A model for adjustment of the retinotectal mapping, using Eph-dependent ephrin regulation

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The formation of a topographically ordered map in the retinotectal system, independent of neural activity, has long been thought to rely on the matching of molecular cues between the innervating retinal ganglion cell (RCG) axons and their targets in the tectum [1, 2]. EphA receptors are expressed in a decreasing gradient along the naso-temporal axis of the retina while their ephrin A ligands increase along the caudal-rostral axis of the tectum. In principle this allows a retinal axon to be targetted to a particular termination zone within the tectum. There are several plausible mechanisms for how this targetting might occur, including models based on multiple "counter-gradients" [3, 4], "set-points" [5, 6, 7], and counter-gradients together with axonal branching [8] - these essentially pre-assign an optimal tectal position to each axon and are known as Type I models [9]. By contrast in Type II models axon-axon competition plays an essential role (e.g. [10, 12]): for example, the ephrin profile can generate a general tendency for all axons to move down the gradient, while the strength of this tendency can be modulated by the Eph level in the RGC. Axonal competition for space in the tectum is then invoked to prevent all axons converging at the low-ephrin boundary. While these models are able to account to varying degrees for recent key findings [11, 12], they do not address a number of experiments carried out even before the discovery of Eph-ephrin signalling, involving recovery of the topographic projection following severe surgical interventions (summarised in [2, 13]). In "expansion" experiments half of the retina is removed prior to formation of the map. The projection that results is a topographic map from the remaining retina to the entire tectum, whereas in most cases the above models would predict a map to only one half. In "contraction" experiments half the tectum is removed, resulting in a topographic map from the entire retina spread out evenly across the remaining tectum [14], contrary to what a Type I model would predict. Another phenomenon is "ectopic targetting", in which RCG axons entering the tectum via abnormal trajectories can still find their appropriate termination sites [15] (although this hasn't been tested for in the expansion/contraction scenarios). This paper shows how Type I models can be augmented with an adaptive process that allows them to account for these experiments in a simple way.

Like other models we treat the retina as a discrete array whose i^{th} RGC expresses EphA at a level R_i. We treat the axon as innervating a single point y_i in a continuous tectum, at which there is a level of ephrin $L(y_i)$. The discussion is restricted to the 1 dimensional case here.

RGC axons exhibit (at least) three different tendencies. Firstly, they terminate somewhere in the tectum. Secondly, they tend towards locations that are monotonically related to their position of origin in the retina - for example, in "set-point" models [5, 6, 7] they move so as to match $R_i L(y_i)$ to a constant, *ie.* $L_i^\star = S/R_i$. Thirdly, they appear to compete for space on the tectum: they may be repelled from one another, or perhaps merely attracted towards areas of tectum that lack innervation. One can think of all these tendencies in terms of "forces". *Region forces* push axons towards the tectum if they are outside it. *Mapping forces* cause axons to gravitate towards locations in the tectum with a certain $L_i^\star$. *Competition forces* would lead to axons distributing themselves evenly over the available tectum, in the absence of other forces.

If competition forces are on a par with mapping forces the two are liable to be in conflict, leading to a large number of local attractors in the the associated dynamics, corresponding to multiple minima of the associated energy function. Most such minima will not correspond to a topographic mapping in that the rank ordering will not be preserved. Intuitively this is because competition forces (such as repulsion) prevent axons from "sliding past" one another to more topographically ordered positions. Thus it is difficult to ensure coverage first and rank ordering second. From a dynamical systems standpoint it is much easier to ensure that ordering is correct first, and then move the system toward better coverage without perturbing it so strongly that the ordering is disrupted, as follows.

Suppose that mapping forces *always* strongly dominate competition. Provided that both R and L profiles and the "set-point" function relating them are monotonic, the energy function will have a single minimum, in which the rank ordering of termination sites is correct. To a first approximation we will see $L(y_i) \approx L_i^\star$, although in reality this will be slightly perturbed by the other forces present such as

competition (and attraction to the tectal region in general if y_i is outside it). That is, the dynamics of y seeks to match L_i to its set-point value, but is perturbed away from it.

Now suppose that the L profile changes so as to match L_i to its set-point value at the termination sites, and that a smoothing process occurs over the L profile within the tectum. The target $L_i^\star$ values are in rank order and so monotonicity of the L profile is retained regardless of its initial form. Once the L profile adapts in this way, the perturbing forces will push the termination sites y slightly further, whereupon the L profile can be updated again, and so on. Although described here as an iterative 2-stage process it is perhaps better thought of as a two parallel processes that occur continuously. It stabilises once the termination sites reach locations such that the perturbing forces are zero: for example if competition is implemented via repulsion, it will eventually be balanced by containment forces at the edge of the tectum. In this way we can have competition forces which are small enough not to introduce local minima, yet still allow them to move the system arbitrarily far from its initial condition, distributing axons uniformly over whatever tectal area is available.

An alternative way to ensure both ordering and coverage is to begin with low competition and increase it, in an process analogous to the highly successful "elastic net" family of optimisation algorithms [16]. This allows an initial ordering to establish itself, after which increasing competition forces each area of the tectum to acquire its share of retinal input. Ultimately such models pit one substantial force against another, and would have difficulty accounting for ectopic targetting: if a "new" retinal ganglion cell is introduced and sends out an axon, it will not in general find its way to the correct position in the tectum, instead becoming stuck in one of many "pockets" generated by the presence of local competitive forces.

We now describe an implementation of the above idea. The retina is modeled as a 1-dimensional discrete array of cells. The Eph level expressed by each cell is a decreasing exponential, $R_i = R_{\text{nasal}} e^{-Kx_i}$ where x is the position in the retina. The simulations followed 20 retinal ganglion cells, with x ranging from 0 to 10, $R_{\text{nasal}} = 5$ and K set such that $R = 2$ at the temporal boundary. The tectal cells at the termination point of the i^{th} axon express ephrin at a level $L(y_i)$. The normal tectum region was $0 \leq y \leq 10$. The initial profile of ligand expression (as per [11, 8]) is a rising exponential $L(y) = L_{\text{caudal}} e^{\kappa y}$ such that the initial set-point positions fit snugly within the nominal boundaries. RGC axons are initialised at random positions near the tectum. $f_i^{\text{region}} = \alpha\epsilon^2$ for axons terminating outside the tectum and zero for those terminating inside, with ϵ the distance from the nominal edge of the tectum. The set-point value $L^\star = S/R$, and $f_i^{\text{mapping}} = \beta[R_i - 1/L(y_i)]$. Competition is implemented via a repulsion force between axons of $\gamma e^{-(y_i - y_j)^2}$. $\alpha = 1$, $\beta = 1$, $\gamma = 0.01$, and $S = 1$. These processes were simulated by alternating between solving 2 ODEs. The first updates the destinations of RGC axons to a zero of the nett axonal forces. The second simultaneously pulls the ephrin levels at axon termination sites towards their ideal values $L_i^\star$ and smooths the ephrin profile across the entire tectum. This was iterated 1000 times, allowing y and L to stabilize. Figure 1 shows the outcome in a hypothetical "expansion" experiment, in which half the retina has been ablated. Figure 2 shows a "contraction", in which half the tectum is removed.

To summarise, the model features (*a*) regulation of ephrin expression in cells that are innervated from the retina, with changes being in the direction that minimizes the mismatch between the current ephrin value $L(y_i)$ and $L_i^\star$; (*b*) smoothing of ephrin levels in the tectum via a local diffusion process. It also

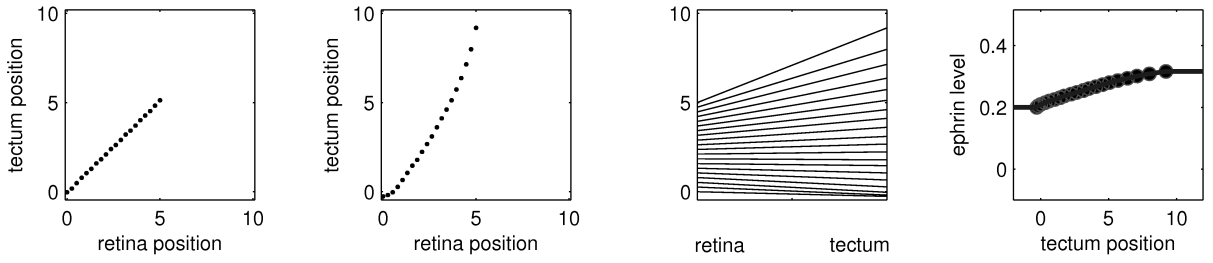

Figure 1: *Expansion*. Half the retina has been removed. The first two panels show the destinations of axons after the initial transient and at the end of the simulation respectively. The mapping forms to the corresponding half of the tectum, but later it expands to the whole. The third panel shows the mapping explicity with retina on the left and tectum on the right. The right-hand panel shows the ephrin profile at the end of the simulation.

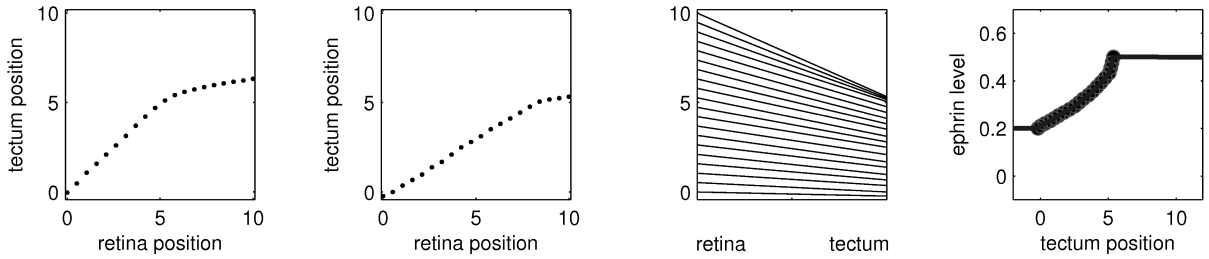

Figure 2: *Contraction*. Half the tectum has been removed, by setting the "region" forces to climb steeply half way across the tectum instead of on its right-hand edge as is normal. Initially the RGC axons bunch up at this new boundary, but later they spread out evenly over the remaining half of the tectum.

incorporates a continuous tectum and "soft" competition between RGC axons for tectal space (listed as desirable features in a recent review [13]), as well as a tendency - rather than a hard constraint - for those axons to terminate in the tectum. It accounts for the expansion and contraction of topographic maps without any fine-tuning of parameters. Since the ephrin levels reset, an axon growing from the retina at a later time will find the correct position in the tectum, and so ectopic targetting would be predicted to occur even following expansion / contraction.

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