Cross-compartmental Modulation of Dendritic Signals for Retinal Direction Selectivity: Part I

David Koren, James Grove and Wei Wei

Aman Chawla

University of Colorado at Denver

September 6, 2018

1. The Starburst Amacrine Cells (SACs) receive glutamatergic inputs from the bipolar cells.
2. From their distal varicosities, they release the neurotransmitters GABA and Acetylcholine so as to provide output to Direction Selective Ganglion Cells (DSGCs).
3. The directionally selective response of the SACs is unexplained.

1. The Starburst Amacrine Cells (SACs) receive glutamatergic inputs from the bipolar cells.
2. From their distal varicosities, they release the neurotransmitters GABA and Acetylcholine so as to provide output to Direction Selective Ganglion Cells (DSGCs).
3. The directionally selective response of the SACs is unexplained.

1. The Starburst Amacrine Cells (SACs) receive glutamatergic inputs from the bipolar cells.
2. From their distal varicosities, they release the neurotransmitters GABA and Acetylcholine so as to provide output to Direction Selective Ganglion Cells (DSGCs).
3. The directionally selective response of the SACs is unexplained.

1. There are 4 main explanations in the literature:
2. The distribution of active conductances in different sectors of the dendrites.
3. The targeting of proximal regions of the dendrite by bipolar cells to provide their glutamatergic inputs.
4. The segregation of inputs from distinct bipolar cells.
5. Lateral inhibition from neighboring SACs and non-SAC amacrine cells.

1. There are 4 main explanations in the literature:
2. The distribution of active conductances in different sectors of the dendrites.
3. The targeting of proximal regions of the dendrite by bipolar cells to provide their glutamatergic inputs.
4. The segregation of inputs from distinct bipolar cells.
5. Lateral inhibition from neighboring SACs and non-SAC amacrine cells.

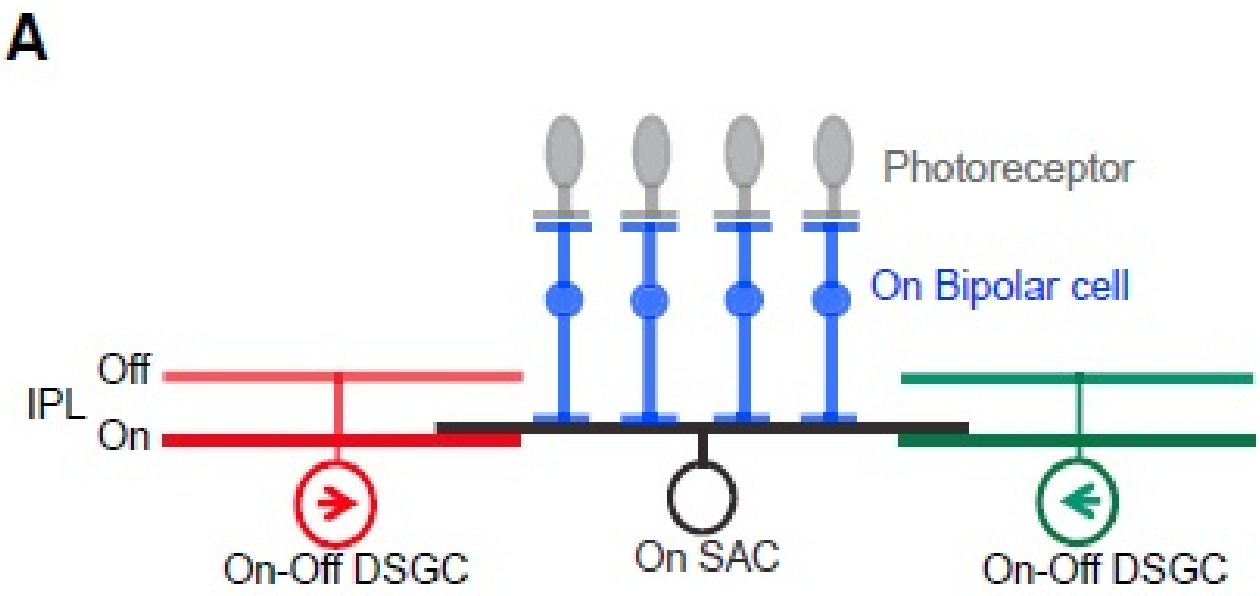
1. There are 4 main explanations in the literature:
2. The distribution of active conductances in different sectors of the dendrites.
3. The targeting of proximal regions of the dendrite by bipolar cells to provide their glutamatergic inputs.
4. The segregation of inputs from distinct bipolar cells.
5. Lateral inhibition from neighboring SACs and non-SAC amacrine cells.

1. There are 4 main explanations in the literature:
2. The distribution of active conductances in different sectors of the dendrites.
3. The targeting of proximal regions of the dendrite by bipolar cells to provide their glutamatergic inputs.
4. The segregation of inputs from distinct bipolar cells.
5. Lateral inhibition from neighboring SACs and non-SAC amacrine cells.

1. There are 4 main explanations in the literature:
2. The distribution of active conductances in different sectors of the dendrites.
3. The targeting of proximal regions of the dendrite by bipolar cells to provide their glutamatergic inputs.
4. The segregation of inputs from distinct bipolar cells.
5. Lateral inhibition from neighboring SACs and non-SAC amacrine cells.

1. Directionally tuned inhibition from SACs to DSGCs is generated by selective wiring between SACs and DSGCs along with the centrifugal preference of the SAC dendrites.
2. A single quadrant of the SAC dendritic tree can form inhibitory synapses with only a single subtype of On-Off DSGC.

1. Directionally tuned inhibition from SACs to DSGCs is generated by selective wiring between SACs and DSGCs along with the centrifugal preference of the SAC dendrites.
2. A single quadrant of the SAC dendritic tree can form inhibitory synapses with only a single subtype of On-Off DSGC.



1

Figure: Structure of the retinal wiring

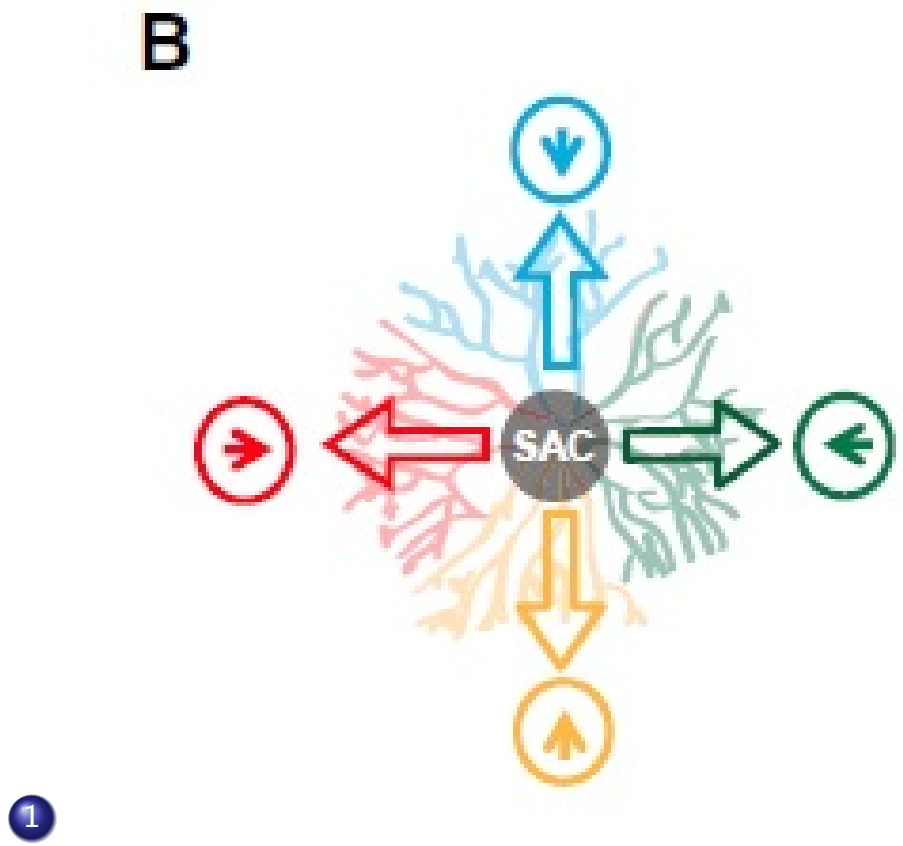


Figure: Top View of the wiring

1. By using stationary light flashes which lit only one sector of the dendritic arbor, the authors were able to demonstrate electrical isolation of SAC dendrites.
2. This isolation is important since otherwise centrifugal activation of an illumined dendrite could spread to a nonillumined area and perhaps cause centripetal activation.

1. By using stationary light flashes which lit only one sector of the dendritic arbor, the authors were able to demonstrate electrical isolation of SAC dendrites.
2. This isolation is important since otherwise centrifugal activation of an illumined dendrite could spread to a nonillumined area and perhaps cause centripetal activation.

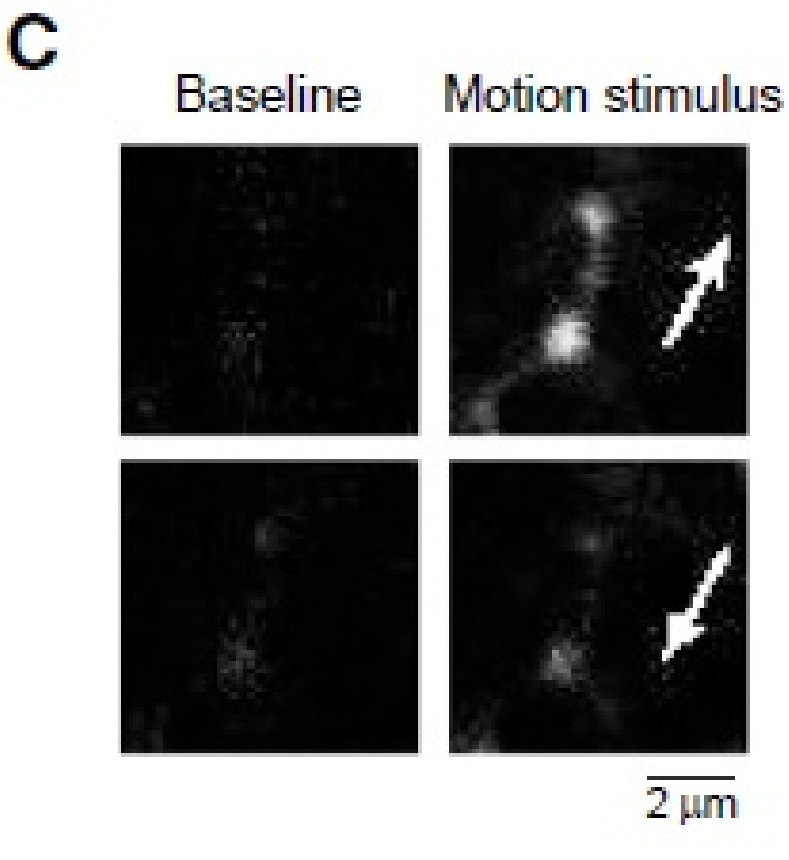


Figure: Baseline vs Motion Stimulus response for Centripetal and Centrifugal cases

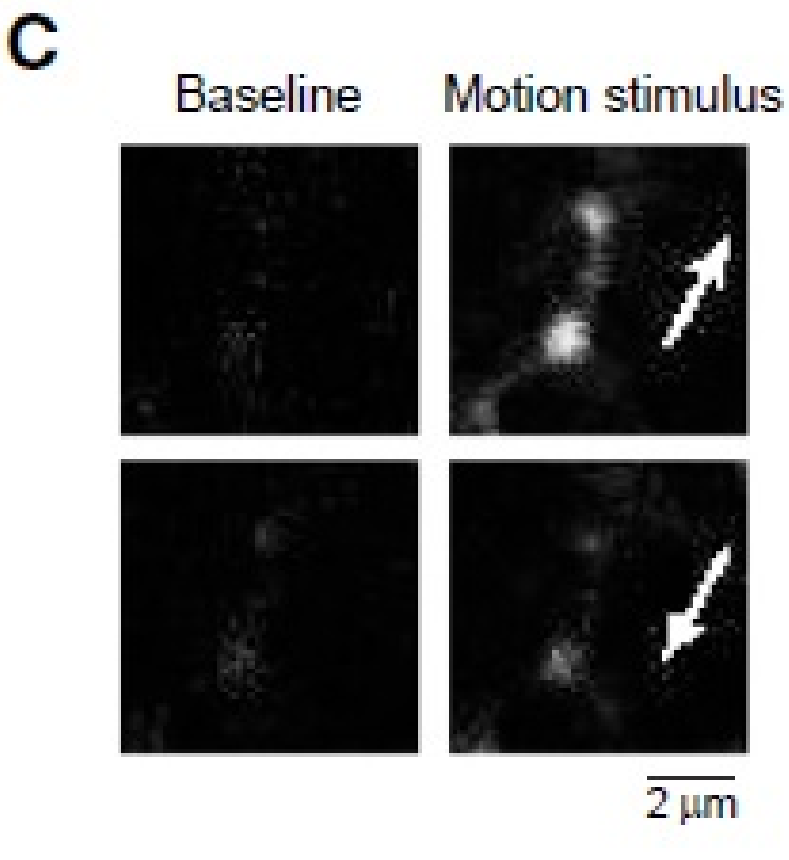
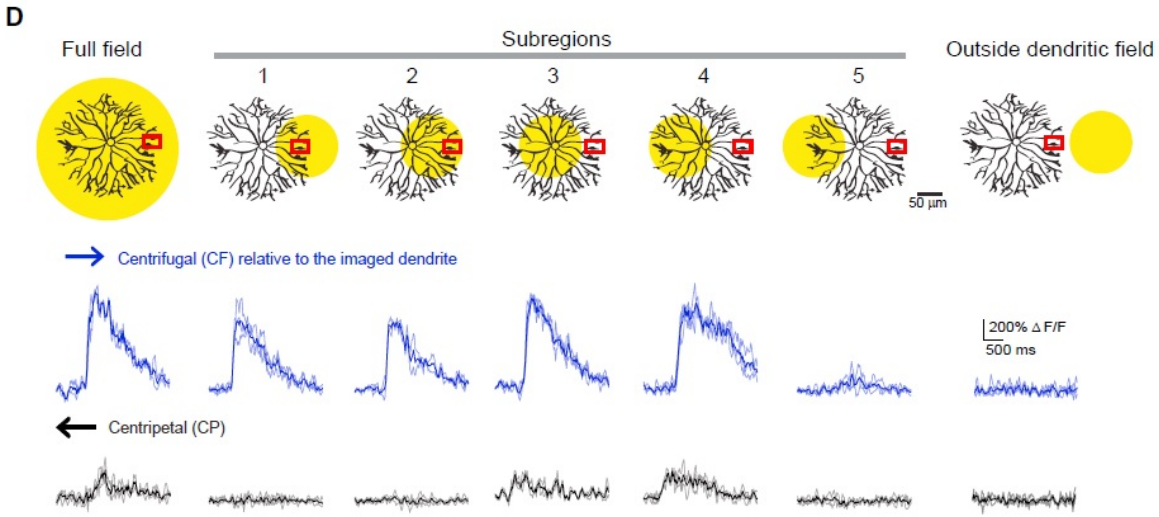


Figure: Baseline vs Motion Stimulus response for Centripetal and Centrifugal cases

1. Because dendritic sectors are electrotonically isolated we think that the strong centrifugal response arises solely from local dendritic processing.
2. However, by favorable spatiotemporal summation, the signals, integrated from multiple dendritic sectors, can enhance the response of a centrifugally stimulated branch.

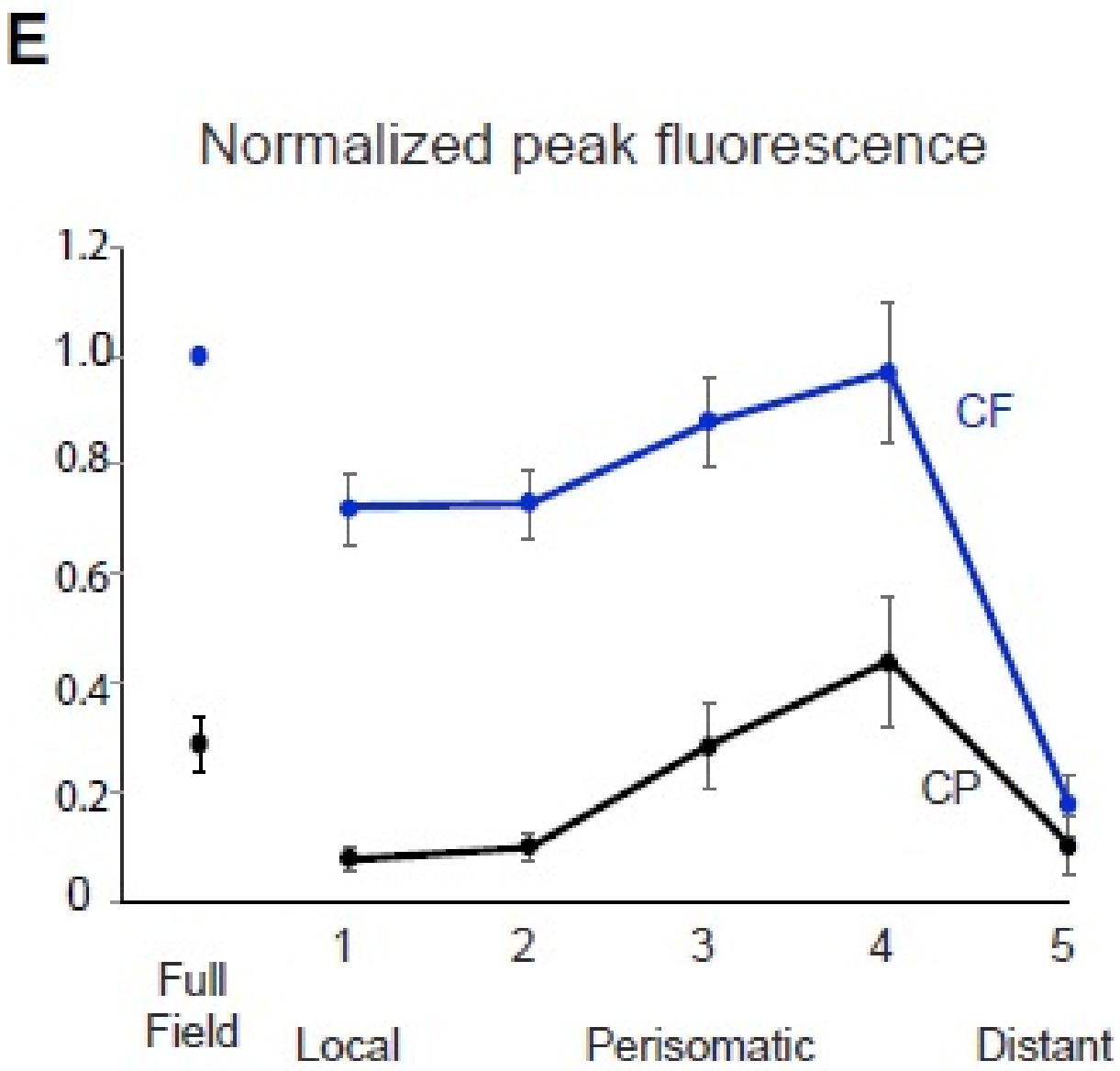
1. Because dendritic sectors are electrotonically isolated we think that the strong centrifugal response arises solely from local dendritic processing.
2. However, by favorable spatiotemporal summation, the signals, integrated from multiple dendritic sectors, can enhance the response of a centrifugally stimulated branch.



1

Figure: Centrifugal vs Centripetal response to various spots, full and local.

1. The importance of multicompartmental signal integration is demonstrated by comparing the response to full-field stimuli with the response to local, single sector stimulation.



1

Figure: Fluorescence of the labeled cell

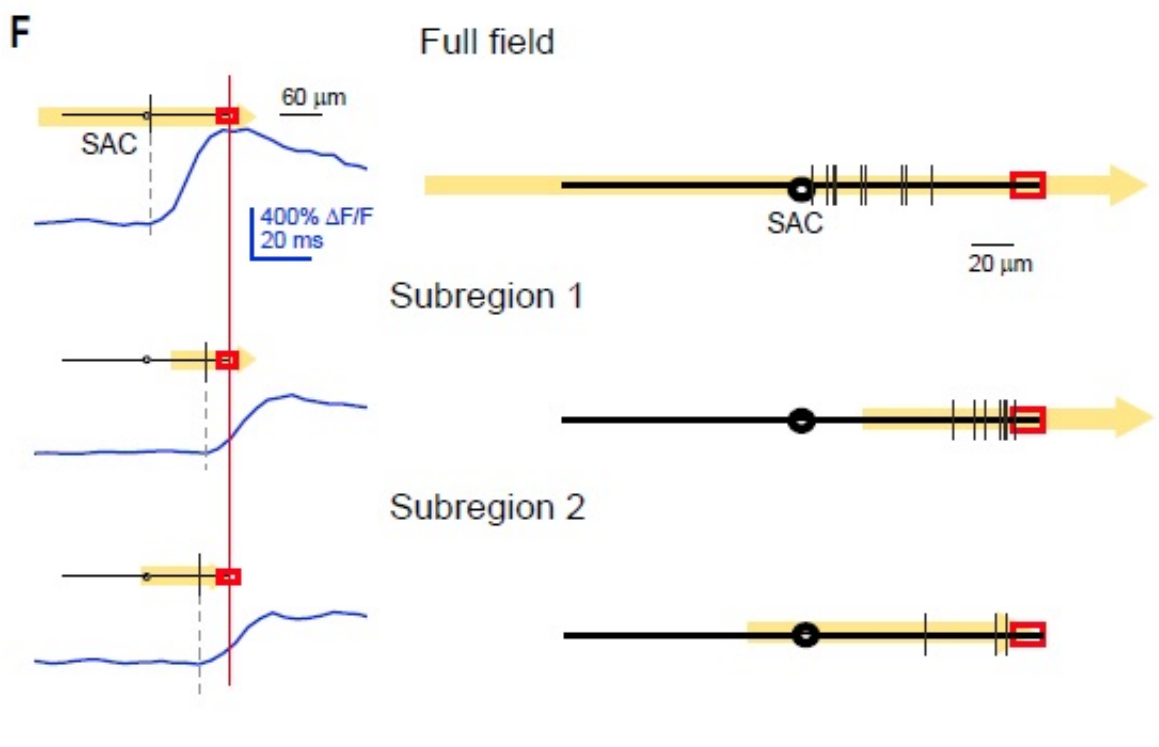


Figure: Earlier onset in full field case in the centripetal direction; later onset and lower amplitude for the local responses.

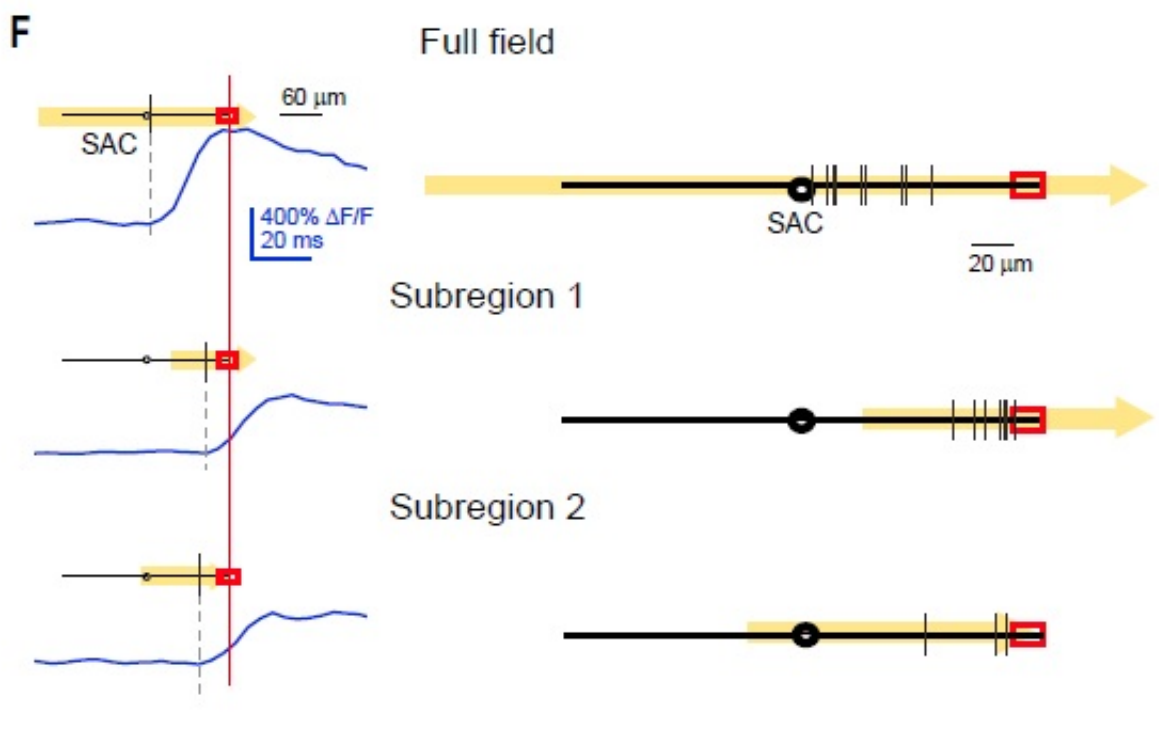


Figure: Earlier onset in full field case in the centripetal direction; later onset and lower amplitude for the local responses.

1. The regulatory mechanism that sets the fine balance between signal isolation and propagation between dendritic sectors is unknown.
2. A prime candidate is metabotropic glutamate receptor 2.
3. It is expressed in SAC dendrites postsynaptically to bipolar cell inputs
4. It promotes neuronal excitability by modulating voltage gated ion channel conductances.
5. It is primarily implicated in cross-sector signal propagation as opposed to local processing.
6. Suppressing mGluR2 signaling alters cross-sector signal propagation which impacts the functional output of the circuit.

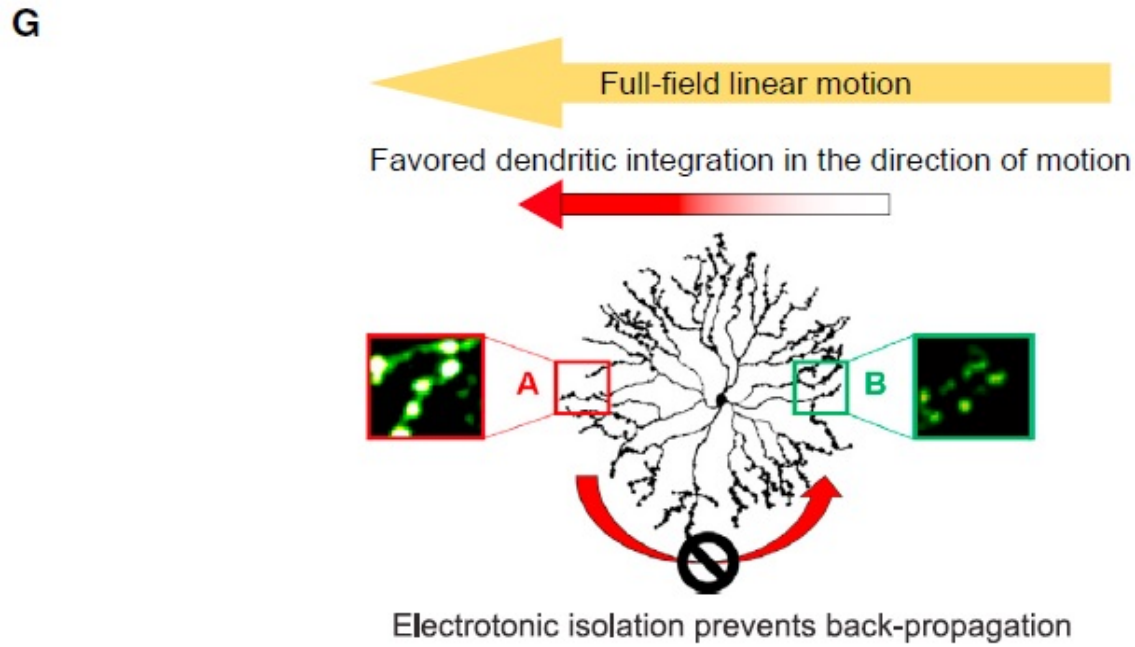
1. The regulatory mechanism that sets the fine balance between signal isolation and propagation between dendritic sectors is unknown.
2. A prime candidate is metabotropic glutamate receptor 2.
3. It is expressed in SAC dendrites postsynaptically to bipolar cell inputs
4. It promotes neuronal excitability by modulating voltage gated ion channel conductances.
5. It is primarily implicated in cross-sector signal propagation as opposed to local processing.
6. Suppressing mGluR2 signaling alters cross-sector signal propagation which impacts the functional output of the circuit.

1. The regulatory mechanism that sets the fine balance between signal isolation and propagation between dendritic sectors is unknown.
2. A prime candidate is metabotropic glutamate receptor 2.
3. It is expressed in SAC dendrites postsynaptically to bipolar cell inputs
4. It promotes neuronal excitability by modulating voltage gated ion channel conductances.
5. It is primarily implicated in cross-sector signal propagation as opposed to local processing.
6. Suppressing mGluR2 signaling alters cross-sector signal propagation which impacts the functional output of the circuit.

1. The regulatory mechanism that sets the fine balance between signal isolation and propagation between dendritic sectors is unknown.
2. A prime candidate is metabotropic glutamate receptor 2.
3. It is expressed in SAC dendrites postsynaptically to bipolar cell inputs
4. It promotes neuronal excitability by modulating voltage gated ion channel conductances.
5. It is primarily implicated in cross-sector signal propagation as opposed to local processing.
6. Suppressing mGluR2 signaling alters cross-sector signal propagation which impacts the functional output of the circuit.

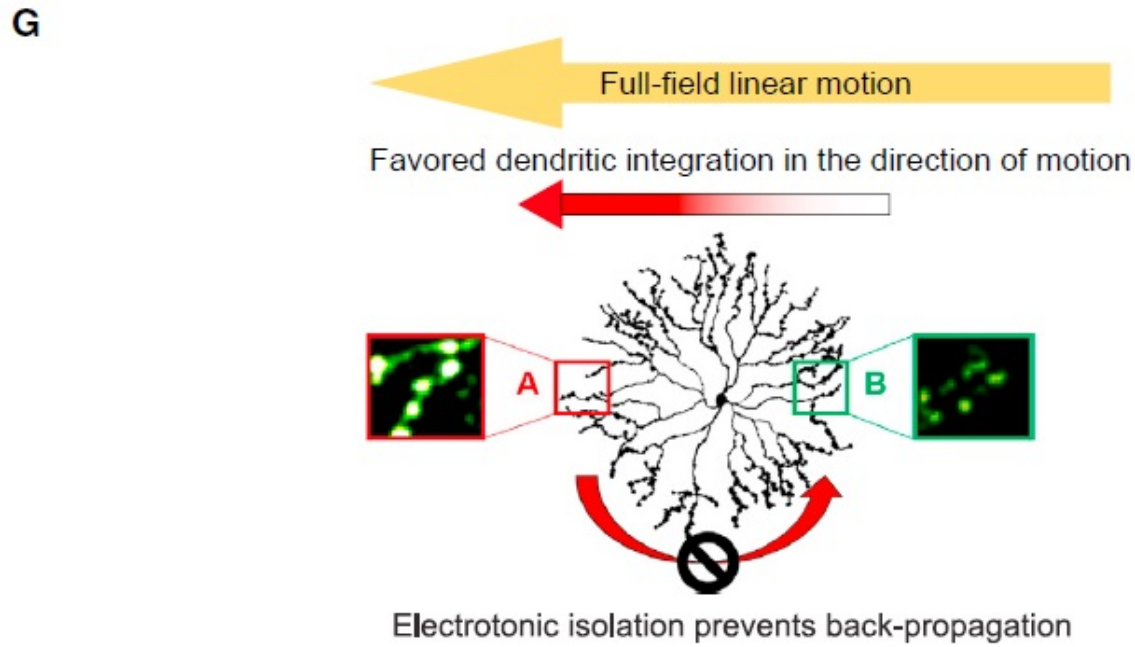
1. The regulatory mechanism that sets the fine balance between signal isolation and propagation between dendritic sectors is unknown.
2. A prime candidate is metabotropic glutamate receptor 2.
3. It is expressed in SAC dendrites postsynaptically to bipolar cell inputs
4. It promotes neuronal excitability by modulating voltage gated ion channel conductances.
5. It is primarily implicated in cross-sector signal propagation as opposed to local processing.
6. Suppressing mGluR2 signaling alters cross-sector signal propagation which impacts the functional output of the circuit.

1. The regulatory mechanism that sets the fine balance between signal isolation and propagation between dendritic sectors is unknown.
2. A prime candidate is metabotropic glutamate receptor 2.
3. It is expressed in SAC dendrites postsynaptically to bipolar cell inputs
4. It promotes neuronal excitability by modulating voltage gated ion channel conductances.
5. It is primarily implicated in cross-sector signal propagation as opposed to local processing.
6. Suppressing mGluR2 signaling alters cross-sector signal propagation which impacts the functional output of the circuit.



1

Figure: No feedback from stronger response side to weaker side, maintains direction selectivity: an example of the balance between signal isolation and signal propagation.



1

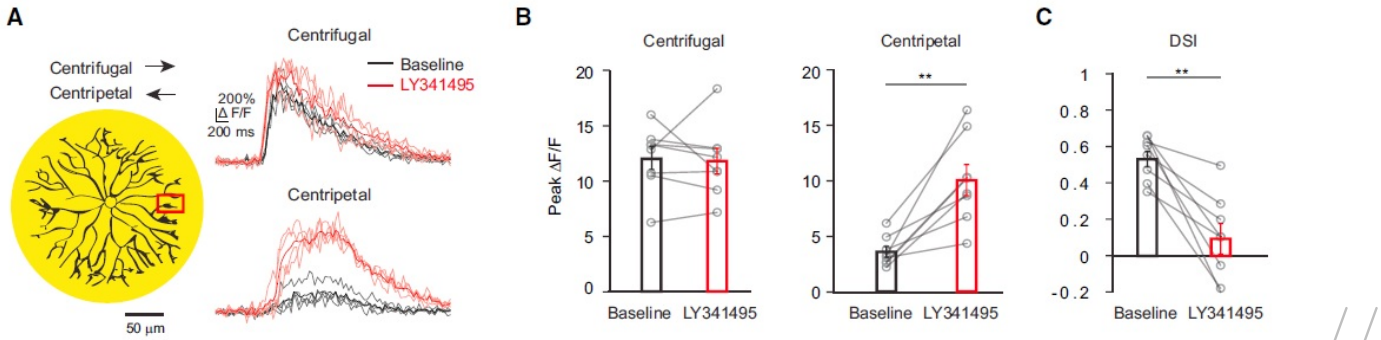
Figure: No feedback from stronger response side to weaker side, maintains direction selectivity: an example of the balance between signal isolation and signal propagation.

1. The response of varicosities in the imaging window were stronger in *their* centrifugal direction.
2. This is consistent with more effective summation of motion evoked signals in the centrifugal direction.
3. The locally generated centrifugal response within a dendrite does not propagate efficiently to the unstimulated side due to electrotonic isolation of dendritic sectors.
4. This prevents the strong centrifugal response in a dendritic sector from contaminating the weak centripetal response of the opposite side.

1. The response of varicosities in the imaging window were stronger in *their* centrifugal direction.
2. This is consistent with more effective summation of motion evoked signals in the centrifugal direction.
3. The locally generated centrifugal response within a dendrite does not propagate efficiently to the unstimulated side due to electrotonic isolation of dendritic sectors.
4. This prevents the strong centrifugal response in a dendritic sector from contaminating the weak centripetal response of the opposite side.

1. The response of varicosities in the imaging window were stronger in *their* centrifugal direction.
2. This is consistent with more effective summation of motion evoked signals in the centrifugal direction.
3. The locally generated centrifugal response within a dendrite does not propagate efficiently to the unstimulated side due to electrotonic isolation of dendritic sectors.
4. This prevents the strong centrifugal response in a dendritic sector from contaminating the weak centripetal response of the opposite side.

1. The response of varicosities in the imaging window were stronger in *their* centrifugal direction.
2. This is consistent with more effective summation of motion evoked signals in the centrifugal direction.
3. The locally generated centrifugal response within a dendrite does not propagate efficiently to the unstimulated side due to electrotonic isolation of dendritic sectors.
4. This prevents the strong centrifugal response in a dendritic sector from contaminating the weak centripetal response of the opposite side.

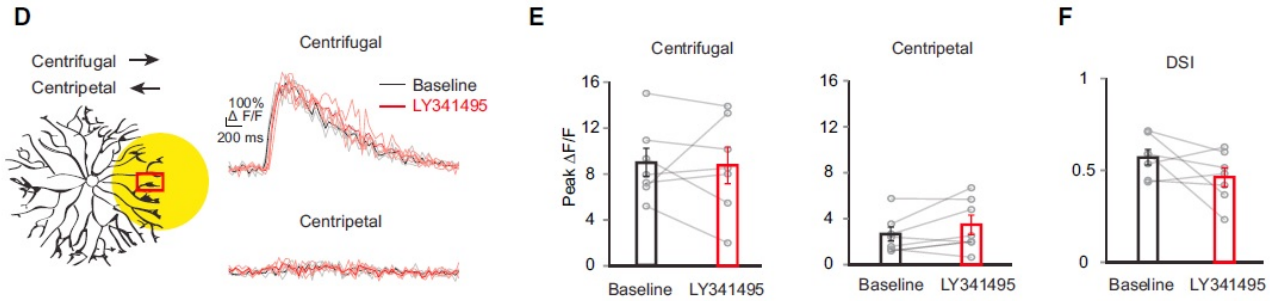

A
Centrifugal
Centripetal
50 µm
Centrifugal
Baseline
LY341495
200%
ΔF/F
200 ms
Centripetal
B
Centrifugal
Peak ΔF/F
20
15
10
5
0
Baseline
LY341495
Centripetal
**
Baseline
LY341495
C
DSI
**
1
0.8
0.6
0.4
0.2
0
-0.2
Baseline
LY341495

1

1. LY341495 is an mGluR2 antagonist or blocker.
2. It increases the centripetal response but doesn't change the centrifugal response.
3. It thus reduces direction selectivity.

1. LY341495 is an mGluR2 antagonist or blocker.
2. It increases the centripetal response but doesn't change the centrifugal response.
3. It thus reduces direction selectivity.

1. LY341495 is an mGluR2 antagonist or blocker.
2. It increases the centripetal response but doesn't change the centrifugal response.
3. It thus reduces direction selectivity.


D
Centrifugal
Centripetal
100%
Δ F/F
200 ms
Centrifugal
Baseline
LY341495
Centripetal
E
Centrifugal
Peak ΔF/F
16
12
8
4
0
Baseline
LY341495
Centripetal
16
12
8
4
0
Baseline
LY341495
F
DSI
1
0.5
0
Baseline
LY341495

1

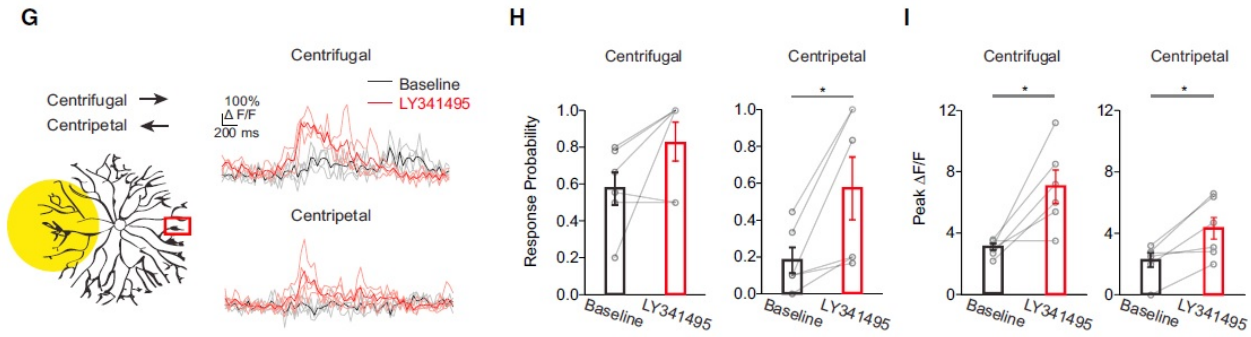
1. Two possible causes of the aberrant centripetal direction response in mGluR2 blockade are:
2. i. A general increase in SAC excitability.
3. ii. End of the isolation between centripetal and centrifugal signal carrying sectors
4. mGluR2 is not required for the intrinsic centrifugal preference which is generated locally.
5. The evidence for this is that the directional calcium response does not get altered when we apply LY341495 to a dendrite and a moving but local stimulus.

1. Two possible causes of the aberrant centripetal direction response in mGluR2 blockade are:
2. i. A general increase in SAC excitability.
3. ii. End of the isolation between centripetal and centrifugal signal carrying sectors
4. mGluR2 is not required for the intrinsic centrifugal preference which is generated locally.
5. The evidence for this is that the directional calcium response does not get altered when we apply LY341495 to a dendrite and a moving but local stimulus.

1. Two possible causes of the aberrant centripetal direction response in mGluR2 blockade are:
2. i. A general increase in SAC excitability.
3. ii. End of the isolation between centripetal and centrifugal signal carrying sectors
4. mGluR2 is not required for the intrinsic centrifugal preference which is generated locally.
5. The evidence for this is that the directional calcium response does not get altered when we apply LY341495 to a dendrite and a moving but local stimulus.

1. Two possible causes of the aberrant centripetal direction response in mGluR2 blockade are:
2. i. A general increase in SAC excitability.
3. ii. End of the isolation between centripetal and centrifugal signal carrying sectors
4. mGluR2 is not required for the intrinsic centrifugal preference which is generated locally.
5. The evidence for this is that the directional calcium response does not get altered when we apply LY341495 to a dendrite and a moving but local stimulus.

1. Two possible causes of the aberrant centripetal direction response in mGluR2 blockade are:
2. i. A general increase in SAC excitability.
3. ii. End of the isolation between centripetal and centrifugal signal carrying sectors
4. mGluR2 is not required for the intrinsic centrifugal preference which is generated locally.
5. The evidence for this is that the directional calcium response does not get altered when we apply LY341495 to a dendrite and a moving but local stimulus.

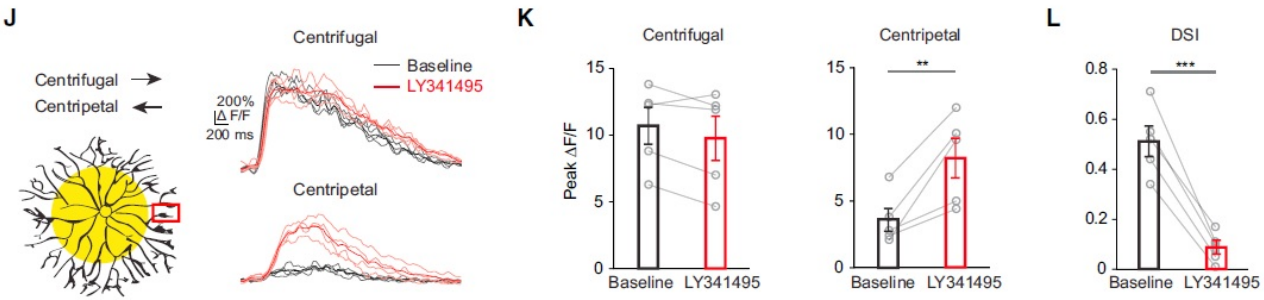

G
Centrifugal
Centripetal
100%
ΔF/F
200 ms
Baseline
LY341495
Centrifugal
Centripetal
H
Centrifugal
Centripetal
Response Probability
1.0
0.8
0.6
0.4
0.2
0.0
Baseline
LY341495
*
I
Centrifugal
Centripetal
Peak ΔF/F
12
8
4
0
Baseline
LY341495
*

1

1. When stimulus is restricted to the opposite sector, LY341495 improves the fidelity of the trans-somatic Ca2+ response.
2. mGluR2 signaling prevents aberrant propagation of depolarization between sectors.
3. mGluR2 signaling does not affect local computation within a sector.

1. When stimulus is restricted to the opposite sector, LY341495 improves the fidelity of the trans-somatic Ca2+ response.
2. mGluR2 signaling prevents aberrant propagation of depolarization between sectors.
3. mGluR2 signaling does not affect local computation within a sector.

1. When stimulus is restricted to the opposite sector, LY341495 improves the fidelity of the trans-somatic Ca2+ response.
2. mGluR2 signaling prevents aberrant propagation of depolarization between sectors.
3. mGluR2 signaling does not affect local computation within a sector.


J
Centrifugal
Centripetal
Centrifugal
Baseline
LY341495
200%
ΔF/F
200 ms
Centripetal
K
Centrifugal
Peak ΔF/F
15
10
5
0
Baseline
LY341495
Centripetal
**
15
10
5
0
Baseline
LY341495
L
DSI
***
0.8
0.6
0.4
0.2
0
Baseline
LY341495

1

Towards a Mathematical Theory of DS Computation in SAC Dendrites

1. Rall (1969) shows that, if τ_0 is the passive membrane time constant and τ_n is the nth equalizing time constant
2. Then, the electrotonic length (which captures the passive spread of the membrane potential) is given by:
3. $$L = \frac{n\pi}{\sqrt{\frac{\tau_0}{\tau_n} - 1}} \tag{1}$$

Towards a Mathematical Theory of DS Computation in SAC Dendrites

1. Rall (1969) shows that, if τ_0 is the passive membrane time constant and τ_n is the nth equalizing time constant
2. Then, the electrotonic length (which captures the passive spread of the membrane potential) is given by:
3. $$L = \frac{n\pi}{\sqrt{\frac{\tau_0}{\tau_n} - 1}} \tag{1}$$

Towards a Mathematical Theory of DS Computation in SAC Dendrites

1. Rall (1969) shows that, if τ_0 is the passive membrane time constant and τ_n is the nth equalizing time constant
2. Then, the electrotonic length (which captures the passive spread of the membrane potential) is given by:
3. $$L = \frac{n\pi}{\sqrt{\frac{\tau_0}{\tau_n} - 1}} \tag{1}$$

Towards a Mathematical Theory of DS Computation in SAC Dendrites 2

1. We can use L or some fraction thereof, as defining the compartment or sector size.
2. This divides the dendrite into various compartments.
3. Local processing is then well defined to be that which is within the compartment.
4. Global processing would be that which corresponds to a larger electrotonic length, spanning twice the dendrite length.
5. We thus need two electrotonic lengths.

Towards a Mathematical Theory of DS Computation in SAC Dendrites 2

1. We can use L or some fraction thereof, as defining the compartment or sector size.
2. This divides the dendrite into various compartments.
3. Local processing is then well defined to be that which is within the compartment.
4. Global processing would be that which corresponds to a larger electrotonic length, spanning twice the dendrite length.
5. We thus need two electrotonic lengths.

Towards a Mathematical Theory of DS Computation in SAC Dendrites 2

1. We can use L or some fraction thereof, as defining the compartment or sector size.
2. This divides the dendrite into various compartments.
3. Local processing is then well defined to be that which is within the compartment.
4. Global processing would be that which corresponds to a larger electrotonic length, spanning twice the dendrite length.
5. We thus need two electrotonic lengths.

Towards a Mathematical Theory of DS Computation in SAC Dendrites 2

1. We can use L or some fraction thereof, as defining the compartment or sector size.
2. This divides the dendrite into various compartments.
3. Local processing is then well defined to be that which is within the compartment.
4. Global processing would be that which corresponds to a larger electrotonic length, spanning twice the dendrite length.
5. We thus need two electrotonic lengths.

Towards a Mathematical Theory of DS Computation in SAC Dendrites 2

1. We can use L or some fraction thereof, as defining the compartment or sector size.
2. This divides the dendrite into various compartments.
3. Local processing is then well defined to be that which is within the compartment.
4. Global processing would be that which corresponds to a larger electrotonic length, spanning twice the dendrite length.
5. We thus need two electrotonic lengths.

Towards a Mathematical Theory of DS Computation in SAC Dendrites 3

1. Let L_{PSP} define the electrotonic length corresponding to an excitatory post synaptic potential. Let this be global.
2. To obtain L_{local} we bring mGluR2 into play.
3. We say that L_{local} is formed by the interaction between L_{PSP} and mGluR2, which curtails the spread of the PSP.

Towards a Mathematical Theory of DS Computation in SAC Dendrites 3

1. Let L_{PSP} define the electrotonic length corresponding to an excitatory post synaptic potential. Let this be global.
2. To obtain L_{local} we bring mGluR2 into play.
3. We say that L_{local} is formed by the interaction between L_{PSP} and mGluR2, which curtails the spread of the PSP.

Towards a Mathematical Theory of DS Computation in SAC Dendrites 3

1. Let L_{PSP} define the electrotonic length corresponding to an excitatory post synaptic potential. Let this be global.
2. To obtain L_{local} we bring mGluR2 into play.
3. We say that L_{local} is formed by the interaction between L_{PSP} and mGluR2, which curtails the spread of the PSP.

Towards a Mathematical Theory of DS Computation in SAC Dendrites 4

1. Once we have L_{local} and L_{global}, we can write two PDEs, one for each, showing the passive membrane potential spread
2. By the interaction of these two PDEs, perhaps direction selectivity arises under the Reichardt setting?
3. Note that L is related to the time constant, the time when a signal reaches its peak - which has implications for when these two PDEs' signals sum.

Towards a Mathematical Theory of DS Computation in SAC Dendrites 4

1. Once we have L_{local} and L_{global}, we can write two PDEs, one for each, showing the passive membrane potential spread
2. By the interaction of these two PDEs, perhaps direction selectivity arises under the Reichardt setting?
3. Note that L is related to the time constant, the time when a signal reaches its peak - which has implications for when these two PDEs' signals sum.

Towards a Mathematical Theory of DS Computation in SAC Dendrites 4

1. Once we have L_{local} and L_{global}, we can write two PDEs, one for each, showing the passive membrane potential spread
2. By the interaction of these two PDEs, perhaps direction selectivity arises under the Reichardt setting?
3. Note that L is related to the time constant, the time when a signal reaches its peak - which has implications for when these two PDEs' signals sum.

Preview of Part 2

1. We will see the influence of mGluR2 signaling on voltage-gated Calcium channels
2. We will see the influence of mGluR2 blockade on the timing and amplitude of the inhibition provided to preferred direction DSGCs
3. We will study the case of higher motion speed.
4. We will study models they propose for direction selectivity based on the authors' experimental work.
5. We will continue our discussion of a mathematical theory.

Preview of Part 2

1. We will see the influence of mGluR2 signaling on voltage-gated Calcium channels
2. We will see the influence of mGluR2 blockade on the timing and amplitude of the inhibition provided to preferred direction DSGCs
3. We will study the case of higher motion speed.
4. We will study models they propose for direction selectivity based on the authors' experimental work.
5. We will continue our discussion of a mathematical theory.

Preview of Part 2

1. We will see the influence of mGluR2 signaling on voltage-gated Calcium channels
2. We will see the influence of mGluR2 blockade on the timing and amplitude of the inhibition provided to preferred direction DSGCs
3. We will study the case of higher motion speed.
4. We will study models they propose for direction selectivity based on the authors' experimental work.
5. We will continue our discussion of a mathematical theory.

Preview of Part 2

1. We will see the influence of mGluR2 signaling on voltage-gated Calcium channels
2. We will see the influence of mGluR2 blockade on the timing and amplitude of the inhibition provided to preferred direction DSGCs
3. We will study the case of higher motion speed.
4. We will study models they propose for direction selectivity based on the authors' experimental work.
5. We will continue our discussion of a mathematical theory.

Preview of Part 2

1. We will see the influence of mGluR2 signaling on voltage-gated Calcium channels
2. We will see the influence of mGluR2 blockade on the timing and amplitude of the inhibition provided to preferred direction DSGCs
3. We will study the case of higher motion speed.
4. We will study models they propose for direction selectivity based on the authors' experimental work.
5. We will continue our discussion of a mathematical theory.