Faithful Retinotopic Maps with Local Optimum Rules, Axonal Competition, and Hebbian Learning

Jean-Philippe Thivierge† and Evan Balaban
Department of Psychology
McGill University
Montreal, QC Canada H3A 1B1
†jpthiv@ego.psych.mcgill.ca

Abstract - **Innervation of the visual midbrain by axons from the retina can be described as a stochastic mapping process that maintains topography and polarity between the two regions. Previous work has identified a number of mechanisms that insure proper guidance of the axons. In the current report, we combine three of these mechanisms, servomechanical guidance with local optimum rules, axonal competition, and Hebbian plasticity. Although each of these separate processes are stochastic and therefore subject to imprecision, their combination guides growth cones to precise termination points.**

I. INTRODUCTION

During the course of development, the vertebrate visual system extends new connections from retinal ganglion cells to the midbrain (optic tectum in fish, amphibians, reptiles and birds, or superior colliculus in mammals). Within these projections, retinal axons maintain their topographic relations to one another, but undergo an anterior-posterior reversal (see Figure 1a). Retinotopic midbrain projections are initially formed in the absence of any external activation of the retina by patterned light stimulation. Thus, before the retina starts receiving stimulation, the pattern of topographically faithful projections is well established, despite a lack of precision. Activity is thought to provide later refinement, making projections very precise [1].

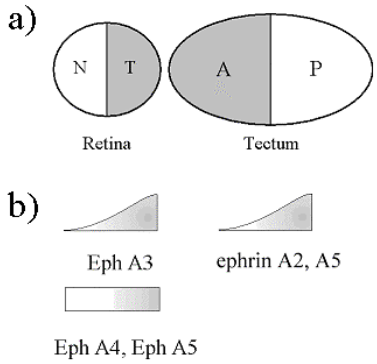

Figure 1. (a) Normal retinotopic projections are characterized by a reversal in anterior-posterior topography. N=nasal; T = temporal; A = anterior; P = posterior. Light and shaded areas indicate mutually connected regions. (b) Expression of anterior-posterior ephrins and Eph receptors (guidance molecules) on the retina and tectum.

In order to enable adequate axon guidance, we combine servomechanical guidance with three interacting mechanisms: (1) local optimum rules; (2) axonal competition; and (3) activity-dependent refinement.

Although each of these separate processes is stochastic and therefore imprecise, their combination provides precise guidance of retinal growth cones to their targets on the tectum.

The framework used here for axonal guidance is the servomechanism model, an established account of axonal growth [2][3]. This model integrates recent findings in Eph/ephrin molecular expression (signalling molecules for axonal guidance; Figure 1b), as well as axonal competition. The servomechanism model adequately captures the directed growth features of axons that distinguish their trajectories from a random walk. Despite slight random variations of direction, the overall trajectory of axons generally approaches a straight line, or a line predominantly curved in one direction [4].

II. SERVOMECHANISM MODEL

A. Local optimum rules

The servomechanism model utilizes the law of mass action to compute the final destination of an axon. According to this principle, the interaction of retinal receptors (R_i) and tectal ligand (L_j) densities generates a topographic signal G following a second order kinetic equation:

$$G(u,v) = \sum_{i,j} h_{ij} R_i(u) L_j(v), \quad (1)$$

where u is a retinal position, v is a tectal position, h_{ij} is a constant scaling factor, and i and j are indexes denoting retinal and tectal cells respectively. A number of biologically plausible ligand functions can be employed [4], including logistic and hyperbolic functions (further empirical data is required to determine the exact shape of ligand gradients). Applying a local optimum rule to this signal (Thivierge & Balaban, in prep.), a traveling axon stops when $\partial G(u,v) / \partial v \cong 0$. In other words, the axon stops growing when the topographic signal stops fluctuating, which means that the target destination is near. The following formula provides $\partial G(u,v) / \partial v$:

$$\frac{\partial G(u,v)}{\partial v} = R_1(u) L'(v), \quad (2)$$

where the apostrophe (‘) indicates a derivative with respect to inputs. Details of the servomechanism algorithm are described in Appendix A. We now provide a description of the migration progress along the anterior-posterior axis. A similar mechanism applies to the dorso-ventral axis, and can be described separately because migration along one axis does not appear to influence migration along the other axis [5]. Migration of the retinal cone occurs in random steps Q, and is biased towards progressing forward by making $Q = (1 + Q) / 2$, where Q is obtained according to

$$Q = \eta \frac{\partial G(u,v)}{\partial v}, \tag{3}$$

and η is a learning parameter. For a given migration step, the start position is given by $d_1^{start} = (R_1(u)L_1(v)-M_1)^2$, and the end position is given by $d_1^{end} = (R_2(u)L_2(v)-M_2)^2$, where M is the maximum receptor saturation of a given retinal growth cone. If $d_1^{start} < d_1^{end}$, the axon remains at its start position. Otherwise, it moves to the new position, which becomes the start position of the next migration step. This mechanism insures that the end position of a given migration step increases the proportional receptor occupation of a growth cone. The probability of migration of an axon is given by $p^{end}/(p^{end} + p^{start})$ where $p^{start} = p(d_1^{start})$, $p^{end} = p(d_1^{end})$, and p is a Gaussian function (see Appendix A for pseudo-code).

B. Axonal competition

A further modification of the servomechanism model allows for a competitive process among axons traveling towards their termination sites. Competition enables axons to avoid a tectal location where the density of retinal projections is high, and favor neighboring locations instead. This has been used to account for abnormal topographic projections in knock-in mice with increased EphA3 receptors [3]. Pseudo-code for the competitive process is presented in Appendix B.

C. Combining local optimum rules and competition

Several experiments were modeled using competitive servomechanical guidance, including regeneration experiments, as well as stripe assays [2]. An example of the anterior-posterior migration of five axons is presented in Figure 2. As shown, all four nasal axons innervate the posterior part of the tectum. In addition, the tectal projections are characterized by a topographically correct but rotated map. Other results (Thivierge & Balaban, in prep.) have shown details of the activity-independent process, and show that faithful maps can be obtained by a combination of local optimum rules and axonal competition, but not by set-point rules [2], or without competition.

The decrease in distance between the current topographic signal G and the maximum saturation M (averaged over all four axons) is shown in Figure 3. It is characterized by a quick decrease to a point near the optimal location (the final value is $\bar{d}$ = 5.0). In order to decrease further the $\bar{d}$ value obtained by the activity-independent process, we now turn to an activity-dependent process.

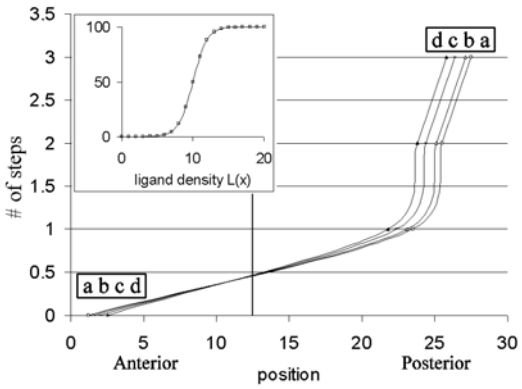

Figure 2. Competitive guidance of four nasal retinal axons using servomechanism. Each axon is labeled by a letter (*a*, *b*, *c*, *d*). A logistic gradient was used on both the retina and tectum (shown in the inset): $L(v) = \left(1/1 + e^{-\beta x}\right) + \alpha$, with β = 25 representing the width of the gradient. The tectum was represented by a 25x25 grid. The following values were employed: M = {90, 92, 94, 96}, R = {1.2, 1.5, 2.0, 2.5}, and $\eta = 0.1 \cdot$

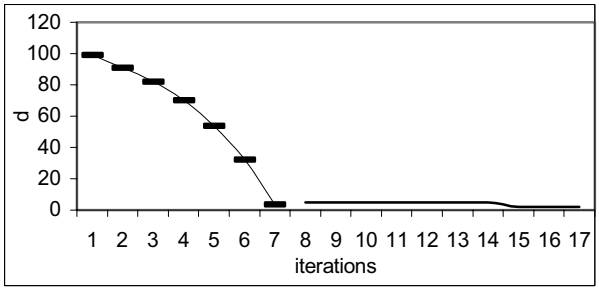

Figure 3. Average decrease in *d* according to activity-dependent (solid line) and independent processes (dashed line) for four nasal axons.

D. Activity-dependent refinement

Although the growth of axons initially occurs independently of activity-dependent synaptic plasticity, such mechanisms can account for the refinement of their position on the tectum [1][6]. Activity caused by light stimulation of the retina makes it possible for axons to find tectal sites that minimize further the d distance between their topographic signal G and the maximum receptor saturation M. The synaptic strengths of axons connecting the retina and tectum can be controlled by Hebbian learning, with the idea that a connection w_{jm} between the j^{th} retinal neuron and the m^{th} tectal neuron is strengthened if

these two neurons fire in synchrony, and weakened otherwise [7]:

$$B(J,M) = -\frac{1}{S}\sum_{j=1}^{J}\sum_{m=1}^{M} v_m^s \left(x_j^s - w_{jm}\right)^2, \quad (4)$$

where *B(J,M)* is a Hebbian rule. Here we assume a linear gradient on the retina for simplicity of notation. The activity of tectal neurons is represented by v_m^s. Eq. 4 depends on the activation of the retina by patterns x_j^s, where *s* is a pattern of activity.

This Hebbian rule reflects the idea that a sending neuron has a high probability of making a target neuron fire if it sends out activation during the resting phase of that neuron. If a sending neuron consistently sends out activation at that time, this activation will be highly correlated with the activation of the target neuron. In this case, and for the purposes of our current discussion, the sending and target neurons will be said to fire in synchrony.

Input patterns are presented to the retina as spatially organized patterns of "activity waves" expanding out radially from spontaneously active sites [8] (see Figure 4).

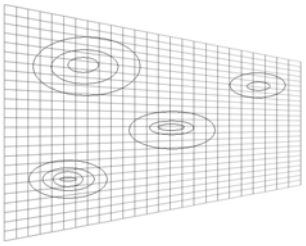

Figure 4. Instances of spatially organized pattern of 'activity waves' expanding out radially from spontaneously active sites. These patterns activate the retina, represented by a grid of neurons.

The entire process of retinotopic innervation thus includes: (i) an activity-independent process according to the servomechanical model with axonal competition; and (ii) an activity-dependent process according to Hebbian synaptic plasticity. In order for the activity-dependent process not to move axons too far out of their position, we propose a weight update rule that accounts for the continued influence of the activity-independent process, even after light stimulation is introduced. In addition, the weight update rule contains a term (*H*) that allows for the activation of one given tectal neuron to partially activate its neighbors, according to a Gaussian function (see Appendix C). The complete weight update rule is given as:

$$\Delta w_{jm} = \eta \frac{\partial G(u,v)}{\partial v} + \gamma \frac{\partial B(J,M)}{\partial w_{jm}} + \varphi \frac{\partial H(J,M)}{\partial w_{jm}}, \quad (5)$$

where η, γ and φ are free parameters. The influence of activity-dependent refinement on $\bar{d}$ (average distance) is shown in Figure 3. As depicted, the axons slightly refine their position in order to finally attain a value of $\bar{d}$ lower than that obtained with the activity-independent process (from $\bar{d}$ = 5.0 to $\bar{d}$ = 2.0).

The refinement in final position by the activity-dependent process is due to the characteristic configuration of connection strengths w_{jm}. Through synaptic modification, these connections markedly increase their slope when compared to their initial distribution (Figure 5a vs. 5b). The justification for this behavior can be illustrated using a logistic gradient on the retina (Figure 6a). With a curved distribution of weights (Figure 6b), a distortion of the original gradient reaches the tectum (Figure 6c). Hence, the synaptic strengths act as weighting factors on the retinal distribution. As such, they can influence which part of the gradient's distribution should have more or less influence on the tectum. With a logistic gradient, the steep part in the middle of the distribution is more informative than the flat parts on the extremes with respect to final position of an axon. This is due to the use of derivatives to calculate a termination point. With a flat derivative, it is impossible to determine where the axon is located and where it should go next. However, with a steep derivative, an axon can quickly move to its target destination. As a result of combining a distribution of weights as in Fig. 6b with a logistic gradient, the retinotopic system maximizes the importance it gives to the steep part of the gradient, while minimizing the importance it gives to the flat part of the gradient.

The weight transformation shown in Figure 6 only needs to capture first order relationships between the activity of the retina and tectum. This is true because the final distribution of connection strengths (Figure 6c) is obtained by $R(u)\cdot W$, where *W* is the matrix of weights obtained in Figure 6b. Learning this linear relationship involves finding *W* such that first-order information in *R(u)* is maximized. A Hebbian-type mechanism is sufficient to learn such relationship.

Hebbian plasticity generates the weight distribution of Fig. 5b according to a specific principle. Given a retinal gradient *R* and a tectal gradient *L* (Figure 7), the goal of Hebbian plasticity is to maximize the strengths of connections between the retinal and tectal neurons that fire in synchrony. However, because neurons in the steep portion of the gradients (located in "b") are already close to their target destination by the activity-independent mechanism, they tend to already fire in synchrony prior to the influence of the activity-dependent mechanism. Conversely, neurons in the flat portion of the gradient (located in "a") may not fire in such a synchronous way, because they may not be in their correct location. Thus, when the activity-dependent mechanism is turned on, the connections of neurons in "b" are strengthened because

those neurons fire in synchrony. The connection strengths of neurons in "a" are reduced, because those neurons do not fire synchronously.

E. Putting it all together: Activity dependence and axonal competition

Recent work (Thivierge & Balaban, in prep.), has assessed the impact of competition in the activity-independent process. The main result is that axonal competition allows for projections with the correct reversal of polarity, and conservation of topography. Without competition, axons from the anterior portion of the retina remain in the anterior portion of the tectum, and do not show a reversal of polarity. However, with competition, these axons migrate to the temporal portion of the tectum, and show a reversal of polarity. These results suggest that competition has an impact on the activity-independent process. Does the same mechanism of competition in the activity-independent process have an impact on the activity-dependent process? As argued previously, the activity-dependent process acts by functionally increasing the slope of the gradient (Figures 5a and 5b). Without competition, however, the initial distribution of connection strengths takes on a drastically different shape (Figure 5c). In addition, removing the activity-independent competition once the activity-dependent process starts leads to a distribution similar to the original distribution (Figure 5d). In other words, without competition, the activity-dependent process cannot efficiently increase the slope of the gradient.

In summary, modifications were made to allow for activity-dependent mechanisms to refine the retinotopic projections, and thus bring the retinal axons closer to their target position on the tectum. This is made possible by the synaptic strengths functionally increasing the slope of the retinal gradient, thus giving more weight to regions of the gradient with more information regarding where the axon should travel next. The retinal gradient gets naturally more curved by Hebbian plasticity, because neurons that are in highly informative regions of the retina tend to fire in synchrony with neurons in highly informative regions of the tectum. Simulations also argued for the importance of competition processes between axons. This competition makes it possible for axons to refine their position on the tectum.

III. CONCLUSIONS

The present report combined several mechanisms for

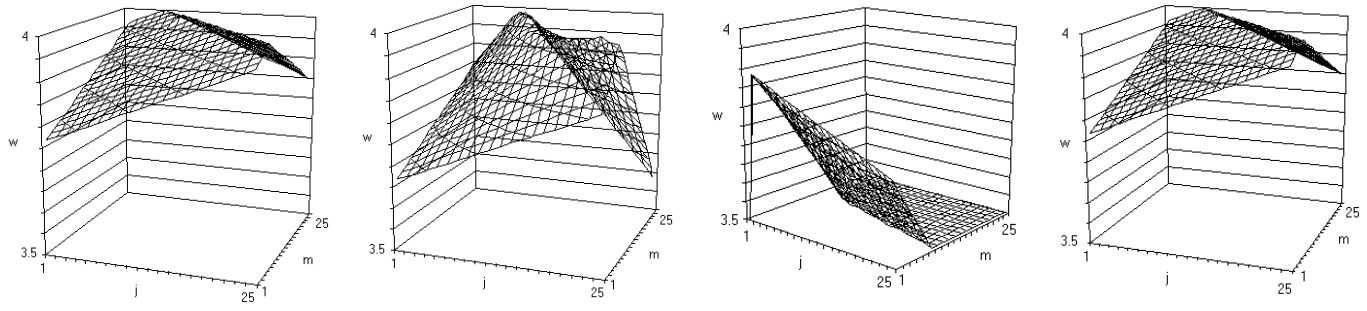

Figure 5. Weight distribution along the tectum (a) at the start position after some activity-independent movement; (b) after 8 iterations of the activity dependent process; (c) after introduction of the activity-dependent process, without initial activity-independent axonal competition. With this type of distribution, the average distance of axons with respect to their final position can't be reduced. Connection strengths do not favor regions where the gradient is steeper (i.e., in the middle of the distribution). (d) Connection strengths after introduction of the activity-dependent process, with prior activity-independent competition, but with the activity-independent competition removed once the activity-dependent process begins. In this case, the curve is not made steeper than the original distribution in (a), and $\overline{d}$ is not reduced further. *w* indicates the weight value from a retinal to a tectal location (scaled down by a factor of 100).

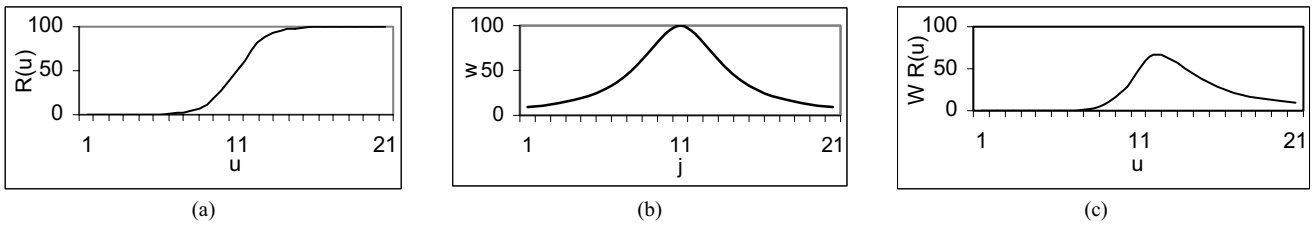

Figure 6. Refinement of final axon position by an activity-dependent mechanism. (a) a possible retinal gradient; (b) a weight column linking the retina to the tectum; (c) a representation of the retinal gradient on the tectum, after weighted transformation.

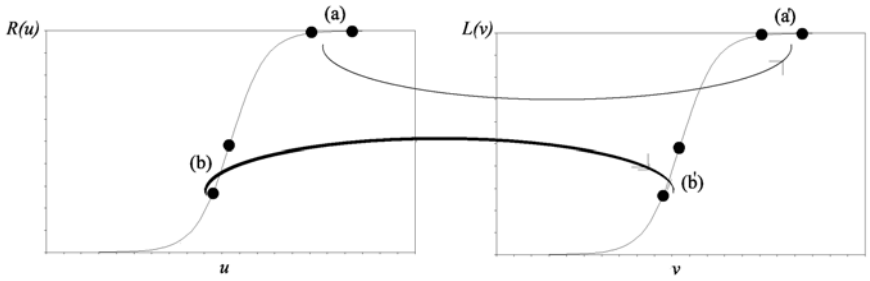

Figure 7. Strengthening of weights according to an activity-dependent process (see text). A thick arrow signifies strengthening of synaptic connections between the retina and tectum.

axonal guidance, including local optimum rules, competition, and activity-dependent synaptic plasticity. An activity-independent component was based on intrinsic knowledge of the appropriate targeting location, derived from ephrin gradients across the tectum. A refinement of this process distributes axons more evenly across the tectum by biasing against regions of high axonal density. Finally, a Hebbian rule enables further refinement of this mapping via input correlations. Activity-independent rules are maintained to limit the ability of the activity-dependent process to redefine the map. Although in isolation these stochastic mechanisms are not immune to failure, their combination leads to maps that are topographically faithful, with axons in close proximity to their target destinations.

Current empirical evidence suggests that the Eph/ephrin molecules that are important in the formation of retinotectal projection formation play similar roles in the formation of other long-range projection systems in the developing brain, including the hippocampus-septum pathway (important for memory processing), thalamocortical sensory pathways, and vomeronasal (olfactory) pathways [5]. Thus, it is plausible that the development of projections between many areas of the nervous system depends on combinations of activity-independent and activity-dependent guidance mechanisms that are similar to the one we have described here. It remains to be determined if these principles can account for axonal projection behavior in all these brain areas.

IV. ACKNOWLEDGEMENTS

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APPENDIX A: PSEUDO-CODE FOR AXONAL MIGRATION ACCORDING TO THE SERVOMECHANISM MODEL

Do define the tectal area as a square matrix [x,y] involving an anterior-posterior (x) and ventral-dorsal (y) axis.
Do define unit migration of the retinal cone in random steps along the x- and y-axis: $(1+Q_x)/2$ and $(1+Q_y)/2$, where Q varies from 0 to 1.
For each migration step, **For** each axon

Get start position: $d_1^{start} = | R_1(u)L_1(v) - M_1 |$,

and end position: $d_1^{end} = | R_2(u)L_2(v) - M_2 |$.

If $d_1^{start} > d_1^{end}$, **Then** the axon moves to d_1^{start},

Else, it moves to d_1^{end}, according to a Gaussian probability.

End For

APPENDIX B: PSEUDO-CODE FOR AXONAL COMPETITION ACCORDING TO THE SERVOMECHANISM MODEL

For each migration step, **For** each axon
Do define 2 neighboring sites at random on the tectum, j and j+1.
Do define n_c, a constant defining the critical population density at a given site.
Do define repulsiveness as $| R_iL_j-M_i |$.
If repulsiveness of end location is lower than start location
If j or j+1 has larger density than n_c,
Then the axon migrates from the site of higher density to the site of lower density.
End if
End if

End for

APPENDIX C: NEIGHBORHOOD ACTIVATION *H* FOR THE ACTIVITY-DEPENDENT PROCESS

We introduce a function *H* to represent the idea that, as neighbouring neurons become more active, centering neurons tend to decrease the distance between *J* (retinal neurons) and *M* (tectal neurons), and fire more strongly:

$$H(J,M) = -\frac{1}{M}\sum_{j=1}^{J}\sum_{m=1}^{M}\phi_j^m\left(x_j^s - w_{jm}\right)^2, \tag{A1}$$

where x_j^s is an input into the retinal surface, w_{jm} is a connection between the j^{th} retinal neuron and the m^{th} tectal neuron, v_m^s is an activation of the tectal neuron, and

$$\phi_j^m = \sum_{\forall m} p(m)\exp\left(-\frac{d_{jm}^2}{2\sigma_2^2}\right), \tag{A2}$$

where σ_2 denotes the width of the topological neighborhood. The probability *p(m)* is introduced to denote the fact that if a neuron fires strongly, it affects the firing of its neighboring neurons. The lateral distance d_{jm} between the j^{th} and m^{th} neurons is given as:

$$d_{jm} = \left\|\mathbf{r}_j - \mathbf{r}_m\right\|, \tag{A3}$$

where the discrete $\mathbf{r}_j$ vector denotes the j^{th} neuron's position in a two-dimensional lattice.