Toward On-chip Functional Neuronal Networks: Computational Study on the Effect of Synaptic Connectivity on Neural Activity

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***Abstract*—This paper presents a new unified computational-experimental approach to study the role of the synaptic activity on the activity of neurons in the small neuronal networks (NNs). In a neuronal tissue/organ, this question is investigated with higher complexities by recording action potentials from population of neurons in order to find the relationship between connectivity and the recorded activities. In this approach, we study the dynamics of very small cortical neuronal networks, which can be experimentally synthesized on chip with constrained connectivity. Multi-compartmental Hodgkin-Huxley model is used in NEURON software to reproduce cells by extracting the experimental data from the synthesized NNs. We thereafter demonstrate how the type of synaptic activity affects the network response to specific spike train using the simulation results.**

I. Introduction

Despite great advances in micro and nanotechnologies pertaining to development of in-vivo multichannel electrical recording devices, the design and implementation of micro- and nanoelectrodes that is penetrated in the brain to recode electrical activities from single neurons through an invasive manner is not possible. On-chip synthetic neuronal networks platform provide a viable way to reach to this objective in-vitro through building a pre-designed network structure. Investigating the synaptic plasticity in very small networks [1] or recording spontaneous and evoked activities from a set of connected neurons using MEA and patch clamp [2] are performed on on-chip patterned neuronal networks. Functional connectome and recording every action potential from every neuron in a neuronal network is the main goal for the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) project [3]. To date, C.elegans is the only organism whose connectome has been completed, however, the electrical activities mapping associated with all 302 neurons of this worm is an unmet challenge [4, 5] and this is because of the difficulty of in-vivo studies for recording from all of the organ neurons. On-chip neuronal networks platform and computational modeling when combined could bring about a way of unraveling the basic rules governing the network dynamics and generalize it to more complicated 3D model organs.

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It has been argued that some of the neurological and psychiatric diseases have roots in altered connectivity of the brain. This alteration can be induced in a very small network of cells that lead to a malfunction in the brain's activity. On-chip neuronal network techniques offer the ideal platform to study these alterations in the network that lead to a significant change in functionality of the nervous system. Development of Biological computers and Bio-inspired computers (Neuromorphic) in future can revolutionize the human world toward faster computers, bio-compatible computers, and extremely intelligent algorithms. On-chip platforms for making synthetic neuronal networks is a promising approach to build computers with neuron-based-logic gates such as AND [6] instead of solid-state devices.

In this paper, we present an approach to overcome the above mentioned technical problem. This so-called unified computational-experimental approach (See Figure 1.) allows us to accurately model small NNs including a few neurons by extracting the experimental data from the same NNs synthesized on chip. This approach offers the advantage of combining small NNs to model more complex in vivo neural networks in order to achieve a complete functional connectivity (functional connectome) of an organ at the single cells level [3]. **Error! Reference source not found.**t shows the unified computational-experimental platform for functional NN study. This system is used to stimulate and record neurons. The experimental data can also be extracted to enhance a computational model.

Another advantage of the proposed approach is to study network disease computationally such as epilepsy [7] or Alzheimer's disease [8]. For instance, temporal lobe epileptic focal area in the brain includes about 50,000

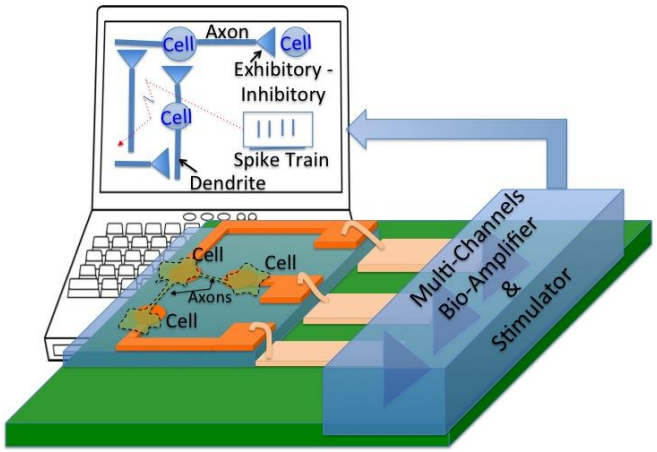

Figure 1. On-Chip neuronal networks and computational models for synthetic neuronal network

inhibitory and excitatory cell types. The hyperexcitability of the network is modeled using NEURON [7]. The main hypothesis beyond this disease is the mal connection because of cell loss and axon sprouting. The simulation of this network disease has been reported but the synthesis of cells to mimic the epilepsy has not been reported.

Many groups have studied the culture of neural cells on chip to study the neural tissue construction [9], but a few attention has been made to culture neural cells with predefined interconnections/pathways for axonal growth and synapse formation in order to study the effect of connectivity on the network activity instead of studying randomly organized neurons on culture [10].

With controlling the properties of surface chemistry mainly by patterning the certain proteins on chip, it could be possible to synthesize simple 2D neuronal networks on chip. Among various techniques are micro-contact printing that is used to control the surface biochemistry in order to study long-term network dynamics and the activity of individual neurons in the network [10], the role of substrate on the network activity [11], functional connectivity in an *in vitro* network [2], synaptic plasticity [1], spontaneous bursting activity, coincident activity, and spike trains from patterned network [12]-[13]. Another similar patterning technique is the conventional soft-lithography. Soft-lithography technique can be employed to pattern PDL to enhance the cell adhesion in some regions of the surface in order to study the frequency and oscillations (firing and bursting activities) in small clusters of neurons (neuro-glia) and their collective activity [14]. In another effort reported by [15] non-biological substrate DETA is used to control attachment and growth of hippocampal neurons to examine synaptic communication in a two-cell bidirectional polarity circuit. Microfluidic system in PDMS can also be used to pattern adhesion molecules on surface of MEA to study the relationship between structure and function of neuronal networks [16].

On the other hand, several computational approaches are used to study different properties of neuronal activities. Firing-rate models are used to describe behavior of a network by avoiding short time scale dynamics for simulation of action potentials [17]-[18]. Conductance-based models are also applied to describe production and propagation of action potential in compartments of a single neuron based on Hodgkin-Huxley model [19]. This model is the basis for generation and propagation of action potentials in the NEURON simulation environment [20]. Another computational study of network is calculation of functional connectivity to analyze the correlation of neural activities [21], [22], [23].

To date, several papers investigated functional connectivity by determining the relationship between anatomical connectivity and function of a network [2], [24] using NNs on chip. However, less attention was paid to describe the neural activity of the network based on the conductance-based multi-compartmental models of single neurons. In this paper the effect of the type of synaptic connections (inhibitory or excitatory) on the network function is investigated. It is shown that the type of synapse plays role in the activity of the neurons in a small networks and changing the synaptic activity changes the networks activity in small neuronal networks with constrained connectivity that are patterned on chip. NEURON simulation environment is used to provide a basic computational study for the neural activity of small patterned neuronal networks in vitro based on multi-compartmental Hodgkin-Huxley model. The experimental data for the synaptic connectivity and neural activity are extracted from the cortical networks that are patterned with the micro-contact printing method in [1].

II. Methods

A. Multi-Compartmental Neuron Model, Synapses, and NEURON software

The models of neurons are made of active and passive compartments. Somas and axons are active compartments that follow Hodgkin-Huxley model [19] for generation of action potential and dendrites are passive compartments. In Hodgkin-Huxley model each component of cell is represented by an electrical element such as capacitances, conductances, voltage sources, and current sources. The mathematical expression of current passes through membrane based on the Hodgkin-Huxley [19] model is:

$$I = C_m \frac{dV_m}{dt} + g_K(V_m - V_K) + g_{Na}(V_m - V_{Na}) + g_l(V_m - V_l)$$

In this equation I is the total membrane current, C_m , g_k , g_{Na} and g_l consequently are membrane capacitance per unit area, potassium conductance per unit area, sodium conductance per unit area, and leak conductance per unit area respectively. V_k , V_{Na} , and V_l are consequently the potassium reversal potentials, sodium reversal potentials, and leak reversal potential. V_m is the difference between membrane potential and resting potential.

Cells are connected in a network with chemical synapses. Two kinds of chemical synapses that were detected in the patterned cortical networks of [1] are GABAergic and glutamatergic synapses. The former is mainly an inhibitory synapse and the latter is an excitatory synapse. Stimulation in the pre-synaptic cell induces a current in the post-synaptic cell that is recorded experimentally in [1]. Based on the SEM geometrical data, biophysical properties of cells, and the properties of synaptic connections a network model is built for the neural structure and activity of small on-chip neuronal networks.

B. On-chip patterned network conceptual model

On-chip study of neuronal networks helps computational models to be improved based on real recorded data from organ cells that are difficult to study in vivo. It is a way to consider more details about neural cells and synapses in neuronal network modeling for a certain study. This approach is new from this point of view.

Based on the experimental data a conceptual network model has been created (Figure 2.). The model is composed of a stimulus which is a spike train, three neurons, two excitatory synapses, and two other synapses that can be excitatory or inhibitory. Since it is not specified that in a particular patterned network of [1] which synapse is excitatory (E) and which one is inhibitory (I) four cases are considered in which the first label shows the synaptic connection to "Cell1" and the second label demonstrates the synaptic connection to "Cell2": I-E, E-E, E-I, and I-I. The functional behavior of the network can be different for each case.

C. Network Dynamics

The network dynamics is represented by the action potential of each cell as the result of spike train that is given to the network as input. The stimulation inputs to the network from the dendrite of Cell1 and Cell3 that are connected by a chemical synapse.

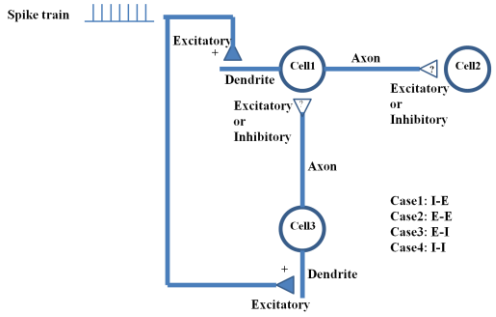

Figure 2. Conceptual model for a simple micro-patterned network composed of cells and synapses

For each choice of synaptic type the dynamics of neurons and the network function can be different.

III. Results

A. Network parameters

The network is composed of three neurons with different sizes for somas, axons, and dendrites according to the SEM images from [1]. In the computational model for Cell1 the diameter of soma is supposed to be 10 µm, the length and diameters of axon are 25 µm and 0.75 µm, and the length and diameter of dendrite are 25 µm and 0.5 µm respectively. Cell2 is only a soma with diameters 7 µm and 4 µm. For Cell3 the soma has diameter of 10 µm, the length of axon is considered to be 40 µm and its diameter is set to 0.75 µm, and the dendrite has the length of 25 µm and diameter of 0.5 µm. Somas and axons are active compartments and follow Hodgkin-Huxley model but dendrites are passive components. The synapses are of two types, inhibitory (GABAergic) and excitatory (glutamatergic). For the inhibitory synapses the decay time is 25.6 ms and for excitatory neurons it is 5.3 ms. The synaptic weight is considered 0.62 for excitatory synapses and 1 for inhibitory synapses. The spike train is composed of 10 spikes with the frequency of 0.8 Hz.

B. Analysis

The experimental results of neural activity for each case (1-4) are shown in Figure 3. . Each figure is composed of three curves that show the activity of Cell1, Cell2, and Cell3 in response to the spike train. Figure 3. (on the left side) is for the case that the synaptic connection to Cell1 is inhibitory and the synaptic connection to Cell2 is excitatory. In this case Cell1 is the postsynaptic neuron for the inhibitory synapse with the axon of Cell3 that is excited by the spike train. Figure 3. (on the right side) shows the activities of cells when both of the synapses are excitatory. In this case Cell2 is post-synaptic cell for an excitatory synapse. Comparison between the activities of neurons in Figure 3. shows that by changing an inhibitory synapse to an excitatory synapse the activity of the postsynaptic neuron changes. When the synapse is inhibitory the post-synaptic potential reaches to the steady state faster. Figure 4. (on the left side) shows the case that the synaptic connection to Cell1 is excitatory and for Cell2 is inhibitory. The difference between this case and the previous one is the change in the activity of post-synaptic Cell2. The inhibitory synapse inhibits the activity and doesn't allow a spike to occur.

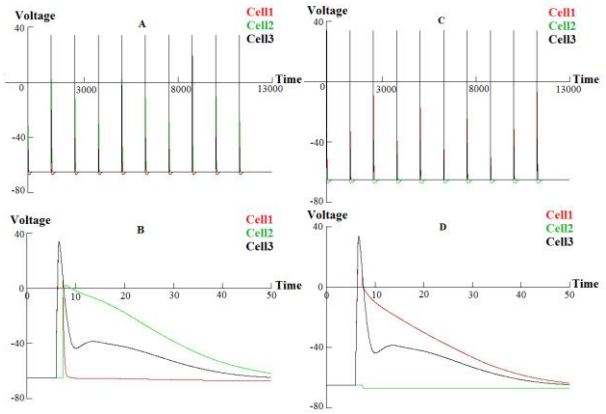

Figure 3. Neural activity in Case1: I-E (left) and Case2: E-E (right). A and C) Spiking activities of Cell1, Cell2, and Cell3. B and D) The action potentials of Cell1, Cell2, and Cell3 that are generated as a response to the first spike.

Figure 4. (on the right side) represents the activity of neurons when both synapses are inhibitory. This case differs from case3 in the type of connection to Cell1. As it is obvious the post-synaptic potential of Cell1 reaches to the steady state faster. The frequency of all cases is the same as the frequency of the input spiking train.

IV. Conclusion

In this paper the network activity of micro-patterned cells were studied using a computational platform to investigate the role of synaptic activity on the network behavior. The results show that synaptic type affects the activity of post-synaptic neurons and as the result the functionality of the

network. In the experimental platforms for building synthetic neuronal networks controlling the formation of synapses plays an important role in making network with arbitrary function. So, new scientific efforts are needed toward on-chip neural networks with controlled topology and controlled synaptic types to bring us ability of designing synthesized networks with specific function.

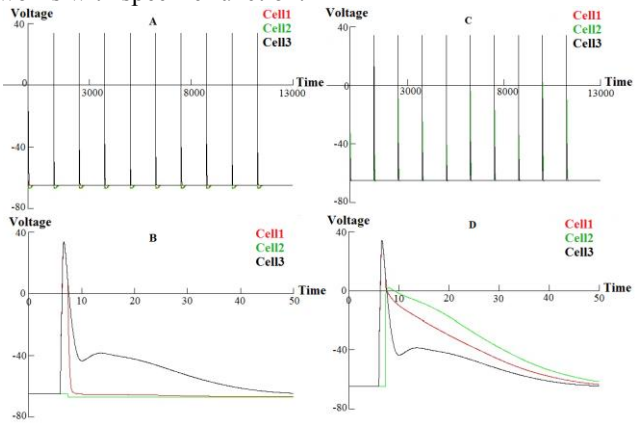

Figure 4. Neural activity in Case3: E-I (left) and Case4: I-I (right). A and C) Spiking activities of Cell1, Cell2, and Cell3. B and D) The action potentials of Cell1, Cell2, and Cell3 that are generated as a response to the first spike.

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