Symmetric Interactions Within a Homogeneous Starburst Cell Network Can Lead to Robust Asymmetries in Dendrites of Starburst Amacrine Cells

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Münch, Thomas A. and Frank S. Werblin. Symmetric interactions within a homogeneous starburst cell network can lead to robust asymmetries in dendrites of starburst amacrine cells. J Neurophysiol 96: 471–477, 2006. First published April 5, 2006; doi:10.1152/jn.00628.2005. Starburst amacrine cells in the mammalian retina respond asymmetrically to movement along their dendrites; centrifugal movement elicits stronger responses in each dendrite than centripetal movement. It has been suggested that the asymmetrical response can be attributed to intrinsic properties of the processes themselves. But starburst cells are known to release and have receptors for both GABA and acetylcholine. We tested whether interactions within the starburst cell network can contribute to their directional response properties. In a computational model of interacting starburst amacrine cells, we simulated the response of individual dendrites to moving light stimuli. By setting the model parameters for “synaptic connection strength” (cs) to positive or negative values, overlapping starburst dendrites could either excite or inhibit each other. For some values of cs, we observed a very robust inward/outward asymmetry of the starburst dendrites consistent with the reported physiological findings. This is the case, for example, if a starburst cell receives inhibition from other starburst cells located in its surround. For other values of cs, individual dendrites can respond best either to inward movement or respond symmetrically. A properly wired network of starburst cells can therefore account for the experimentally observed asymmetry of their response to movement, independent of any internal biophysical or biochemical properties of starburst cell dendrites.

INTRODUCTION

The starburst amacrine cell, a retinal interneuron, plays a critical role in the circuit of direction-selective (DS) ganglion cells (Fried et al. 2002, 2005; Yoshida et al. 2001). DS cells spike vigorously when a visual stimulus transverses their receptive field in one direction but remain silent when the same stimulus travels in the opposite direction (Barlow and Levick 1965). Individual dendrites of starburst cells also show directional responses (Euler et al. 2002): The observed calcium signal in the tip of starburst dendrites was strongest when motion was directed “outward,” or centrifugal, i.e., from the cell body to the tip of the process. The response was minimal for opposite movement (inward, centripetal, from the tip to the cell body). This makes starburst cell dendrites some of the earliest components in the DS circuit that express directional response properties.

Several possible explanations of this phenomenon have been given. These include geometrical properties of starburst dendrites that lead to biophysical properties that favor centripetal movement (Borg-Graham and Grzywacz 1992; Tukker et al. 2004); asymmetric distribution of chloride co-transporters along the dendrites that lead to spatially asymmetric chloride currents and hence to directional asymmetries (Gavrikov et al. 2003); or cell-internal biochemical processes, calcium-induced calcium currents, which lead to stronger calcium signals for outward movement (Barlow 1996). These mechanisms are consistent with each other and could function synergistically.

These studies all account for the directional behavior of starburst dendrites by invoking intrinsic directional properties of starburst cell dendrites. However, it is not possible to determine if starburst cells are intrinsically directional because we study them deeply embedded within the retinal circuitry. Theoretically, however, we can define how intrinsic directional behavior could be distinguished from extrinsically imposed directional behavior. To do this, we imagine a starburst cell with all its synaptic input sites. We then activate these synapses sequentially, as if a light bar is sweeping across the cell, and compare the activity of a dendrite when the activity sweeps in opposite directions. It is important that the activity of any individual synapse does not depend on the direction of the sweep. We would consider the starburst cell to have intrinsic directional properties if, under these hypothetical conditions, the response of a dendrite is different for sweeps in opposite directions.

In this report we investigate if the retinal network can impose directional behavior on starburst cell dendrites, when the dendrites do not have intrinsic directional properties. To approach this problem, we constructed a computational model of an interacting network of starburst cells. The following two well-established findings about the geometric arrangement of starburst cells within the retina were incorporated in our model: first, starburst dendrites receive synaptic input along the whole length of the dendrite, but they release transmitter only at their distal third (Famiglietti 1991). Second, the dendritic trees of starburst cells overlap strongly (Famiglietti 1983; Vaney 1984). While the dendritic trees have diameters of ~300 μm, the distance between neighboring cell bodies is on the order of only 30 μm. This creates a dense dendritic network with many possible sites of interaction between starburst cells. Moreover, those interactions could be excitatory and inhibitory because starburst cells release both acetylcholine and gamma-aminobutyric acid (GABA) (Brecha et al. 1988; O’Malley et al. 1992) and also have receptors for both of these neurotransmitters (Feller 2002; Zhou and Fain 1995).

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MODEL DESCRIPTION

We tested the influence of such excitatory and/or inhibitory network interactions on the directional response properties of starburst dendrites. For simplicity, our model network is one dimensional, consisting of starburst cells with only two dendrites: one dendrite pointing to the left, the other dendrite pointing to the right (Fig. 1A). The two dendrites of a cell are modeled to be functionally independent of each other, i.e., there is no “diffusion” of activity between the two dendrites of a cell. In this one-dimensional case, there are two configurations for a pair of interacting dendrites: the two interacting dendrites can point in the same direction (like cells A and B in Fig. 1B) or they point in opposite directions (cells B and C).

Our model is a discrete-time model. In each time step, we calculate the state of all starburst dendrites based on the state of all starburst dendrites at the previous time step and on the current “light stimulus”, which is a user-generated input to the model.

The state of each dendrite is represented by a number which can take on positive values (interpretation: “activated”, “depolarized”), zero (“resting state”), or negative values (“suppressed”, “hyperpolarized”). There are no boundaries built into the model as to how large or small this number can become. We chose not to impose absolute boundaries because any boundary would have to be set arbitrarily; interfering with the behavior of the model for some sets of parameters but not for others (see following text for a description of the parameters of the model). Compare, for example, the three graphs in Fig. 3B that show the model behavior for three sets of parameters. An arbitrary boundary of 100 would not affect the behavior in the first and third graph, whereas the cells in the second graph reach a maximum of ~130. However, it is worth pointing out that due to our restriction of the parameter space (see RESULTS), the cells in the model do behave bounded, despite the lack of an absolute imposed boundary. Although the maximum and minimum values that are reached depend on the particular set of parameters, it is therefore possible to interpret the state value as a (not necessarily linearly related) measure of membrane potential, or intracellular calcium, or synaptic release.

Dendrites in the model are connected with rectifying synapses, i.e., a dendrite in the model can influence other dendrites only if its state is larger than zero. In addition, the effect that a particular dendrite can have on other dendrites is proportional to the length of the physical overlap between the release sites of that dendrite and the input sites of the receiving dendrites (Fig. 1B); in other words, we assume an even distribution of synapses along the contact sites. A trivial consequence of this model property is that nonoverlapping dendrites do not contact each other.

There are three free parameters in our model. The “decay factor” d determines how much of the activity of every dendrite decays from time step to time step. The second and third parameters (cs and cs_o) reflect the synaptic connections between starburst cells, the “connection strength” (cs). cs can be set to positive values (reflecting excitatory interactions through acetylcholine) or negative values (reflecting inhibitory interactions through GABA) or it can be zero, indicating that there is no interaction. Relatively large positive or negative values of cs can be interpreted as high density of synapses along the dendrite and/or as high efficacy of the synapses. In our model, we allow the connection of two dendrites to depend on the direction in which they point. If two dendrites point in the same (“s”) direction (like cells A and B in Fig. 1B), their synaptic connection strength is determined by the parameter cs. If the dendrites point in opposite (“o”) directions (like cells B and C), they interact synthetically with strength cs_o. The total connection strength between any two dendrites is then determined by the model parameter cs_s, cs_o, and cs (depending on the relative direction of the dendrites), multiplied by the length of overlap between the output and receiving sites of the two dendrites. This geometric overlap, and therefore the degree of interaction between a pair of dendrites, is not necessarily symmetric (see Fig. 1B). We tested the directional behavior of the starburst cells in the model for all plausible combinations (see following text) of d, cs_s, and cs_o.

The behavior of each dendrite in our model is therefore determined by the following equations (given for a left dendrite in the model)

\[ L_s(t) = \text{light}(t) + (1 - d) L_s(t - 1) + cs \sum_{j=1}^{N} \text{overlap}_{L_s \rightarrow L_j} \cdot [L_j(t - 1)] + cs_o \sum_{j=1}^{N} \text{overlap}_{L_s \rightarrow R_j} \cdot [R_j(t - 1)] \]

\[ L_o(t) = 0, i = 1, \ldots, N \]

A corresponding equation can be defined for the right dendrites of starburst cells in the model.

![Fig. 1. Layout of the model. A: geometric properties of individual starburst cells. Each dendrite receives inputs at its distal 110 µm and makes output synapses with its distal 50 µm. We chose to exclude input sites from the proximal 40 µm because we wanted to focus on interactions between starburst cells, and the proximal region of starburst dendrites does not lie in the “starburst stratum” of the inner plexiform layer (Famiglietti 1991). B: top: geometric properties of the starburst network. The amount of overlap between individual dendrites is determined by the geometry. For example, the release region of the left dendrite of cell A (L_A) overlaps with the input region of L_B by 20 µm, whereas, conversely, the release region of L_A overlaps with the input region of L_B by 50 µm. Overlapping starburst dendrites can point in the same direction (the dendrites of cells A and B) or in opposite directions (cells B and C). Starburst cells receive input from an array of bipolar cells (gray) spaced 30 µm apart. Bottom: 2 confocal micrographs showing 2 reconstructed starburst cells each. Left: cell pair is located closely together, therefore its dendrites point in the same direction. Right: cell pair is far apart, their overlapping dendrites point in opposite directions. Images courtesy of Professor David Vaney.](image-url)
RESULTS

We used the following strategy to investigate the influence of network interactions on directional starburst cell behavior: first, we restricted the parameter space to reasonable values (see following text). Second, we scanned the complete remaining parameter space and quantified the directional behavior for each parameter combination. We then discuss the behavior of the model starburst cells and provide some intuition about the model properties that lead to directional behavior of our cells. We also compare our model to the behavior of real starburst cells, to predict actual connectivity within the starburst cell network, and the influence of that connectivity on the directional behavior of starburst cells.

Restriction of parameter space

The decay constant \(d\) has the trivial boundaries 0 (no decay between time steps) and 1 (complete decay). The parameters \(c_s\) and \(c_o\) have no such natural boundaries, and the abstract and general design of the model does not provide us with boundaries dictated by the biology of the system. We found boundaries for parameters \(c_s\) and \(c_o\) by applying two different criteria to the model behavior: boundedness and robustness.

Because our starburst model is a network of interacting elements, unbounded behavior is easily achieved. For example, if all dendrites in the model were to excite each other strongly, all dendrites would reinforce each other and the values \(L_i(t)\) and \(R_i(t)\) would soon approach infinity. To test for boundedness, we simply let the system run with the light stimulus set to 0 (gray). This will lead to baseline release from the model bipolar cells; the starburst cells will interact and eventually either reach some steady state, or their behavior will be unbounded (Fig. 2A, top). Parameter combinations \(d-c_s-c_o\) which lead to unbounded behavior, were excluded.

With a uniform background illumination, all dendrites in the model should in theory behave absolutely identically because, by design, the model is completely symmetric and homogeneous. In some cases, however, we observed that small numerical rounding errors caused very different behavior of left and right dendrites in the model (i.e., for those parameter combinations the system was not robust against rounding errors). To test for robustness, we therefore started with a system where all right dendrites in the model were set to a different initial value (= 0) than the left dendrites (= 1, but the specific value has no influence on the outcome of this test), whereas the light stimulus was still a uniform gray. Parameter combinations \(d-c_s-c_o\) for which the difference between left and right dendrites diminished and approached 0 were considered robust. All other parameter combinations were excluded (Fig. 2A, bottom).

Parameter combinations \(d-c_s-c_o\) that are both bounded and robust (according to the tests described in the preceding

\[ R_i(t) = \text{light}(t) + (1 - d)R_i(t - 1) + c_s \sum_{j=1}^{N} \text{overlap}_{jkh} \cdot [R_j(t - 1)] \]

\[ + c_o \sum_{j=1}^{N} \text{overlap}_{jkl} \cdot [L_j(t - 1)] \]

\[ R_i(0) = 0, i = 1, \ldots, N \]

with

\[ L_i(t), R_i(t) \]: state of the left an right dendrites of cell \(i\) at time \(t\).

\(N\): number of starburst cells in the model;

\(c_s, c_o\): parameters of the model, see above. The \(c_s\)-parameters are given in mm^-1; and

\[ \text{overlap}_{jkh}: \] length of overlap between input sites of dendrite \(x\) and output sites of dendrite \(y\) given in micrometer. These numbers are determined purely by the geometric layout of the model (Fig. 1B); the overlap between most dendritic pairs is 0 \(\mu m\). To avoid boundary effects, the model is both large (large \(N\)) and circular, with cell 1 coming to lie next to cell \(N\). Note also that the input to a starburst dendrite from other dendrites depends on their activity at the previous time step (before the decay of their activity determined by parameter \(d\)).

\(\text{light}(t)\): stimulus that the model receives at time \(t\). The light stimulus is a user-defined array of values between –1 (black) and +1 (white). The standard background intensity is 0 (gray). The stimulus is passed through a balanced spatial Mexican hat filter (difference of Gaussians, center sigma = 90 \(\mu m\), surround sigma = 240 \(\mu m\)) before being passed on to an array of “bipolar cells”. The output of the bipolar cells is a rectified version of the light stimulus, according to the equation \(\text{output} = 1/(1 + e^{\frac{2x-2y}{\text{surround}\ \text{sigma}}})\), yielding no output to black (= –1) stimuli, some baseline release under background (= 0) conditions [corresponding to baseline glutamatergic input that starburst cells receive (Peters and Masland 1996)], and maximum release to white (= 1) stimuli. The bipolar cells are evenly spaced every 30 \(\mu m\), and each starburst dendrite sums all activity of those bipolar cells that overlap with its input sites (Fig. 1B).
text) represent an upper bound of parameters that can be expected to reasonably describe “biological” behavior in our model. Those parameters lie within a convex region of the \( dc_\text{s} - dc_\text{s}_o \) space (Fig. 2B). We have therefore restricted the reasonable parameter space to a manageable size and are able to scan the complete space to observe the behavior of the starburst cells for each possible parameter combination.

**Directional behavior of starburst network**

We tested the directional behavior of the starburst cells with a white bar moving across the model network (Fig. 3A). We compared the behavior of the left and the right dendrites that are located in the center of the model (for \( n = 61 \) cells, this is \( R_{28} \) and \( L_{34} \)). The bar is moving from left to right; therefore \( R_{28} \) sees outward or centrifugal movement, and \( L_{34} \) sees inward or centripetal movement. Figure 3B shows three individual examples for three different sets of parameters. The first pair of traces shows the behavior of \( R_{28} \) and \( L_{34} \) when \( c_\text{s} = c_\text{s}_o = 0 \). In other words, there is no interaction within the starburst network; the starburst dendrites receive input exclusively from the bipolar cells. \( R_{28} \) and \( L_{34} \) do not behave differently in this case, consistent with the design of the model in which the starburst dendrites have no intrinsic directional behavior. The other two examples illustrate the two possible asymmetries that the cells in the model can express: the starburst dendrites can either respond more strongly to outward movement (\( R_{28} > L_{34} \), Fig. 3B, middle), or they can prefer inward movement (\( R_{28} < L_{34} \), Fig. 3B, bottom). We quantified the directional preference by calculating the directional index \( DI = \frac{Max_{R_{28}}}{Max_{L_{34}}} \). Values of \( DI > 1 \) indicate preferred outward movement, \( DI = 1 \) indicates nondirectional behavior, and \( DI < 1 \) indicates preferred inward movement. Figure 3C shows the distribution of the directional index over the parameter space. We find that the value of the decay factor \( d \) is not critical for the directional behavior of starburst dendrites in the model. As a general rule, whenever \( c_\text{s} \) is larger than \( c_\text{s}_o \), the dendrites prefer outward movement. When \( c_\text{s} \) is smaller than \( c_\text{s}_o \), the dendrites respond stronger to inward movement (Fig. 3D).

**DISCUSSION**

It has long been a hot topic of discussion whether directionally asymmetric behavior in the nervous system requires a neuron with intrinsic directional properties or if directional behavior can emerge as a circuit property, even if there are no intrinsically directional neurons in the circuit. The dendrites of starburst amacrine cells in the retina are one of the earliest building blocks in the circuit of DS cells that show directional behavior. Many studies have explained this behavior with intrinsic properties of starburst cells. In this report, we show that the directional behavior can emerge from network interactions, independent of intrinsic directional properties of starburst dendrites.

**How does the model generate directional selectivity?**

The starburst dendrites in our model do not behave asymmetrically unless there is some directional bias in the synaptic circuitry. For example, let us consider the right dendrite of cell B in Fig. 1B. It may receive inputs from dendrites that point in the same direction (e.g., the right dendrite of cell A) and from dendrites that point in opposite direction (e.g., the left dendrite of cell C). If these synaptic connections have the same strength (i.e., \( c_\text{s} = c_\text{s}_o \)), then the starburst network will not impose directional behavior on the right dendrite of cell B (Fig. 3, C and D). If there is a bias, however, to favor excitation (or inhibition) for like-wise oriented dendrites, then this bias will result in a directional behavior of the starburst dendrite: it will either favor outward or inward movement, depending on the bias.

At first glance, it may seem surprising that the dendrites in our model can behave directionally because the detection of movement direction inherently requires the “analysis” of the change of position of an object over sequential time points. How can a dendrite in our model do this, although it is modeled as a single compartment, and does therefore not have the ability to distinguish between different spatial positions? The answer is that a dendrite cannot do this—the directional behavior is a network property (reflected in the behavior of the
individual dendrites) and not the property of any single dendrite.

It is worth to provide some intuition about the network interactions that underlie the directional behavior. Let’s first consider the two dendrites A and B in Fig. 4A. They are at the same spatial location but point in opposite directions. We now show a brief stimulus (lasting only 1 time step) that lies just to the left of both dendrites (solid outline, Fig. 4A), so that it causes no additional input to either dendrite A or B beyond the steady-state background input that all dendrites receive. The stimulus will, however, excite the three gray dendrites shown above dendrite A. At the next time step, the stimulus disappears. Dendrites A and B still receive the steady-state background input and, in addition, input from the three gray dendrites that can be either positive, negative, or zero depending on the values of \(c_s\) and \(c_{so}\). For simplicity, we set \(c_s = 0\) (so that dendrite B will receive no input from the gray dendrites), and consider the cases \(c_{so} > 0\), which leads to positive input to dendrite A (and hence we will get \(A > B\)) or \(c_{so} < 0\), which leads to negative input to dendrite A (and \(A < B\)). In each case, dendrites A and B have now different values. Likewise, if we set \(c_{so} = 0\), we can consider similar scenarios for positive and negative values of \(c_{so}\), and will again get different activity of dendrites A and B.

This example shows the underlying basis for the directional behavior of the model. Even a brief stationary stimulus sets up different activity patterns in the left- and right-pointing dendrites surrounding the stimulus location (as long as \(c_s \neq c_{so}\)), which will lead to directional behavior for a moving stimulus. The crucial property of the model is therefore the ability of starburst cells to influence other cells that are displaced from the stimulus location; they can perform “action at a distance”. By this mechanism, the dendrites A and B of the preceding example integrate information about the activity at a different location at the previous time step (mediated by the gray dendrites).

How does this concept (action at a distance with a delay of 1 time step) lead to directionally selective behavior when the stimulus is actually moving? Figure 4, B and C, shows a specific example that illustrates the underlying interactions. For simplicity, this example is modeled with no outer retinal preprocessing of the stimulus (as opposed to the traces shown in Fig. 3) with \(c_s\) set to 0 and positive \(c_{so}\) (\(c_{so} = 5\)). For illustrative purposes, we set \(d = 1\) (complete decay between time steps, so that the state value of a dendrite reflects only its current inputs and is not directly dependent on its own past). The 17 positions of the rightward moving stimulus bar (positions \(-8\) to \(+8\)) are shown in Fig. 4B, top (these are the same positions as for the stimulus used in Fig. 3), and C shows the responses of the central dendrites \(R_{28}\) and \(L_{34}\). We use a slowly moving stimulus [stepping 1 spatial unit (\(= 30 \mu \text{m}\)) every 12 time steps, indicated by the gray vertical lines] that clearly reveals the interactions underlying the directional behavior. For comparison, Fig. 4C, left inset, shows the responses when the stimulus moves at the same speed as in Fig. 3, i.e., stepping one spatial unit each time step.

Note the transient peaks in the response of \(R_{28}\) during the first half of the movement (up to position 0). These peaks are signatures of coincidence detection that is happening in the network. Consider for example the transient peak as the stimulus steps from position \(-1\) to position 0. This peak is caused by an increase in the bipolar input to \(R_{28}\) because the stimulus has just moved to the right and is covering more of the input region of dendrite \(R_{28}\). At the same time, \(R_{28}\) is still receiving strong input from the likewise oriented dendrites (compare the gray dendrites in Fig. 4A) where the stimulus has been at the previous time step. The decay after the peak is due to decreased input to \(R_{28}\) from those likewise-oriented dendrites after the stimulus has stepped away. Importantly, this decreased network input “reaches” \(R_{28}\) one time step delayed compared with the increased bipolar input. In other words, the transient peak is due the coincidence of strong input from two sources: the increased direct bipolar input and the not-yet decreased input from the likewise oriented neighboring dendrites. Each time the stimulus steps to the right, it causes such a transient peak in the dendrites directly underlying the stimulus, as described in the preceding text. But even dendrites further away from the stimulus will eventually “see” this event because of successive network transmission through the likewise-oriented dendrites. For example, dendrite \(R_{28}\) eventually reports the step of the stimulus from position \(-8\) to position \(-7\), even though this event is happening far to the left of the input sites of \(R_{28}\).

The transient “negative dips” in the response of \(L_{34}\) in the second half of the movement (after position 0) are not due to any negative connections. Instead, those dips correspond to the stimulus moving away from the left-pointing dendrite \(L_{34}\), so that it gets (instantaneously) less bipolar input. Then the response grows again due to inputs from other left-pointing dendrites located further to the right (network effect that is delayed by 1 time step). Again, such an event is transmitted to \(L_{34}\) through likewise oriented dendrites even if it happens further to the right of \(L_{34}\).

A fast-moving stimulus, like shown in the left inset, will emphasize the transient aspects of the responses (like the peaks in the response of \(R_{28}\)), so that the directional difference is more pronounced than during the slowly moving stimulus. In fact, the steady-state values of \(R_{28}\) and \(L_{34}\) (after a stimulus has been at a position for a while) are not different, as is most easily seen at position 0, but also at any other pair
of corresponding symmetric positions (e.g., the responses of $R_{28}$ at position $-2$ and of $L_{34}$ at position $+2$; the steady-state responses are the same, even though the stimulus gets to both positions from the left, i.e., outward for $R_{28}$ and inward for $L_{34}$).

It can be shown mathematically that there are two general requirements for the discrimination of movement direction (see for example the classical model of directional selectivity of Barlow and Levick 1965). One requirement is the comparison of the activity at two spatial locations ($\Delta s$) at two different time points ($\Delta t$). This requirement is fulfilled in our model by the “action at a distance” of starburst cells ($\Delta t$) that they perform with the delay of one time step ($\Delta t$) as described in the preceding text. Physiologically, this delay can be interpreted as the delay and/or persistence of synaptic release. The second requirement is at least one nonlinearity in the analysis. The only nonlinearity in our model is the rectification of release from starburst cells, which only kicks in for negative values of the state value. For most parameter combinations in our model, however, the starburst cells stay in the positive range, that is, there is no nonlinearity involved. How can the cells in our model still distinguish the direction of movement? The answer is that there is a hidden nonlinearity in the way we quantify the response: we compare the maximum of the of the cells’ responses, which is equivalent to a thresholding operation. If we were to compare the total activity of the cells, i.e., the “area under the curve” of the responses, we would find no difference between inward and outward movement. Fig. 4C, right inset, illustrates this linearity. Note also that the areas under the curves shown in Fig. 3B are the same for the responses of $R_{28}$ and $L_{34}$.

It should also be mentioned that the Mexican hat filter of the “outer retina” is not crucial for the directional behavior of the model. If we run the simulation with no outer retinal preprocessing, as exemplified by Fig. 4, the results are very similar. The same is true when the bar moves at twice the speed as shown in Fig. 3 (data not shown).

What does the model tell us about the biology of starburst cells?

We know from experimental results that starburst dendrites do indeed respond more strongly to outward movement (Euler et al. 2002). The strongest prediction of our model is therefore that there should be no connectivity bias that would favor inward movement (i.e., we should not find $c_{ss} < c_{cs}$) because then, even if starburst cells do have intrinsic properties, these properties would have to be strong enough to overcome such a bias imposed by the network. It seems unlikely to us that network and internal properties compete with each other.

What is known about connectivity of starburst cells in the retina? Zhou and colleagues (Zheng et al. 2004) recently reported that in the maturing rabbit retina, cholinergic nicotinic synapses between starburst cells slowly disappear, whereas GABAergic connections remain present. In the terminology of our model, this means that both $c_{ss}$ and $c_{cs}$ are nonpositive in the mature retina. Negative $c_{ss}$ corresponds to an inhibitory surround of the starburst cell (note that cell C in Fig. 1B is in the position to supply surround-input to cell B and vice versa). The question then is whether $c_{ss}$ is more negative than $c_{cs}$, or, in other words, if any given starburst cell receives stronger inhibitory input from the starburst cells with cell bodies lying in its surround ("surround-cells") than from those starburst cells with cell bodies that lie within its dendritic field ("non-surround cells"). If this is the case, our model predicts that we can attribute at least some of the directional behavior of starburst dendrites to the retinal circuitry. Zhou and colleagues (Lee and Zhou 2005) also performed double patch experiments and found inhibitory connections between starburst cells that were close together (non-surround cells, like cells A and B in Fig. 1B) and also between cells that were far apart (surround-cells, like cells B and C). Unfortunately, these experiments do not allow us to strictly answer the question if $c_{ss} < c_{cs}$ because one can only measure the overall synaptic input to the cells and not the strength of the synaptic input to an individual dendrite. It is likely that a cell pair A–B, which is spatially almost completely co-incident, has more synapses in common than a cell pair B–C, which has a much smaller region of overlap. This would result in stronger inhibitory currents measured in a double-patch experiment between cells A and B than between cells B and C (which could be interpreted as $c_{ss} > c_{cs}$). If we were able to measure the inhibitory input to an individual dendrite, the result may or may not be opposite.

It was shown that the directional behavior of starburst dendrites remains intact in the presence of blockers of GABA$_A$ receptors (Euler et al. 2002) as well as GABA$_C$ receptors (Haussett et al. 2004). Based on these findings and those of Zhou and colleagues (that there are no nicotinic synapses between starburst cells in the adult retina), one might conclude that network interactions cannot underlie the directional behavior of starburst cells. If we allow only direct and electrogenic synapses between starburst cells (using nicotinic acetylcholine receptors, and GABA$_A$ and GABA$_C$ receptors), this seems indeed to be the case. The conclusion of our model would then be: the directional behavior of starburst cells has to be, at least in part, due to internal properties of the dendrites.

However, we cannot exclude the possibility that other types of connectivity exist in the starburst network; even indirect connections between starburst cells (through an additional interneuron) have been proposed in the literature. There are therefore other possible mechanisms of how one starburst dendrite can have a “positive” or “negative” influence on another: a positive value of $c_{ss}$ in our model could be interpreted as cholinergic enhancement of glutamate release from bipolar cells (Yamada et al. 2003), as inhibition of an inhibitory amacrine cell (dissinhibition), or as a nonelectrogenic muscarinic excitation between starburst dendrites (through receptors other than M2) (see Wasselius et al. 1998). None of these indirect or nonelectrogenic connections could be easily detected by common electrophysiological techniques. Similarly, one starburst cell could have “negative” influence on another starburst cell through nonelectrogenic connections through GABA$_A$ receptors (Zucker et al. 2005), the reduction of glutamate release from bipolar cells (Linn and Massey 1992), or cholinergic excitation of a presynaptic GABAergic or glycinergic amacrine cell (indirect inhibition) (Neal and Cunningham 1995). Again, these indirect connections are not easily observed by standard electrophysiological techniques.

In summary, we conclude that interactions within a homogeneous network of starburst cells can impose a directional bias on (intrinsically nondirectional) starburst cell dendrites. If we only consider direct synaptic connections between starburst...
cells, such a directional bias can in principle be generated by a symmetrical inhibition from surrounding starburst cells with processes that point toward the central starburst cell. Previous experimental results suggest that this could not be the only mechanism that generates directional behavior in starburst dendrites. But the influence of the circuitry does not have to be confined to direct connections between starburst cells. This would allow for even more sophisticated directional network processing.

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