

# Study of Robustness of Synchronized Bursting Behaviors for Spike Neural Network Motifs

Chao-Yi Dong\*, Xiao-Yan Chen  
 School of Electric Power  
 Inner Mongolia University of Technology  
 Huhhot, China  
 Email: dongchaoyi@imut.edu.cn

**Abstract**—The understanding of the physiological basis of basic functions of brains requires detailed information about the functional structures of neuronal networks. Feedback loops are crucial dynamic motifs playing a pivotal role in the regulation and control of many important physiological and biochemical processes such as gene transcription, signal transduction, and metabolism (intracellular processes), and neuronal coding and decoding (intercellular processes). In the study, we focus on investigating a prerequisite for generating the synchronizations in spike neural networks and also a crucial structure for inducing the most robust synchronized network behaviors. Based on simulations for synthetic spiking neuronal network models, it is shown that only the networks with positive feedback loop (PFL) motifs can arrive at synchronizations under a variety of initial states. Importantly, coupled direct and indirect PFL motifs induce most robust synchronized bursting behaviors, which are one of the most remarkable characteristics of biological neuronal networks. This result may infer a crucial structural module for designing both *in vitro* and *in vivo* neuronal networks.

**Index Terms**—feedback loop, coupled direct and indirect positive feedback loops, synchronized bursting behaviors, robustness

## I. INTRODUCTION

It is well accepted that the basic functions of brains, for examples, perceptions, decisions, learning, and memory, are all encoded in trains of action potentials which are often known as “spiking times”. Indeed, the investigation of the physiological basis of these spike codes requires both a detailed knowledge about network topology and a proper connection between certain of spiking patterns and specific neuronal network structures. Many previous studies verified that a wide variety of biological neural networks exhibit a highly deterministic characteristic of network connectivity. This non-randomness is usually represented by the special local linking structures termed as “network motifs”. For instance, the structure and connectivity of the nervous system of the nematode *Caenorhabditis elegans* was deduced by White, revealing that neurons generally make synaptic connections with many of their neighbors, and that one of striking features of the connectivity diagrams is a sort of “network motif” like triangular connections linking three functional classes [1]. Later, Reigl used statistical analysis to reconfirm that some inter-connectivity patterns

containing two, three and four (but not five) neurons are significantly over-represented relative to the other inter-connectivity patterns [2]. The similar deterministic characteristics of network structures are also found in the mammalian cortical regions. Such networks present highly local clustering with short path lengths (small world topology) or power law distributed connectivity (scale-free topology), and nonrandom distributions of connection strength. Moreover, the analysis made by Sporns and Kotter suggests the hypothesis that brain networks might maximize both the number and the diversity of functional motifs, while the repertoire of structural motifs remains limited [3].

The large cultured cortical networks developed *ex vivo* provide appropriate experimental models for studying the network functions and structures due to their advantages: extensive sampling, easy manipulation, little interference, and wide timescale. The most prominent activities in *ex vivo* cortical networks are the synchronized bursting spikes happening in the processes of development [4, 5] and maturation [6]. Such activities of much functional significance *in vivo* were also reported in the cortical and sub-cortical regions of diverse species: rhesus monkey [7]; macaque monkey [8]; turtle [9]; pigeons [10]; rats [11]; and cats [12]. Usually, the adjustments of synaptic connections are considered highly correlated with the synchronized activities. For example, a rapid increase in the number of synaptic structures coincides with the development of spontaneous electrical activity [13]. Whereas, the process of functional network maturation is accompanied by an overall decline in the number of synapses that start in the fourth week and continue for approximately 40 days in culture [14]. A question might be raised as: what are the main structural characteristics related to the synchronized bursting behaviors of the neural network?

Feedback loops are considered to be closely related to the self-sustainable homeostasis of biological systems under internal and external changes [15-18]. The underlying feedback mechanisms of synchronizations have been also widely discussed in multimedia information retrieval, coupled lasers and liquid crystal light modulators, and coupled chaotic systems in the context of engineering. In the paper, we focus on investigating a prerequisite for generating the synchronizations in spike neural networks and also a crucial structure for inducing the most robust

synchronized network behaviors. In the present study, we hypothesize that the motifs with positive feedback loop (PFL motifs) defined in section 2 are a prerequisite. It turns out that only the networks with PFL motifs can arrive at synchronizations under a variety of initial states. For the synchronizations of spontaneous activities in cultured neural networks. To investigate this hypothesis, we apply artificial pulsed neural networks to fabricate neural networks with PFL motifs or without PFL motifs. It turns out that only the networks with PFL motifs can arrive at synchronizations under a variety of initial states. In addition, comparing to “direct” PFL motifs, coupled “direct” and “indirect” PFL motifs have higher “parameter robustness” for achieving synchronized bursting behaviors. This may further infer that the coupled direct and indirect PFL motifs might be the underlying mechanism to realize the robust synchronizations in the cultured neural networks.

II. METHODS

A. The definition of functional feedback motifs

We begin this section by a discussion which will motivate our definition of feedback motif, then propose the hypothesis that coupled positive feedback motifs might be the underlying mechanism to form synchronizations after investigating the functional properties of such motif in artificial pulsed neural networks. Milošević gave a formal definition of “network motif” as the patterns of interconnections occurring in complex networks at numbers that are significantly higher than those in randomized networks [19]. This definition is primarily based on anatomical building blocks, which are commonly present frequently in the biological networks. Sporns and Kotter later stressed on a distinction between structural and functional concepts [3], thus defined the functional motifs as a specific combination of nodes and connections (contained within structural motifs) that may be selectively recruited or activated in the course of neural information processing. In another word, the definition of functional motifs is entirely based on overall regulatory effects, i.e., control and information flows among different network nodes, instead of dealing with detailed anatomical structures. This standpoint is raised in some extent by the formidable complex of biological networks, which often daunts the efforts to investigate their exact topological structures, especially, in biological neural networks. Limiting the problems to the study of the functional interactions between biologically measurable signals rather than anatomical linkages might be a compromised but efficient way to study specific network functions.

The definition of feedback motifs suggested by us also follows the context of functional motifs and it reads as: The feedback motif is a feedback loop (including both a feedforward and a feedback regulatory effect) or a coupling of multiple such feedback loops in complex networks. For example, in terms of a simple synthetic network depicted in Fig. 1 (a), we can recognize the feedback loops as (2, 5), (3, 4), and (1, 3, 4). Some

attributes, for instance, positive or negative, direct or indirect, and coupled or uncoupled, can be assigned to classify those feedback loops as shown in Fig. 1 (a) (see Table 1 ). The sign of a feedback loop is determined as  $(-1)^q$ , where  $q$  is total number of the inhibitory paths in the loop. We thus define the feedback motifs which include at least one positive feedback loop as positive feedback loop motifs (PFL motifs). If a feedback loop is only composed of 2 nodes, we say it is a “direct” feedback, otherwise, “indirect”. When a feedback loop has at least one common node with the other feedback loops, it is considered as “coupled”. While it is entirely separated from the other feedbacks, it is “uncoupled”. Therefore, Fig. 1 (a) includes two feedback motifs, which are shown in Fig. 1 (b).

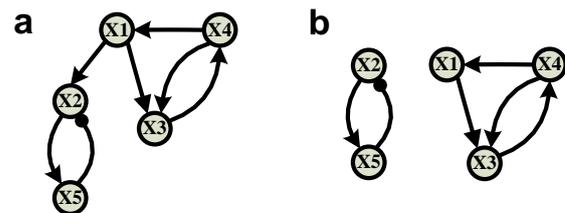


Fig. 1 (a) A synthetic 5-node network with 3 feedback loops. The interactions between nodes are represented by directed edges. The arrows denote the excitatory regulations, while the line dots denote the inhibitory regulations. (b) Two feedback motifs extracted from (a). One is an uncoupled direct negative feedback motif, and the other one is a coupled PFL motif, composed of one direct positive feedback loop and one indirect positive feedback loop.

Table 1  
Classification of different feedback loops in Fig. 1 (a) by their attributes. Three types of attributes are currently considered, which are “positive or negative”, “direct or indirect”, “uncoupled or coupled”.

Property\Feedback loop	(2,5)	(3,4)	(1, 3, 4)
Positive feedback	No	Yes	Yes
Negative feedback	Yes	No	No
Direct effect	Yes	Yes	No
Indirect effect	No	No	Yes
Coupled	No	Yes	Yes
Uncoupled	Yes	No	No

We start with networks where the interactions between nodes are represented by directed edges (either excitatory or inhibitory) and each network was scanned for all possible  $n$ -node subgraphs (in the present study,  $n = 2, 3$ , and 4). For example, the all possible schemes of connections for 2, 3-nodes networks are given in Fig. 2 (a), in which the empty arrows are not containing any information about whether the interactions are “positive” or “negative”. The first five schemes have no feedback loops, while the last 10 schemes each have at least one feedback loop. Based on those basic schemes of feedback loops, a list of all possible 2-node and 3-node feedback motifs can be presented in Fig. 2 (b). Herein, we consider the possibility of either excitatory or inhibitory interactions for a single path, the number of possible feedback motifs are therefore extended to 80.



Fig. 2 (a) The basic schemes of connections for 2, 3-nodes networks. The empty arrows only indicate the regulatory direction rather than its attribute. First 5 schemes (counted by row direction) are free of feedback loops, while the last 10 ones all have at least one feedback loop. (b) The total possible feedback motifs in 2, 3-nodes networks. If the attribute of excitatory or initiatory is considered in the last 10 schemes in (a), we have 80 different feedback motifs. (c) The feedback motifs of positive feedback loops.

Because we are seriously interested with the functions of PFL motifs, the feedback motifs including at least one positive feedback loop are singled out and form Fig. 2 (c). Thus, we can further compare the characteristics of these PFL motifs with the negative feedback loop motifs and also the cases free of feedback loops.

**B. Pulsed neural networks**

To infer the relation between a type of feedback motif and its network behaviors, we construct typical feedback motifs based on pulsed neural networks and observe their raster plots by randomly giving the initial states and parameters of the simulations. The pulsed neural networks, also called as third generation of artificial neural network, are based on spiking neurons, or “integrate and fire” neurons [20, 21]. These neurons use recent insights from neurophysiology, specifically the use of temporal coding to pass information between neurons [7, 8, 22-25]. Therefore, pulsed neural networks are commonly applied to study the properties of simulated neural networks.

For a spiking neuron  $i$ , the state, or say membrane voltage, can be described by a state variable  $x_i$ . The

neuron is said to be fired, if  $x_i$  reaches a threshold  $\delta$ . The moment of threshold crossing corresponds to a firing time  $t_i^k$ . The set of all firing times of neuron  $i$ , commonly called spike train, is represented by

$$\Phi_i = \{t_i^k; 1 \leq k \leq n\} = (t | u_i(t) = \delta), \tag{1}$$

where  $t_i^n$  is the most recent spike before the current time  $t$ . There are two different processes which contribute to the value of  $x_i$ . The first contribution is a negative-value function  $\Psi_i(t - t_i^k)$  indicating an immediate “reset” after each firing time in  $\Phi_i$ . In the biological context,  $\Psi_i$  is used to account for neuronal refractoriness. The second contribution is the inputs from pre-synaptic neurons  $j \in \Psi_i$  where

$$\Psi_i = \{j | j \text{ presynaptic to } i\}. \tag{2}$$

A pre-synaptic spike at time  $t_j^k$  increase (or decrease) the state  $x_i$  of post-synaptic neuron  $i$  for  $t > t_j^k$  by summing up a weighted kernel function as  $w_{ij} \varepsilon_{ij}(t - t_j^k)$ . The signs can be put in the synaptic efficacy and use

$w_{ij} > 0$  for excitatory synapses and  $w_{ij} < 0$  for inhibitory synapses. The kernel  $\varepsilon_{ij}$  describe the response of  $x_i$  due to a pre-synaptic potentials at  $t_j^k$ . This can be viewed as a synthetic effect of axon transmission property and membrane transmission property.

Therefore, the state of neuron  $i$  at current time  $t$  is given by the linear superposition of two main contributions,

$$x_i(t) = \sum_{t_i^k \in \Phi_i} \Psi_i(t-t_i^k) + \sum_{j \in \Psi_i} \sum_{t_j^k \in \Phi_j} w_{ij} \varepsilon_{ij}(t-t_j^k). \quad (3)$$

The equations (1)-(3) are referred as the Spike Response Model (SRM) [21]. They together with the connectivity topology of neural network form a simple simulated mechanism of a biological neural network. In many cases, we also induce the noise into the SRM by adding on the right-hand side of (3) an effect of a stochastic noise current  $I_i^{noise}(t)$ . Then (3) can be altered to

$$x_i(t) = \sum_{t_i^k \in \Phi_i} \Psi_i(t-t_i^k) + \sum_{j \in \Psi_i} \sum_{t_j^k \in \Phi_j} w_{ij} \varepsilon_{ij}(t-t_j^k) + \int_0^\infty e_i(s) I_i^{noise}(t-s) ds, \quad (4)$$

where kernel function  $e(s)$  mimics the dynamic from the local current stimulation to the membrane voltage for neuron  $i$ . In usual, we adopt several mathematical formulations (also illustrated in Fig. 3) to describe refractoriness  $\Psi_i$ , postsynaptic potential (PSP)  $\varepsilon_{ij}$ , and membrane dynamics  $e_i$ . For instance,

$$\varepsilon_{ij}(t) = \frac{1}{1 - (\tau_s / \tau_m)} \left[ \exp\left(-\frac{t - \Delta_{ax}}{\tau_m}\right) - \exp\left(-\frac{t - \Delta_{ax}}{\tau_s}\right) \right] H(t - \Delta_{ax}), \quad (5)$$

where  $\tau_s$  and  $\tau_m$  are time constants describing axon transmission dynamics and membrane dynamics, and  $\Delta_{ax}$  is the axonal transmission delay.  $H(t - \Delta_{ax})$  is the Heaviside step function which vanishes for  $t \leq \Delta_{ax}$  and take a value 1 for  $t > \Delta_{ax}$ .

$$\Psi_i(t) = \begin{cases} -\delta \exp(-\frac{t}{\tau}), & \text{for } t > T_{refractory} \\ -\infty, & \text{for } t \leq T_{refractory} \end{cases}, \quad (6)$$

where  $T_{refractory}$  is the absolute refractory period of neuron  $i$ . In such a period, the neuron would never be fired regardless of the value of membrane voltage.

$$e_i(t) = \frac{1}{\tau_m} \exp(-\frac{t}{\tau_m}) H(t). \quad (7)$$

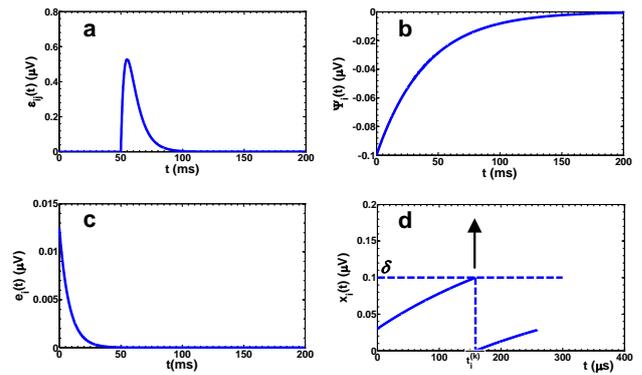


Fig. 3 (a) The kernel  $\varepsilon_{ij}(t)$  describing the response of  $x_i(t)$  contributed by a pre-synaptic spike at  $t = 0$ .  $\Delta_{ax} = 5ms$ ,  $\tau_s = 0.35ms$ , and  $\tau_m = 0.8ms$ . (b) The function  $\Psi_i(t)$  reflecting refractoriness after a spike emitted at  $t = 0$ .  $\delta = 0.1\mu V$  and  $\tau = 4ms$ . (c) The kernel  $e(t)$  representing the dynamic from the local current stimulation to the membrane voltage of a neuron. The time constant equals to the  $\tau_m$  in (a). (d) The membrane voltage  $x_i(t)$  firing at time  $t_i^k$  until it reaches a threshold voltage  $\delta = 0.1\mu V$ . After firing, it is to be reset by the function  $\Psi_i(t)$  and then accumulated by the pre-synaptic spike inputs  $w_{ij} \varepsilon_{ij}(t-t_j^k)$  again.

### III. RESULT

Simulations of above specified SRMs (2, 3, 4-node networks) show that only PFL motifs have a possibility to yield synchronized bursting activities. We follow the simulation protocols that all neurons share an identical parameter set  $\{\tau_s, \tau_m, \Delta_{ax}, \tau, \delta\}$  and the synaptic efficacies  $w_{ij}$  are randomly selected from a uniform distribution  $[-W_{max}, W_{max}]$ . Then, 100 times of simulations are run for each possible synaptic connective structure, i.e. “motifs”. Note that in order to reflect the essence of spontaneous behaviors only related to the network topology, we just consider the deterministic simulations for networks. Effects of stochastic noise current  $I_{noise}(t)$  thus are excluded in these cases. The initial conditions for network can be any  $P$ -bit binary number, where  $P$  is the number of neurons. For instance, for a 3-node network, the initial conditions can be any number for state “000” to state “111”, where state “1” indicates a “spike” at time  $t = 0$ , while state “0” indicates no “spike” at time  $t = 0$ . There are four typical network behaviors which appear during simulations. They are instantaneous response activities, synchronized bursting activities, asynchronized bursting activities, and hyper-excitable activities.

Table 2

The possibility distribution of the four mentioned behaviors for 12 typical 2, 3, 4-node feedback motifs. The values in table indicate the numbers of occurrences of certain activity from 100 simulations by randomly assigning the initial state and synaptic efficacies.

Behaviors \ Feedback motifs	1	2	3	4	5	6	7	8	9	10	11	12
Instantaneous response activity	21	20	3	5	2	0	1	2	51	18	3	5
Synchronized bursting activity	12	13	8	18	15	5	28	25	1	2	1	5
Asynchronized bursting activity	48	53	33	21	11	2	7	15	43	74	62	45
Hyper-excitable activity	19	14	56	56	72	93	64	58	5	6	35	45

By our protocols of simulations, the “synchronized bursting activities” is defined as a situation when the time distances between the first spike in “bursting events” of different neurons are less than the given axonal transmission delay  $\tau_{ax}$ , which are generally short as a few milliseconds. Otherwise, if the time distances are greater than  $\tau_{ax}$  and there are still some “bursting events”, we consider those situations as asynchronized bursting activities. The hyper-excitable activities are the cases that all nodes permanently fire with an interval of absolute refractory period  $T_{refractory}$ . Fig. 4 illustrates these four typical activities commonly appeared in simulations.

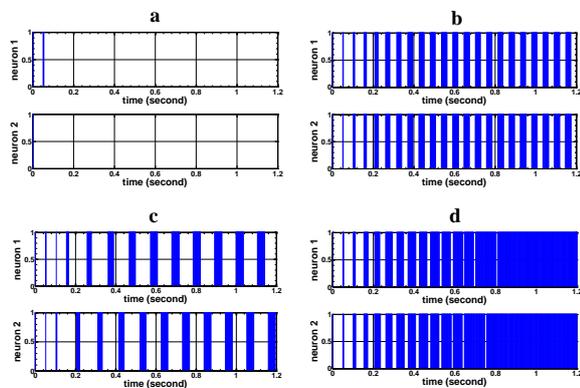


Fig. 4 Four typical behaviors for a 2-nodes PFL motif when different synaptic efficacies are arranged. The initial state takes (1,1) at  $t=0$ . (a) Instantaneous response activity. (b) Synchronized bursting activity. (c) Asynchronized bursting activity. (d) Hyper-excitable activity.

The simulations indicate: The motifs without any feedback loop (the first 5 schemes in Fig. 2 (a)) and the motifs with only negative feedback loops in Fig. 2 (b) are not able to show the synchronies, asynchronies, and hyper-excitabilities, whatever synaptic efficacies are adjusted; the PFL motifs shown as in Fig. 2 (c) can generate all four activities if we set appropriate synaptic efficacies. Therefore it is deduced that the PFL motifs be the underlying mechanism for the sustainable oscillatory and synchronized behaviors.

Robustness is one of the favorable characteristics of biological systems. Numerous reports have been published on how robustness is involved in various biological processes and on mechanisms that give rise to robustness in living systems [26-28]. The property is

generally quantified as a ratio of alterations of dynamic behaviors to an alteration of system parameters. For the investigation of parameter robustness of PFL motifs with respect to synchronized bursting behaviors, we use the possibility of maintaining synchronies while rearranging all synaptic efficacies randomly in  $[-W_{max}, W_{max}]$  to evaluate the “parameter robustness”. The results show the coupled direct and indirect positive feedback loop motifs have higher possibilities to maintain the synchronized bursting behaviors than the other PFL motifs have.

Table 2. shows the possibility distribution of the four mentioned behaviors for 12 typical 2, 3, 4-node feedback motifs. The comparisons of activity distributions among those motifs are further illustrated in Fig. 5 (a). Motif 4, 7, and 8, all of which include coupled direct and indirect positive feedback loops, have much higher possibilities to yield synchronized bursting behaviors than the other motifs have. For motif 7, the percent of synchronized bursting activities is 28%, which reaches more than one fourth of all 100 simulations. While the positive paths are increased, the possibility of hyper-excitabilities climbs up significantly (see Fig. 5 (b)). Motif 6, being the fully-connected case for 3-node network, has 93% possibility to generate hyper-excitability, which is the highest one among all 12 motifs. The introduction of inhibitory synapse to PFL motifs can remarkably increase the possibility of asynchronized bursting activities, whereas decrease the possibility of synchronized bursting activities. This point can be shown in the pair comparisons between motif 4 and 9, motif 4 and 10, motif 5 and 11, and motif 6 and 12 in Fig. 5 (c). The possibility of hyper-excitabilities goes down when the inhibitory synapses are added into motifs 4, 5, and 6. In summary, compared with the other PFL motifs, the coupled direct and indirect PFL motifs have strongest parameter robustness for synchronized bursting behaviors, and the introduction of inhibitory paths deteriorates such robustness rather than improve it. Seriously interested with such coupled PFL motifs, we develop an efficacy method to identify the feedback loops in spike neural networks. For more detailed introductions for the feedback loop identification method, see references [29-31].

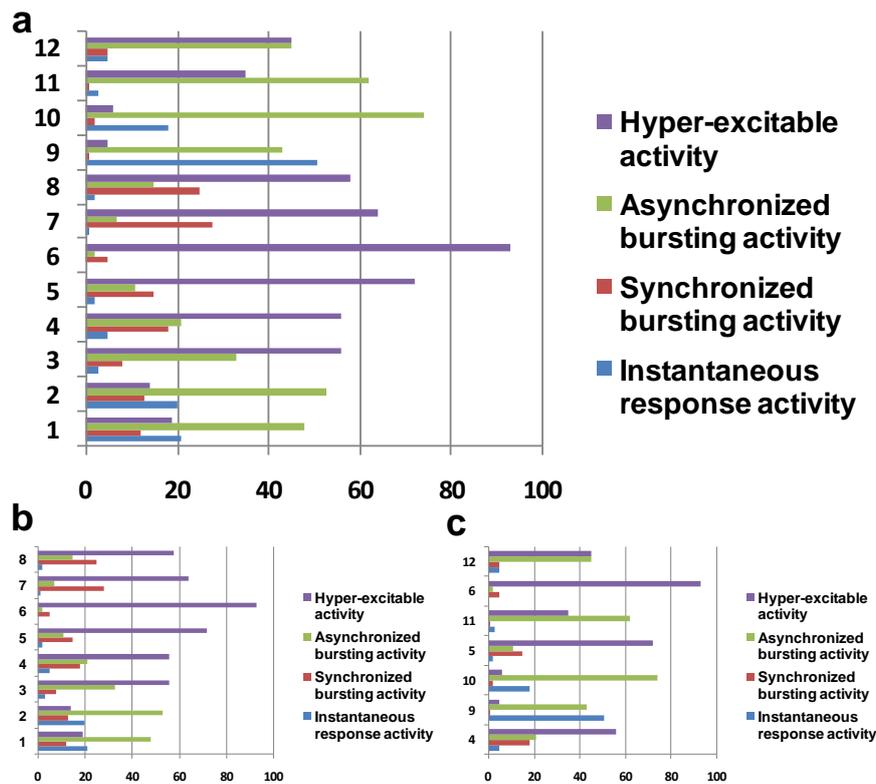


Fig. 5 (a) The comparisons of activity distributions among 12 typical motifs. (b) The comparison of activity distributions among all-positive-path PFL motifs. Motif 4, 7, and 8 have highest possibilities to yield synchronized bursting behaviors which are 18%, 28%, and 25%. Motif 6 has the highest possibility of hyper-excitability, which are 93%. (c) The comparison of the cases before an introduction of inhibitory synapses and after an introduction of inhibitory synapses. The synchronies and hyper-excitability are inhibited significantly while the asynchronies increase dramatically.

#### IV. CONCLUSION

Synchronized bursting behavior is one of remarkable phenomena in neural dynamics. Identification of its underlying functional structure is crucial in understanding the mechanism of synchronized bursting behavior at a system-level. Feedback loops are commonly used basic building blocks in engineering circuit design, especially for synchronization, and they have also been considered as important regulatory network motifs in systems biology.

Interested with the underlying mechanism of synchronized bursting activities among in vitro and in vivo neuronal networks, we compare the different network behaviors of 3, 4-node network motifs in synthetic networks. Through extensive simulations of synthetic spike oscillation models, we found that a particular structure of feedback loops, coupled direct and indirect positive feedback loops, can induce robust synchronized bursting behaviors.

It is shown that all spontaneous responses from the simulated motifs can be categorized into four typical modes: instantaneous response activity; synchronized bursting activity; asynchronized bursting activity; hyper-excitable activity, which are all robust to a variety of initial “binary” states. Only the networks with PFL motifs have possibilities to arrive at sustainable oscillations and synchronies, while sole negative feedback motifs and

feedback free motifs cannot bring out such network behaviors. Most importantly, comparing to “direct” PFL motifs, coupled “direct” and “indirect” PFL motifs have higher “parameter robustness” for achieving synchronized bursting behaviors. It is thus suggested that coupled “direct” and “indirect” PFL motifs may be underlying mechanism for to realize the robust synchronizations in the cultured neural networks.

The method used here is based on plenty of Mont Carol simulations. That is, the weight values of synaptic connections are randomly perturbed and the network topologies are arbitrary arranged for covering all different possible mechanisms to induce network behaviors of 2, 3, or 4-node spiking neural network motifs. The complexity of computation will increase exponentially with the increase of network scale. The cases may be handled by the use of cluster computation or GPU devices, which have higher computational abilities. However, it is quite interesting to extend the study of robustness to larger scale networks, which contain such basic network motifs, for checking whether the major conclusions in this paper are still maintained or some other emergent properties come out. Those endeavors will finally contribute to the final goal, the understanding of the functional structures of neuronal networks.

## ACKNOWLEDGMENT

This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea Ministry of Education, Science & Technology through the Systems Biology grant (M10503010001-07N030100112), the Nuclear Research grant (M20708000001-07B0800-00110), the 21C Frontier Microbial Genomics and Application Center Program (Grant MG08-0205-4-0), Inner Mongolia University of Technology grants (X20416).

## REFERENCES

- [1] J. G. White, E. Southgate, J. N. Thomson, and S. Brenner, "The structure of the nervous system of the nematode *Caenorhabditis elegans*", *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* (1934-1990), vol. 314, pp. 1-340, 1986.
- [2] M. Reigl, U. Alon, and D. B. Chklovskii, "Search for computational modules in the *C. elegans* brain", *BMC Biol.*, vol. 2, p. 25, 2004.
- [3] O. Sporns and R. Kotter, "Motifs in brain networks", *PLOS Biology*, vol. 2, pp. 1910-1918, 2004.
- [4] A. Habets, A. M. J. Dongen, F. Huizen, and M. A. Corner, "Spontaneous neuronal firing patterns in fetal rat cortical networks during development in vitro: a quantitative analysis", *Experimental Brain Research*, vol. 69, pp. 43-52, 1987.
- [5] H. Kamioka, E. Maeda, Y. Jimbo, H. P. C. Robinson, and A. Kawana, "Spontaneous periodic synchronized bursting during formation of mature patterns of connections in cortical cultures", *Neuroscience Letters*, vol. 206, pp. 109-112, 1996.
- [6] E. Maeda, H. P. Robinson, and A. Kawana, "The mechanisms of generation and propagation of synchronized bursting in developing networks of cortical neurons", *Journal of Neuroscience*, vol. 15, pp. 6834-6845, 1995.
- [7] E. Vaadia, I. Haalman, M. Abeles, H. Bergman, Y. Prut, H. Slovin, and A. Aertsen, "Dynamics of neuronal interactions in monkey cortex in relation to behavioural events", *Nature*, vol. 373, pp. 515-518, 1995.
- [8] A. Riehle, S. Grun, M. Diesmann, and A. Aertsen, "Spike synchronization and rate modulation differentially involved in motor cortical function", *Science*, vol. 278, p. 1950, 1997.
- [9] J. C. Prechtl, L. B. Cohen, B. Pesaran, P. P. Mitra, and D. Kleinfeld, "Visual stimuli induce waves of electrical activity in turtle cortex", *Proceedings of the National Academy of Sciences*, vol. 94, pp. 7621-7626, 1997.
- [10] S. Neuenschwander, A. K. Engel, N. P. K. O, W. Singer, and F. J. Varela, "Synchronization of neuronal responses in the optic rectum of awake pigeons", *Visual Neuroscience (Print)*, vol. 13, pp. 575-584, 1996.
- [11] A. Bragin, G. Jando, Z. Nadasdy, J. Hetke, K. Wise, and G. Buzsaki, "Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat", *Journal of Neuroscience*, vol. 15, pp. 47-60, 1995.
- [12] C. M. Gray and W. Singer, "Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex", *Proceedings of the National Academy of Sciences*, vol. 86, pp. 1698-1702, 1989.
- [13] K. Muramoto, M. Ichikawa, M. Kawahara, K. Kobayashi, and Y. Kuroda, "Frequency of synchronous oscillations of neuronal activity increases during development and is correlated to the number of synapses in cultured cortical neuron networks", *Neuroscience Letters*, vol. 163, pp. 163-165, 1993.
- [14] F. Van Huizen, H. J. Romijn, and A. Habets, "Synaptogenesis in rat cerebral cortex cultures is affected during chronic blockade of spontaneous bioelectric activity by tetrodotoxin", *Brain Research*, vol. 19, pp. 67-80, 1985.
- [15] M. T. Laub and W. F. Loomis, "A molecular network that produces spontaneous oscillations in excitable cells of *Dictyostelium*", *Molecular Biology of the Cell*, vol. 9, pp. 3521-3532, 1998.
- [16] M. Maeda, S. Lu, G. Shaulsky, Y. Miyazaki, H. Kuwayama, Y. Tanaka, A. Kuspa, and W. F. Loomis, "Periodic signaling controlled by an oscillatory circuit that includes protein kinases ERK2 and PKA", *Science*, vol. 304, pp. 875-878, 2004.
- [17] S. H. Strogatz, *Nonlinear dynamics and chaos: with applications to physics, biology, chemistry, and engineering*. New York: Perseus Books Group, 2000.
- [18] R. Thomas and M. Kaufman, "Multistationarity, the basis of cell differentiation and memory. I. Structural conditions of multistationarity and other nontrivial behavior", *Chaos*, vol. 11, pp. 170-179, 2001.
- [19] R. Milo, S. Shen-Orr, S. Itzkovitz, N. Kashtan, D. Chklovskii, and U. Alon, "Network motifs: simple building blocks of complex networks", *Science*, vol. 298, pp. 824-827, 2002.
- [20] W. Maass, "Networks of spiking neurons: The third generation of neural network models", *Neural Networks*, vol. 10, pp. 1659-1671, 1997.
- [21] W. Maass and C. M. Bishop, *Pulsed Neural Networks*: Bradford Book, 1999.
- [22] G. T. Buracas, A. M. Zador, M. R. DeWeese, and T. D. Albright, "Efficient discrimination of temporal patterns by motion-sensitive neurons in primate visual cortex", *Neuron*, vol. 20, pp. 959-969, 1998.
- [23] Z. F. Mainen and T. J. Sejnowski, "Reliability of spike timing in neocortical neurons", *Science*, vol. 268, pp. 1503-1506, 1995.
- [24] J. O'Keefe and M. L. Recce, "Phase relationship between hippocampal place units and the EEG theta rhythm", *Hippocampus*, vol. 3, pp. 317-330, 1993.
- [25] S. Thorpe, D. Fize, and C. Marlot, "Speed of processing in the human visual system", *Nature*, vol. 381, pp. 520-522, 1996.
- [26] M. A. Savageau, "Mathematics of organizationally complex systems", *Biomed Biochim Acta*, vol. 44, pp. 839-44, 1985.
- [27] U. Alon, M. G. Surette, N. Barkai, and S. Leibler, "Robustness in bacterial chemotaxis", *Oncogene*, vol. 15, pp. 899-910, 1997.
- [28] H. Kitano and K. Oda, "Robustness trade-offs and host-microbial symbiosis in the immune system", *Molecular Systems Biology*, vol. 2, 2006.
- [29] C. Y. Dong, K. H. Cho, and T. W. Yoon, "Identification of Intra-Cellular Feedback Loops by Intermittent Step Perturbation Method", in *IFAC, 2008 Seoul*, 2008.
- [30] C. Y. Dong, J. S. Lim, Y. K. Nam, and K. H. Cho. "Systematic analysis of synchronized oscillatory neuronal networks reveals an enrichment for coupled direct and indirect feedback motifs", *Bioinformatics*, vol. 25, pp. 1680-1685, 2009.
- [31] C. Y. Dong, T. W. Yoon, D. Bates, and K. H. Cho. "Identification of feedback loops embedded in cellular circuits by investigating non-causal impulse response components", *Journal of Mathematical Biology*, vol. 60, pp. 285-312, 2009.



**Chao-Yi Dong** received his B.S. degree in Electrical Engineering from Heifei University of Technology in 1997. He received his Ph.D. degree in Electrical Engineering from Korea University, Korea in 2009. He is currently an assistant professor at the Department of Automatic Control at Inner Mongolia University of Technology, Huhhot, People's Republic of China. From 2006

to 2009, he has worked with Dr. Kwang-Hyun Cho at the Laboratory for Systems Biology and Bio-Inspired Engineering (SBIE), Kaist on developing identification methods for biological feedback network feedback motifs. His current research interests include development, integration, and adoption of information technologies for inferring biological neural network topology, and also include robust control for power electronic devices.