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Mutual inhibition of lateral inhibition: a network motif for an elementary computation in the brain

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A series of classical studies in non-human primates has revealed the neuronal activity patterns underlying decision-making. However, the circuit mechanisms for such patterns remain largely unknown. Recent detailed circuit analyses in simpler neural systems have started to reveal the connectivity patterns underlying analogous processes. Here we review a few of these systems that share a particular connectivity pattern, namely mutual inhibition of lateral inhibition. Close examination of these systems suggests that this recurring connectivity pattern ('network motif') is a building block to enforce particular dynamics, which can be used not only for simple behavioral choice but also for more complex choices and other brain functions. Thus, a network motif provides an elementary computation that is not specific to a particular brain function and serves as an elementary building block in the brain.

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Introduction

Animals are routinely faced with the challenge of responding to available sensory information with an appropriate action that increases their chances of survival. One aspect of this challenge lies in the uncertainty of stimulus information [1]. In nature, animals are exposed to multiple and often competing sensory stimuli, each of which potentially calls for a different action. Even with respect to a single stimulus, it is often necessary to decisively categorize the stimulus so as to choose the appropriate action.

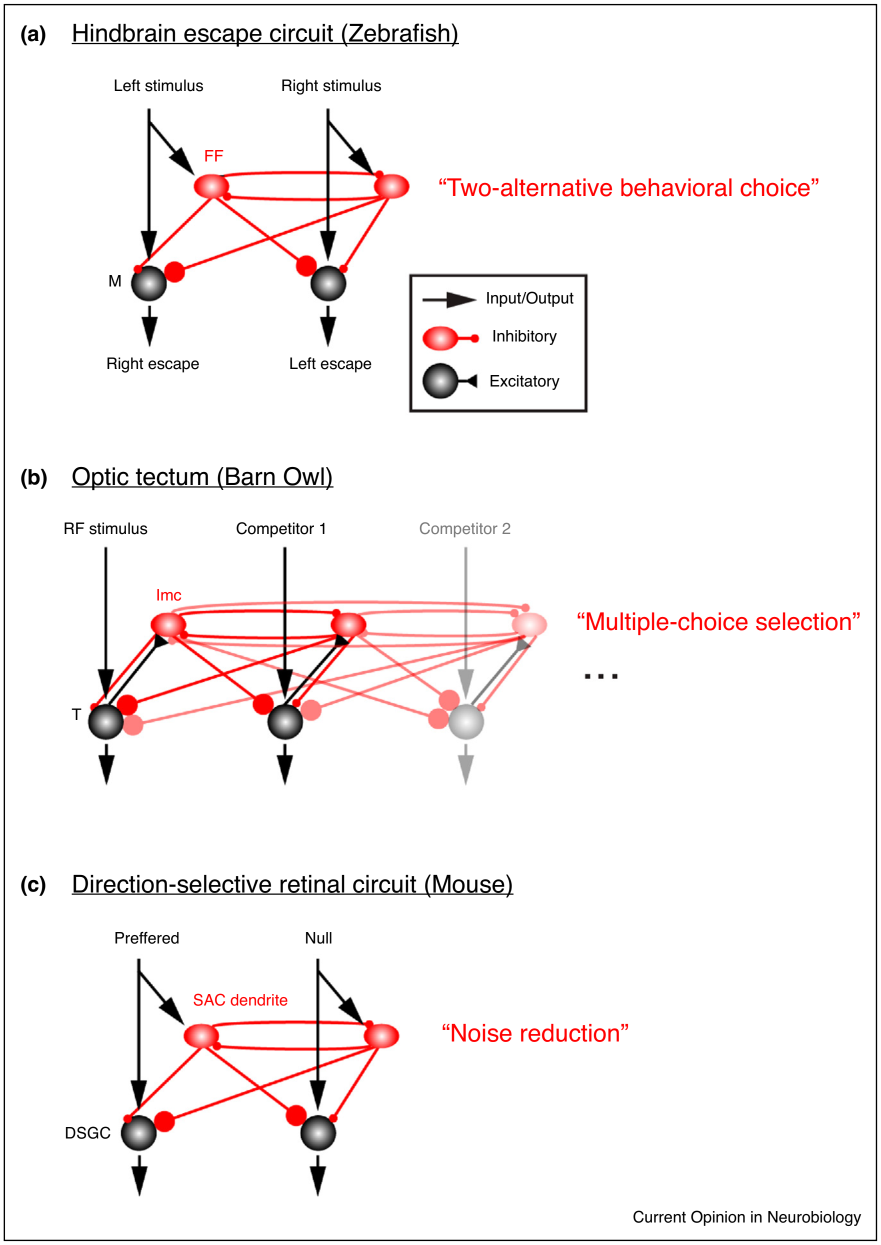
A series of classical studies in non-human primates has revealed the dynamics of neurons underlying such decision-making processes [2,3]. This inspired biophysical models that suggest potential circuit mechanisms [4–7]. However, the experimental evidence for these circuit mechanisms is still largely absent.

Recent detailed circuit analyses in simpler systems have started to reveal connectivity patterns involved in analogous processes [8••,9,10••,11••]. Here we review a few of these systems and note that they share a common connectivity pattern, namely mutual inhibition of lateral inhibition. Close examination of these systems further suggests that this connectivity pattern is a building block that enforces particular neuronal dynamics, and provides an elementary computation that can be used not only for simple behavioral choice but also for other brain functions. Such recurring patterns of interconnections in complex networks are often referred as network motifs [12] and have been shown to perform specific elementary computations in transcriptional networks [13]. Our review provides a concrete example of a 'network motif' in the nervous systems that performs a specific elementary computation and further suggests that 'network motifs' provide a useful level of abstraction to understand and communicate about circuit mechanisms in the brain.

A circuit mechanism for a two-alternative behavioral choice: mutual inhibition of lateral inhibition

The fast escape response in fish is a simple form of two-alternative behavioral choice [14]. To escape away from a potential predator (stimulus), fish choose the side of the initial large body bend based on the direction of the stimulus with respect to its own position [15]. However, in natural conditions, the direction of a stimulus is often ambiguous. For example, an auditory stimulus will enter both ears and the fish must choose which side to escape to based on possibly a small difference in the inputs from the two ears. How is this accomplished in the brain? Thanks to the relatively simple circuit organization controlling this behavior, experiments by Koyama and colleagues have provided insights into the underlying circuit mechanisms [8••]. The critical component of this circuit is a pair of large hindbrain descending neurons called Mauthner cells (M-cells) [14] (Figure 1a). A single action potential in one M-cell elicits the initial large body bend of escape by directly activating contralateral spinal motoneurons. Thus, the direction of escape is, to a large extent, determined by which M-cell spiked. In the auditory pathway, each M-cell directly receives excitatory inputs from the ipsilateral auditory nerve. However, inhibitory inputs come from both sides through bilaterally

Figure 1



Simplified diagrams of circuits with mutual inhibition of lateral inhibition. **(a)** Escape circuit in zebrafish. Connections from feedforward inhibitory neurons (FF) are highlighted in red. FF neurons strongly inhibit FF neurons and Mauthner cell (M) on the other side and play a critical role in two-alternative behavioral choice mediated by the circuit. **(b)** Tectum circuit in barn owl. Connections from midbrain inhibitory neurons in Isthmi Pars Magnocellularis (Imc) are highlighted in red. Imc neurons provide global inhibition to other Imc neurons and tectum output neurons (T) except the one that provided input and play a critical role in multiple-choice selection computed by the circuit. **(c)** Direction-selective circuit in mouse retina. Connections from starburst amacrine cells (SAC) are highlighted in red. SAC dendrites inhibit other SAC dendrites and direction-selective ganglion cells (DSGC) with opposite direction selectivity and make motion processing robust against noise.

projecting feedforward inhibitory neurons (FF neurons). This suggests that the balance of ipsilateral and contralateral inhibition may play a key role in the decision of escape direction.

By making triple whole-cell recordings of an FF neuron and bilateral M-cells, Koyama and colleagues showed that FF neurons inhibit the contralateral M-cell more strongly than the ipsilateral one [8••]. Biophysical simulations indicated that, at the level of postsynaptic potentials in M-cells, this lateral inhibition can accentuate the difference between the two sides. However, the simulations also indicated that strong bilateral stimulation recruits a large number of FF neurons from both sides and prevents