Functions of neuronal network motifs

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It was recently found that neuronal (and many other) networks contain some significantly recurring wiring patterns, termed "network motifs," which are believed to be basic building blocks of these networks and to perform important functional roles in them. We study the functions of neuronal network motifs by computational modeling. We use both the firing-rate and integrate-and-fire models to model the neuronal network motifs. Several interesting functions and dynamics are found in the neuronal network motifs, such as the acceleration and delay of response and long- and short-term memory.

Complex networks are ubiquitous in nature. Recent research has uncovered that complex networks share some common statistical features, such as the small-world effect and the scale-free property. In addition, it was recently found that many networks contain some significantly recurring wiring patterns, termed "network motifs." Network motifs are patterns that occur in a real network significantly more often than those in a randomized network with the same degree sequence [1,2]. Especially, motifs were found in some biological networks—for example, in gene transcription networks [3], brain functional networks [4], and neuronal networks [1,5,6]. Motifs found in these networks are believed to be basic building blocks and to perform specific functional roles. Moreover, it is found that, in many systems studied so far, the motifs are linked to each other in a way that does not spoil the independent function of each motif [7]. That means that the network dynamics might be understood as combinations of these elementary computational units [8]. Elucidating these motifs' functions is the first step to understand the behaviors of whole networks. The dynamics and functions of genetic network motifs have been intensively studied in recent years [2,3], but to our knowledge, the functions of neuronal network motifs have not yet been addressed. It is interesting to know what the functions of the neuronal network motifs are [2].

In [1,5,6], several *common redundant* network motifs, as shown in Figs. 1(a)–1(d), were found in different neuronal networks inferred by using different approaches. Several other connection patterns might also be recognized as network motifs in some specific neuronal networks, but the four patterns shown in Figs. 1(a)–1(d) are the most significant ones commonly occurring in different networks. In [1,5] the authors considered the wiring diagram of the *C. elegans* brain, in which the connections among the neurons were obtained from serial-section electron microscopic reconstructions. In [6], the connections among neurons were inferred by simultaneous quadruple whole-cell recordings from layer-5 pyramidal neurons in the rat visual cortex. Interestingly, in [6], it was further found that the connections among neurons in the network motifs tend to be *stronger* than the other connections. "The network may be viewed as a skeleton of stronger connections in a sea of weaker ones" [6]. Thus, it is reasonable to believe that neuronal network motifs play some important roles in the networks and the individual functions of the network motifs are likely to be preserved when they are connected to other neurons, which means that the network function and dynamics might be understood as combinations of these elementary computational modules.

In this Brief Report, we study the functions of neuronal network motifs by computational modeling. Since the mutually connected two-neuron motif [Fig. 1(d)] is in fact contained in the triple-neuron mixed-feedforward-feedback loop (MFFL) motifs [Figs. 1(b) and 1(c)], we study here only the functions of the three triple-neuron network motifs: the FFL [feedforward loop, Fig. 1(a)], the MFFL1 [Fig. 1(b)], and the MFFL2 [Fig. 1(c)] network motifs.

We model the neurons in the motifs and perform simulations in two levels [9]. We use the firing-rate model, which is intuitive, and the integrate-and-fire (IF) neuron model, which can mimic the action potential firing dynamics of biological neurons, in investigating the motif functions.

The firing-rate model is described by the following equation [10]:

$$\frac{dr_i}{dt} = -\frac{r_i}{\tau} + f\left(\sum_j W_{ij} r_j - T_i\right) + I_i, \quad (1)$$

where r_i is the firing rate of the ith neuron, τ is the time constant, and W_{ij} is the connection weight from neuron j to neuron i. When neuron j is excitatory, $W_{ij}=1$; when neuron j is inhibitory, $W_{ij}=-1$; and when there is no connection from neuron j to neuron i, $W_{ij}=0$. The constant T_i is the threshold, which is 0 Hz for excitatory neurons and 10 Hz for inhibitory neurons. I_i is the input. Without loss of generality, the response function $f(\cdot)$ is as follows:

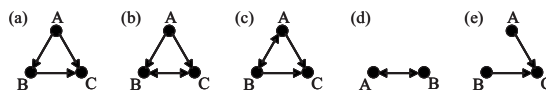$$f(x) = \begin{cases} 0, & x \leq 0, \\ \tanh(x), & x > 0. \end{cases}$$

FIG. 1. Connection patterns: (a)–(d) triple-node and two-node neuronal network motifs; (e) simple drive of C by A and B as a comparison of the feedforward loop.

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The integrate-and-fire model is described as follows [10]:

$$\frac{dv_i}{dt} = (V_{\text{rest}} - v_i)/\tau_1 + I_s + I_i, \qquad (2)$$

where I_i is the applied current, τ_1 is a time constant, and the resting membrane potential $V_{\text{rest}} = -65$ mV. The synaptic current I_s is defined as $I_s = \Sigma_j g_j(E - v_i)$. The reversal potential $E = 0$ mV if neuron j is excitatory and $E = -75$ mV if neuron j is inhibitory. When a neuron fires, the synaptic conductance g of its postsynaptic target neuron is increased, $g = g + P_{\text{max}}(1 - g)$, and in the other time $dg/dt = -g/\tau_2$. The fixed parameters $\tau_1 = 10$ ms, $\tau_2 = 15$ ms, and $P_{\text{max}} = 0.5$. Whenever the membrane potential reaches a threshold $V_{\text{th}} = -50$ mV, an action potential is generated and the membrane potential is reset to the resting potential V_{rest}, where it remains clamped for a 2-ms refractory period. The above parameter values in the two models are widely used in the literature.

It should be noted that we are interested in qualitative functions of the network motifs and we did not consider the quantitative correspondence between the two types of models in setting the parameters. By using other spiking neuron models—for example, the Izhikevich model [11]—we can also obtain similar results. For simplicity, we present the results of the IF neuron model in this Brief Report.

Since we do not know whether the neurons in the motifs in Figs. 1(a)–1(c) are excitatory or inhibitory, we consider all possible combinations of excitatory and inhibitory neurons in the motifs. In all motifs, we consider A as the input neuron and C as the output neuron. We use E and I to represent excitatory and inhibitory neurons, respectively.

The FFL is one of the most significant network motifs in many networks [1]. In the FFL, neuron A drives neuron B, and A and B both drive neuron C. As in [12], in studying the function of the FFL, we use the "simple drive" of C by A and B [Fig. 1(e)] as a reference of comparison.

Depending on whether neurons A and B are excitatory or inhibitory, there are four possible structural configurations of the FFL, but we have only found interesting results (in this Brief Report, by "interesting results," we mean that we can distinguish *functional* roles from these results) in the FFL with $(A, B, C) = (E, I, E)$ neurons, which is the so-called incoherent type-1 FFL (I1-FFL) [12]. It is interesting to notice that many neuron types in biological neural networks are indeed wired as I1-FFL [13].

In the firing-rate model, we let the time constant $\tau = 5$ ms. The input $I(t)$ to neuron A is shown in Fig. 2(a), and the input to neuron B is set to $I_y = 1$ for all times, in both the FFL and the simple drive. With the above setting of the parameters, the steady states of neuron C (when the input is ON) of the FFL and the simple drive are the same. In the integrate-and-fire model, we let the input to neuron A be a random variable of uniform distribution in $0-10$ nA during the ON period (between 20 ms and 60 ms) and the input to B as a constant of 10 nA. We use random input here simply because constant input will induce a trivial spike pattern. It should be noted that when constant input is applied to neuron A, we can get the same conclusion on the functional role. The simulation results are shown in Fig. 2. In Fig. 2(b) we show the firing rate of neuron C based on the firing-rate
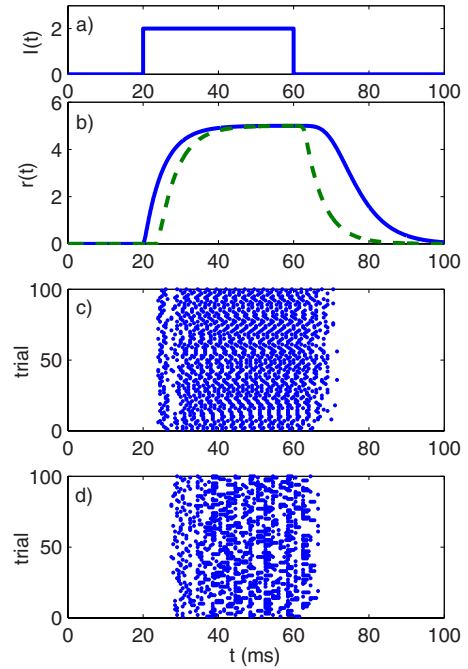

FIG. 2. (Color online) Functions of the feedforward loop (FFL): (a) Input to neuron A. (b) The firing rate of neuron C in the firing-rate model. Solid line: FFL. Dashed line: simple drive of C by A and B [Fig. 1(e)]. (c) Spike raster of the FFL of 100 trials. (d) Spike raster of the simple drive of 100 trials.

model. As we see, the FFL can both accelerate the response to the ON step and delay the response to the OFF step of the input to neuron A. The spike rasters of 100 trials produced by the integrate-and-fire model, as shown in Figs. 2(c) and 2(d), confirm the above observation.

In the case of the integrate-and-fire model, the spiking frequency of the output neuron is obviously affected by both the input current and the refractory period, so the absolute value of the spiking frequency is nonsensical. Besides, we are considering the qualitative logic function of the motif, and the quantitative spiking frequency will not affect our conclusion, so in this Brief Report, we do not calculate the spiking frequency.

Next, we study the motifs MFFL1 and MFFL2 shown in Figs. 1(b) and 1(c). We do not consider reference connection patterns here since, on the one hand, we did not find an appropriate comparison pattern; on the other hand, the dynamics (memory) does not depend on a comparison. In both network motifs, we set the time constants in Eq. (1) as $\tau = 10$ ms. There is no external input to neurons B and C.

In the MFFL1 motif, we let the input to neuron A of the IF model as a random variable of uniform distribution in $0-10$ nA during the ON period (between 20 ms and 60 ms).

When neurons $(A, B, C) = (E, E, E)$, the input to the firing-rate model, the firing rate of neuron C, and the spike raster are shown in Figs. 3(a)–3(c), respectively. As we see, in this connection configuration, the motif serves as a long-term memory circuit.

When neurons $(A, B, C) = (E, E, I)$, the motif functions as a short-term memory, as shown in Fig. 4. When the time constants τ in the firing-rate model and τ_1 and/or τ_2 in the
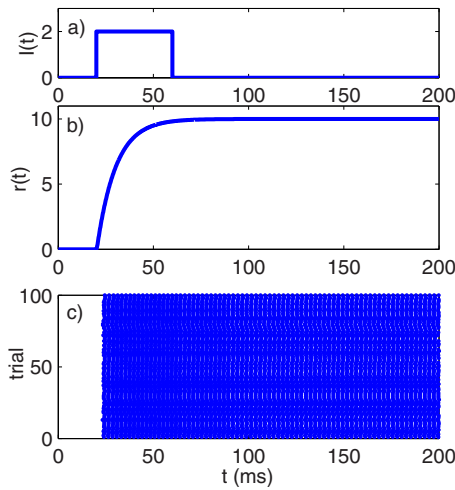
FIG. 3. (Color online) MFFL1 with neurons (A,B,C) $=(E,E,E)$ functioning as long-term memory: (a) the input to the firing-rate model, (b) the firing rate of neuron C, and (c) the spike raster of neuron C of 100 trials.

integrate-and-fire model are increased, the memory period will also be increased. For example, when the neurons $(A,B,C)=(E,E,I)$ and $\tau=\tau_1=\tau_2=20$ ms, the dynamics of the motifs are shown in Fig. 5, which confirms the above statement (when compared with Fig. 4).

In the MFFL2 motif, we need a strong input to active both neurons B and C in some connection configurations. We let the input to neuron A of the IF model be a random variable of uniform distribution in $0-50$ nA during the ON period (between 20 ms and 60 ms). Since in this motif both neurons A and B drive neuron C, we only need to consider whether neurons A and B are excitatory or inhibitory. When neurons $(A,B)=(E,E)$ and (E,I), the motifs can also function as long-term and short-term memories, respectively. The simulation results are shown in Figs. 6 and 7. When neurons $(A,B)=(E,I)$, by increasing the parameter values of τ and τ_1
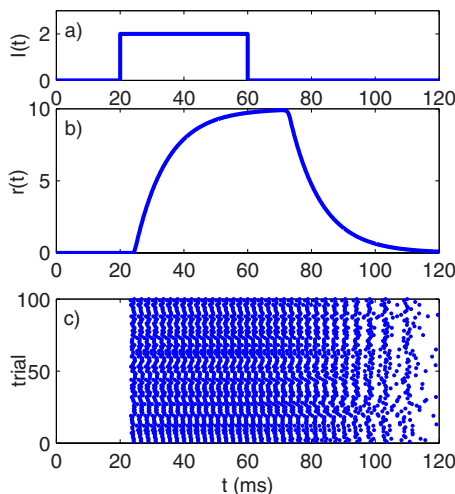

FIG. 4. (Color online) MFFL1 with neurons (A,B,C) $=(E,E,I)$ functioning as short-term memory: (a) the input to the firing-rate model, (b) the firing rate of neuron C, and (c) the spike raster of neuron C of 100 trials.
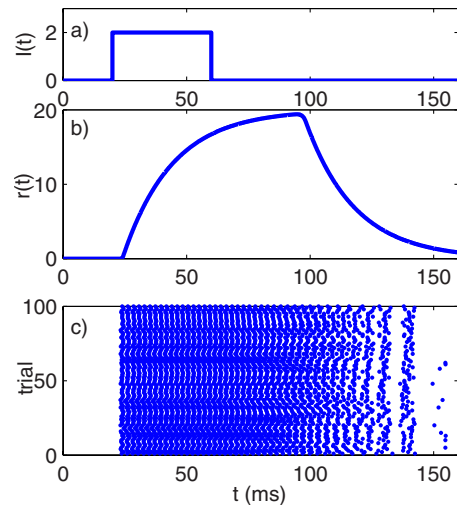

FIG. 5. (Color online) MFFL1 with neurons (A,B,C) $=(E,E,I)$ and $\tau=\tau_1=\tau_2=20$ ms: (a) the input to the firing-rate model, (b) the firing rate of neuron C, and (c) the spike raster of neuron C of 100 trials.

and/or τ_2, the memory period can also be prolonged. Since the results are quite similar to those in the above MFFL1 case, we omit the results here.

We did not find interesting functional roles in the other configurations of the MFFLs. Since long-term and short-term memories play important roles in almost all neural computation and cognition tasks, the above findings might to a certain degree explain the redundance of the MFFLs.

In summary, in this Brief Report, we studied the functions of neuronal network motifs and we have found some (though not as many as had been expected) interesting functional roles for them. We did not obtain as many functions as in genetic network motifs at least due to the following two reasons: (i) The experimental results on motifs in neuronal network are not as extensive as in genetic networks, so the number of motifs found in neuronal networks is itself less
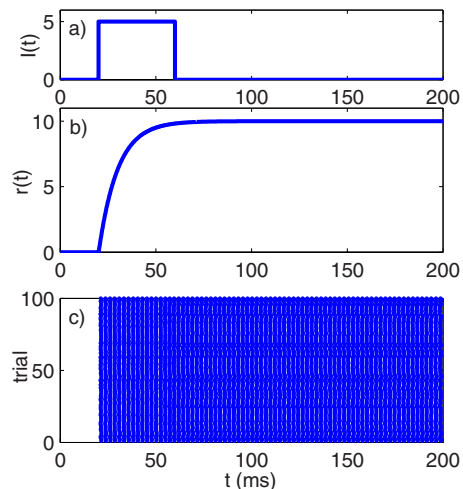

FIG. 6. (Color online) MFFL2 with neurons $(A,B)=(E,E)$ functioning as long-term memory: (a) the input to the firing-rate model, (b) the firing rate of neuron C, and (c) the spike raster of neuron C of 100 trials.
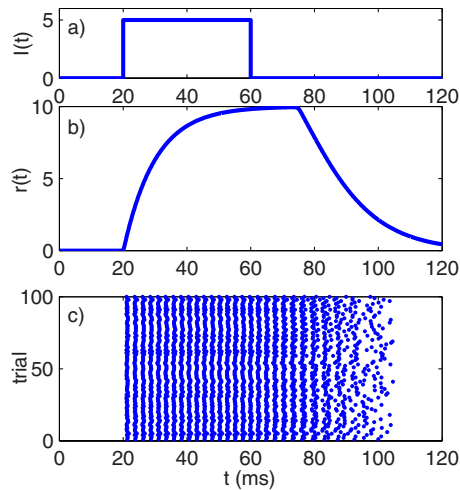
FIG. 7. (Color online) MFFL2 with neurons $(A,B)=(E,I)$ functioning as short-term memory: (a) the input to the firing-rate model, (b) the firing rate of neuron C, and (c) the spike raster of neuron C of 100 trials.

than that in genetic networks. (ii) In neuronal networks, the configurations of connection patterns are characterized by the excitatory and inhibitory properties of the neurons, but in genetic networks, the configurations are characterized by the activation and repression of the links, so the number of con-

figurations in neuronal network motifs is less than that in genetic network motifs. For example, in the FFL, if neuron A is excitatory, then it can *only excite* both neuron B and neuron C [though a (small) portion of neuroscientists do not agree with this]; in other words, the links $A \rightarrow B$ and $A \rightarrow C$ are both excitatory. But in genetic networks, the links (regulations) $A \rightarrow B$ and $A \rightarrow C$ are independent, so that gene A can *active* and *repress* genes B and C independently. Nevertheless, by the results found in this Brief Report, we can conclude that, as in genetic networks, motifs in neuronal networks can also play important functional roles. We do not exclude other possible functions. When more experimental results become available, by using more detailed models of neurons and synaptic connections, other dynamics and functions might be found.

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