A biophysical model for the developmental time course of retinal orientation selectivity

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Abstract

A quantitative study of the time course of development of the percentage of orientationally selective and isotropic ganglion cells in turtle retina has recently been performed. This study revealed that as soon as ganglion cells start responding to light, a large percentage of them are selective to the orientations of moving visual stimuli. This percentage decreases with age to reach a minimum around hatching, increases dramatically after birth and finally, decreases again following the first month of life to reach adult level. Concomitantly, the percentage of cells responding isotropically to the orientation of elongated stimuli increases monotonically until about 30 days after birth, stabilizing afterwards. To account for both time courses, we propose a biophysical model implementing features ubiquitous to developing vertebrate retinas. These features include early dendritic and synaptic spatial polarization, dendritic growth, and waves of activity generated spontaneously or by visual stimulation sweeping across the inner plexiform layer (IPL). The model also assumes a physiologically plausible Hebbian rule, which includes long-term potentiation and depression. Computer simulations of this model yield good fits of the data. The quality of these fits confirms and extends results from an earlier model using computationally-simple mechanisms, which suggested that early dendritic polarization might be the seed for mature orientation selectivity. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Keywords: Retina; Inner plexiform layer (IPL); Receptive field development; Orientation selectivity; Computational model

1. Introduction

The time course of development of ganglion-cell receptive fields in the turtle’s retina has recently been investigated [1]. At stage S23 (approximately embryonic Day 40 (E40) in an approximate 60-day-long gestation period), which is when light responses emerge, a large percentage of ganglion cells demonstrate selectivity to the directions of motion and orientations of visual stimuli. As the embryo develops, this percentage decreases to reach a minimum around the time the turtle hatches. This minimum is then followed by an outburst in the percentage of orientationally (but not directionally) selective ganglion cells. Because this outburst is significantly less dramatic under dark rearing than normal rearing, visual stimulation appears to contribute to the outburst [2]. In contrast, the spontaneous waves of activity, which are ubiquitous to developing retinas [3], do not appear to contribute directly to the outburst, since their chronic blockade does not prevent the outburst from reaching a normal magnitude [2].

In parallel to the development of orientation selectivity, the percentage of ganglion cells responding isotropically to stimulus orientation (hereinbelow called ‘orientationally isotropic cells’) also varies with turtle development [1]. At S23, this percentage is insignificantly small. Besides orientationally and directionally selective cells, at this stage there are many cells that respond well to motions in a small (more than two) number of directions or to stimuli in a small (more than two) number of orientations. We call these cells the ‘multi-axis anisotropic cells’. As the turtle develops, these cells slowly disappear, being replaced by more and more orientationally isotropic cells. The percentage of the latter grows continuously until about postnatal Day 30 (P30).

While genes undoubtedly participate in the development of retinal receptive-field structures, the complexity
of these structures is so large that the genetic information must be in large part tacit [4,5]. Models of self-organization that rely on epigenetic factors such as, for instance, spontaneous neural-activity patterns, have previously been proposed to explain the formation of orientation selectivity in cortex [6–9]. These models assume static multi-layer feedforward architectures. Hebb-like rules for synaptic maturation, and uncorrelated random noise on the first layer. Unfortunately, these models are not directly applicable to the retina for at least two reasons: (1) Ganglion-cell orientation selectivity (and other complex receptive-field properties) seems to involve a single synaptic layer, the inner-plexiform layer (IPL) [10] but see ref. [11]. (2) The network's connectivity is dynamic, since intense growth and remodeling of the ganglion-cells' dendritic tree can be observed [12–14]. Early in development, immature retinal cells have small, poorly branched, and polarized dendritic trees [15,12,16–18], but most of these cells acquire an approximately symmetric shape with maturation by addition of new dendrites. Besides these two reasons, the spontaneous input activity in the ganglion-cell layer is specific to retinal development. Multi-electrode and optical-recording studies in developing retinas of cat and ferret provide evidence that instead of uncorrelated random noise, the early retinal noise consists of spontaneous waves of activity propagating across the ganglion-cell surface and IPL [19,20], correlating the activity of neighbor cells5. Spontaneous bursts of activity in ganglion cells of developing retinas have also been reported in rabbit [21], rat [22] and turtle [23,24], with evidence for correlation in the spontaneous discharges of neighboring ganglion cells being provided for the latter two species.

The goal of this paper is to inquire whether a biophysical model including early dendritic-tree polarization, dendritic growth, waves of activity and a physiologically plausible Hebbian rule leads to results consistent with retinal development. We will discuss two types of waves, the spontaneous ones and, after birth, light evoked ones. (There are two reasons for saying that visual stimulation will evoke waves of activity. The first is that responses to objects moving in a scene will be prominent at their edges and thus will be propagating along with them. The second is that as the animal walks, swims, or moves its head or eyes, the retinal projections of edges in scenes will propagate in the retina.) Quantitative fits of model to experimental data [1] on the time course of development of orientationally selective and isotropic cells in turtle retina will be used to assess the applicability of our model. Possible extensions of it to account for the development of directional selectivity will be discussed. Preliminary findings of the work reported here have been published in abstract form [29].

2. Model

We built a biophysical model of the IPL. In this model, straight amacrine dendro–dendritic processes [30] of random orientation appeared at random times according to a Poisson process with average rate λ until a maximal number (m) of dendrites was reached. These dendro–dendritic processes made synaptic contacts through their endings with ganglion cells (Fig. 1). The model did not specify the number or types of amacrine cells contributing to the receptive field of one ganglion cell, only the number of their synaptic contacts at each age through parameters λ and m. In other words, the 'unit of computation' was the amacrine dendrite not the cell itself. We assumed that neither the primary dendrites nor the very endings of the dendritic trees represents this unit, and thus 'm' corresponds to the total number of branches of relatively parallel dendrites. To find out how many cells participate, one would have to specify their dendritic structure, which is outside the scope of this paper. Contacts anywhere in the dendritic tree of the ganglion cell could have the same effects on the ganglion-cell response. We thus assumed that the dendritic spread does not significantly affect the development of orientation selectivity, except by modulating the number of amacrine contacts. As for the increase in the number of amacrine contacts, it could be caused either by the growth of ganglion-cell dendrites or by the growth of amacrine-cell dendrites [1], these cases being indistinguishable in our model. All contacts were assumed to be excitatory (this excitation could involve acetylcholine—Masland and Ames [25]—, early GABA excitation—Bahring et al. [31]—and other neurotransmitters from amacrine cells—Strettoi and Masland [32]). However, a discussion of one of the roles of inhibitory contacts appears in Section 5.5. Finally, no bipolar-cell processes were considered in this model, since orientation selectivity depends mainly on wide lateral contacts, which bipolar cells are not well suited to provide. Synaptic maturation was described according to a Hebbian rule consistent with the physiology of long-term potentiation (LTP) and long-term depression (LTD) in hippocampus [33]. Similar to the covariance rule (see refs. [34,35]), this synaptic maturation depends on the product of the pre- and post-synaptic activity levels. However, different from the covariance rule, synaptic weights are implicitly bounded between 0 and 1 due to limited availability of substrate in some enzymatic reactions, and changes in synaptic weights are turned on and off by an enzymatic switch [36].

5 The mechanism of spontaneous-wave propagation appears to involve cholinergic nicotinic synapses [25–28,24] and efflux of K+ from cells during bursting [23,26,27].
simplified version of this physiological rule, less demanding in computation time but retaining most of its original properties, was derived in the Appendix. According to this version, changes in synaptic weights, \( w_i \) (\( 0 < w_i < 1 \)), of the \( i^{th} \) amacrine dendritic process were expressed as

\[
\frac{d}{dt} w_i = k_1 \frac{-w_i F_i^A F_i^G + k_2 w_i^\mu(1 - w_i)(F_i^A F_i^G)^\mu}{w_i F_i^A F_i^G + k_2 w_i^\mu(F_i^A F_i^G)^\mu} \tag{1}
\]

where \( k_1 \) is a parameter determining the rate of synaptic maturation, \( k_2 \) is a parameter determining the transition point between long-term depression and potentiation, \( \mu > 1 \) specifies the steepness of this transition, \( F_i^A \) and \( F_i^G \) are the levels of activity in the \( i^{th} \) amacrine process and ganglion cell, respectively and the overbar denotes average over a large number of waves (spontaneous or light evoked). For large correlations between amacrine and ganglion-cell activities, the quantity \( (F_i^A F_i^G)^\mu \) made the numerator of this equation positive, causing an increase in synaptic weight (LTP). Conversely, small correlations made the numerator negative, causing a decrease in synaptic weight (LTD). The denominator prevented LTP and LTD from happening too fast.

For simplicity, and following other models for the development of orientation selectivity [37,6,7,9,38], the ganglion-cell response depended linearly on the inputs, namely.

\[
F_i^G = \beta \sum_{\mu=1}^\mu w_i F_i^A \tag{2}
\]

where \( \beta \) is a constant and \( \mu (1 \leq \mu \leq m) \) is the number of amacrine dendrites contacting the ganglion cell.3 Also for simplicity, we assumed that the wave is one dimensional and that the response to it of the \( i^{th} \) dendrite is

\[
F_i^A = \gamma \cos p x_i \tag{3}
\]

where \( \gamma \) and \( p \) are constants (\( p \) being an integer), and \( x_i \) is the angle between the orientations of the wavefront and the \( i^{th} \) dendrite with \( x_i = 0 \) or \( \pi \) when they are parallel. This assumption was not arbitrary as in cursory computer simulations, it approximated well the time integral of the transmitter release from the end of a dendritic cable [39] stimulated by a propagating perturbation in extracellular K\(^+\) concentration (such a

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3Because all the quantities in Eq. (2) are positive, the model in this paper does not have surround inhibition. This is not to say that we assert that the maturation of surround inhibition is independent of the spontaneous activity. However, we neglect surround inhibition here, since it is present as soon as light responses emerge in turtle [1]. Therefore, these data are suggestive that surround inhibition might be a direct genetic feature of retinal coding and thus independent of activity. In any event, the main point here is that one does not need to take surround inhibition into account to explain the development of orientation selectivity.
perturbation was predicted by the model for the spontaneous waves by Burgi and Grzywacz [26,27]). Similar simulations showed that Eq. (3) is a good approximation for this integral when a wave of synaptic-conductance changes activates the dendrite (such a wave was an example of what might happen to the dendrite when a moving edge stimulates the retina). Some intuition for why Eq. (3) approximated well the results of these simulations came from the following observation: When \( \xi = 0 \) or \( \pi \), the entire dendrite was depolarized at once when hit by a wave, since their orientations were parallel. Such a massive simultaneous depolarization caused the synapse at the end of the dendrite to overcome the threshold for transmitter release. In contrast, when \( \xi = \pm \pi / 2 \), different portions of the dendrite depolarized at different times as the wave passed. Therefore, at any given instant, the synapse’s depolarization was smaller than for the parallel case, thus making it less likely for this synapse to release its transmitter.

Under the assumptions underlying Eq. (2) (postsynaptic activity) and Eq. (3) (presynaptic activity), \( (F^y)^q \) becomes

\[
(F^y)^q = A_q \left( \int_{0}^{2\pi} \cos^q \xi \sum_{j=1}^{n} w_j \cos^q \xi_j d\xi \right)^q
\]

(4)

where \( A_q = \beta^q \) is a positive constant. Although cumbersome, especially for \( q > 1 \), the calculation of this integral involves straightforward algebraic manipulations.

3. Methods

The outcome of receptive-field formation was determined by Eq. (1). To solve this equation, we had to calculate \( (F^y)^q \) for every dendrite, and for \( q = 1 \) and \( q = n \), as specified in Eqs. (1) and (4). Eq. (1) was solved using Runge-Kutta’s method with variable time step [40]. Typically, the time step ranged from 30 min to several days (the shorter time steps occurred when changes in the receptive field were fast, while the longer time steps occurred when the number of dendrites reached its limit). All the simulations started at Day -30, i.e. 30 days before birth. Initial conditions for synaptic weights were homogeneously distributed with a mean of 0.5 and S.D. of 0.06 (cursory simulations showed that this S.D. gave good results, but we verified that varying it by a factor of three up and down did not affect the qualitative behavior of results). Our cell population comprised 100 units. Because the time steps could in principle be different from one cell to another, we determined the time course of development of a class of cells within a population by taking the smallest time step in this population and applying linear interpolation to fill the gaps when necessary.

The parameter space explored in the simulations comprised the transition point between long-term depression and potentiation \( (k) \), the ratio between the rates of arrivals of new dendrites and of synaptic maturation \( (\lambda / k) \), and the maximum number of dendrites \( (m) \). The parameter \( p \) in Eq. (3) was set to eight. This is because cursory simulations with the dendritic model discussed after that equation showed that \( p = 8 \) yields good approximations to the effects of spontaneous and light-evoked waves on the dendritic synapses. Moreover, \( p = 8 \) yielded good fits to the orientation tuning curves of ganglion cells measured experimentally [1]. The effects of varying \( p \) are discussed in Section 5. Finally, the parameters \( A_1 \) and \( A_n \) in Eq. (4) were arbitrarily set to one. This can be achieved without loss of generality, because these parameters can be absorbed into \( k \) in Eq. (1).

The light stimuli used to test whether a cell was orientationally selective or isotropic were translating edges, which elicited responses as in Eqs. (2) and (3). From these responses, polar plots were built such that the angle and radius corresponded to the direction of motion and response amplitude respectively. We used these plots to define two criteria to classify a cell as being either orientationally selective or isotropic. We first performed a principal axes transformation to find this plot’s inertia ellipse [42]. A cell was classified as orientationally selective if the length of the ellipse’s major axis was at least three times that of the minor axis. To be classified as orientationally isotropic, the coefficient of variation across the cell’s polar plot had to be < 0.3 (no cell had a coefficient of variation < 0.3 and a ratio between major and minor axes larger than three simultaneously). Cells that were neither orientationally selective or isotropic displayed multi-axis anisotropy.

The data used to evaluate the model came from Sernagor and Grzywacz [1]. Because our focus was on orientation selectivity, we neglected to include directionally selective behavior in the synaptic equation (Eq.

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4 Light responses are first observed at around day -20 in turtle [1]. Their emergence coincides with the appearance of outer segments and ribbon synapses [41]. However, amacrine conventional synapses precede these processes by several days [41]. We started the simulations at day -30 to see how the receptive fields would look like, if ribbon synapses and photoreceptors were already functional.
Fig. 2. Four examples of polar plots of responses to motion from ganglion cells emerging from the model. The left column shows the cells' responses (angle corresponding to direction of motion and radius to response amplitude, with the constant of proportionality between radius and amplitude being arbitrary, but invariant across examples). Also in the left column is the distribution of orientations of the amacrine dendrites feeding each ganglion cell. Each of these dendrites is represented by straight lines whose lengths are proportional to synaptic weights (0 ≤ w, ≤ 1). When the synaptic weight is depressed to zero, a long dashed straight line is drawn to show its orientation. The right column shows the criteria used to classify a cell as orientationally selective, orientationally isotropic, or multi-axis anisotropic. The ellipse in dashed lines is the polar plot's inertial ellipse, with its scale being chosen arbitrarily for graphical purpose. A cell is classified as orientationally selective if the length of the ellipse's major axis is three times that of the minor axis. The hatched area represents the standard deviation of the cell's response across polar plot. A cell is classified as orientationally isotropic if the coefficient of variation is <0.3. If a cell is neither orientationally selective nor orientationally isotropic, then it is classified as multi-axis anisotropic. (A) Immature multi-axis anisotropic cell 20 days before hatching. This cell has a double-axes-anisotropy and thus, fails to pass the test for being orientationally isotropic (coefficient of variation 0.4) and the test for being orientationally selective (ratio 1.5). (B) Mature orientationally isotropic cell. Because of the small deviations about its mean response (coefficient of variation 0.18), and because of the relative 'circularity' of its inertial ellipse (ratio 1.6), this cell is classified as orientationally isotropic and not orientationally selective. (C) Immature orientationally selective cell 25 days before hatching. This cell attains its selectivity because of chance orientation of the few dendritic inputs it receives. Its inertial ellipse is narrow (ratio 4.3) and its coefficient of variation is high (0.57). None of its input synapses have been suppressed yet. (D) Mature orientationally selective cell. Despite having a large number of dendritic inputs, this cell has one axis of preferred orientation illustrated by a narrow inertial ellipse (ratio 5.0) and a large coefficient of variation (0.7). Five of these cells' dendrites are shown in dashed lines as their associated synaptic weights have been completely depressed.
(3)). Such behavior could arise if one took the dendritic dynamics into account [43]. This is how Sernagor and Grzywacz interpreted their early directional selectivity. If their interpretation were correct, then some of the cells we call orientationally selective would actually be directionally selective in Sernagor and Grzywacz's data. Hence, our paper aggregated Sernagor and Grzywacz's orientationally and directionally selective cells for purpose of comparing their percentages to those of the model.

4. Results

We classified cells as orientationally isotropic, orientationally selective, or multi-axis anisotropic according to the appearance of the polar plots of their responses to motion (angle corresponding to direction of motion and radius to response). Four examples of such polar plots for these classes of cells after they emerged from our model are shown in Fig. 2. At early stages of development, immature cells exhibited either orienta-
tion selectivity or multi-axis anisotropy. The polar plots for the multi-axis anisotropic cells (for instance, Fig. 2A) resembled those obtained experimentally [1]. The modeled multi-axis anisotropic cells (Fig. 2A) failed to pass the criterion for being isotropic because the coefficient of variation across their polar plot was large. They also failed to pass the criterion for being orientationally selective, because their inertial ellipse was almost circular. At later stages of development, they disappeared, while orientationally isotropic cells emerged. These isotropic cells had homogeneous dendritic-input and synaptic-weight distributions (Fig. 2B). Orientation selectivity occurred at all stages of development, always having inhomogeneous synaptic-weight distributions. However, whereas early on, their dendritic inputs were polarized (Fig. 2C), later on, they were not (Fig. 2D).

Good fits to experimental data [1] on the time course of development of the percentage of orientationally isotropic and selective cells are shown in Fig. 3 (as explained in Section 3, we lumped the experimental percentages of orientation and directional selectivities). The model captured the complex features of the experimental time course. In particular, the fits captured the fast-then-slow rise of the percentage of orientationally isotropic cells and the fall-then-rise-then-fall behavior of orientation selectivity. Chi-square tests for these fits gave $0.75 < P(x^2 \geq 1.43) < 0.9$ (four degrees of freedom) for orientationally isotropic cells and $0.999 < P(x^2 \geq 0.06) < 1$ (four degrees of freedom) for orientationally selective cells. We did not apply any optimization techniques to get these fits, but rather performed an exploration of the parameter space.

To obtain the good fits in Fig. 3, we had to set the maximum number of amacrine dendritic contacts ($m$) to 20. The results of varying this number in steps of five appears in Fig. 4. When reduced to 15, dramatic changes in population percentages occurred as no more orientationally isotropic mature cells could be observed and 90% of the mature cells (instead of 30%) were classified as orientationally selective. In contrast, when $m = 25$, the percentage of orientationally isotropic cells increased significantly to the detriment of orientationally selective cells. A similar effect was obtained by varying the transition point between LTD and LTP, i.e. by varying $k_2$ (Fig. 5). A reduction in this parameter by about 20% and an increase by 100% resulted in comparable effects on population percentages as the reduction and increase of $m$ caused in Fig. 4, respectively. This similarity of effects is because an increase in the number of dendrites effectively induces more LTP, by causing more postsynaptic activity.

Doubling the ratio between the rates of dendritic arrival and synaptic maturation ($\lambda/k$) caused orientationally isotropic cells to emerge faster and the minimum in the population percentage of orientationally selective cells, normally observed around hatching (Day 0), to shift towards earlier stages of development (Fig. 6). This condition did not affect much the percentages of mature cells. In contrast, reduction of $\lambda/k$, by a factor of two reduced the number of mature orientationally isotropic cells.

![Orientationally Isotropic Cells](image1.png)

![Orientationally Selective Cells](image2.png)

Fig. 3. Good fit of the model to experimental data on the time course of development of the percentage of orientationally selective and isotropic cells. Experimental data from turtle retina [1] are shown with ○; from left to right, the data points correspond to a total of 16, 19, 34, 10 and 30 cells. Solid lines show the model's fits obtained for $m = 20$, $k_2 = 1.3$ and $\lambda/k = 7.7$. The fits are qualitatively good and account for complex features of the data such as the fall-then-rise-then-fall behavior of the incidence of orientation selectivity.
Fig. 4. Effects of variations of the maximum number of dendrites \( m \) on the time course of development of the percentage of orientationally selective and isotropic cells. The solid line shows the good fit of the model from Fig. 3, \( m = 20 \). In the other simulations, \( m \) is reduced to 15 (dotted lines) and increased to 25 (dotted-dashed lines). The tendency for forming orientationally isotropic cells and against forming orientationally selective cells increases with \( m \).

...cells (about 15%), increased the number of mature orientationally selective cells (about 55%), and resulted in noisy time courses for both classes of cells.

Finally, the time course of the development of the percentages of both classes of cells was investigated in the absence of synaptic maturation (which corresponds to \( k_1 = 0 \) in Fig. 7). This case yielded monotonic time courses with slopes determined by the rate of dendritic growth. When no more dendrites appeared, these time courses leveled off. Consequently, a Hebbian mechanism, such as described by the covariance rule [35] or our own rule (Eqs. (1) and (2)), is important in the model for the rise of the percentage of orientationally selective cells after birth. In addition, in the absence of a Hebbian mechanism, the percentage of orientationally isotropic cells that emerged was lower than normal, to the detriment of orientationally selective cells. Hence, the Hebbian process is important in the model for the transformation of many cells from orientationally isotropic to selective.

5. Discussion

5.1. Possible roles for early dendritic polarization

Perhaps the most important hypothesis emerging from this paper is that the ‘wiring noise’ provided by the poor branching and small number of synapses early in development may provide the seed for mature orientation selectivity. The paradox that this hypothesis may solve is how strong orientation selectivity exists in cells with isotropic dendritic trees, receiving contacts from isotropic cells. If anisotropies in early wiring noise are reinforced by Hebbian mechanisms, they may be imprinted in the synapses for life even if the cells’ dendrites lose their anisotropies. This conclusion confirms and substantially extends a similar conclusion based on a much simpler model of retinal development [38]. That model (itself a modification of an earlier model by Linsker [6]—see also MacKay and Miller [8]) used the computationally simple (but physiologically implausible) linear covariance Hebbian rule [34]. In that work, to determine what kinds of receptive field could emerge, we first determined what the covariance matrix would be if instead of uncorrelated noise (used by Linsker), the noise assumed the form of spontaneous waves exciting ganglion cells through polarized amacrine dendrites. Then, to determine the possible stable state vectors, we performed an eigenvector analysis [8,44]. Despite the covariance-based and eigenvector-analysis simplifications in that work, similar conclusions emerged as in this paper on the role of early dendritic polarization. However, the early model could not account for the time course of development, but just its asymptotic behavior.

Polarization of poorly branched dendritic trees characterize immature cells [15,12,16,17]. Simulations of our biophysical model for the time course of development of receptive fields suggest that dendritic polarization may promote the formation of anisotropic receptive
fields. This provides a simple explanation for the high percentage of anisotropic cells found early in development. Besides having a high incidence of orientation selectivity, immature cells in the model also exhibit multi-axes anisotropy (Fig. 2A), consistently with experimental data from embryonic turtle retina [1]. The model's early anisotropies are due to the small number of dendritic contacts, which thus have a high probability of causing chance anisotropies.

As the number of dendrites grows in the model, dendritic-related orientation biases average out in many cells and thus, the incidence of orientation selectivity falls and that of orientationally isotropic cells rise (Fig. 3). This result of the simulations is consistent with the embryonic time course of development of the percentage of orientationally isotropic and selective cells in turtle retina [1]. The time course of cell populations are found to be directly related to the rate of appearance of new dendrites and their maximal number, which therefore, may be important parameters of development. An anatomical interpretation of this number is that the dendritic components that may contribute to the formation of orientation selectivity are neither the primary dendrites, nor the very endings of the dendritic trees, but small branches of relatively parallel dendrites (see Section 2). When this number is raised in the simulations, it leads to a higher percentage of orientationally isotropic cells (Fig. 4), an effect that matches well experimental conditions where dark-reared turtles have been found to have larger and more branched dendritic
trees (E. Sernagor, personal communication) and correspondingly, higher percentages of orientationally isotropic ganglion cells than normal-reared turtles [24].

5.2. Possible roles for Hebbian mechanisms

Physiological evidence for Hebb-like mechanisms in the retina is still unavailable. Attempts to demonstrate their existence in the development of rabbit directional selectivity failed [45]. However, one can argue that those attempts used rabbits too old to show any developmental plasticity in their retinas [46]. Furthermore, our model had to rely on such plastic (Hebbian) mechanisms to account for the rise in the incidence of orientationally selective cells after Day 0. These mechanisms provided a way by which some particular dendritic configurations had their orientation biases amplified to give rise to mature orientation selectivity. This amplification happened when the number of dendrites reached a critical mass (at around Day 0) and LTP began becoming more prominent than LTD.

5.3. Possible roles for spontaneous and light-evoked waves of activity

In the developing retina, there is evidence for waves of spontaneous discharges propagating across the retinal surface and in the process, correlating the activity of neighboring cells (see Section 1). This correlation is observed during a critical period of synaptogenesis.

Fig. 5. Effects of variations of the transition point between long-term depression and potentiation ($k_2$) on the time course of development of the percentage of orientationally selective and isotropic cells. The solid lines are as in Fig. 4. In the other simulations, $k_2$ is reduced from 1.3 to 1.0 (dotted lines) and increased to 2.0 (dotted--dashed lines). The tendency for forming orientationally isotropic cells and against forming orientationally selective cells increases with $k_2$. 
[47,48], and dendritic growth and remodeling [49]. One must thus ponder on the role that these spontaneous correlating waves of activity may have in the formation of retinal receptive fields. Recent data strongly suggest that waves promote both the formation of orientationally isotropic receptive fields and control of their size. Normally, in turtle, the wave-like activity lasts until about P21 and then disappears [1]. Coincidentally with the disappearance of waves, the receptive-field sizes mature [1]. However, if one dark-rears the turtles, the wave-like activity is stronger and longer lasting (> P30), and the receptive fields become larger and more isotropic [1,24]. Furthermore, the density of growth cones (and thus of dendritic growth) increases under dark-rearing [50]. In turn, if one blocks the waves chronically by implanting in the retina curare-soaked Elvax [2,24], the receptive fields stop growing and become less isotropic.

Although spontaneous waves are key for the development of orientationally isotropic cells, light-evoked waves may be the relevant ones for orientation selectivity. Chronic blockade of spontaneous wave does not prevent the percentage of orientationally selective cells from reaching its normal level [2]. Therefore, if one observes that the outburst of orientation selectivity after birth is fueled by a Hebbian mechanism, then the relevant activity is not spontaneous, but probably light evoked. Why would development wait for light-evoked waves to boost orientation selectivity if it could use spontaneous waves? One reason may be that light-evoked waves have sharper wavefronts than the spontaneous ones. Consequently, the narrower light-evoked waves may be better suited to elicit differential responses from a polarized dendrite (see discussion after Eq. (3)), leading to more orientation selectivity (in other words, p may be larger for light-evoked waves than for spontaneous ones). Burgi and Grzywacz [38] obtained a similar result, i.e. a negative correlation between wave smear and the mature percentage of orientationally selective cells, using the covariance Hebbian rule.

5.4. Are oriented inputs required for the formation of orientation selectivity?

In the discussion above, we postulate that early orientational biases of dendritic trees can be amplified by a Hebbian mechanism so as to lead to mature orientationally selective cells, in spite of the homogenization of the trees. Is this postulate valid for any kinds of input activity, whether correlated and oriented (e.g. waves), or not? In principle, the answer to this question is positive, because uncorrelated spontaneous activity on the first layer can lead to anisotropic receptive fields on the second layer if the dendritic tree is polarized (to be convinced of this, think about a dendritic tree with only one dendrite). However, as shown by Linsker [6], such anisotropic structures cannot be stable if the dendritic tree is symmetrical and the input activity uncorrelated. In addition, extension of Linsker's work to spontaneous waves and uncorrelated activity hitting dendrites has provided evidence that
oriented inputs enormously boost the emergence of orientation selectivity [38] (Fig. 5, bottom panel). Consequently, the final outcome of the receptive fields does not only depend on early dendritic polarization and the Hebbian mechanism, but also depends on the statistics of the input activity to guarantee stability of anisotropic structures.

5.5. Directional selectivity

The time course of the percentages of various types of ganglion cells suggest that mature retinal directionally selective cells emerge from orientationally selective cells existing during the first month of life [1]. Grzywacz et al. [46] postulated that the placement of GABAergic synapses at the output of the amacrine cells giving rise to orientation selectivity could transform the corresponding ganglion cells into directionally selective. This postulate is consistent with recent data on retinal directional selectivity, which show that some of this computation arises at the synapses between cholinergic-amacrine and directionally selective ganglion cells [51]. This consistency is not surprising, because these data were taken into account when we designed our model. We could have placed the dendritic anisotropy relevant for orientation selectivity not on the amacrine inputs, but directly on ganglion-cell dendrites [24]. However, since mature directional selectivity seems to arise in part in amacrine dendrites, and since it may be transformed orientation selectivity, it seemed reasonable to use amacrine dendrites as the source of the anisotropy in our model.

5.6. Speculations on species differences based on the model

Because our model accounts well for the turtle data, we wondered whether a similar model with appropriate parameter changes could explain the relative incidence of orientationally selective and isotropic cells in the retinas of other species. Of particular relevance is a comparative study involving the ratio between conventional and ribbon synapses in the inner-plexiform layer of various species. Conventional and ribbon synapses onto ganglion cells are made by amacrine and bipolar cells, respectively [10]. If the ratio between these synaptic types is large, it suggests a relatively high incidence of ganglion cells that receive polarized amacrine dendritic inputs during development. This ratio was found to be low in primates and cats, and high in rabbits, squirrels and frogs [52]. Based on this finding, our model accounts for the higher relative incidence of complex receptive-field properties such as orientation selectivity in small-brain vertebrates than in large-brain vertebrates (ref. [53]). Hence, the model suggests how retinal developmental mechanisms are adapted to achieve the negative correlation observed between the complexity of retinal physiology and the degree of encephalization of visual analysis [54,55].

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**Fig. 7. Effect of eliminating the Hebbian mechanism ($k_1 = 0$) on the time course of development of the percentage of orientationally selective and isotropic cells. The solid lines are as in Fig. 4. The dotted lines are for the non-Hebbian case. This case yields time courses that are only dependent on the statistics of polarization of the dendritic inputs and thus, for example, does not produce a rise in orientation selectivity after Day 0.**
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Appendix A. Appendix

In a recent paper [33], we derived a Hebbian rule that accounts for basic LTP and LTD phenomenology in hippocampus. In this rule, a feedback messenger \( m \) originating at the postsynaptic site activated presynaptic enzymes controlling synaptic strength \( w \). These enzymes worked by controlling the active and inactive states of a gating molecule. For computational simplicity, it was assumed that the synaptic weight is proportional to the active state's concentration. Moreover, to ensure that no synaptic change occurs in the absence of pre- and post-synaptic activity, we postulated a molecular switch. This switch would operate presynaptically and would be turned on by the messenger \( m \) to allow for synaptic changes. A possible implementation of this switch was described by the following equation

\[
\frac{d[E_{a,i}]}{dt} = -k_a[E_{a,i}] + ([E_{a,0} - [E_{a,i}])k_3 + k_3[m_i][E_{a,i}])
\]

(A1)

where \( 1 \leq i \leq p \) and \( p \) is the number of synapses, \( E_{a,i} \) is the active state of the switch, \( k_1, k_2 \) and \( k_3 \) are the rate constants of the reactions, \( [E_{a,0}] \) is the maximal concentration of active switches, and \( [m_i] \) is the concentration of feedback messenger produced by synaptic activity. This concentration is assumed to be proportional to the local concentration of a postsynaptic agent, such that \( [m_i] = \alpha R w I_i \), where \( I_i \) and \( R \) are pre- and postsynaptic activities, respectively, \( w_i \) is the strength of the \( i \)th synapse, and \( \alpha \) is a constant.

The feedback messenger activates two presynaptic enzymes, which control synaptic strength by shifting the balance of the gating molecule either towards its inactive or active state. One enzyme reduces synaptic strength in proportion to the enzyme's current concentration and is activated by the feedback messenger with a stoichiometry of \( \alpha \), while the other enzyme requires \( n > 1 \) molecules of the messenger to increase synaptic strength (stoichiometry of \( n \)). The switch allows back and forth transitions between the active and inactive states of the gating molecule, depending on the amount of messenger. To achieve this goal, the switch promotes the transitions from these states to a transient unstable metastate. This metastate decays enzymatically back to the active and inactive states with rate constants that depend on the messenger. Assuming that the decay from the metastate is much faster than the arrival to it, one can express the variation of \( w \) as follows (for details, see ref. [33])

\[
\frac{dw_i}{dt} = -k_a[E_{a,i}](k_3 + k_3[m_i])w_i + k_3[E_{a,i}](k_3 + k_3[m_i])w_i - w_i
\]

\[
(k_3 + k_3 + k_3[m_i] + k_3\beta[m_i])
\]

(A2)

where \( w_0 \) is the maximal possible synaptic weight, \( k_3 \) and \( k_3 \) are rate constants of thermic reactions, \( k_3, k_3, k_3 \) and \( k_3 \) are rates of enzymatic reactions, and \( \beta \) and \( \gamma \) are constants linking \( m \) to the enzymes.

Because these two differential equations involve a large number of parameters (16), and because the equations are highly nonlinear, their implementation in a serial digital computer is slow, in particular, when the number of synapses is large. Therefore, we looked for simplifications of these equations. Consequently, in this Appendix, we propose five approximations to obtain a Hebbian rule that reduces to one differential equation (instead of two), with four parameters (instead of 16), and which retains most of the properties of the original Hebbian rule:

1. The thermic effect controlled by the rates \( k_3 \) and \( k_3 \) can be neglected if one assumes that the decay from the metastate is entirely determined enzymatically (and thus \( k_3 = k_3 = 0 \)).

2. The transitions from the active and inactive states of the gating molecule to the transient unstable metastate can, for the sake of simplicity, be taken to have the same reaction rates \( k_3 = k_3 \).

3. The switch can be assumed to be turned on and off by the messenger rapidly and completely, as the switch involves a positive feedback (second term of the right hand side of Eq. (A1)) and \( k_3 < < k_3 \) [33]. Thus, we can assume the active state \( w \) to be dominated by the dynamics of the messenger, an assumption that permits to eliminate Eq. (A1). Instead of this equation, the switch's concentration will be either at its maximal value \( [E_{a,0}] \) when the input is not negligible \( (I_i) \) or at zero when the input is negligibly small.

4. We can assume that Hebbian modulations of synaptic weight are much slower than activity modulations. Therefore, one can replace \( [m_i] \) in Eq. (A2) by \( \alpha w I_i \) and \( [m_i]^n \) by \( \alpha w^n (RI)_i \), where the overlines indicate temporal averages over some suitable period.

5. \( w_0 \) can be absorbed into a new, normalized variable \( \hat{w} = w/w_0 \), without affecting the behavior of the Hebbian rule.

Making these simplifications, one gets
\[ \frac{d\tilde{w}}{dt} = 0 \quad \text{if} \quad \frac{R_I}{c^*} \approx 0 \quad (A3) \]

and

\[ \frac{d\tilde{w}}{dt} = -\tau_{R_I} \tilde{w} + k(1 - \tilde{w}) \tilde{w}^2 \left( \frac{R_I}{c^*} \right)^{\gamma} \quad \text{if} \quad \frac{R_I}{c^*} > 0 \quad (A4) \]

where \( \epsilon = k_{4}[E_{act}] = k_{4}[E_{in}] \) determines the rate of synaptic modification and \( k = k \cdot k_{17}/\beta \cdot x^{n-1} \cdot y^{n-1} \).

The first (negative) and second (positive) terms of the numerator of the right hand side of this simplified equation cause LTD and LTP, respectively. The balance between LTD and LTP is controlled by the parameter \( k \). Finally, regardless of the parameter values, if \( 0 \leq \tilde{w}(t = 0) \leq 1 \), then this condition will be maintained at \( t > 0 \). This is because as \( \tilde{w} \to 1 \), the LTD term converges to zero, stopping \( \tilde{w} \)'s growth, while as \( \tilde{w} \to 0 \), the LTD term converges to zero, stopping \( \tilde{w} \)'s fall.

References


