systems (Liaw and Berger, 1996).

The similarity between the model response and the desired response increased during the GA; however, it reached a plateau after some epochs. The obtained RRTF response is sketched in Fig. 2 by solid line. Table 1 demonstrates the GA optimized and fixed parameter values of the model.

Henceforth, we will refer to the optimized model as the “reference model”.

3.2. Functional analysis

Trains of noise bursts were used as stimulus at eight repetition rates (2, 4, 7, 10, 12.5, 15, 17.5, and 20 pps) in accordance with (Bao et al., 2004). For each repetition rate, the experiment was repeated 10 times. The reference model response, i.e. the sequence of action potentials generated by the third neuron, as well as the stimulus (red lines) is
sketched in Fig. 3a. As it is evident from this figure, the model does not follow the stimulus for repetition rates above 15 pps. Decreasing \( U_1 \) parameters (\( U_{1,1} \) and \( U_{1,2} \)) by 8% mimicked the effect of behavioral learning observed in Bao et al. (2004), so the manipulated model was able to respond to higher repetition rates of the stimulus, as illustrated in Fig. 3b.

To further investigate the effect of variation of \( U_1 \) parameters on the model, we evaluated the RRTF (as defined in analysis methods) at eight repetition rates (2, 4, 7, 10, 12.5, 15, 17.5, and 20 pps), while \( U_1 \) parameters were varying from 90% to 106% of their reference value (see Table 1). The resultant RRTF curves are demonstrated in Fig. 4. As evident in the figure, decreasing \( U_1 \) shifts the RRTF curve toward higher repetition rates (red area) whereas increasing \( U_1 \) moves it toward lower repetition rates (blue area). The apparent grouping of curves in the figure is due to the discontinuity in the repetition rate of the stimulus, as each curve breaks down at one of the aforementioned eight repetition rates.

Despite the high sensitivity of the spectral behavior to \( U_1 \) parameters, the temporal features did not show any considerable variation when \( U_1 \) parameters were varying within ±10% of their reference value. More specifically, the response latency and the single burst response magnitude (as defined in analysis methods) were constant (about 2 ms and 0.28, respectively), when \( U_1 \) parameters were varying from 80% to 107% of their reference value.

In order to better understand the sequence of steps that result in the sharp decrease evident in frequency responses (see Figs. 3 and 4), we plotted the values of the sequential processes influencing the final response (Fig. 5). The plotted quantities involve the post-synaptic response, membrane potential, action potentials, and synaptic efficacy (see Eq. (4)), regarding all neurons and synapses in the model. The values are plotted for two repetition rates just below and just above the descent, i.e. 17.0 and 17.1 pps, respectively. Basically, when we increased the repetition rate, a gradual fade-out of action potentials occurred at the second layer, which eventually resulted in sudden disappearance of the output action potentials. More specifically, while the firing rate at the second layer decreased gradually to the point of what shown in Fig. 5g (left), the output retained its firing rate (Fig. 5k, left), until the spikes at the second layer entirely disappeared (Fig. 5g, right), causing an abrupt outage at the output of the model (Fig. 5k, right). This phenomenon, which is observable when there are at least three layers, has led to the sharp decrease apparent in frequency responses (see Figs. 3 and 4).

Interestingly, when there was a single synapse (two layers), the model was unable to reproduce the sharp decrease evident in real auditory cortical frequency responses. Instead, the model output gradually dropped as we increased the repetition rate (see Fig. 5g). It seems that the nonlinear effect of depression/facilitation mechanisms in synapses, as well as the nonlinear transfer functions of the neurons, plays an important role in the model, conducing to the behavior demonstrated in Fig. 5. However, this behavior appears only when there are at least two synapses, and it plays an important role in our model, allowing it to simulate the sharp decrease of RRTF responses observed in experimental studies (Bao et al., 2004).

### 4. Discussion

The model, however simple, is capable of resembling the behavior of primary auditory cortex in several aspects. In order to maximize this resemblance, we utilized GA to optimize the model parameters. We aimed to have a model with an RRTF similar to the RRTF obtained from naïve rats (Bao et al., 2004). The similarity increased during GA progress; however, it reached a plateau after some epochs. More specifically, the model was unable to precisely mimic the desired response at high repetition rates: while the model response was suppressed to zero at higher repetition rates, the experimental response retained its non-zero value, which led to an approximately 14% difference between the two curves (see Fig. 2). The possible causes can be summarized as follows: (1) The model is simplified. In other words, a huge complicated network of neurons and synapses is modeled by only three neurons and two synapses. It is plausible to assume that among a wide number of neurons, a few of them continue to fire spikes at high repetition rates; as experimental results confirm that a small number of neurons respond to every burst in the entire temporal rate range (Bao et al., 2004). (2) In real biological systems, some neurons fire spikes even when the stimulus is absent. Thus, the response of such neurons is not strictly equal to zero at all, but it decreases to a minimum value, which is called the spontaneous firing rate of that neuron (Rieke et al., 1999).

After the optimization stage, we intended to find out which parameter(s) could be responsible for the changes observed in experimental studies after behavioral learning.
The synaptic parameters seem to claim more responsibility for modifying the spectral behavior of the model. But the question is which of these parameters could be assumed as the basis of A1 responses plasticity? In general, synaptic time constants are able to affect the spectral features of RRTF, as a recent study suggests that the spatial diversity of auditory cortical responses may arise from the variation of synaptic time constants (Elhilali et al., 2004). Nevertheless, the phenomenon does not seem to be responsible for the plasticity of synapses in time (i.e. learning), or at best it seems implausible, because in that case there should be a concordance between the two time constants, $t_{\text{rec}}$ and $t_{\text{facil}}$, whereas each one deals with a separate synaptic mechanism, i.e. depression and facilitation, respectively. The study of Liaw and Berger (1996) in modeling hippocampal synaptic connections is indirectly consistent with this idea. Therefore, we turn our attention to $U_1$.

There are several similarities between the modification of $U_1$ in our model and the effect of behavioral learning observed in experiments:

1. According to Fig. 4, it seems that $U_1$ has the ability to scale the RRTF curve without noticeably distorting its shape. More specifically, when there is a 5% decrease in $U_1$ parameters, the response remarkably becomes more vigorous in higher frequencies (see also Fig. 3). This behavior is very similar to what observed in real A1 neurons (Kilgard et al., 2001; Bao et al., 2004). In both studies, it has been detected that the behavioral training makes the primary auditory cortex more sensitive to higher repetition rates of bursts.

2. The response latency of the model is not conspicuously affected when $U_1$ varies within a limited range, i.e. ±5% of its reference value. The constancy of response
Fig. 4. Displacement of repetition rate transfer function (RRTF) curve due to variation of $U_{1,1}$ and $U_{1,2}$, from 90% to 106% of their corresponding reference value. Each RRTF is obtained by evaluating the normalized response magnitude at eight repetition rates (2, 4, 7, 10, 12.5, 15, 17.5, and 20 pps) and the legend indicates the percentage of change in both $U_{1,1}$ and $U_{1,2}$ parameters.

Fig. 5. Sequence of neuronal and synaptic processes influencing the output of the model, plotted for the reference model, at repetition rates 17.0 pps (left) and 17.1 pps (right). (a) stimulus (post-synaptic current stimulating the first neuron); (b) membrane potential of the first neuron; (c) action potentials generated by the first neuron; (d) synaptic efficacy of the first synapse; (e) post-synaptic current stimulating the second neuron; (f) membrane potential of the second neuron; (g) action potentials generated by the second neuron; (h) synaptic efficacy of the second synapse; (i) post-synaptic current stimulating the third neuron; (j) membrane potential of the third neuron; (k) action potentials generated by the third neuron.

The latency in the mentioned range is well compatible with the experimental results (Bao et al., 2004).

(3) The variation of $U_1$ parameters within ±5% of their reference value does not noticeably change the single burst response magnitude. This behavior is consistent with what has been reported by Bao et al. (2004). However, the single burst response magnitude can be affected by the variation of $U_1$, when it is great enough.
The aforementioned aspects, i.e. RRTF alteration, and the invariability of response latency and single burst response magnitude, direct us to propose that the “long-term” variation of $U_1$, which can be regarded as a long-term synaptic plasticity mechanism, may be responsible for primary auditory cortex enhancement achieved by behavioral training. It was demonstrated through our simulations that a change as small as $-5\%$ in $U_1$ could mimic the temporal plasticity of primary auditory cortex induced by behavioral learning experiments.

It has been theoretically indicated that the value of $U_1$ corresponds to the contribution of facilitation in generating subsequent synaptic responses (Tsodyks et al., 1998). Several experimental results, many of those reviewed by Zucker and Regehr (2002), emphasize that this facilitation in turn relies on the concentration of Ca$^{2+}$ ions in the pre-synaptic area. As stated by the residual Ca$^{2+}$ hypothesis (Katz and Miledi, 1968), facilitation is briefly caused by an action of Ca$^{2+}$ ions remaining in axon terminals after the spike arrival. Based on this hypothesis, one can consider the facilitation time constant $\tau_{\text{facil}}$ as the time course of Ca$^{2+}$ clearance at the axon terminals; and the contribution factor $U_1$ as the amount of Ca$^{2+}$ influx each time an action potential arrives at the nerve terminal $(I_{P, Ca})$. Consequently, the variation of $U_1$ on the other side stands for the modification of Ca$^{2+}$ influx. Although the effect of such modification has been shown to be indispensable in short-term enhancement of synapses (Kreitzer and Regehr, 2000), in the long-term evaluation of synaptic strength it may show a crucial role. Therefore, based on our results, we hypothesize that the temporal tuning of $I_{P, Ca}$ may be responsible for the RRTF enhancement observed in the primary auditory cortex after auditory learning trials. The behavior could be modeled by a simple differential equation as the following:

$$\frac{dI_{P, Ca}}{dt} = x(t),$$  

(9)

while

$$U_1 \propto I_{P, Ca},$$  

(10)

where $x(t)$ represents a feature of the stimulus, e.g. spike rate, which triggers the enhancement or the declination of $I_{P, Ca}$, and $\tau_1$ denotes the time course of this process. Note that the time constant $\tau_1$ should be great enough in order to originate a long-term modification of $I_{P, Ca}$, and subsequently $U_1$.

5. Conclusion and future prospects

Regardless of what really leads to the long-term variation of Ca$^{2+}$ influx (corresponding to $U_1$ in our model), we suggest that this process is possible, as we indicated that it can give rise to the experimentally observed temporal plasticity in cortical cells. If the future laboratory studies verify this suggestion, the role of structural reorganization, i.e. macroscopic synaptic changes, will be attenuated and the attention will be focused on the microscopic changes in synapses in order to explain the spectral alterations in the primary auditory cortex. This will also raise hopes for pharmacological manipulation of synapses in order to modify the spectral behavior of the auditory cortex, a way to auditory perception enhancement.

We believe that measurement of the long-term variation of Ca$^{2+}$ influx at the pre-synaptic area of the cortical cells, in auditory learning trials similar to the study of Bao et al. (2004), would be the first step to validate our hypothesis.

References


