From Retinal Waves to Activity-Dependent Retinogeniculate Map Development

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Abstract

A neural model is described of how spontaneous retinal waves are formed in infant mammals, and how these waves organize activity-dependent development of a topographic map in the lateral geniculate nucleus, with connections from each eye segregated into separate anatomical layers. The model simulates the spontaneous behavior of starburst amacrine cells and retinal ganglion cells during the production of retinal waves during the first few weeks of mammalian postnatal development. It proposes how excitatory and inhibitory mechanisms within individual cells, such as Ca2+-activated K+ channels, and cAMP currents and signaling cascades, can modulate the spatiotemporal dynamics of waves, notably by controlling the after-hyperpolarization currents of starburst amacrine cells. Given the critical role of the geniculate map in the development of visual cortex, these results provide a foundation for analyzing the temporal dynamics whereby the visual cortex itself develops.

Introduction

This article describes a neural model of how spontaneous retinal waves are formed in infant mammals, and how these waves organize activity-dependent development of a topographic map in the lateral geniculate nucleus, or LGN, with connections from each eye segregated into separate anatomical layers of the LGN (Figure 1). Recent work in imaging the retina through multielectrode arrays [1] and fluorescent dyes [2] before eye opening in mammals, and some invertebrates, has cast new light on how these spontaneous traveling waves in the retina are formed. While their existence has been known for over two decades [3], experimentalists have just begun to untangle their molecular basis and functional implications [4–11]. Our model builds upon previous theoretical work [2,12–14] to clarify key properties of these waves and to show how these properties may function to organize the development of the retinogeniculate map. The model includes two key cell types: starburst amacrine cells (SACs) and retinal ganglion cells (RGCs) that interact through time.

Albeit simple, the new model goes beyond earlier modeling efforts by explicitly accounting for the role of intracellular mechanisms such as Ca2+-activated K+ channels, cAMP, and afterhyperpolarization currents (AHPs) in controlling spatiotemporal properties of retinal waves [5]. These results include novel predictions concerning how these intracellular mechanisms regulate retinal waves. For example, the model predicts that decreasing the strength of AHPs, formulated here as an activity-dependent recovery process (see equation (7)), increases the frequency and velocity of the waves generated by SACs, and vice versa for increasing the strength of AHPs. Thus, our model advances current knowledge by simulating how single-cell currents may give rise to emergent dynamical network properties, such as wave velocity, shape, and periodicity.

Retinal waves cause spontaneous bursts of action potentials in RGCs, on the order of 10–100 Hz, that move in a wave-like fashion across 1.5–2 mm² sections of the retina in the first two weeks of postnatal development, just prior to eye opening in cat, ferret, and mouse. There are two stages of retinal waves, normally classified into early (<P8) and late (>P8) stage waves. This article concerns early stage waves only, which have been more fully characterized as spatially correlated patterns of activity that travel across the RGC network. Blockade of nicotinic acetylcholine receptors (nAChRs) in the retina leads to the disruption of waves, as well as of the development of the early visual system [8] (although see [15]). The mature organization of the mammalian LGN thus appears to be both caused [16] and maintained [17] by spontaneous retinal activity. The current model simulates how the retinal waves can organize retinogeniculate map development, leading to a learned map in which each eye activates a different layer (A or A1) in the LGN. Moreover, retinal waves also may play a role in the early formation of receptive field properties and ocular dominance columns in V1 [18].

Materials and Methods

Model Retina

As noted above, the model (Figure 1) incorporates interacting SACs and RGCs, in keeping with experimental data [15] and the
structure of previous models [2,14] about retinal waves. Model SACs occupy the first layer, where they are laterally connected to each other with isotropic distance-dependent Gaussian weighting functions. Anatomical data estimate their effective input radius at approximately 100μm [9]. This lateral communication approximates the function of transmission via nicotinic acetylcholine receptors (nAChRs) during early development, which are thought to be a critical mediator of waves and thereby retinogeniculate development [8,19]. Spontaneous activity within the SACs is generated using a Poisson process.

In (1), subscript l denotes the left eye and r the right eye. In the Poisson distribution in (4) that defines the probabilistic input term \( I_{ej} \), \( Pr \) denotes the probability, and \( \lambda = 0.0025 \). The excitatory recurrent interactions \( \sum_{pq} w_{ijpq} s_{pq}^{+} \) in (3) between SAC cells are mediated by Gaussian connection weights across space:

\[
w_{ijpq} = L^S \frac{1}{2\pi \sigma_1^S \sigma_2^S} \exp \left[ -\frac{(i-p)^2}{(\sigma_1^S)^2} - \frac{(j-q)^2}{(\sigma_2^S)^2} \right],
\]

where \( L^S \) is a scaling factor, and \( \sigma^S \) defines the variance along the x and y axes, which are assumed to be equal, as suggested by data from imaging of SACs [9]. The recurrent signal function in (3) is a half-wave rectified function of cell activity; e.g.,

\[
\left\{ \begin{array}{ll}
S_{leij} = \frac{1}{2} \left( 1 + \text{erf} \left( \frac{X_{leij}}{\sigma_{leij}} \right) \right) & \text{for } X_{leij} > 0 \\
S_{leij} = 0 & \text{for } X_{leij} < 0 
\end{array} \right.
\]

respectively. As in (2), parameter \( A^S \) in (3) is the decay rate; \( B^S \) is the excitatory saturation point; \( I_{lj} \) and \( I_{rq} \) are endogenously active inputs that are defined by a Poisson distribution:

\[
\Pr \{ I_{lj} = k \} = \frac{\lambda^k}{k!} e^{-\lambda}.
\]
In (7), $A^R$ is the rate at which each $r$ increases, analogous to intracellular mechanisms that lead to inhibition as a result of spiking; e.g. Ca$^{2+}$-activated K$^+$ channels [21]. By the same token, $B^R$ defines the rate with which each $r$ decreases, thereby upregulating the excitability of each SAC, similar to the role of cAMP and its correspondent signaling cascades [3,22]. The variable $r$ is similar to the recovery variable used in the Fitzhugh-Nagumo equation to describe the spiking rate of a single neuron [23]. It describes the overall state of activity-dependent intracellular processes that modulate a cell’s firing rate. The variable $r$ increases when the cell begins to fire, and it steadily decreases once the recovery variable has sufficiently suppressed the firing rate. For example, an increase in the SAC cell activity $s_{ij}$ in (3) leads to an increase in $r_{ij}$ in (7) that, in turn, suppresses $s_{ij}$ via (3), leading to a subsequent decrease in $r_{ij}$ until $r_{ij}$ can no longer suppress $s_{ij}$. This interaction qualitatively simulates the recruitment of Ca$^{2+}$-activated K$^+$ channels, which have been shown to control the AHPs of SACs using in vitro whole cell patch clamp [24]. More precisely, an increase in a cell’s firing rate leads to an increase in the intracellular concentration of Ca$^{2+}$ which, in turn, opens Ca$^{2+}$-activated K$^+$ channels that act to electrically shunt the cell by increasing K$^+$ conductance on a slow timescale, decreasing the membrane resistance for tens of seconds. It also appears that these channels are voltage-independent (similar to the small conductance, or SK, channels) and can only be opened by an increase in cytosolic Ca$^{2+}$ [24], although cytosolic Ca$^{2+}$ can be affected by the conductance of voltage-gated Ca$^{2+}$ channels.

**Retinal Ganglion Cells**

The SACs send half-wave rectified signals to the RGCs, which smooth SACs activity through leaky integration. The activities $g_{ij}$ and $r_{ij}$ of RGCs in position $(i, j)$ in the left ($l$) and right ($r$) eyes obey:

$$\frac{dg_{ij}}{dt} = -A^G g_{ij} + (B^G - g_{ij}) \sum_{pq} w_{ijpq}^{G} [s_{pq}]^+,$$

respectively, where $e = l$ or $r$. In (2), the weights $w_{ijpq}^{G}$ are Gaussian functions of distance with the same spatial parameters as in (5). Finally, the RGC output signals to the LGN are thresholded at a positive threshold $\Gamma^G$.

![Figure 2. Depiction of a model wave generated using the parameters given in Table 1 (A) and through randomizing SAC refractory periods (B and C). Model RGCs are shown using an intensity plot where the brightness scales with the firing rate. The waves propagate in a radially symmetric pattern due to the isotropy of the SAC lateral weights, or model dendrites. Other geometries were achieved through randomizing $B^R$ by choosing $B^R$ from a normal distribution centered on 0.9 where $\alpha = 0.3$ (negative values were set to zero). doi:10.1371/journal.pone.0031553.g002](image1)

![Figure 3. Inter-wave interval (IWI) distributions from Ca$^{2+}$-imaging data (A) and the model simulation (B). A comparison the IWI distributions from model simulations with Ca$^{2+}$-imaging data [2]. The Ca$^{2+}$-imaging data is derived from multiple retinas. Likewise, the simulation results are an aggregate of multiple simulations that used different values of $A^R$ (6,6.15,6.3,6.45,6.6,6.75,6.9,7.05). [Experimental data in (A) are reproduced with permission from [2]]. doi:10.1371/journal.pone.0031553.g003](image2)
By (9), model RGCs act as a set of thresholded leaky integrators that remove noise from the SAC layer--that is, the RGCs only relay activity at a sufficiently high firing rate--similar to the model in [2]. Supporting this assumption, experimental data have demonstrated that, outside of bursting related to waves, RGC activity may not be tightly coupled to SAC activity [24]. See Table 1 for the parameters for the model retina.

Lateral Geniculate Nucleus Cells

The RGC outputs activate cells in the dorsal LGN (dLGN) in layers $A$ and $A_1$ whose activities $x_{ij}^A$ and $x_{ij}^{A1}$ at position $(i,j)$ obey the equations:

$$\frac{dx_{ij}^A}{dt} \sim \begin{cases} A_L x_{ij}^A + (B_L - x_{ij}^A) \sum_{pq} w_{eijpq} f(g_{epq}) & \text{if } g_{epq} > G^G \\ 0 & \text{otherwise} \end{cases}$$  \quad (10)$$

and

$$\frac{dx_{ij}^{A1}}{dt} \sim \begin{cases} A_L x_{ij}^{A1} + (B_L - x_{ij}^{A1}) \sum_{pq} w_{eijpq} f(g_{epq}) & \text{if } g_{epq} > G^G \\ 0 & \text{otherwise} \end{cases}$$  \quad (11)$$

respectively. The adaptive weights $w_{eijpq}^A$ and $w_{eijpq}^{A1}$ in (10) and (11) from the RGC at position $(p,q)$ and eye $e=(l,r)$ to the dLGN cell at position $(i,j)$ and layer $d=(A,A_1)$ are initially chosen at time 0 to obey the equations.

Figure 4. Comparison of waves per minute (A), and velocity (B), between simulations while increasing $B^R$ in (8), a parameter analogous to excitatory intracellular mechanisms (e.g. cAMP-related signaling cascades) in experiments conducted under various levels of cAMP. In (A), the average waves per minute (WPM) is compared between the model (right) and an experiment (left) under forskolin treatment, an agonist of cAMP [5]. Here, WPM monotonically increases as a function of $B^R$, similar to the forskolin treatment in vitro. In (B), the average velocity is given for model simulations (right) and cAMP perturbations in the same experiment (left). Generally, velocity increases with $B^R$ in the model, which is also observed under pharmacological manipulation of cAMP levels. For the model, the mean movement of the centroid of the wave across time is used as a measure of velocity, as in (25).

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Figure 5. Single cell dynamics of a model SAC when setting $B_R^R$ in (8) low (A), and high (B), to .09 and .095, respectively. Shown are the dynamics of a single cell in a full simulation of the model retina over 1000 seconds. Here, $s$ is the firing rate of the model SAC, and $r$ the amount of inhibition due to intracellular processes. By setting $B_R^R$ high, the decay rate of inhibition decreases, analogous to the application of forskolin to acute retinal slices. This has the effect of increasing both the WPM and the wave velocity (see Figure 4).
doi:10.1371/journal.pone.0031553.g005

Figure 6. The effect of changing model parameters on waves per minute (WPM). The effects on WPM of varying the following parameters were studied: leak $\lambda^S$ and maximum excitability $B^S$ in model starburst amacrine cells (SACs)–see (3); similar parameters $\lambda^G$ and $B^G$ in model retinal ganglion cells (RGCs)–see (10); and other intracellular excitatory $B^R$ and inhibitory $A^S$ mechanisms in the AHP currents–see (8). Increasing $A^S$ or $B^G$ decreases WPM, while increasing $B^R$ or $B^S$ increases WPM. The parameters $A^G$ and $B^G$ governing the behavior of model RGCs have no significant effect on WPM, indicating that SAC dynamics alter WPM. Means of WPM across multiple simulations are shown, with error bars indicating the standard deviation.
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\[ w^{d}_{eijpq} = b^d_{ijpq} (g_{ijpq} + N^d_{eijpq}), \]  
where \[
x_{ijpq} = \begin{cases} 
    z^L & \text{if } p = i \text{ and } q = j - 1, j, or j + 1 \\
    0 & \text{otherwise}
\end{cases}
\]  
and \[ N^d_{eijpq} \] is a random number drawn uniformly from \([0, \eta]\).

This defines a noisy topography where arborization from retinogeniculate axons undershoots and overshoots its target along the dorsoventral axis in early development [25,26]. The eye-specific bias terms \(b^d\) in (12) multiply the afferents from the left eye to layer A and the right eye to layer A1 by an eye-specific scaling factor with parameter \(b^A_L\) for the projections from the left (right) eye to layer A and \(b^A_R\) for projections from the right (left) eye to layer A1. As a result, afferents from both eyes contact both layers of the LGN, albeit with a slight bias to the eye that eventually dominates, prior to the critical stage of mammalian retinogeniculate development of eye-specific layers [26,27].

The activity-dependent release of learning-inducing neurotrophins from dLGN cells is modeled by sigmoid signals of LGN activities:

\[ X^A_{ij} = \frac{(x^A_{ij})^2}{10 + (x^A_{ij})^2}, \]  
and

\[ X^{A1}_{ij} = \frac{(x^{A1}_{ij})^2}{10 + (x^{A1}_{ij})^2}. \]

Retinogeniculate Map Learning

Learning in the adaptive weights \(w^{d}_{eijpq}\) and \(w^{A1}_{eijpq}\) in equations (10) and (11), from the eyes \(e = (L, R)\) to the LGN layers A and A1 is gated on and off by these neurotrophic signals, and obeys the following equations:

\[
\begin{align*}
\frac{dw^A_{eijpq}}{dt} &= A^RLX^A_{ij} f(g_{pq}) \left[ B^{RL} - \sum_{p'q'} w^{A}_{eijpq} \right] - w^A_{eijpq}, \\
\frac{dw^{A1}_{eijpq}}{dt} &= A^{RL}X^{A1}_{ij} f(g_{pq}) \left[ B^{RL} - \sum_{p'q'} w^{A1}_{eijpq} \right] - w^{A1}_{eijpq},
\end{align*}
\]

Retinal Waves and Retinogeniculate Map Development

Learning in the adaptive weights \(w^{d}_{eijpq}\) and \(w^{A1}_{eijpq}\) in equations (10) and (11), from the eyes \(e = (L, R)\) to the LGN layers A and A1 is gated on and off by these neurotrophic signals, and obeys the following equations:

\[
\begin{align*}
\frac{dw^A_{eijpq}}{dt} &= A^RLX^A_{ij} f(g_{pq}) \left[ B^{RL} - \sum_{p'q'} w^{A}_{eijpq} \right] - w^A_{eijpq}, \\
\frac{dw^{A1}_{eijpq}}{dt} &= A^{RL}X^{A1}_{ij} f(g_{pq}) \left[ B^{RL} - \sum_{p'q'} w^{A1}_{eijpq} \right] - w^{A1}_{eijpq},
\end{align*}
\]

Figure 7. The effect of changing model parameters \(A^S, B^S, A^G, B^G, A^R, B^R\) on wave velocity. The effects on velocity are weak, but statistically significant. As with WPM, increasing \(A^S\) and \(A^G\) decreases velocity, and vice versa for \(B^S\) and \(B^G\). Unlike the periodicity of waves, their velocity is significantly modulated by the properties of the model RGCs via \(A^R\) and \(B^R\).
Equations (17)–(20) define a self-normalizing instar learning law [28–30] wherein $A^{RL}$ is a learning rate and $B^{RL}$ a limited growth factor released by coincident LGN bursting $\langle X_{ij}^d \rangle$, where $d$ equals $A$ or $A1$, and RGC bursting $f(g_{opp})$. Learning and forgetting are both gated by postsynaptic activity $\langle X_{ij}^d \rangle$. This process could be carried out through the use of a limited growth factor, such as BDNF or NT-4 [31,32], when there is a coincident rise in the firing rates of RGCs and dLGN cells [33,34]. Competition for a limited neurotrophin is shown herein to cause bounded synaptic growth. It allows for the eye with a slight initial advantage to dominate a given layer of the dLGN. In particular, as weights with a slight bias grow, they prevent the growth of other competing weights.

Models that rely on inter-synaptic competition have used explicit divisive or subtractive normalization to achieve similar

![Figure 8. Simulation of retinogeniculate development.](image)

(A) The normalized dominance of the initially biased eye grows. For both layers A and A1, the eye that is initiated with weights slighter larger than the other comes to ‘dominate’ that layer over the course of 5,000 s of waves (see (22)). (B) Additionally, the mean distance of the CoM from an ideal CoM for the retinogeniculate weights decreases, indicating that the weights projecting to each dLGN cell become increasingly refined; in particular, ectopic projections are pruned away.

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Results

Retinal Wave Simulations

Retinal waves [10] were simulated in order to tease apart the effects of excitatory and inhibitory intracellular mechanisms; e.g., the cAMP and Ca$^{2+}$ currents that are represented in (7). These intracellular mechanisms are assumed to control the AHP of SACs that modulate wave velocity and periodicity. The model replicates the general spatiotemporal properties of waves observed in vitro in a number of animals, including mice and ferrets. A sample wave is depicted in Figure 2. The properties most commonly observed and quantified are the inter-wave interval (IWI), or the time between waves, and the wave velocity [1,2,5]. These properties were the focus of the simulations. Wave events were identified by determining if the number of active cells at a given time point exceeded a predetermined threshold, similar to a method used to quantify neuronal avalanches [36], which are neural events quite similar to retinal waves. The movement of the center of mass (CoM) of cell activity across time was used to measure wave velocity [14], where the CoM for each retina c is defined by:

$$\text{CoM}_c = \frac{\sum_{pq} \text{pos}_{pq} f(g_{pq})}{\sum_{pq} f(g_{pq})},$$  \hspace{1cm} (21)$$

where pos$_{pq}$ denotes position [p, q] and the RGC outputs f(g$_{pq}$) are defined in (9).

First, model simulations were compared to Ca$^{2+}$-imaging data from [2] that were corroborated using a 512 electrode array [1]. The model was numerically integrated for 40000 seconds (approximately 11 hours) using Euler’s method with a time step of 20 ms, and the output of the RGC layer was stored for subsequent analysis. Since the model parameters could not be directly fit to biophysical data (e.g., the batch concentration of forskolin, which increases the intracellular concentration of cAMP), they were determined empirically.

In all the retinal simulations, waves were detected by counting the number of active cells at each time step and comparing with a pre-determined threshold. The algorithm assumes that the beginning and end of a wave are marked by crossing the threshold of 10 cells going active. Thus, if more than ten cells (out of 576) burst, a wave begins, and the wave ends as soon as less than ten cells are bursting. Each time step in between these two events is considered part of a single wave. This algorithm eased the significant computational load of analyzing the simulation results (24$^2$ values over 200000 time steps). Hundreds of identified target waves were checked by eye to ensure the validity of the algorithm.

Figure 3 shows a good qualitative match of IWI distributions between the model and experiment. Increasing parameter $B^R$ in equation (7), analogous to increasing the level of intracellular cAMP or other intracellular excitatory mechanisms, decreases AHPs in model SACs, and thereby shifts both the IWI and velocity distributions to the right (Figure 4). Additionally, the single cell dynamics of model SACs is significantly altered; SAC cells enter an active, or bursting state (i.e., a state of sustained high firing rate) more frequently (Figure 5). Thus, model SACs control IWI, velocity, and SAC firing characteristics using activity-dependent intracellular processes.

To more comprehensively understand how model parameters affect the IWI and velocity, simulations systematically explored the parameter space (see Figures 6 and 7). The results demonstrate that the inhibitory and excitatory terms in the two SAC equations modulate waves in complementary ways: Increasing the SAC decay rate $A^S$ and the excitatory saturation potential $B^S$ in (3) decrease and increase waves per minute (WPM, inversely proportional to IWI) and wave velocity, respectively, and similarly for $A^R$ and $B^R$ in (7). These results predict that upregulating the decay rate or intracellular inhibitory mechanisms (e.g., cytoplasmic Ca$^{2+}$ concentration) of SACs should decrease wave velocity and WPM, while increasing maximum excitability (e.g., density of voltage-gated Na$^+$ channels) or intracellular excitatory mechanisms (e.g., intracellular cAMP concentration) should increase velocity and WPM. Additionally, these simulations show a significant relationship between velocity and WPM, which has been observed in experiments [5] and other theoretical work [2].

![Figure 9. Change in CoM for the model retinogeniculate pathway (from the left retina to layer A1 of the dLGN, both layers develop simultaneously but all results are shown in one pathway for convenience). Using the method of visualizing retinogeniculate weights from [34], the CoM of the weights projecting to a given dLGN cell (see (23)) is depicted as a node connected to its 4 nearest neighbors in solid black (2 for cells at the edge, since the boundaries are non-periodic). The ideal topography is visualized by the dotted grid defined by the points in (23).](doi:10.1371/journal.pone.0031553.g009)
Whereas all SAC parameters influence wave periodicity and velocity, the RGC parameters $A^G$ and $B^G$ only affected wave velocity. This is due to the fast-slow dynamics present in the SACs and the assumption that RGCs merely filter SAC activity en route to the dLGN.

Retinogeniculate Map Development Simulations

Simulations were carried out to demonstrate that waves generated within the model retina can drive the development of a retinogeniculate map whose connections from each eye are segregated into distinct LGN layers A and A1 [37,38] (see Figure 10).

Figure 10. Retinogeniculate development accelerates as wave velocity and wave frequency increases by increasing $B^R$ (see Figure 4). (A) The CoMs approach the ideal grid at a faster pace with accelerated waves, also shown by the sharper decrease in the mean distance of the CoM from their targets (B). doi:10.1371/journal.pone.0031553.g010
equations (10)–(20), Molecular guidance cues, e.g. EphA and EphB [39], presumptively form the initial topography of the retinogeniculate projection while a second stage of activity-dependent refinement prunes ectopic axonal arbors (i.e., arbors that resulted in a breakdown of retinotopy) [25,40,41]. The model retinogeniculate pathway focuses on this second stage of development.

The simulations demonstrate that retinal waves can drive the development of eye-specificity in dLGN layers (Figure 8) as well as refinement of dLGN topography in a single hemisphere (Figure 9). To measure eye-specificity, a normalized measure of the difference in total magnitude (DOM) between the weights projecting from each eye is used:

\[
DOM_A = \frac{\sum_{ipjq} w^A_{ipjq} - \sum_{ipjq} w^D_{ipjq}}{\sum_{ipjq} w^D_{ipjq}}
\]

\[
DOM_A1 = \frac{\sum_{ipjq} w^{A1}_{ipjq} - \sum_{ipjq} w^{D1}_{ipjq}}{\sum_{ipjq} w^{D1}_{ipjq}}
\]

Figure 11. A proper topography fails to develop in the absence of structured retinal input. In these simulations, the dLGN received interleaved Poisson noise from each eye instead of retinal waves (thus preserving the anti-correlated activity between retinas). (A) The CoMs do not approach the grid as in Figures 9 and 10 (normal and accelerated waves), yet (B) the proper eye-specificity develops. doi:10.1371/journal.pone.0031553.g011
distribution centered at .09 with retinogeniculate projections at the expense of the opposite retina, and the right retina to dLGN layer A) quickly dominated the biased to project to each dLGN layer (left retina to dLGN layer A1 retinas. Under these conditions, the retinas that were slightly active at a time and consecutive waves occurred in different parameters to generate retinal waves (see Table 1), and each wave and its correct retinotopic position (i = p, j = q) (see Figure 9B).

Then, topography was assayed as the summed Euclidean distance between the center-of-mass (CoM) of the weights from the RGC at position [p,q] and projecting to all dLGN cells [i,j] in layers A and A1, respectively:

\[
\text{CoM}^A_{pq} = \sum_j w^A_{ijpq} \]

\[
\text{CoM}^{A1}_{pq} = \sum_j w^{A1}_{ijpq} \]

and its correct retinotopic position (i = p, j = q) (see Figure 9B).

First, development of the retinogeniculate pathway was simulated for 5,000 seconds (simulated time) using the standard parameters to generate retinal waves (see Table 1), and each wave was distributed between the retinas such that only one retina was active at a time and consecutive waves occurred in different retinas. Under these conditions, the retinas that were slightly biased to project to each dLGN layer (left retina to dLGN layer A1 and the right retina to dLGN layer A) quickly dominated the retinogeniculate projections at the expense of the opposite retina, indicated by the sharp rise in DOM for layers A and A1 in the first 500 seconds of the simulation (see Figure 8). At the same time, yet on a much slower timescale, the topography of the dLGN was refined (see Figure 9). Thus, the learning rule used in the model retinogeniculate pathway accounts for the development of both layer-specificity and a refined topography.

Waves were also generated using different sets of parameters to simulate perturbations to the retina and their effect on retinogeniculate development. First, \(B^R\) (see (7)) was increased from .12 to .2 to generate faster waves with smaller inter-wave interval distributions (see Figures 3 and 4). This sped up the formation of layer-specificity and, more dramatically, the topography refinement proportional to the increase in \(B^R\) (see Figure 10). When \(B^R = .2\), the topography refinement is sped up dramatically, with a noticeable increase in the speed of the initial rise in DOM for both layers. These parameter settings are analogous to the use of forskolin to accelerate waves in vivo [3].

Next, to divorce layer-specificity from topography refinement, ‘random’ waves were generated by replacing the activity of RGCs with Poisson noise (\(\lambda = .5\)), and then interleaving the noise between the two retinas, where each retina was active for one second with the other completely inactive. Intuitively, this would cause the biased retinas to dominate the appropriate layers in the dLGN since the two eyes were still anti-correlated, yet the topography would not be refined due to the lack of spatially local input. Indeed, this is what happened in the model, as DOM increased similar to the other simulations, yet the CoM for each dLGN cell did not approach its ideal position on the grid (Figure 11).

Finally, waves of different geometries were simulated by randomizing the afterhyperpolarization period of the SACs by setting \(B^R\) for each cell to values drawn from a Gaussian distribution centered at .09 with \(\sigma\) set to .15, .2 and .3 (example waves are shown in Figure 2), with negative values set to zero. A small amount of variability \(\sigma = .15\) had a minimal effect on retinogeniculate development, while setting \(\sigma = .2, .3\) prevented full refinement of the dLGN topography, with the CoMs forming a “crumpled” pattern (Figure 12).

**Discussion**

Tables 2 and 3 compare the proposed model with previous models. One innovation of the retinal dynamics in the current model is the use of a recovery variable, \(r\), as in (7), to approximate the dynamics of Ca\(^{2+}\)-activated and CAMP-sensitive K\(^+\) channels. Godfrey and Swindale [14] described a simpler model that utilizes an activity-dependent refractory period. Their model employs a countdown mechanism whereby a cell necessarily spikes after a variable decays to zero. This hypothesis does not help to explain mechanistically how the intracellular processes that underlie SAC AHPs govern wave dynamics. Another recent model of retinal waves from Hannig et al. [12] uses the idea that SACs are

**Table 2. Comparison of retinogeniculate models.**

| Reference                | Dynamical retina | Activity-dependent refractoriness | Retinogeniculate simulation |
|--------------------------|------------------|-----------------------------------|-----------------------------|
| Haith, 1995              |                  |                                   |                             |
| Eglen, 1999              |                  |                                   |                             |
| Elliot and Shadbolt, 1999|                  |                                   |                             |
| Feller et al., 1997      |                  |                                   |                             |
| Godfrey and Swindale, 2007|                 |                                   |                             |
| Hannig et al., 2009      |                  |                                   |                             |
| Proposed model           |                  |                                   |                             |

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**Table 3. Comparison of models that simulate the dLGN.**

| Reference                | Dynamical dLGN cell simulation | Competition for neurotrophin |
|--------------------------|-------------------------------|------------------------------|
| Haith, 1995              |                               |                              |
| Eglen, 1999              |                               |                              |
| Elliot and Shadbolt, 1999|                               |                              |
| Hannig et al., 2009      |                               |                              |
| Proposed model           |                               |                              |

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governed by intrinsic cellular noise and slower activity-dependent Ca²⁺ processes that dictate afterhyperpolarization periods. This is more similar to our model and is quite biophysically realistic. Our approach captures most of the dynamics present in this spiking model, yet is significantly simpler and is more amenable to embedding in a larger model of retinogeniculate development, which is not simulated by Hennig et al. More precisely, in our model, the recovery variable r simulates lumped intracellular inhibitory mechanisms, based on whole-cell patch clamp data [24] and Ca²⁺-imaging [5] data. Similar to the role of the recovery variable in the Fitzhugh-Nagumo model of a spiking neuron, r suppresses the firing rate of SACs after a prolonged period of heightened firing. This approximates the process of slow Ca²⁺ accumulation in the cytosol during bursting, which progressively opens K⁺ channels that electrically shunt a given SAC. As the channels are slow to close, the SAC remains hyperpolarized or refractory for tens of seconds during the AHP, which regulates the periodicity of retinal waves observed in vitro. Additionally, upregulating cAMP through either uncaging techniques or bath application of forskolin reduces AHPs [5,24], an effect simulated by the model (see Figure 4). Thus, the pacemaking mechanism of the model retina is cell-autonomous since it is regulated by intracellular processes and is affected by both Ca²⁺ and cAMP, which agrees with whole-cell patch clamp data [24] wherein SACs rhythmically depolarized even after the complete blockage of synaptic transmission.

This foundation enables our simulation of retinogeniculate development to use a biologically plausible dynamical system with activity-dependent refractoriness to generate retinal waves. Some models simply move the center of pre-computed distributions (e.g., a Gaussian) to approximate the bump of activity that sweeps across the retinal sheet during waves [13,35], while others use a pre-determined refractory period that is not governed by a dynamical process [2,34] (e.g., their model SACs are forced to not fire for a given interval after bursting). Our model also demonstrates how a simple, but biologically realistic post-synaptically gated learning rule [20] based on competition for a growth factor, as in equations (17)–(20), can simultaneously lead to eye-specificity and to the refinement of the retinogeniculate projection. That is to say, the model waves lead to LGN activity, which, in turn, induces learning where the correlations between LGN and RGC activity are the strongest. This competition obviates the need for a biologically unrealistic explicit divisive normalization term such as is used in [13,34,35].

In summary, the proposed model builds on and goes beyond previous work by being the first to include both: (1) a fully dynamical explanation and simulation of retinal waves that clarifies the functional role of intracellular AHP currents, and (2) a learning rule that exploits competition for a limited neurotransphin to induce topography refinement and the dominance of one eye over the other in each dLGN layer. Testing the model's predictions can provide additional experimental data with which to develop future model refinements (see Table 3).

Author Contributions
Conceived and designed the experiments: JM YC SG. Performed the experiments: JM YC SG. Analyzed the data: JM YC SG. Contributed reagents/materials/analysis tools: JM YC SG. Wrote the paper: JM YC SG.

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