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Impaired homeostatic regulation of feedback inhibition associated with system deficiency to detect fluctuation in stimulus intensity: a simulation study

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ABSTRACT

Information processing in animals' brain requires the balance between excitatory and inhibitory neural circuits. Feedback inhibition is involved in many sensory processes; however, the role of inhibition in system efficiency is not fully understood. Moreover, the regulation of inhibition intensity in response to different stimulus intensity is not fully studied in normal and pathological cases. In this work, a geometrical measure for system efficiency is defined that measures the system ability to discriminate between similar stimulus intensities. For this purpose, we developed a simulation of a two-layer feedforward neural system constrained by electrophysiological data. The effect of inhibition on system efficiency was studied for different feedback inhibition parameter values. The simulations show that inhibition is critically required to detect fluctuations in stimulus intensity, especially for high stimulus intensities. Moreover, simulations demonstrate that incremental change of inhibition parameter value (by a hypothetical homeostatic regulation mechanism) to detect fluctuations in incremental stimulus intensity is critically required to obtain high level of system efficiency. This work assigns a vital role for feedback inhibition in system efficiency of feedforward neural systems.

1. Introduction

The central question of modern neuroscience is how information concerning quality and intensity of stimuli in the environment are being processed within neural circuits in the animal's brain. Furthermore, neural systems are able to encode different stimulus intensities which serve as a pivotal capability to live in natural environments [1–5]. Examples of biological neural systems in which detection of stimulus intensity plays an important role are the visual system [6] and the *Drosophila* olfactory system which enables flies to learn to differentiate various concentrations of odors [7].

A challenge in computational neuroscience is to describe the computations performed by single neuron as well as neural populations. Moreover, how the spiking pattern of a neuron or neural layer elicits a specific behavior is under research [8,9].

At the molecular level, the neural circuits of the brain generate spatial and temporal patterns of activity [10]. By doing so, the neural systems remain highly sensitive to sensory inputs [11]. In addition, connectivity rate between neural layers may play important role in information processing and so is an important parameter in all neural systems [12]. The connectivity rate is defined as mean number of connection of each neuron in first layer to neurons in the second layer.

The synaptic excitation and inhibition are inseparable events in all neural processes including sensory systems. Concomitant occurrence of synaptic excitation and synaptic inhibition enables neural systems to process the complicated information received from environment [13–16]. For example, cortical processing reflects the interplay of synaptic excitation and inhibition [17]. Evidences highlighting the critical role for feedback inhibition for our understanding of information processing in the brain are rapidly accumulating [18]. Inhibition has also demonstrated direct involvement in the generation of oscillations in cortical neurons [19]. Feedforward inhibitory circuits are involved in both the suppression of excitability and timing of action potential generation in principal cells in area CA3 of the hippocampus [20]. An example of critical role of feedback inhibition in information processing is the role of GABAergic neurons in the *Drosophila* olfactory system [21]. Some models have been proposed to study the role of feedback inhibition in neural information processing [22,23].

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In the vertebrates' brain, microcircuits in hippocampus are other examples for existing feedback inhibition. Pyramidal cells in the hippocampus are part of a small neuronal network which consists of principal cells and various forms of feedback inhibition that performs computations on external input. Experimental evidence has indicated distinct inhibitory feedback loops in the CA3 area of the hippocampus. Several GABAergic cell types contribute to feedback circuits in the hippocampus [24].

In the CA1 region of the hippocampus a population of interneurons that contribute to feedback inhibition have their dendrites in the stratum project to the apical dendrites of pyramidal neurons in stratum lacunosum/molecular (O-LM cells) [25]. In addition, the Hippocampome project (see: http://hippocampome.org) has shown the possibility of existing such feedback inhibition in many regions of rodent's hippocampus.

Thus inhibition and the details of the microcircuit organization play an important role in the information processing of the small neuronal circuit in the hippocampus. Local inhibitory interneurons can perform quite distinct functions: interneurons that receive feedforward inhibition operate differently from those that participate in feedback loops [26].

Studies have demonstrated that the total number of hippocampal neurons in the pyramidal cell layer is normal in schizophrenia, but the number of inhibitory interneurons is reduced [27]. These studies have provided strong evidence for a specific defect of hippocampal inhibitory feedback and feedforward neurons in schizophrenia. Moreover, these results have implications for emerging models of hippocampal dysfunction in information processing in schizophrenia [27,28]. Theoretical studies and simulations may help link abnormal behavior associated with disorders such as schizophrenia to the altered physiological and structural features of inhibitory neurons in hippocampus or other regions of patients' brain.

Theoretical as well as experimental studies of neural systems have illustrated that interaction between excitation and inhibition orchestrates the flow of information through neuronal networks involved in sensory information processing [29]. Moreover, a hypothesis assumes that the elevation in the ratio of cortical cellular excitation-inhibition ratio through increased activity in excitation or reduction in inhibition could lead to the social and cognitive deficits observed in disorders such as autism [30,31].

To reveal the role of feedback inhibition in information processing in the brain, it is imperative to have a measure for system efficiency that considers the connectivity of neural layers as well as physiological parameters simulating different neural systems. Information theory has been used to define the system efficiency by measuring mutual information [32,33].

To model information processing in a two-layer feedforward neural network in insect brains, mutual information has been used to study the role of connectivity rate of layers and firing threshold as digits from 1 to 20 in system efficiency to encode incremental intensity of stimulus. The results of the simulation assign a pivotal role for feedback inhibition in information processing such that an optimal value of inhibition intensity has been found to encode different stimulus intensity which is pivotal to live in dynamical environments [33].

Alternatively, geometric approaches can be employed to measure the similarity of spike trains [34–38]. One way to study neural responses is to convert the spike train to a sequence of ones and zeroes, indicating the presence or absence of a spike in the corresponding time bin. The binary sequence is then split into a set of short intervals, called 'words' to measure mutual information [39].

In this study, we introduce a geometrical measure of system efficiency based on spike train analysis [39]. For this purpose, a neural network model for simplified sensory system was constructed using two feedforward neural layers simulated by an 'integrate and fire' neuron model using electrophysiological data (Fig. 1). The feedback inhibitory neuron activity with different parameters value is modeled to study its role in information processing in the presented neural system. Simulations are performed to study the role of feedback inhibition with different parameter values to search for optimal parameter value to obtain maximum system efficiency in detecting fluctuation in stimulus intensity. Moreover, a hypothesis about the role of intrinsic change of inhibition parameter (homeostatic regulation of inhibition) in system efficiency is introduced.

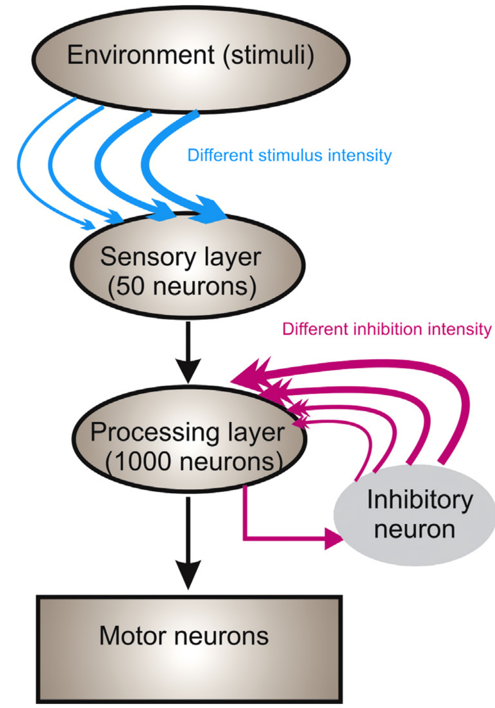

Fig. 1. Network model structure. The information of stimulus is transferred from environment to sensory neural layer (50 neurons). The firing rate of this layer is determined by stimulus intensity. The sensory layer is connected to processing layer (1000 neurons) according to the connectivity rate between layers. The processing layer is connected to motor neuron (is not modeled here). The processing layer is fully connected to inhibitory neuron which triggers it to inhibit activity of processing layer as a feedback inhibition.

2. Methods

2.1. Structure of neural system and neuron spiking model

A simplified sensory neural system was constructed to detect and process the stimulus within the environment. This neural system is composed of two sensory and processing layers with 50 and 1000 neurons, respectively, and one inhibitory neuron (Fig. 1). The parameters of the system are 'connectivity rate of sensory and processing layers', 'stimulus intensity' and 'inhibition parameter value'. The Connectivity rate between sensory and processing layers is modeled as the probability of connecting each neuron in the sensory layer to neurons in the processing layer. In the other words, connectivity rate determines the average percentage of connected neurons in the processing layer to each neuron of sensory layer. The inhibitory neuron is fully connected to the processing layer to receive inputs of stimulus then inhibits the spiking of processing layer with different intensity.

Stimulus intensity as a value in interval of zero and one determines the probability of spiking of neurons in sensory layer in each time bin. The stimulus is presented to the system for 10 s