Asymmetric Inhibitory Connections Enhance Directional Selectivity in a Three-layer Simulation Model of Retinal Networks

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ABSTRACT

In this paper, we found that spatial and temporal asymmetricity of excitatory connections are able to generate directional selectivity which can be enhanced by asymmetrical inhibitory connections by reconstructing a hexagonally-arranged 3-layered simulation model of retina by NEURON simulator. Asymmetric excitatory inputs to ganglion cells with randomly arborizing dendrites were able to generate weaker directional selectivity to moving stimuli whose speed was less than 10 μm/msec. By just adding asymmetric inhibitory connections via inhibitory amacrine cells, directional selectivity became stronger to respond to moving stimuli at 10 times faster speed (< 100 μm /msec). In conclusion, an excitatory mechanism appeared to generate directional selectivity while asymmetric inhibitory connections enhance directional selectivity in retina..

INTRODUCTION

The directional selectivity is a unique function relating to agility that some portion of ganglion cells in the retina respond to moving light stimuli with specific direction and speed [*Ariel and Daw*, 1982; *Barlow et al.*, 1964]. It has been reported that inhibitory synaptic outputs from starburst amacrine cells to bistratified directional selective ganglion cells are playing critical role to make directional selectivity in the rabbit retina [*Taylor et al.*, 2000; *Fried et al.*, 2002]. Starburst amacrine cells have been a favorite subject for retina researchers since Tauchi and Masland reported [*Tauchi and Masland*, 1984], and several mechanisms for directional selectivity have been proposed [*Fried et al.*, 2005; *He and Masland*, 1997; *Euler et al.*, 2002; *Hausselt et al.*, 2007; *Poznanski*, 2005; *Yoshida et al.*, 2001; *Borg-Graham*, 2001; *Gavrikov et al.*, 2003; *Lee and Zhou*, 2006]. Recently, especially in rodent retina, several types of retinal ganglion cells were found to show directional selective light responses [*Kim et al.*, 2008; *Weng et al.*, 2005; *Huberman et al.*, 2009]. There might be not one, but several directionally selective ganglion cells involved to generate directional selectivity so that the mechanism for generating directional selectivity in retina was thought to be more complicated.

In the present study, to address a common mechanism capable of elucidating directional selectivity in the retina, we established theoretical hypothesis and conducted 3-layer simulation model for directional selectivity by using NEURON simulator [*Hines and Carnevale*, 2001].The reconstructed hexagonally-arranged retina consisted of bipolar cells and ganglion cells as well as inhibitory amacrine cells that sent inhibitory feed-forward signals to retinal ganglion cells. We proposed the hypothesis that asymmetric inhibitory inputs from amacrine cells to ganglion cells might play an important role in enhancing the sensitivity of directional selectivity, although these

inhibitory inputs were not necessarily required to generate directional selectivity. We have already reported the fundamental idea of this theoretical hypothesis previously from the theoretical point of view [*Takayasu et al.*, 2005]. Here, we provide details of our simulation to reinforce our theoretical hypothesis and present further discussion with recent advances in retinal neurophysiology.

METHODS

Neural network simulation using NEURON simulator

Three layers were reconstructed in the NEURON simulator [*Hines and Carnevale*, 2001]: bipolar cells layer, amacrine cells layer, and ganglion cells layer (see Figure 2). In each layer, neurons were located on a triangular lattice, and their somas were separated 100 μm apart. Three layers were overlapped with 50 μm distances. Glutamatergic excitatory synaptic inputs from photoreceptors to the bipolar cells were imitated by the alpha equation (tau = 2 msec, maximum conductance = 15 mS/cm^2). In order to simplify the model photoreceptors sent only excitatory synaptic outputs to bipolar cells when they received light stimuli. All bipolar cells depolarized with glutamate synaptic inputs in this simulation. Amacrine cells and ganglion cells received glutamate inputs from bipolar cells (maximum conductance = 400 $\mu S/cm^2$). Excitatory receptive fields of amacrine and ganglion cells were assumed to form symmetric soma-centered circle of diameter 800 μm. Anatomically, it is known that excitatory bipolar cells connecting to ganglion cells were located in a pattern of asymmetrical mosaic within a receptive field of ganglion cell. In order to take into account such non-uniform effect we chosen active connection with probability 50% from 61 input sites in the receptive filed by connecting these inputs sites with randomly arborizing dendrites of ganglion cells.

In this simulation, we made inhibitory amacrine cells which received excitatory inputs from 61 bipolar cells and sent feed-forward inhibitory outputs to ganglion cells. The amacrine cells were assumed to be starburst amacrine cells which have been shown to contribute to directional selectivity [*Fried et al.*, 2002; *Tauchi and Masland*, 1984; *Euler et al.*, 2002; *Yoshida et al.*, 2001], although the morphological features were not

necessarily consistent with those of real starburst amacrine cells. Inhibitory output signals from amacrine cells to ganglion cells were determined as GABAergic inhibitory synapses (maximum conductance = 50 μS/cm^2). In our numerical model the length of dendrites which conveyed inhibitory signal from amacrine cells to ganglion cells were limited to be less than 1000 μm, and their directions were chosen randomly. A single amacrine cell possessed three dendrites for inhibitory outputs to release inhibitory synaptic outputs to ganglion cells. The direction and length of output dendrites of each amacrine cell were determined randomly. In the model each bipolar cell has soma (diameter 10 μm, length 31.8 μm) and axon (diameter 3 μm, length 100 μm). An amacrine cell had soma (diameter 20 μm, length 20 μm) and dendrites (diameter 0.7 μm, various lengths). A ganglion cell had soma (diameter 20 μm, length 20 μm) and dendrites (diameter 0.7 μm, various lengths).

Electrophysiologically bipolar cells possessed only passive parameters (passive conductance 50 μS/cm^2, membrane capacitance 1 μF/cm^2, cytoplasmic resistance 100 Ωcm). Amacrine cells possessed passive parameters (passive conductance 50 μS/cm^2, membrane capacitance 1 μF/cm^2, cytoplasmic resistance 100 Ωcm) and four types of ionic currents; Hodgkin-Huxley type Na current (maximum conductance, gNa = 10 mS/cm^2), K current (gK = 3 mS/cm^2), persistent Na current (gNaP = 3 μS/cm^2) and Ca current (gCa = 35 μS/cm^2) and their properties were determined to be consistent with electrophysiological data reported previously [*Koizumi et al.*, 2001]. These mechanisms and parameters of active conductances were the same as that we used previously [*Koizumi et al.*, 2005]. In this simulation, other types of active conductances, which were found in the starburst amacrine cells, were not included because the simulation represented a caricature model of retinal directional selectivity. In the numerical model

these amacrine cells were able to generate action potentials with temporal delay preceded by the action potentials of ganglion cells when they received simultaneous synchronous light stimuli. Ganglion cells possessed passive parameters; two types of Hodgkin-Huxley type Na current ($gNa = 100\ mS/cm^2$) and K current ($gK = 10\ mS/cm^2$) generating the action potential with a certain threshold (around -45 mV). Simultaneous stimulation of all bipolar cells generated a single action potential in every ganglion cell at the onset of stimulation (ON type response). All ganglion cells had a center-ON (excitatory, 800 μm diameter) and surround-OFF (inhibitory) receptive field.

The total numbers of cells in our numerical simulation are 721, 397 and 397 for bipolar, amacrine and ganglion cells, respectively. This size was assumed to correspond to a retina tissue of radius 1500 μm.

RESULTS

The theoretical hypothesis: temporal and spatial asymmetricity of excitatory connections generate directional selectivity which can be enhanced by inhibitory asymmetrical connections.

First, we describe theoretical hypothesis that asymmetric excitatory and inhibitory connections can generate directional selectivity, but they have different roles. Especially, the hypothesis advances the excitatory mechanism for directional selectivity.

The fundamental idea of our hypothesis for directional selectivity [*Takayasu et al.*, 2005] can be understood by a simple diagram of retina's neural network schematically shown in Figure 1a. In the schematic drawing, photoreceptors send excitatory signal when they receive light stimuli. Bipolar cells receive excitatory signals from photoreceptors and send excitatory signals to both amacrine cells and ganglion cells. These amacrine cells are inhibitory and send feed-forward inhibitory signals to the ganglion cells.

Simplified schema is shown in Figure 1b where only a retinal ganglion cell and its inputs from two bipolar cells and an amacrine cell are shown. The time delay of inputs from the two bipolar cells (TA and TB) and the amacrine cell (TC) are supposed to be caused by synaptic delay along the neural network connections from photoreceptors and by latency of synaptic integration at each neuron. Spatial distance between two bipolar cell inputs (A and B) is determined as d and spatial distance between the bipolar cell (B) and the amacrine cell (C) is determined as d'.

First, we considered responses of the ganglion cell to a moving stimulus at the speed v, without the inhibitory input (C) to the ganglion cell (Figure 1b). We assumed that the ganglion cell's threshold level is a little above one-excitatory-input-level; the

ganglion cell can generate action potentials when two excitatory inputs overlap. When a moving stimulus moves from A to B with time difference *d/v*, the ganglion cell can respond if the inequality, TA – T0 < d/v + TB < TA+T0, is satisfied, where T0 is the duration time of an excitation (Figure 1c Top, Left). In the case that the moving stimulus moves from B to A, the condition that ganglion cell can respond is given similarly as, TB – T0 <*d/v* + TA<TB+T0, (Figure 1c, Top, Right). When T0 is larger than TA or TB, the left-hand sides of the previous inequalities are replaced by 0. When only one of these two conditions is satisfied, directional selective responses can be observed. For example, when TA>TB the ganglion cell responds only for a moving stimulus from left to right if the speed of moving stimulus *v* lies in the range between d/(T0+TA-TB) and d/(T0+TB-TA), while it does not respond to neither directions if the speed is smaller than d/(T0+TA-TB). However, the directional selective responses from the ganglion cell were lost for a high-speed movement satisfying v > d/(T0+TB-TA) (Figure 1c, Middle).

The case with an asymmetric inhibitory input (C) is shown in Figure 1b (dotted area). In this case, the ganglion cell receives two excitatory and one inhibitory inputs with time delays, TA, TB and TC, respectively. As shown in the bottom of Figure 1c the inhibitory input can shorten the duration time T0 of an excitatory input, and the directional selective function becomes active for much higher speed because the practical value of T0 can take a small value by tuning the distance and the time delay TC. Thus, the asymmetric inhibitory connection can enhance the response speed of directional selectivity in the retina.

In summary, from this theoretical hypothesis, we concluded that asymmetric excitatory inputs can generate directional selective responses in ganglion cells to

moving stimuli within a limited range of moving speed. Asymmetric inhibitory input can shorten the duration of excitation and make the ganglion cell respond to much higher speed of moving stimuli.

The hexagonally-arranged 3-layered simulation model of retina

In order to confirm these basic results of directional selectivity in the theoretical hypothesis, we reconstructed properties of retina as an ensemble of huge number of neurons by using NEURON simulator[*Hines and Carnevale*, 2001]. The NEURON simulator is a well-established numerical simulator of neural networks, in which electrophysiological properties of neurons can be described accurately. Here, we reconstructed a hexagonally-arranged 3-layered retinal neural network with 721 bipolar cells, 397 amacrine cells and 397 ganglion cells (Figure 2, see Methods in detail). We incorporated passive and active properties into these neurons. In order to simplify the model, we assumed that photoreceptors were just a receptor of light stimuli and sent glutamergic outputs to depolarize bipolar cells. Bipolar cells were non-spiking neurons, while ganglion cells were determined as spiking neurons. A bipolar cell sent excitatory outputs when it was excited. The bipolar cells had synaptic connections directly with ganglion cells and/or with amacrine cells. In this simulation, the speed of the signal spread on dendrites of inhibitory amacrine cells was determined as approximately 100 μm/msec according to previous models of cultured cells [*Koizumi et al.*, 2005; *Y Yamada et al.*, 2002]. In fact, in starburst amacrine cells, the speed of cytosolic calcium spread has been reported to reach 100 μm per 100 msec [*Poznanski*, 2010a]. (We will discuss the effect of the speed of signal spread on dendrites of amacrine cells later in Figure 5 and Discussion). Thus, initiation and spread of signals on dendrites of these

amacrine cells made temporal delay in synaptic outputs to ganglion cells. In addition, asymmetric expansion of dendrites of amacrine cells made asymmetric synaptic outputs to ganglion cells.

Asymmetricity of excitatory inputs was achieved by randomly arborizing dendrites of ganglion cells. Ganglion cells received excitatory inputs from bipolar cells which were only from bipolar cells above the randomly arborizing dendrites. The spatial randomness due to randomly arborizing dendrites caused time delays such as TA and TB with various distribution of distance *d* in the simulation model. Connections between ganglion cells and amacrine cells were randomly chosen. These randomly chosen inhibitory connections made temporal and spatial asymmetricity of inhibitory inputs to ganglion cells.

Asymmetric excitatory inputs were able to generate weaker directional selectivity

Figure 3a shows an example of spatial distribution of bipolar cells connected with a ganglion cell having asymmetric dendritic arbor receiving excitatory inputs but not with any inhibitory inputs from amacrine cells. Responses of this ganglion cell to moving stimuli at 5 μm/msec were displayed in Figure 3b for 6 directions. As expected the directional symmetry was broken due to the randomly arborizing dendrites. However, the strength of directional selectivity was rather small. Directional Selectivity Index (DSI) was calculated by dividing the length of the vector sum by the summed lengths of the component vectors [*Taylor et al.*, 2000]. DSI value of 1 would indicate complete directional selectivity. In Figure 3c, the distribution of DSI for 397 ganglion cells represented in a polar coordinate in the case of no inhibitory connections. Virtually all of ganglion cells showed less than 0.2 DSI.

Asymmetric inhibitory inputs enhanced the strength of directional selectivity

By adding an inhibitory connection as shown in Figure 4a the ganglion cell's response became more sensitive to the direction difference as demonstrated in Figure 4b. In Figure 4a, an inhibitory amacrine cell's dendritic field was surrounded by the blue dotted circle, while a blue line represents the connection between the amacrine cell and the ganglion cell. Responses of this ganglion cell to moving stimuli at 10 μm/msec were displayed in Figure 4b for 6 directions. In Figure 4b, blue shaded area in the circular graph represented the case with the inhibitory connection, and the red line in the circular graph represented the case without the inhibitory connections of the same ganglion cell. We found that the strong directional selective function of the ganglion cell disappeared only by neglecting the inhibitory connections. Comparing the distribution of the strength of DSI of all 397 ganglion cells in Figure 4c with Figure 3c where every ganglion cell had the same parameters except the inhibitory connections, it is clear that the inhibitory connections drastically enhanced the selective function.

The sensitivity for the speed of the moving stimuli was also enhanced by inhibitory connections.

Asymmetric inhibitory connections also enhanced the sensitivity for the speed of moving stimuli as well as the strength of DSI. In the case of no inhibitory connection the characteristic speed of directional selective function was estimated by the ratio of the interval of bipolar cells connecting to the same ganglion cell over the excitation input duration time, i.e., 100 μm (the minimum distance between bipolar cells) / 10 msec (an approximate duration time of excitation) = 10 μm/msec, in this simulation. In

our model retina the directional selective function could not be found for the moving speed faster than this characteristic speed for the case without the inhibitory bypass as shown in Figure 5a (red line).

In contrast, the directional selective function became active for more than 10 times higher speed by simply adding the inhibitory connections (blue curve in Figure 5a). The time delay of inhibitory connections, namely TC in Figure 1, was a key factor for making the wide range of speed sensitivity in this simulation. The main part of time delay TC consisted of two types of time delays in amacrine cells: excitation time delay and signal spread time delay (Figure 5b). In our simulation, excitation time delay was estimated as almost 10 msec. Time delay of signal spread depended on the speed of signal spread on dendrites of amacrine cells. Because in this simulation, the speed of the signal spread on dendrites of amacrine cells was approximately 100 μm/msec. When the speed of moving stimuli exceeded the speed of the signal spread on dendrites, the directional selectivity should disappear. Taken together, that is a reason why, in our simulation, the maximum speed of moving light stimuli was approximately 100 μm/msec (see Figure 5a).

DISCUSSION

We have found that temporal and spatial asymmetricity of excitatory inputs and inhibitory inputs have different roles in shaping directional selectivity in retina.

First, asymmetricity of excitatory inputs was enough to generate directional selectivity. However its generation was limited to moving stimuli at a certain range of speed. In addition, directional selective index was lower. Second, the inhibitory asymmetricity had important role in enhancing the agility of directional selective

responses. Inhibitory connection made ganglion cells more sensitive to moving stimuli with wide range of speed, about 10 times more agile. However, in our hypothesis, the speed of signal spread on dendrites of inhibitory amacrine cells determined the maximum speed of moving stimuli that were able to make directional selective responses in ganglion cells. These kinds of limitations probably were not in real retina. There should be more factors, which we ignored in this simulation, to enhance directional selectivity in retina.

In this simulation, we determined the speed of the signal spread on dendrites of amacrine cells as approximately 100 μm/msec. In starburst amacrine cells, Poznanski (2010a) has shown that speeds of cytosolic calcium spread can reach 100 μm per 100 msec under the hypothesis of the starburst amacrine cell having continuous endoplasmic reticulum. Of course, these speeds are not as fast as those used in this simulation; however, this suggests that calcium-mediated potentials might be propagating within such a speed in the dendrites of starburst amacrine cells given that cytosolic calcium is always an order or two slower than voltage.

One of the factors to potentially enhance the agility which we ignored here in this theoretical simulation was presynaptic feed-back inhibition from amacrine cells to bipolar cells. For example, transient local feed-back inhibitory mechanism was found in dendritic varicosities of A17 amacrine cells [*Chavez et al.*, 2006; *Grimes et al.*, 2010] and in starburst amacrine cells [*E S Yamada et al.*, 2003]. If such a transient local feed-back inhibitory mechanism works in between bipolar cells and amacrine cells which contribute to generate directional selectivity, the time delay in amacrine cells, namely Tc, could be much shorter and excitatory inputs themselves could be asymmetrically modulated. Anatomical and nerurophysiological evidences also supported this

prediction of the effect of presynaptic feed-back inhibition on directional selectivity [*Fried et al.*, 2005; *Borg-Graham*, 2001; Poznanski, 2010b]. These mechanisms very possibly also contribute to enhance directional selectivity in real retina.

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Figure legends

Figure 1 Theoretical hypotheses: how asymmetric excitatory and inhibitory connections make directional selectivity in the retina.

(a) Schematic view of information flow in the retina. Photoreceptors (dark rectangles) send synaptic outputs to bipolar cells (red circles) responding to moving stimuli. A bipolar cell has synaptic connections either directly with a ganglion cell (brown circle) or with an amacrine cell (blue circle) that makes an inhibitory output to the ganglion cell. **(b)** Simplified figure of the information paths. Two direct paths A and B, each having time delays TA and TB respectively, are located at distance *d*. An amacrine cell's inhibitory connection C located at distance *d'* from B transmits an inhibitory signal to the ganglion cell with time delay TC. **(c)** Time evolution of responses to moving stimuli at A, B and C paths, and the amplitude of integrated response at the ganglion cell (A+B+C). Each dark triangle indicates the time that the photoreceptor receives moving stimulus. Top: (Left): In the case the stimulus moves from A to B the sum of synaptic inputs exceeds the ganglion's threshold level (dotted line) and the ganglion cell fires (shaded area), however, in the opposite direction case the ganglion cell does not fire (Right). Middle: (Left and Right) When the speed of the stimulus is high enough the ganglion cell fires for both directions. Bottom: Adding the inhibitory synaptic input through path C the ganglion cell fires for the stimulus moving from A to B to C as before, however, it does not respond to the high speed stimulus motion from C to A, namely, the directional selectivity recovers.

Figure 2. The hexagonally-arranged 3-layered simulation model of retina.

(a) Three layers, bipolar, amacrine and ganglion cells, were reconstructed. This figure simply shows partial connections between cells, ignoring dendritic structure of each cell. **(b)** In each layer, cells were located on a triangular lattice, and their somas were separated 100 µm apart. Three layers were overlapped with 50 µm distances. See Methods in detail.

Figure 3. Response of ganglion cells without inhibitory connections.

(a) An example of randomly arborizing dendrites of a ganglion cell and resulting asymmetric spatial distribution of connecting bipolar cells. **(b)** Direction dependence of the ganglion cell's responses. The speed of the moving stimulus was 5 µm/msec on the retina. The circular graph shows a polar coordinate representation of the numbers of output pulses for each direction. For comparison, the case that all bipolar cells were stimulated simultaneously the ganglion generated action potential (Synchronous). **(c)** The distribution of directional selectivity indices (DSI) for 397 ganglion cells represented in a polar coordinate. Each DSI is defined by the vector sum of the polar diagram in (b) normalized by the total spike numbers. The DSI value is 1 when the ganglion cell fires in only one direction.

Figure 4. Response of ganglion cells with inhibitory connections.

(a) An example of randomly arborizing dendrites of a ganglion cell and an inhibitory input via an amacrine cell. **(b)** Direction dependence of the ganglion cell's response. The speed of the moving stimulus was 10 µm/msec on the retina. The blue shaded part in the circular graph shows the case with inhibitory connections and the red line

represents the case neglecting the inhibitory connection with identical bipolar cells' connection. **(c)** The distribution of DSI for 397 ganglion cells.

Figure 5. The maximum DSI values as functions of speed of the moving stimuli. **(a)** A blue line shows an typical example of ganglion cell's directional selective response with the inhibitory connection and a red line is that with no inhibitory connection.**(b)** Schematic vertical view of an amacrine cell. Time delay in amacrine cells, namely TC in Figure 1b, consisted of two components: excitation time delay and signal spread time delay. In this simulation, the speed of directional selective moving stimuli could not exceed that of the signal spread on dendrites (100 μm/msec).

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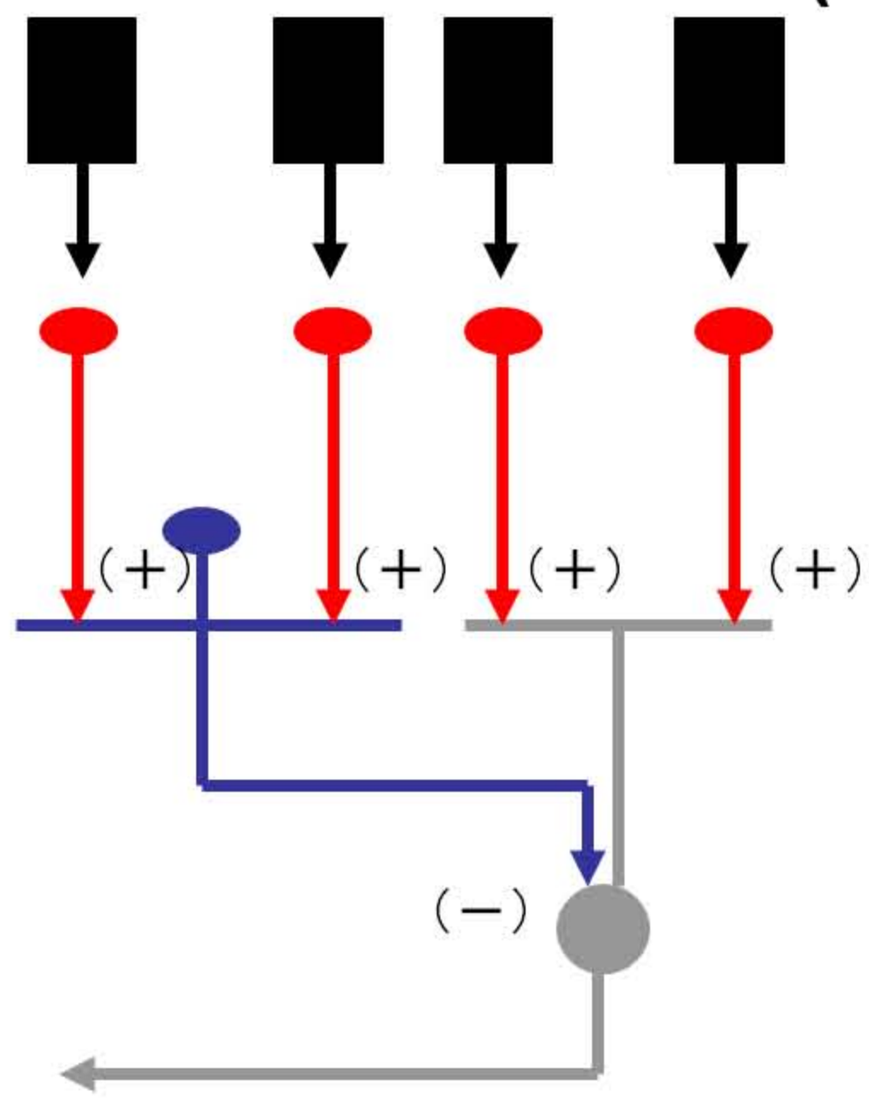
(a)



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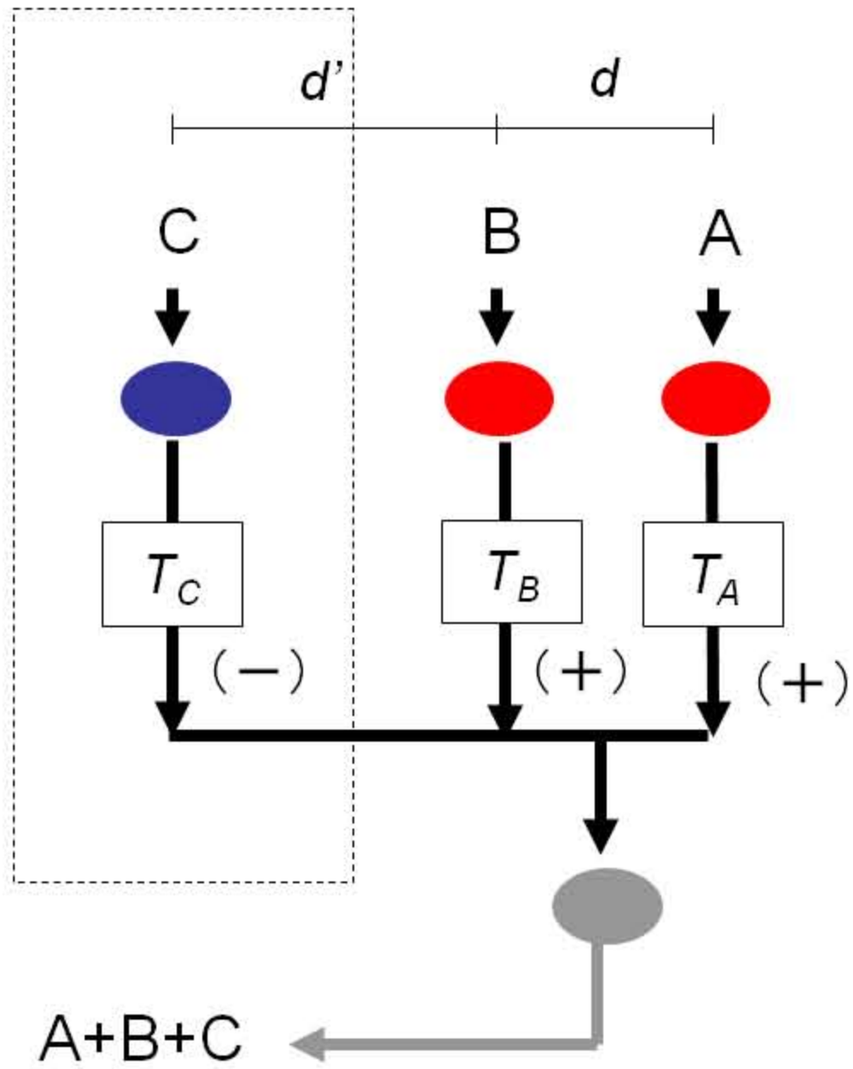
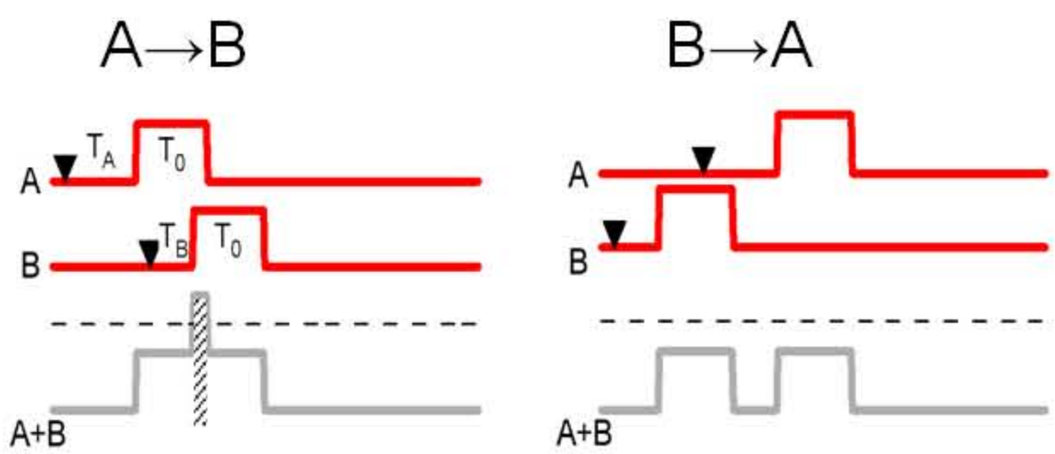


(c)

No Inhibitory Input
Low Speed Stimulus



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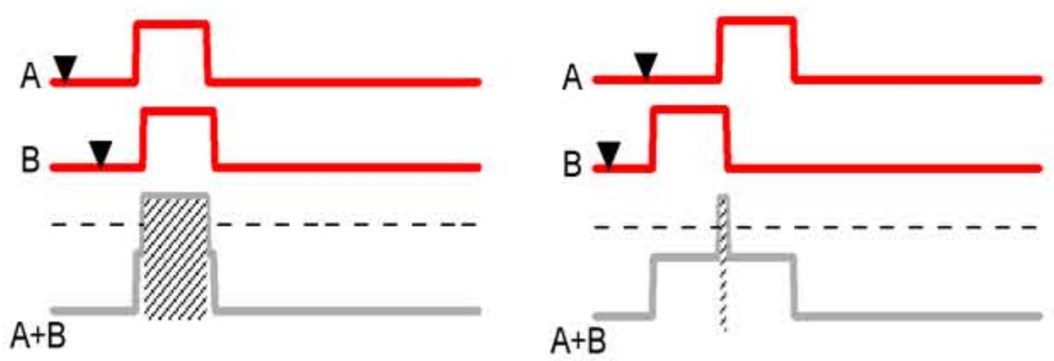

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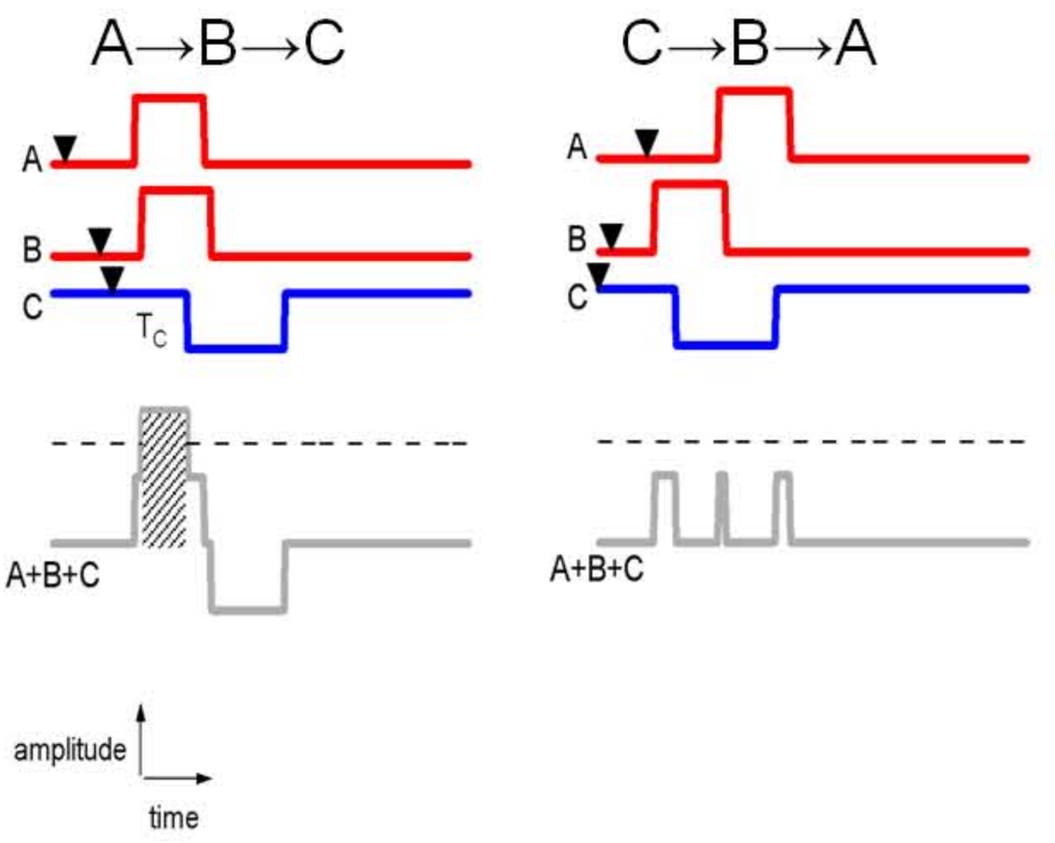


Figure 1

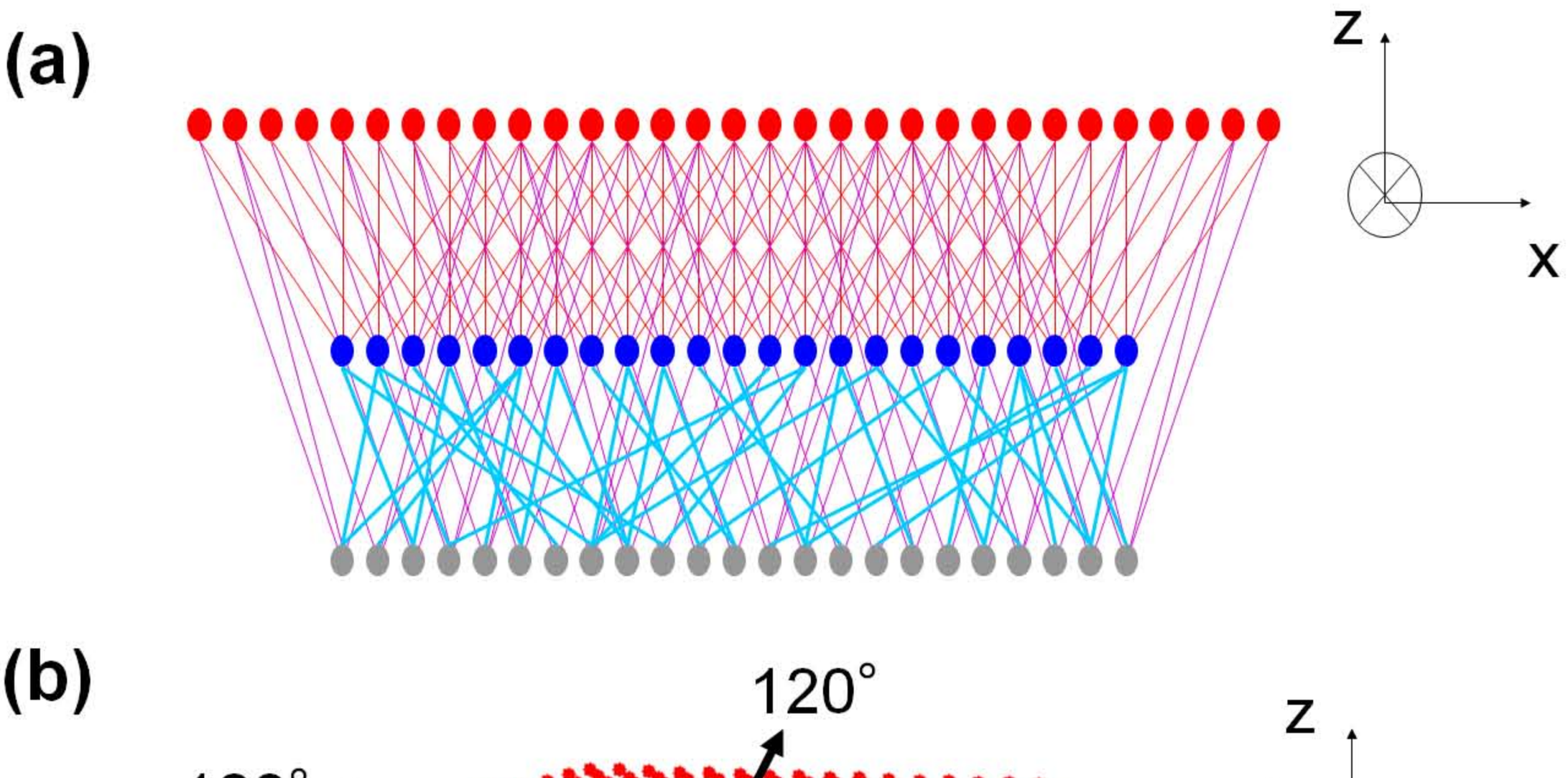
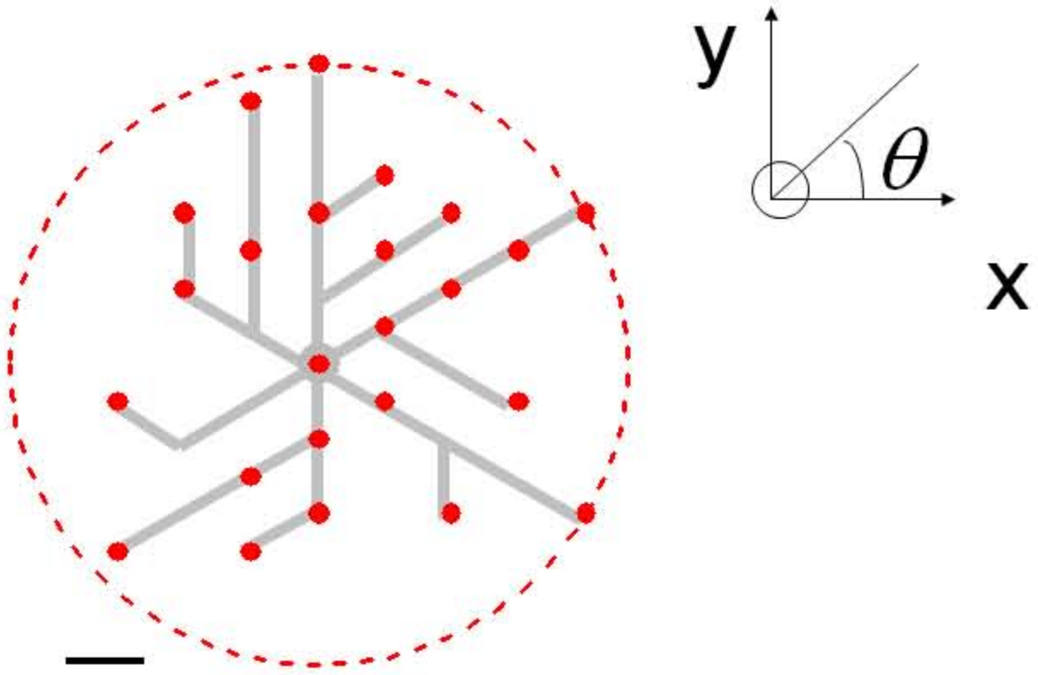
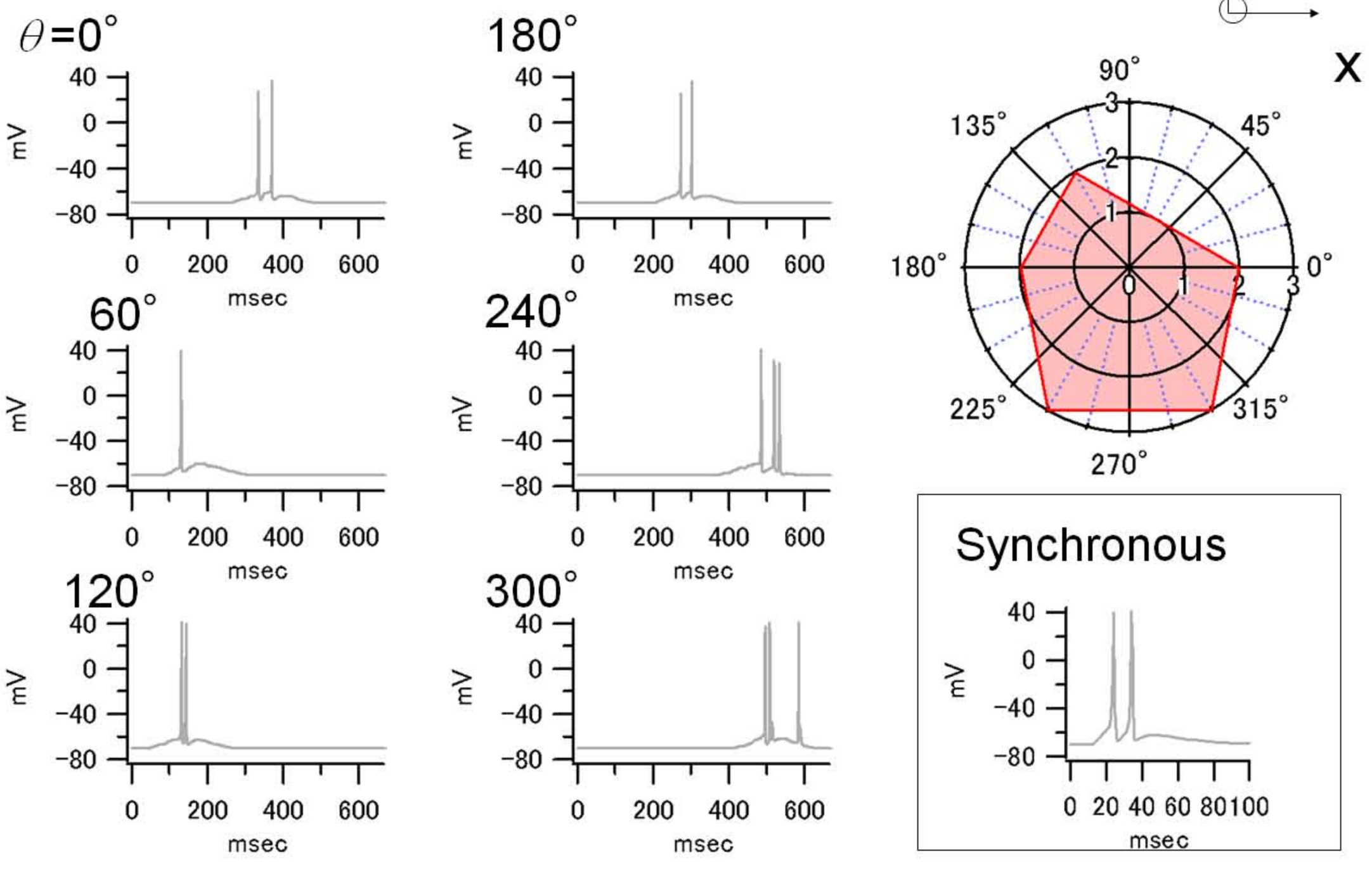


Figure 2

(a)



(b) v = 5 μm/msec



(c)

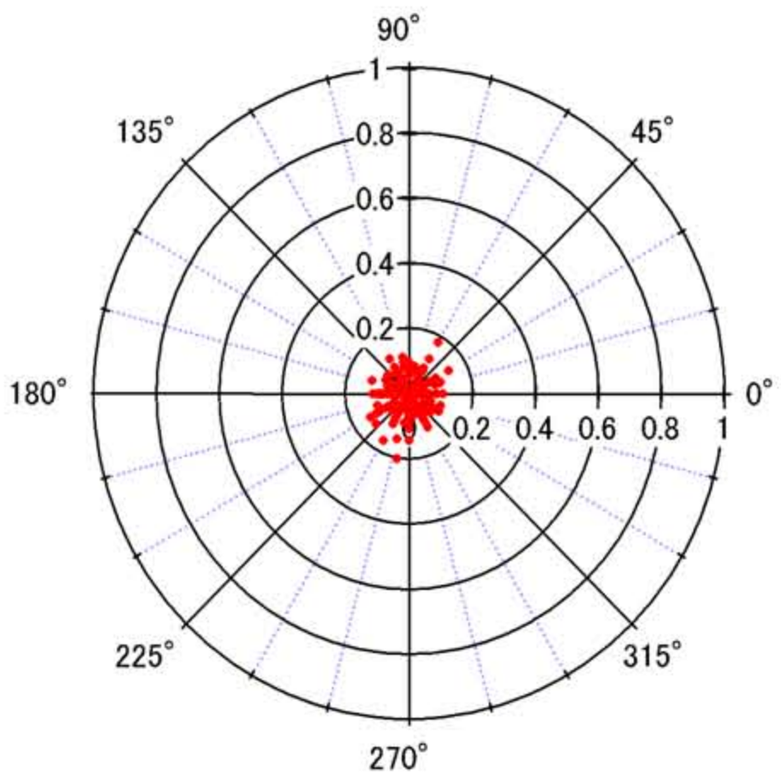
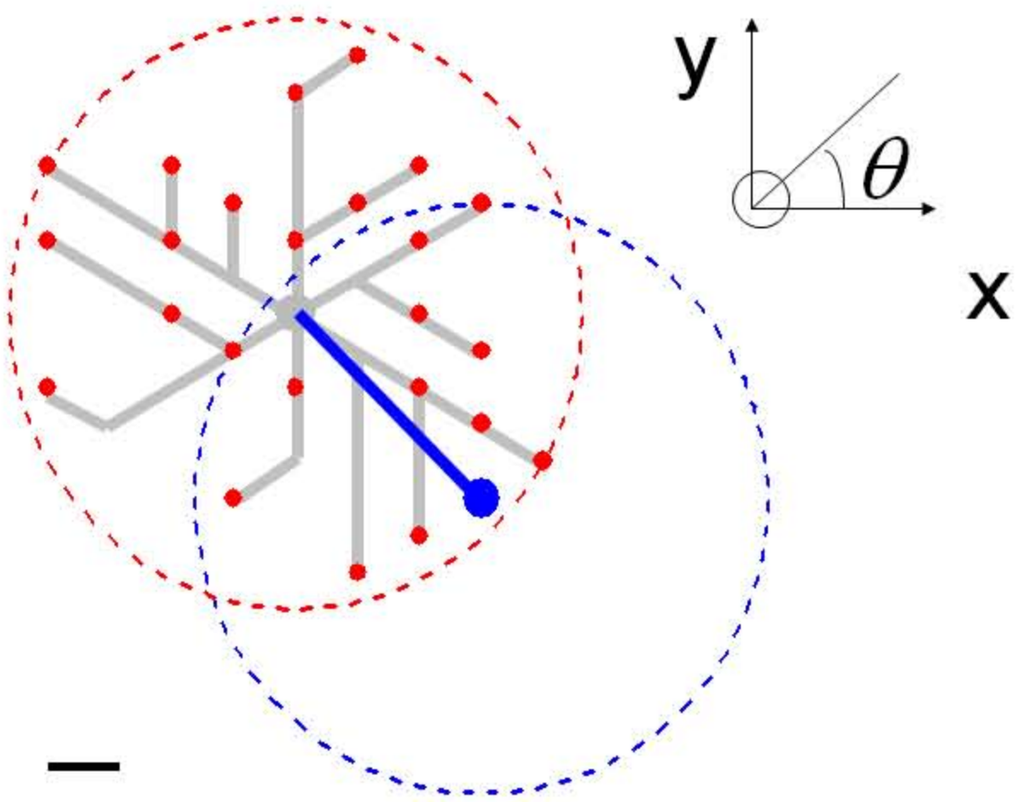


Figure 3

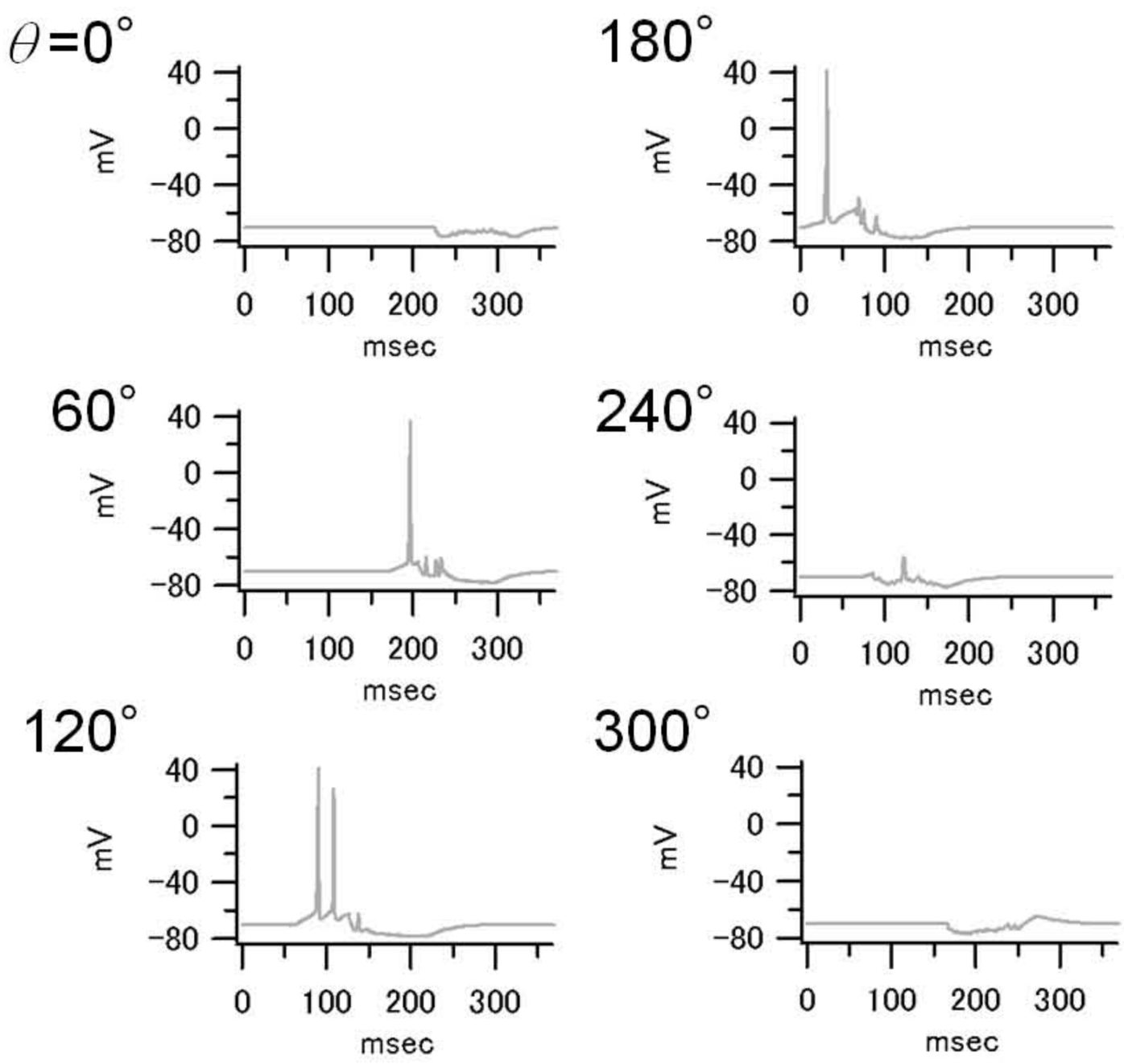
(a)

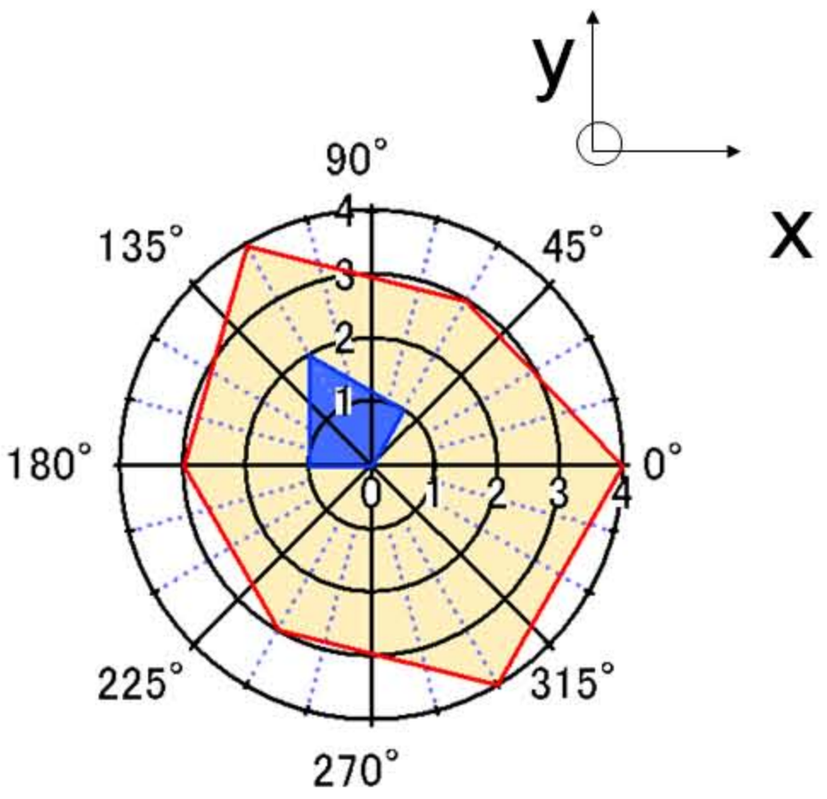


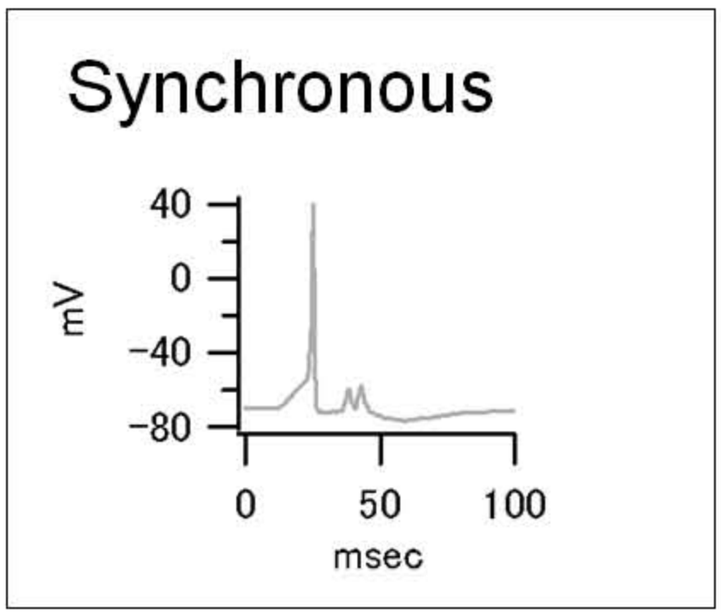
100 μm

(b)

v = 10 μm/msec







(c)

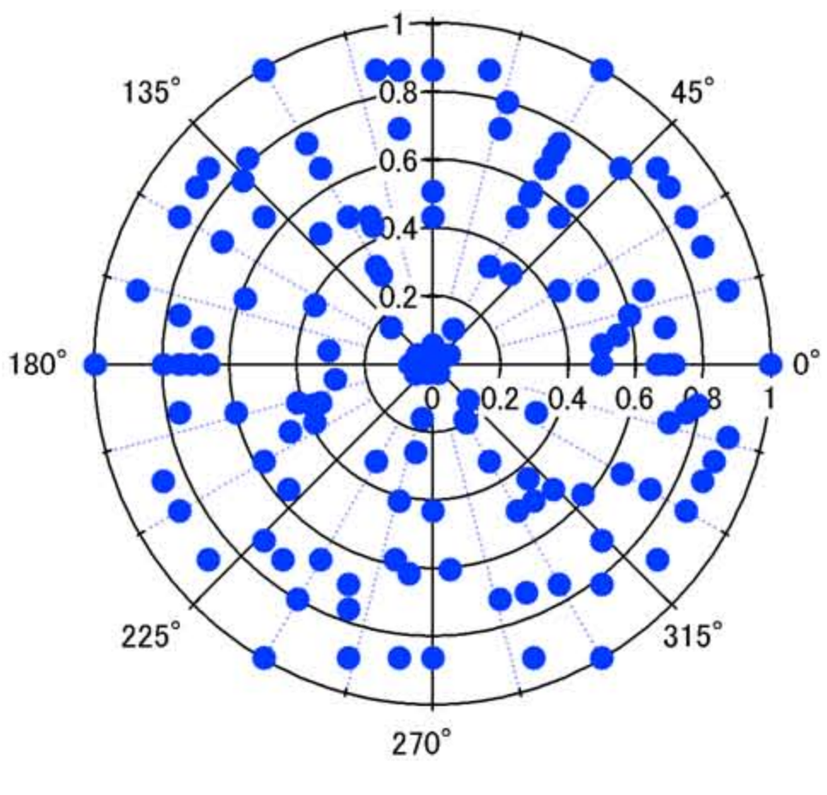


Figure 4

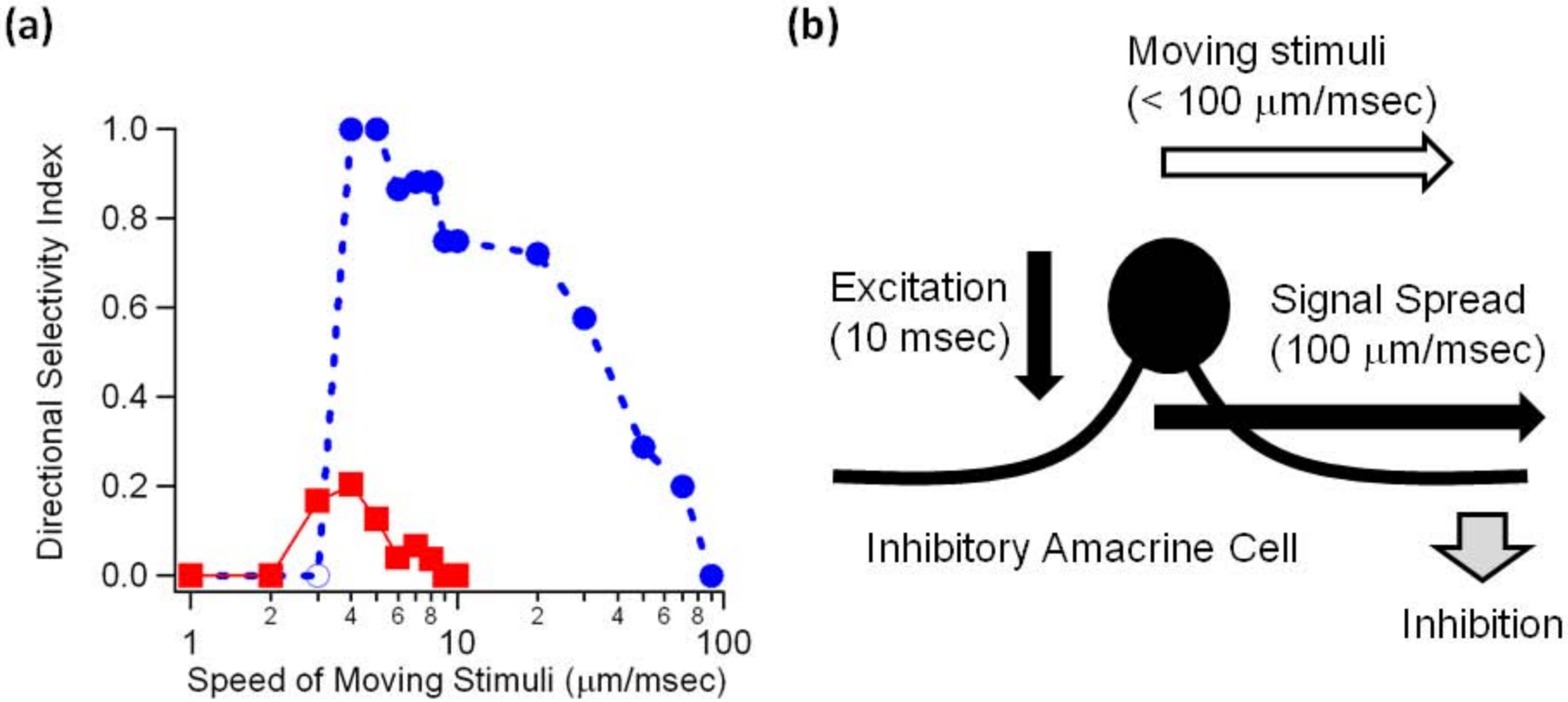

(a)
Directional Selectivity Index
1.0
0.8
0.6
0.4
0.2
0.0
1
2
4
6
8
10
2
4
6
8
100
Speed of Moving Stimuli (μm/msec)
(b)
Moving stimuli
(< 100 μm/msec)
Excitation
(10 msec)
Signal Spread
(100 μm/msec)
Inhibitory Amacrine Cell
Inhibition

Figure 5