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TOPICAL REVIEW

The development of retinotectal maps: A review of models based on molecular gradients

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Abstract
Information about the world is often represented in the brain in the form of topographic maps. A paradigm example is the topographic representation of the visual world in the optic tectum/superior colliculus. This map initially forms during neural development using activity-independent molecular cues, most notably some type of chemospecific matching between molecular gradients in the retina and corresponding gradients in the tectum/superior colliculus. Exactly how this process might work has been studied both experimentally and theoretically for several decades. This review discusses the experimental data briefly, and then in more detail the theoretical models proposed. The principal conclusions are that (1) theoretical models have helped clarify several important ideas in the field, (2) earlier models were often more sophisticated than more recent models, and (3) substantial revisions to current modelling approaches are probably required to account for more than isolated subsets of the experimental data.

Keywords: *Topographic maps, axon guidance, ephrins, Eph receptors, computational model*

Introduction

Even simple biological nervous systems display impressive computational abilities. This probably requires precise patterns of connections between neurons. Such wiring forms during development using a combination of cues, some molecular and some dependent on neural activity. A better understanding of how this wiring forms will give an insight into the computational operations performed by the adult nervous system, lead to improved treatments for developmental disorders, produce methods for appropriately reconnecting the damaged nervous system after injury, and hopefully inspire algorithms for the autonomous wiring of artificial computing devices.

A particularly important type of connection pattern that forms in the nervous system of many species is a topographic map. In its simple form, this means a 1–1 mapping between a

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two-dimensional input structure and two-dimensional output structure such that neighbouring points in the input structure map to neighbouring points in the output structure and vice versa. ("Topographic map" is also sometimes used to describe a one or two-dimensional representation of a space of input features which has more than two dimensions (see Swindale 1996; Chklovskii & Koulakov 2004 for reviews). Topographic maps are an extremely common method used in the brain to represent information about the world. Such representations are probably crucial for efficient information processing, though exactly why is not definitively known (for some suggestions, see Cowey 1979; Linsker 1989; Durbin & Mitchison 1990).

The paradigm example of topographic map formation in the brain is the projection from the eye to the optic tectum, or superior colliculus (SC) in mammals. This is often referred to as the "retinotectal map", and in this context, "topography" is sometimes referred to as "retinotopy". Experimentally, this is the best studied and most completely characterized of all topographic projections. The mechanisms underlying retinotectal map formation may also be important in establishing connections in the retinogeniculocortical pathway, along which all the visual information we are consciously aware of enters our brain. Similar mechanisms are probably also crucial for establishing topography in other sensory pathways (Feldheim et al. 1998; Vanderhaeghen et al. 2000; Ellsworth et al. 2005), and between more central brain structures (e.g., Gao et al. 1996). Deciphering retinotectal map formation is therefore likely to increase our understanding of topographic map formation in the brain more generally, and thus our understanding of the basic information processing strategies used by nervous systems.

This review focuses on theoretical models of retinotectal map formation. By a theoretical model, we mean one or more hypothesized principles underlying map formation stated as mathematical equations, usually accompanied by an analytical and/or computational demonstration of the consequences of these principles. These types of models offer several advantages over the "qualitative" models that are more common in biology in general. First, they force underlying assumptions to be made explicit rather than merely implied. Second, such models reveal which ranges of parameters are consistent with the desired outcome. Third, such models allow richer predictions for future experiments than are obtainable from qualitative models. These can include behaviours that do not appear to follow intuitively from the original idea, subtle quantitative effects not predictable from a purely qualitative model, and suggestions for new types of experiments that had not been inspired by purely qualitative reasoning. Theoretical models of this type are ubiquitous, and extremely successful, in physics (e.g., Greene 2004) but as yet have made fewer inroads in biology (for a sociological discussion of models in developmental biology, see Keller 2003). However, retinotectal map formation is an area where an unusually large and varied set of theoretical models were proposed in the 1970s and 1980s. The last 10 years have seen rapid progress in the experimental data and some new models, but the way in which these data and models relate to earlier theoretical proposals has not been much discussed. It is thus timely to do so now.

We begin by reviewing the relevant experimental data. Retinotectal map development depends on both guidance of axons by molecular cues and refinement of synaptic strengths by neural activity. Conventionally, these have been regarded as two sequential phases of development, though they may also act in concert (Ruthazer & Cline 2004). To maintain a manageable scope, this review focuses entirely on activity-independent processes; for reviews of relating modelling focusing more on activity-dependent development, see Swindale (1996) and van Ooyen (2001). We then review the most significant theoretical models that have attempted to address subsets of this data (no model has yet attempted to address it all). Finally, we summarize the key ideas underlying modelling in this area and how these relate to experimental data, and make some suggestions for future modelling.

Experimental data

Mapping in the adult

In vertebrates, including fish, amphibians, and birds, the main visual centre in the brain is the optic tectum, part of the midbrain, which receives projections from the axons of retinal ganglion cells. In these species, retinal projections are mostly crossed (decussated) at the optic chiasm, meaning that left eye axons project mostly to the right (contralateral) tectum, with no fibres projecting to the left (ipsilateral) tectum, and vice versa for the right eye. In mammals, the retinal projection is split between the SC (the equivalent of the optic tectum) and the lateral geniculate nucleus of the thalamus. In addition, there is only a partial decussation of projections at the optic chiasm. The degree of decussation roughly correlates with the degree of binocular vision, i.e., the extent to which information from different eyes represents the same part of the world. For simplicity, we will sometimes use "tectum" to also mean the SC.

The optic tectum and SC are layered structures. Within the layer to which retinal ganglion cell axons project, there is a topographic map of the visual world. This is oriented such that the nasal–temporal and dorsal–ventral axes of each retina map to the caudal–rostral and ventral–dorsal axes of each tectum, respectively (see Figure 1). This topographic map is crucial for visual function. For instance, in a classic body of work from the 1940s, Sperry showed that rewiring the projection so that it was inverted caused frogs to misplace visual targets by 180° (reviewed in Sperry 1963). In mammals, the retinogeniculocortical pathway is more important for behaviour, and in humans it is the route for our conscious awareness of visual information. However, the projection to the SC is significant for the coordination of eye movements, which relies on a topographic representation of visual space aligned with maps of auditory and somatosensory space in other layers (reviewed in King 2004).

Normal development of the pathway

We do not discuss the development of retinal ganglion cells, or the guidance of ganglion cell axons out of the eye, along the optic nerve, across the optic chiasm, into the tectum, and into a specific tectal layer. Each of these stages of development relies on distinct molecular

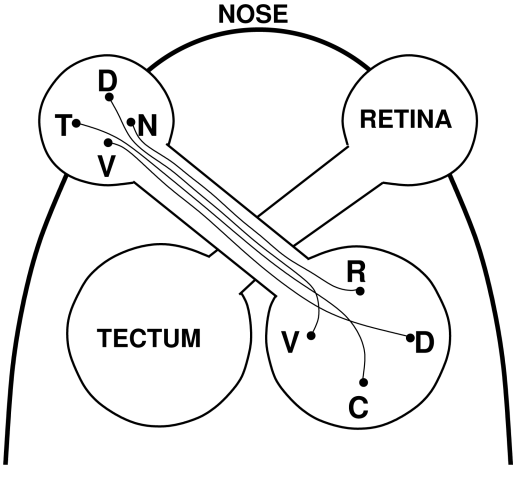

Figure 1. Schematic view of the retinotectal map in adult frogs and fish. N, nasal; T, temporal; D, dorsal; V, ventral; R, rostral; C, caudal. Note that for clarity, the retina has been rotated by 90° around the N–T axis in this view: the dorsal edge should be standing up out of the picture, with the ventral below. The optic nerves are drawn much larger than their actual size relative to the retinae and tecta.

cues, the identity of which is currently being uncovered (for reviews, see Holt & Harris 1993; Mey & Thanos 2000; Thanos & Mey 2001; Mann et al. 2004). There is a wide variation between species in the degree of topographic order existing in the optic nerve prior to tectal innervation. However, it is almost always the case that the final map in the tectum is ordered to a greater extent than the optic nerve (reviewed in Udin & Fawcett 1988).

Once axons have reached the tectum, they often branch. Some controversy has surrounded the degree to which axonal branching plays a role in retinotectal map formation. One hypothesis is that axons grow directly to their correct targets and arborize there (Holt 1983, 1984; Fujisawa 1987; Harris et al. 1987; Thanos & Bonhoeffer 1987; Stuermer 1988; Kaethner & Stuermer 1992). An alternative hypothesis is that axons instead tend to overshoot their targets, then produce side-branches from the axon shaft into the target, followed by pruning of the aberrant intial projection (Nakamura & O'Leary 1989; Simon & O'Leary 1992a, 1992b; Yates et al. 2001). It is possible that the relative importance of each mechanism may be somewhat species-dependent, with the former predominating in amphibians and fish, and the latter in chicks and rodents.

Chemoaffinity hypothesis

The most important organizing principle in the study of activity-independent map development in the last several decades has been the concept of chemoaffinity (sometimes called chemospecificity). Discussing the exquisite precision of axon guidance in the developing nervous system in general, Langley (1895) said:

> The only feasible explanation appears to me to be that ... there is some special chemical relation between each class of nerve fibre and each class of nerve cell, which induces each fibre to grow towards a cell of its own class and there to form its terminal branches.

Although, in the early part of the 20th century, alternative hypotheses temporarily gained greater prominence (reviewed in Purves & Lichtman 1985), seminal experiments by Roger Sperry in the 1940s (reviewed in Sperry 1963) reinstated chemoaffinity as the dominant hypothesis in the field. In particular, Sperry showed that axons regenerating after optic nerve section grew to their original locations in the tectum, even if optic nerve fibres had been artificially scrambled, or if the eye had been rotated by 180°. This led to his classic statement of the chemoaffinity hypothesis (Sperry 1963):

> The establishment and maintenance of synaptic associations [is] conceived to be regulated by highly specific cytochemical affinities that arise systematically among the different types of neurons involved via self-differentiation, induction through terminal contacts, and embryonic gradient effects ... [I propose] an orderly cytochemical mapping in terms of two or more gradients of embryonic differentiation that spread across and through each other with their axes roughly perpendicular. These separate gradients successively superimposed on the retinal and tectal fields and surroundings would stamp each cell with its appropriate latitude and longitude expressed in a kind of chemical code with matching values between the retinal and tectal maps. The inversion of the retinal map on the tectum suggests complementary relations in the affinity forces involved in linking the corresponding points in the two fields.

A crucial corollary to this hypothesis is that the concentration gradients that specify the position of tectal cells could also be used to guide retinal axons to their targets. That is, besides providing a scalar signal giving location, tectal gradients could also provide a vector signal to retinal axons indicating the direction in which they should grow.

Systems-level experiments to test the chemoaffinity hypothesis

If the chemoaffinity hypothesis is correct, there must exist molecular gradients in the retina which interact with molecular gradients in the tectum at an appropriate time in development. Furthermore, perturbing these gradients should lead to perturbations in the map. However, such a direct attack on the problem did not yield significant fruit until the 1990s. Although some molecules were identified earlier that exist in gradients in the retina (9-*O*-acetyl GD3 (Constantine-Paton et al. 1986); TOP (Trisler et al. 1981); TRAP (McLoon 1991)) and in the tectum (RGM (Stahl et al. 1990)), a clear role for these in the formation of retinotectal topography was not established. Therefore, from the 1960s to the 1980s, the paradigm driving most experiments investigating retinotectal mapping was to perturb normal development or regeneration at the systems level by surgical manipulations. From the form of the resulting map when challenged in this way, inferences could be drawn about the mechanisms underlying normal development, particularly the role played by the putative molecular gradients.

We now briefly review some of these results (also reviewed in Gaze & Keating 1972; Fraser & Hunt 1980; Meyer 1982; Trisler 1982; Purves & Lichtman 1985; Schmidt 1985; Udin & Fawcett 1988; Fraser & Perkel 1990; Jacobson 1991; Holt & Harris 1993; Goodhill & Richards 1999). These results are summarized schematically in Figure 2. We refer to these as the "systems level" data to distinguish them from more recent molecular approaches, though the latter also often involve analysis at the systems level. The focus is on mapping along the rostral-caudal axis of the tectum. An important issue we do not emphasize is the distinction between development and regeneration. Owing to the early stage at which the retinotectal map normally forms, many of the experiments described below actually investigated the pattern of regeneration rather than de novo development of retinal axons. Although it is possible that these processes might occur by different mechanisms, it seems more likely that the results of regeneration experiments provide relevant constraints on the mechanisms of during normal development. We also do not emphasize species differences, and describe experiments performed in *Xenopus*, goldfish, chicks, and rodents. At a general level, similar principles probably apply to map formation in all species; however, the degree to which generalizations can be made between species at a finer level of detail is not always clear.

Ectopic targeting. Retinal axons entering the tectum via abnormal trajectories can still find their appropriate termination sites (Finlay et al. 1979b; Harris 1982, 1984). This suggests the presence of vector signals throughout the tectum pointing axons towards their correct termination sites.

Shifting connections. In some fish and amphibians, the retina grows by addition of new neurons around the ciliary margin, while the tectum grows by addition of cells to its caudomedial edge (Gaze et al. 1974; Fraser 1983).The retinotectal map remains ordered throughout this time, indicating that the retinotectal projection is continually shifting caudally. This suggests that, at least in these species, either chemoaffinity gradients do not irreversibly specify the map or the gradients must evolve with time.

Rotation experiments. If a *Xenopus* presumptive tectum is rotated early enough during development, a map is formed that is normal relative to the whole animal, whereas later rotations lead to a rotated map (Chung & Cooke 1978). Initially, it was thought that eye rotation could also lead to both a normal outcome, if performed early enough, and a rotated outcome, if

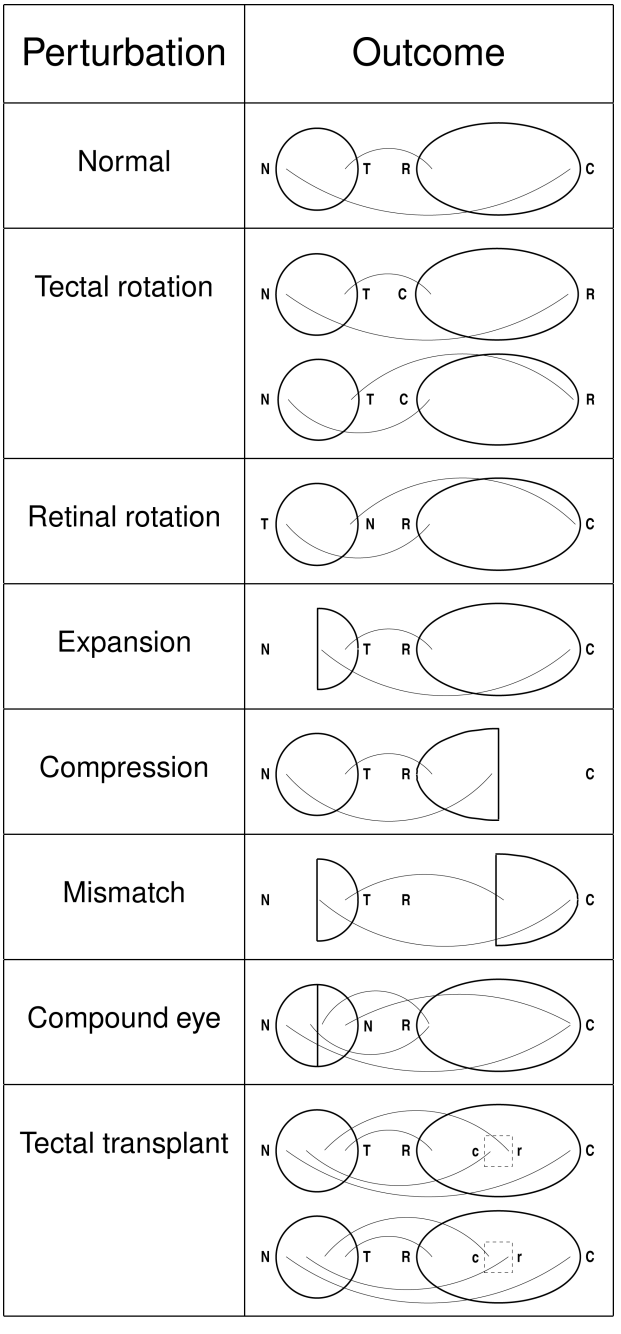

Figure 2. Summary of the outcomes of surgical manipulation experiments in the retinotectal system. The circle represents the retina, and the ellipse represents the tectum. N, nasal; T, temporal; R, rostral; C, caudal. See text for more details.

performed later (Jacobson 1967; Hunt & Jacobson 1972). However, later experiments always found rotated maps (reviewed in Jacobson 1991; Holt & Harris 1993). These experiments show that the normal direction of the gradient in retina or tectum provides an overwhelming cue for the overall orientation of the map. The obvious interpretation of a normal map

following very early tectal rotation is that the gradient had not formed by that point; however, this has not been directly demonstrated in this context.

Map compression and expansion. The map formed after removal of half the retina initially covers half the tectum (Attardi & Sperry 1963), but then gradually expands to fill the whole tectum (Schmidt et al. 1978). The axon terminal density remains the same (Schmidt et al. 1978). If the optic nerve is then made to regenerate again, an expanded map is immediately formed (Schmidt 1978). If half the tectum is ablated, the regenerated map is compressed into the remaining tectal space (Yoon 1971; Sharma 1972; Cook 1979; Finlay et al. 1979a). If "mismatched" halves of the retina and tectum are ablated, a topographic map still forms (Horder 1971). These experiments suggest that there is not a rigid match between retinal and tectal locations, and some plasticity of the map is possible. In particular, they suggest a role for *competition* between retinal axons for tectal space (Gaze & Keating 1972). Retinal fibres compete for space in the tectum, and since each fibre has equal competitive strength, they spread out to fill the entire space available, be that larger or smaller than the normal case.

Translocation. If two parts of the tectum are reciprocally translocated, regenerating retinal axons innervate their normal piece of tectum (Gaze & Hope 1983), and also appropriately reverse their order if the tectal fragment is rotated (Yoon 1980). However, in some cases, a map can be formed that ignores the translocation, i.e., the fibres tend to align with fibres in the surrounding tectum, regardless of the orientation of the transplant (Hope et al. 1976). Although the former results imply a strong determining role for tectal gradients in map formation, the latter results indicate an important role for *fibre–fibre interactions*, at least in some cases. Such interactions could also help explain ordering in the optic nerve (Bonhoeffer & Huf 1985).

Compound-eye experiments. When a whole eye is created by fusing together two half eye rudiments before connections are made, the two halves being from opposite eyes but of the same type (e.g., nasal, ventral or temporal), they each map across the whole tectum in the mirror image of each other (Gaze et al. 1963; Hunt & Jacobson 1973; Straznicky et al. 1974). When fragments smaller than half a retina are substituted early in development ("pie slice" eyes), the retinal fragments map appropriately for their original position (Willshaw et al. 1983), though they can also show some degree of reprogramming (Cooke & Gaze 1983). These results generally argue for a strong determining role of retinal gradients in map formation.

The overall conclusions. Drawn from these results (see for example, the review articles cited above) were that (1) the chemoaffnity gradients predicted by Sperry are not always stable and can sometimes be modified in response to experimental manipulation, and (2) competition and fibre–fibre interactions are also important. However, in the 1980s, attention shifted to the development of simplified *in vitro* assays allowing examination of individual retinal axons under very controlled conditions and, with the advent of the necessary tools, the identification of molecules that actually implement the gradients.

In vitro *assays for studying retinotectal mapping*

Friedrich Bonhoeffer and colleagues developed an important simplification by treating the mapping problem as binary rather than continuous: the nasal half-retina maps to the temporal half-tectum, and the temporal half-retina maps to the rostral half-tectum. This approach led to the influential *membrane stripe assay* (Walter et al. 1987b). Here, retinal axons growing

in vitro in two dimensions are confronted with a series of narrow alternating lanes of fragments of anterior and posterior tectal membranes. This makes easily visible any preference retinal axons have for the two types of membrane, and it was found that temporal axons prefer anterior tectum, while nasal axons show no preference. This effect was explained by positing a *repulsive* component in posterior tectal membranes (Walter et al. 1987a). This interpretation was later supported by the finding that posterior tectal membranes can cause growth cone collapse of temporal retinal axons (Cox et al. 1990). Essentially, these authors proposed that the map arises because nasal axons are repelled less than temporal axons by a low-anterior high-posterior tectal gradient. Bonhoeffer's group subsequently identified a 33 kDa glycoprotein preferentially expressed in posterior tectal membranes that could be the substrate for this repulsion (Stahl et al. 1990). This was recently cloned and named (Repulsive Guidance Molecule) (RGM) (Monnier et al. 2002); however, the functional role RGM plays in map formation is still unclear.

The membrane stripe assay used only uniform concentrations of anterior or posterior tectal membranes. Baier and Bonhoeffer (1992) subsequently developed an assay for growing axons on gradients of density of membrane fragments. They first applied a gradient of posterior tectal membranes to a two-dimensional surface, followed by a gradient of anterior tectal membranes pointing in the opposite direction, and then allowed retinal axons to grow on this carpet. To ensure the axons grew in straight lines, they used an alternation between narrow stripes of the gradient and stripes of a non-adhesive substrate which axons avoided. While nasal axon growth was not affected by the gradient in this assay, temporal axons grew an amount that was negatively correlated with the steepness of the gradient (i.e., the steeper the gradient, the shorter the axons). Using a more refined version of this technique, Rosentreter et al. (1998) then suggested that temporal axons grow up a gradient of posterior tectal membranes until they have travelled a fixed increment of concentration that is independent of both the slope of the gradient and the starting concentration. However, this conclusion relies on strong quantitative inferences drawn from somewhat qualitative criteria for assessing the stopping point of the front of axons within a lane. These results are reviewed in Loschinger et al. (2000).

More recently, Hansen et al. (2004) developed an assay that goes beyond the binary approach of the stripe assay to analyse more graded effects. Here, retinal explants were cut into eight strips parallel to the dorsal–ventral axis, and these were grown on membrane carpets transfected with uniform levels of ephrin-As, molecules now known to be expressed in gradients in the tectum and to be important for retinotectal mapping (see later). A matrix of outgrowth was then constructed, with one dimension being the nasal–temporal origin of the axons and the other being the ephrin-A concentration. With no ephrins, all axons grew equally. For low concentrations of ephrin-A2, starting from the nasal retina, outgrowth increased and then fell, moving towards the temporal retina. For high concentrations of ephrin-A2, outgrowth fell monotonically moving from the nasal to the temporal retina. This demonstrated a smoothly graded effect not apparent in the standard stripe assay, and a surprising promotion of outgrowth for low ephrin-A2 concentrations compared to zero concentration (see later). However, *in vivo* axons grow over ephrin gradients, not uniform levels of ephrins, so it is not obvious how to interpret this result in terms of an *in vivo* mapping mechanism.

Overall, these *in vitro* approaches have constituted an important step forward in the controlled analysis of the behaviour of isolated retinal axons when confronted with tectal membranes. On the other hand, neither a simple correlation between amount of growth and gradient steepness, nor growth of temporal axons for a fixed increment of concentration, nor a graded effect on outgrowth on uniform levels of ephrin-As, provides a mechanism for

topographic mapping. In addition, such assays do not illuminate systems-level behaviours such as competition and the role of fibre–fibre interactions in mapping.

Identification of molecules involved in retinotectal mapping

An important step forward in understanding the molecular basis of retinotectal map formation was the discovery of a role for the erythropoetin-producing hepatocellular (Eph) family of receptor tyrosine kinases, and their associated ligands, the ephrins (Cheng et al. 1995; Drescher et al. 1995). There are two families of Eph/ephrins, A and B, with promiscuous binding between receptors and ligands within a family. Though there was initially thought to be little affinity between families, more recent work has shown some interaction (Himanen et al. 2004). It now appears that the A family is most important for mapping along the rostral–caudal axis of the tectum, while the B family is most important for mapping along the dorsal–ventral axis. The Eph/ephrins are crucial in many other biological contexts besides map formation (recently reviewed in Klein 2004). Although initially, each member acquired multiple names, the terminology has since been standardized (Eph Nomenclature Committee 1997; http://eph-nomenclature.med.harvard.edu/table_1.html). We now briefly summarize the Eph/ephrin data relevant to understanding retinotectal map formation (also reviewed in Tessier-Lavigne 1995; Friedman & O'Leary 1996a; Tessier-Lavigne & Goodman 1996; Flanagan & Vanderhaeghen 1998; Goodhill & Richards 1999; O'Leary et al. 1999; Wilkinson 2001; Knöll & Drescher 2002; McLaughlin et al. 2003a; O'Leary & McLaughlin 2005). Some of the Eph/ephrin gradients currently known in chick are summarized in Figure 3. The specific Eph receptors and ephrin ligands expressed vary between species, but the theme remains the same.

Repulsive interactions. Interactions between Eph receptors and ephrins are generally repulsive (reviewed in Orioli & Klein 1997). The molecular details by which this repulsion occurs are

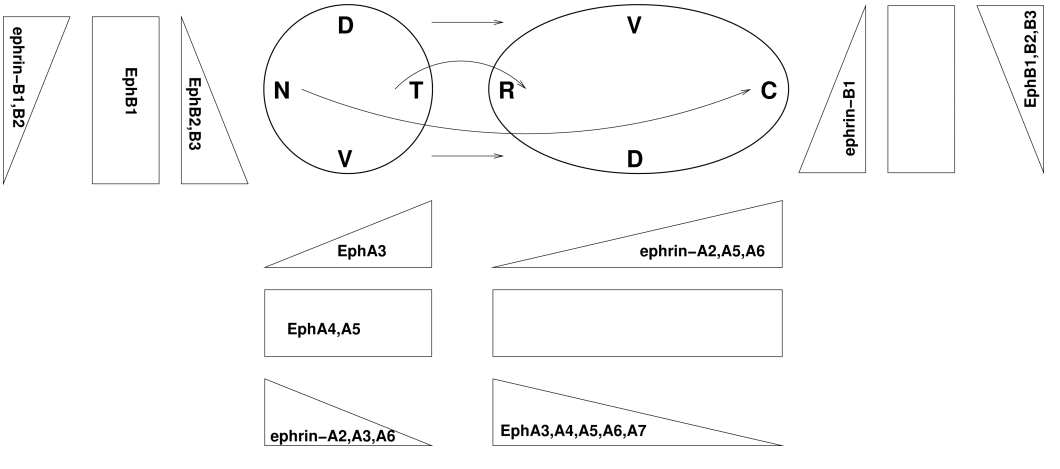

Figure 3. Some of the Eph/ephrin gradients in the chick retinotectal system. N, nasal; T, temporal; D, dorsal; V, ventral; R, rostral; C, caudal. For conceptual clarity, empty boxes are included for gradients that might in principle exist but are not currently known. The pattern is similar in mouse, though some of the Eph receptors involved are different. In *Xenopus*, the role of EphB/ephrin-B along the DV to ML axis is reversed, with ephrin-B1 expressed in a retinal gradient and EphBs expressed in a tectal gradient (Mann et al. 2002). Species differences are also discussed in McLaughlin et al. (2003a).

discussed in Hattori et al. (2000). Surprisingly, signalling can also be bidirectional, i.e., ephrin-As can act as receptors (Knöll & Drescher 2002).

Retinal gradients. So far, only distributions of Eph and ephrin mRNAs have been measured, not actual protein levels. In chick, Eph receptors are expressed in the retina and on the growth cones of retinal ganglion cells (Cheng et al. 1995; Monschau et al. 1997). EphA3 is expressed in an increasing nasal to temporal gradient, while EphA4 and EphA5 are uniformly expressed. In mouse, EphA4, A5 and A6 are expressed in the retina, with EphA4 being expressed uniformly and EphA5 in an increasing nasal to temporal gradient (Marcus et al. 1996; Connor et al. 1998; Feldheim et al. 1998; Reber et al. 2004). Ephrin-A2 and Ephrin-A5, ligands for most EphA receptors, are also expressed in a low-temporal to high-nasal gradient in the retina and on corresponding ganglion cell axons (Connor et al. 1998; Hornberger et al. 1999). Along the dorsal-ventral axis, EphB1 is expressed uniformly, while EphB2, EphB3, and EphB4 are expressed in a high ventral to low dorsal gradient (Holash & Pasquale 1995; Braisted et al. 1997; Connor et al. 1998; Hindges et al. 2002).

Tectal gradients. Ephrin-A2 and A5 are both expressed in an increasing rostral to caudal gradient in the tectum (Cheng et al. 1995; Drescher et al. 1995). In chick, levels of both ephrin-A2 and ephrin-A5 rise from rostral to caudal, with the latter being restricted to more caudal locations and rising more steeply. In mouse, levels of ephrin-A5 rise from rostral to caudal, while levels of ephrin-A2 drop off at both ends of the SC (Frisén et al. 1998). In general, retinal axons expressing high levels of EphA receptors therefore project to regions of SC expressing low levels of ephrin-As, and vice versa. EphA3 is also expressed in a gradient running in the opposite direction to the ephrin-A gradients (Marcus et al. 1996; Connor et al. 1998). Ephrin-B1 is expressed in a high-dorsal to low-ventral gradient (Braisted et al. 1997; Hindges et al. 2002). Therefore, retinal axons expressing high levels of EphB receptors project to regions of SC expressing high levels of ephrin-Bs, and vice versa.

Eph/ephrin misexpression studies

The principal evidence that the above-mentioned Eph and ephrin gradients are actually involved in retinotectal mapping comes mainly from experiments where one or more of the gradients are disrupted in mice or chicks. The effect on the mapping is then examined by focal injections of fluorescent dye into retina for anterograde labelling of SC, and focal injections of dye into SC for retrograde labelling of retina. This set of data is rapidly growing as refinements in molecular techniques make more subtle manipulations possible. For brevity, we do not discuss experiments manipulating Vax2 and Tbx5, transcription factors controlling EphB and ephrin-B expression, respectively (reviewed in McLaughlin et al. 2003a).

Ephrin-A2 and A5 knockouts. Knockout of ephrin-A5 (*ephrin-A5* $-/-$) alone causes several effects (Frisén et al. 1998). Some temporal retinal axons (nasal axons were not examined in this study) overshoot the caudal margin of SC and penetrate the inferior colliculus, some axons target normally in rostral SC, and some axons aberrently target caudal SC. Since the ephrin-A5 gradient in normal mice actually declines at the caudal end of the SC, this means that the targeting of temporal retinal axons in the ephrin-A5 knockout is correlated with regions of low ephrin-A2 expression. Feldheim et al. (2000) also analysed the projections of nasal axons and found that most had an aberrent termination zone in rostral SC in addition to the normal termination zone in caudal SC. Knockout of ephrin-A2 alone (Feldheim

et al. 2000) showed a similar phenotype to knockout of ephrin-A5, except for an absence of overshoot at the caudal margin of the SC. *Ephrin-A2−/−*; *ephrin-A5−/−* mice had more substantial defects than each knockout individually (Feldheim et al. 2000). Many axons had both a normal and an aberrent termination zone, with little apparent preference for the aberrent termination site for temporal axons and a broad distribution of sites for nasal axons, though generally avoiding far-rostral SC. Retinal axons still filled the SC. This was interpreted as evidence for competition: the movement of nasal axons away from their normal termination sites is caused by the occupation by temporal axons of regions of the SC normally occupied only by nasal axons (discussed in Goodhill 2000). Stripe assays were also used to show that retinal axons show no lane preference when the tectal membranes come from double-knockout mice. Defects were also found in dorsal–ventral targeting in some of the mutant animals. Together, these results show that ephrin-A2 and ephrin-A5 gradients do indeed play an important role in specifying the topographic map in the SC, and that they each play a distinctive though additive role.

EphA loss of function. Feldheim et al. (2004) disrupted retinal EphA gradients in both mouse and chick retina. This caused a reduced responsiveness of temporal retinal axons to caudal tectal membranes, though no change in the responsiveness of nasal axons in the stripe assay. *In vivo* it caused a caudal shift in temporal axons and a rostral shift in nasal axons. This provides direct evidence that Eph gradients are involved in retinotectal mapping.

Disruption of the ephrin-A2 gradient. Based on the hypothesis that ephrin gradient expression in tectum is controlled by earlier gradients of Engrailed (En) genes (e.g., Logan et al. 1996), Friedman and O'Leary (1996b) misexpressed En genes in developing tectum. Nasal axons formed a very diffuse projection with many aberrent termination sites, while temporal axons tended to avoid regions of high En expression. Direct misexpression of ephrin-A2 (Nakamoto et al. 1996) led to similar results.

EphA knock-in. In mouse retina, EphA3 is not normally expressed. Using a subtle molecular manipulation, Brown et al. (2000) expressed EphA3 in just a subset of ganglion cells spanning the retina. This created two sets of retinal axons competing for space in the SC: those with normal total EphA expression levels, and those where total EphA expression levels were increased by a constant amount. Quantitative analysis showed that in the homozygous mutant this caused the formation of two almost non-overlapping topographic maps in the SC: one in the rostral part from the axons with normal EphA expression, and one in the caudal part from axons with elevated levels of EphA expression. In the heterozygous mutant, there were two, more overlapping, topographic maps in the caudal part of the SC, collapsing to one map at the rostral end of the SC, corresponding to about 76% of the nasal–temporal axis. These results were interpreted as supporting a "relative signalling" model, whereby whether one or two maps form depends on the ratio of EphA expression levels between the two populations of axons. In nasal retina, EphA levels are low, the induced EphA3 expression provides a large ratio between the two populations, and two maps form. In temporal retina, EphA levels are high, the ratio is lower, and in the heterzygote this leads to a collapse to one map at a particular critical location. A more recent paper from the same group analysed the maps formed when similar manipulations in EphA3 levels were performed in EphA4 heterzoygous and homozygous mice (Reber et al. 2004). According to the relative signalling model, these reductions in overall EphA levels should shift the collapse point for the two maps. This was indeed found: it shifted to a position corresponding to 88% of the nasal–temporal axis in

the EphA4 heterzgote, and entirely to the temporal pole in the EphA4 homozygote. Reber et al. (2004) were able to quantitatively predict these values from a simple mathematical formulation of the relative signalling model, discussed in the Models section.

Branching and EphB misexpression. In a modification of the membrane stripe assay, Roskies and O'Leary (1994) showed that a GPI-linked molecule, possibly ephrin-A5 (Ciossek et al. 1998; O'Leary et al. 1999), in rostral tectum can preferentially induce branch formation of temporal retinal axons in chicks. Ephrin-A5 has also been shown to act as a promotor of axonal branching in the formation of layer-specific circuits in the cortex (Castellani et al. 1998). Mice deficient for both EphB2 and EphB3 show defects in mapping along the dorsal–ventral axis (Hindges et al. 2002), particularly involving the extension of lateral branches of axons along the dorsal–ventral axis towards their correct termination zones. Ectopic expression of ephrin-B1 caused axon branches to be directed away from regions of high ephrin-B1 expression (McLaughlin et al. 2003b). It was concluded from these studies that EphB/ephrinB signalling can promote both branch attraction and repulsion. The same group subsequently proposed a computational model for this process (Yates et al. 2004), discussed later. In Xenopus, where the roles of the EphBs and ephrin-Bs are reversed, disrupting EphB/ephrin-B interactions produced results consistent with attraction by EphBs of dorsal retinal axons expressing ephrin-Bs (Mann et al. 2002).

Computational models for retinotectal map formation

With no other constraints, there are many possibilities for how a mapping could be established by gradients in the normal unaltered, case. Modelling from the 1970s to the early 1990s tried to refine this space of possibillities by focusing on the systems-level experimental data then available. These data provide many constraints, and in response these models became quite sophisticated. However, the discovery of Eph and ephrin gradients and their role in retinotectal mapping generated a return, at least initially, to much simpler ideas about mapping, focusing mostly just on the normal case. The systems-level data and the insights gained from earlier modelling work, for example regarding the role of competition, were not considered (discussed in Goodhill & Richards 1999). However, as gene misexpression studies started to find maps in perturbed situations which called more simplistic ideas into question, interest in earlier modelling work was revived, and it is thus timely to review these models here.

A detailed understanding of the assumptions of each model comes only from studying its equations. Unfortunately, the models do not generally share enough of a common framework for a unified set of equations and parameters to be formulated, and presenting all equations for all models, each with their associated terminology, would be unmanageably long. For each model, we therefore give only a broad outline of the assumptions involved, but remind the reader that words are at best only an approximation to the mathematics.

Prestige and Willshaw (1975)

Prestige and Willshaw (1975) were the first to formalize notions of chemospecific matching suggested by Sperry's hypothesis, and to computationally investigate the importance of competition in this context. They defined a crucial distinction between two forms of chemical matching, termed "type I" and "type II". In type I (which they also refer to as "direct") matching, each presynaptic cell has an affinity for just a small neighbourhood of postsynaptic cells, with a peak affinity for the topographically matching cell in the postsynaptic sheet.

While such a rigid scheme can form a map under normal conditions, it cannot account for much of the systems-level experimental data without assuming that the underlying molecular signals are appropriately respecified in each case. In type II matching,

> . . . *all* axons have maximum affinity for making and retaining contacts at one end of the postsynaptic sheet of cells, and progressively less for the cells at greater distances from that end. Similarly, all postsynaptic cells have maximum affinity for axons from one end of the postsynaptic set, and axons remote from this end have correspondingly less likelihood of retaining *any* contact. We may thus talk of *graded affinity* within both pre- and postsynaptic sets. The contact behaviour of individual cells and axons will now be highly dependent on the presence or absence of their neighbours.

To explore type II matching computationally, Prestige and Willshaw (1975) considered the mapping between a one-dimensional array of presynaptic cells and a one-dimensional array of postsynaptic cells. Each presynaptic cell could make several contacts, and each postsynaptic cell could receive several contacts. Graded affinity was expressed in terms of the lifetime of a contact. A simplified version of the events taking place at each discrete timestep in the model is that a presynaptic and postsynaptic cell are selected at random and assumed to make a connection, the clock starts ticking on the lifetime of that connection determined by the prespecified matrix of affinities, and all connections for which time has run out are removed. There was no requirement that each retinal or tectal cell maintain any contacts. The size of the simulations was modest by modern standards due to the limited computing power available (roughly a million times less than today), and the length of the retina and tectum were each in the range of 10–30 cells. However, this was sufficient to recognize the importance of constraints on the number of connections that each cell can make or receive. If this number is not limited, then no map results, but introducing *competition* by restricting the total number of contacts (normalization) does lead to a map. In particular, Prestige and Willshaw (1975) assumed that each presynaptic cell could make only a fixed number of contacts N_{pre} among the postsynaptic cells, and similarly each postsynaptic cell could support only a fixed number of contacts N_{post} from presynaptic cells (simulation values for N_{pre} and N_{post} were generally in the range of 5–10). This then ensures an even spread of connections: without competition for postsynaptic sites, every presynaptic cell would connect only to the highest-affinity end of the postsynaptic array, while without competition for presynaptic sites, every postsynaptic cell would receive connections only from cells at the highest-affinity end of the presynaptic array (for a more recent discussion of this concept, see Goodhill 2000). They then investigated whether compression and expansion of retinotectal maps could be explained within this framework. They found that it was necessary to make the additional assumption ("regulation") that N_{pre} and N_{post} were also altered. For instance, if half the postsynaptic array is removed, then unless N_{post} is increased, connections will only be made from the highest-affinity end of the presynaptic array.

Overall, this model was expressed purely in terms of attractive gradients, and the implementation of affinities in terms of lifetime of connections now seems unlikely. However, this work was significant in that it was the first quantitative investigation of the principles of retinotectal mapping, particularly competition. More general discussions of competition and normalization in models of neural development can be found in Wiskott and Sejnowski (1998) and van Ooyen (2001).

The Arrow model (1976)

Hope et al. (1976) took a more abstract approach to the mapping problem than Prestige and Willshaw (1975). The model did not consider multiple connections between a retinal

and tectal array; rather, each tectal location was occupied by at most one retinal axon. As described by Hope et al. (1976):

> The arrow model is best explained by an analogy. Suppose that there is a row of soldiers lined up side by side, facing the same way. The order of the soldiers is initially random with respect to their height. The problem is to give a set of instructions which, if obeyed, will cause the soldiers to be lined up with the tallest man on the far left, the next tallest to his immediate right and so on, until the smallest is on the far right.

Here, height correlates with retinal location, and position corresponds to tectal location. Starting from initially random connections, two retinal axons that terminate next to each other in the tectum are chosen at random. Their retinal positions ("heights") are compared, and if appropriate the sites of termination of the axons are exchanged. This is a type II mechanism with competition: all axons try to migrate to one end of the tectum, but each tectal site supports only one connection. The algorithm used is actually bubblesort (Friend 1956), one of the least efficient sorting algorithms available (reviewed in Knuth 1998). Hope et al. (1976) ran this algorithm in two dimensions, starting from random initial conditions and assuming two independent gradients of positional information along the two orthogonal retinal and tectal axes. Some tectal sites were allowed to be empty, i.e., the retinal and tectal arrays were not required to be the same size. Since the exchange rules only applied to occupied sites, they also included a random walk component in the model, allowing retinal axons to invade unoccupied sites. Hope et al. (1976) showed that besides forming normal maps, appropriately rotated maps could be formed when a piece of tectum was rotated (assuming the gradient of positional information in that piece of tectum points in the opposite direction). However, the model obviously failed to account for the translocated map experiments, since it relies exclusively on local rather than global information. Overall, the model assumes that retinal fibres that terminate next to each other in the tectum are able to compare their relative positions of origin, and then exchange positions if necessary; however, the way in which these processes might be implemented biologically was not discussed.

Tea Trade model (1977, 1979)

Von der Malsburg and Willshaw (1977) proposed a model based on the idea that map formation might somehow be dependent on induction of molecules from the retina into the tectum (Willshaw and von der Malsburg 1979; von der Malsburg and Willshaw 1981a, 1981b; von der Malsburg 1989). The model is expressed in terms of molecular markers, but markers intrinsic only to the presynaptic sheet. There are no pre-existing markers encoding position in the postsynaptic sheet: it is assumed that presynaptic markers are transported to the postsynaptic sheet via induction along presynaptic axons. Some experimental evidence for such a mechanism was presented around the same time by Schmidt (1978) and Schmidt et al. (1978). In the model, several markers are assumed to exist in the presynaptic sheet, the sources of which are spaced out in the presynaptic sheet at fairly regular intervals. An analogy presented to explain the working of the model was the import of tea from plantations in India to British towns, hence the name "Tea Trade model".

Initially, markers diffuse in the presynaptic sheet until a stable distribution is established. Each presynaptic axon then makes contacts of equal strength with the postsynaptic sheet across a broad but topographically appropriate range (generally about half the width of the postsynaptic sheet). This slight overall bias in the connection strengths is required initially in order to provide a global orientation for the map, since no intrinsic polarity is specified in the postsynaptic sheet (a rigorous analytic basis for this requirement was presented by Häussler and von der Malsburg 1983). It is then assumed that each presynaptic axon induces the

vector of markers existing at that point in the presynaptic sheet into the postsynaptic sheet, where the markers diffuse as in the presynaptic sheet. The rate of induction at each synapse is proportional to the strength of that synapse. Synaptic strengths are updated periodically according to the degree of similarity between the vector of markers each axon carries and the vector of markers already existing at those points it contacts in the postsynaptic sheet. Synaptic updating occurs with a molecular analogue of the Hebb rule: the strength of connection between a presynaptic cell and a postsynaptic cell is increased in proportion to the similarity of their vectors of molecular markers, rather than on the basis of the correlations in their activities as originally proposed by Hebb (1949). Synaptic strengths are normalized so that each presynaptic cell can only support a fixed total strength of connections. This ensures that every presynaptic axon makes contacts in the postsynaptic sheet. Weak synapses are eliminated, and axons making strong synapses then put out branches to neighbouring postsynpatic cells.

Willshaw and von der Malsburg (1979) simulated this using discrete, one-dimensional presynaptic and postsynpatic arrays, each of length 80 cells. These simulations showed that the model reaches a stable state of dynamic equilibrium, with new branches constantly being extended and then retracted. In Willshaw and von der Malsburg (1979), a large body of results with the algorithm are presented (the paper contains 20 figures). Besides forming appropriate maps under normal conditions, they showed that the model also correctly predicts the outcome of a wide range of results for the retinotectal system under abnormal conditions, including mismatch, tectal graft, and compound eye experiments. In addition, some regeneration experiments (e.g., Schmidt 1978) can be accounted for under this scheme by assuming that when regeneration occurs, the postsynaptic sheet holds a "memory" of the previous pattern of innervation in terms of the previous stable distribution of markers.

Subsequent experimental discoveries (reviewed above) have made it clear that there are preexisting gradients in the tectum and that these play a crucial role in retinotectal mapping. The Tea Trade model is however quite elegant mathematically and, along with the Neural Activity model from the same authors (Willshaw and von der Malsburg 1976), had a significant impact on the development of general-purpose topographic map formation algorithms in the artificial neural network literature. The Tea Trade model equations later inspired the development of the elastic net algorithm (Durbin & Willshaw 1987), which has been very successful at modelling the formation of feature maps in primary visual cortex (e.g., Durbin & Mitchison 1990; Carreira-Perpiñán et al. 2005). The Tea Trade model was the first in this context to include axonal "branching" and set a high standard for the level of detail at which the experimental data could be engaged.

Willshaw subsequently spent several years doing purely experimental work in the retinotectal system (e.g., Fawcett & Willshaw 1982; Willshaw et al. 1983). More recently, Willshaw (Willshaw & Price 2003; manuscript in preparation) has proposed a modified form of the Tea Trade model to address recent data on Eph/ephrins, particular the EphA3 knock-in experiments of Brown et al. (2000) and Reber et al. (2004). This model assumes that ephrin gradients are either weak or non-existent before the arrival of retinal axons, and it is the arrival of Eph receptors on these axons that overwrites or upregulates ephrin levels in the tectum. With such a mechanism, a quantitative match can be obtained with the mapping results of Brown et al. (2000) and Reber et al. (2004).

Extended branch-arrow model (1982)

Overton and Arbib (1982) presented a model originally motivated by the arrow model (Hope et al. 1976), but substantially more sophisticated. They modelled the tectum as a

(one-dimensional) continuum rather than a discrete array of positions. Each retinal axon was imagined to form several branches in the tectum, with a small circle surrounding each branch indicating the area of tectum within which it could interact with branches from other axons. In the "branch-arrow model", at each timestep, the movement of each branch was given by a weighted vector sum of three terms. The "interaction" term was a smoothed version of the exchange term in the original arrow model: all other branches with intersecting circles of influence are taken into account in terms of whence they originated in the tectum, with a weight that declines with distance in the tectum. The "boundary effect" term was introduced to help model the effect of tectal grafts: it decreases the influence of branches on each other across a graft boundary (and is also used to encode the position of the boundary of the tectum itself). The "average influence" term is itself a weighted sum of interaction and boundary effect terms over all branches from the same retinal axon. Thus, in total, each branch moves according to the retinal position of origin of nearby branches from other axons, the state of the tectum nearby, and what the rest of the axonal tree is doing. In the "extended branch-arrow model", an additional term is added to the movement vector which provides some absolute information about position, rather than just the local information utilized in the arrow and branch-arrow models (i.e., a mixed type I/type II model). This was needed to help account for the translocation experiments.

Overton and Arbib (1982) presented the results of extensive computer simulations of the extended branch-arrow model, accounting for the majority of systems level experimental results then known. This is much more realistic than the original arrow model, and is relatively unusual amongst models in treating the tectum as continuous.

Multiple-constraint model (1980, 1985, 1990)

The multiple-constraint model was first introduced by Fraser (1980, 1985), and explored most fully by Fraser and Perkel (1990). It is based on the idea that the state of a retinotectal map can be described by an "adhesive free energy" G, which depends on how successfully a number of constraints are satisfied, and that during map formation the system tries to mimimize this energy. In the final version of the model (Fraser & Perkel 1990), the constraints employed (in order of decreasing weighting in G) are (1) a position-independent adhesion between retinal and tectal cells, (2) a general competition among retinal axons for tectal space, (3) a tendency for neighbouring axon terminations in the tectum to stabilize if they come from neighbouring positions in the retina, (4) a dorsoventral gradient of adhesive specificity in retina and tectum, and (5) an anteroposterior gradient in retina and tectum. It is thus a mixed type I/type II model with competition. The tectum is continuous, and each of 2500 retinal axons is considered to occupy a small circular region of diameter about 10% of the total diameter of the tectum (axonal branching is not explicitly considered). The form of the final mapping is found from minimizing G by the general-purpose optimization algorithm simulated annealing (Kirkpatrick et al. 1983). At each timestep, one randomly chosen possible movement of one randomly chosen axon is considered. If this movement would decrease G, it is implemented; however, if it would increase G, it may still be implemented, with a probability that decreases with both the size of the increase of G and the time elapsed in the simulation.

Fraser and Perkel (1990) presented both a relatively comprehensive summary of the experimental systems level results then known and a systematic catalogue of computer simulations addressing these results, for the most part successfully. It was suggested that the type I specificity could be implemented by gradients of different molecules running in opposite directions in the tectum. One weakness of this model is the abstractness of its rules for moving axons: a developmental mechanism which could perform the minimization of G was not presented.

Cowan's model (1981, 1991, 1997)

There has generally been a clean separation between theoretical models addressing activity-dependent and activity-independent effects in retinotectal maps formation, making it possible to focus this review only on activity-independent models. However, one model which has tried to integrate both effects should be mentioned here. Whitelaw and Cowan (1981) combined a gradient of adhesive specificity (i.e., a type II mechanism (Prestige and Willshaw 1975)) with an activity regime and synaptic updating as in the Neural Activity model (Willshaw & von der Malsburg (1976). Changes in synaptic strengths are now however multiplied by the degree of "adhesion" between the corresponding pre- and postsynaptic cells. Competition is implemented by both pre- and postsynaptic normalization of synaptic strengths. One-dimensional simulations successfully accounted for a wide range of the experimental literature, including expansion and compression, mismatch, rotation, and compound-eye experiments.

The first version of this model however lacked fibre–fibre interactions, i.e., a tendency for retinal axons to attract each other and fasciculate (Schmidt and Easter 1978; Meyer 1979, 1982; Hayes and Meyer 1988b). This meant there were certain experimental results the model did not explain. The addition of such an axon–axon interation rule to the model, which helps balance the repulsive competitive force, led to perhaps the most complete account of the experimental data available up the late 1980s (Cowan and Friedman 1990, 1991). In a subsequent version of the model (Weber et al. 1997), the axon–axon interaction rule is implemented as the product of a gaussian function of separation in the retina multiplied by a gaussian function of separation in the tectum (which is a version of the function for measuring topography proposed by Goodhill & Sejnowski 1997). Overall, this model represents one of the most concerted and successful efforts to address the system-level experimental data in full detail and is the only model to attempt to fully integrate activity-dependent and activity-independent effects.

Gierer's model (1983, 1987)

Gierer (1983, 1987) proposed a model based on the matching of pre-existing gradients in retina and tectum based closely on Sperry's original chemoaffinity hypothesis. We review it here in some detail, as this model has been widely cited in the Eph/ephrin literature. The basic idea of this model is well summarized in Gierer (1987):

> A recent study of requirements for projections by gradient mechanisms (Gierer 1981, 1983) demonstrates that countergraded effects are necessary in each of the two dimensions to generate a spatial distribution of a guiding parameter p with a minimum at a position *within* the tectal field. Two gradients with opposite slope, or two substances graded in the same direction, one activating and one inhibiting, or even a single gradient which is read by the axonal growth cone in two different manners, exerting an activating and an inhibitory effect, could create a minimum. . . . Experimental evidence on the sign of the guiding gradients is not yet available and the choice of sign does not strongly affect model properties.

Note that "countergradients" here means two gradients running in opposite directions in the tectum; in the more recent Eph/ephrin literature, this term often means a retinal and a tectal gradient which run in opposite directions along the mapping axis. In particular, Gierer (1983) imagined that mapping is controlled by the concentration of an inhibitory substance $p(x, u)$, where x indicates the tectal position and u indicates the retinal position. p is produced by a reaction of the graded distribution of a retinal marker present on retinal axons with a graded distribution of a tectal marker. Axons then grow down the gradient of p to a minimum, stopping when $\frac{\partial p}{\partial x} = 0$. For this to form a map, it is required that the

position of this minimum vary smoothly as a function of retinal origin u; in the simplest case when $x = u$. There are clearly an infinite number of combinations of gradient shapes and reaction rules that accomplish this: two specific possibilities Geirer discusses are that the retinal gradient is given by $e^{-2\alpha u}$, the tectal gradient by $e^{-\alpha x}$, and that

$$p(x, u) = \frac{e^{-2\alpha u}}{e^{-\alpha x}} + e^{-\alpha x},$$

or alternatively

$$p(x, u) = \frac{e^{-\alpha u}}{e^{-\alpha x}} + \frac{e^{-\alpha x}}{e^{-\alpha u}}.$$

Simulations were presented using such rules demonstrating that they indeed can lead to a topographic map.

This was so far purely a type I model which did not account for the systems-level experimental data available at the time. Gierer (1983) also therefore suggested a possible mechanism for gradient change in response to surgical manipulations such as retinal or tectal ablation. Reminiscent of the Tea Trade model, the idea is that

> "retinal fibre terminals induce, in the tectum, a slow increase in source (e.g., an enzyme) producing an additional contribution to p, and that the rate of increase is proportional to the local density of retinal fibre terminals. If the sources thus produced persist on the tectum while fibre terminals continuously move to respecified positions of minimal p, this process will eventually smooth out differences in the density of fibre terminals, giving rise to compression or expansion in the dimensions of ablation."

Specifically, he considered the modified equations

$$p(x, u) = \frac{e^{-\alpha u}}{e^{-\alpha x}} + \frac{e^{-\alpha x}}{e^{-\alpha u}} + r(x, t),$$

$$\frac{\partial r}{\partial t} = \epsilon \rho(x, t),$$

where ρ is the local density of fibre terminals and t is time. Simulation results suggested that this could be an effective mechanism for gradient regulation.

Gierer (1987) presented essentially the same model, though leaving out inductive effects and the possibility of gradient change. This paper focused on the trajectories axons might follow in such a gradient field and also considered a role for probabilistic axonal branching in map formation, both at the tip of the axon and from further back on the axon shaft. Simulated trajectories and branching patterns resembling those seen experimentally were presented, though full algorithmic detail for how these were generated was not presented. This work was the first to discuss type I specificity implemented by dual gradients, and to present axonal trajectories and branching patterns across the tectum. However competition and axon–axon interactions were not considered, and the rigidity of the matching in Gierer (1987) strongly limits its explanatory power. This work has had little impact on models of topographic mapping in general in the artificial neural network literature. It has however been widely cited in the experimental literature and, in some experimental papers, is the only computational model mentioned.

Mass action models (1996–)

The discovery of gradients of EphA receptors and ephrin-A ligands in the retinotectal system led to many qualitative speculations in the experimental literature for how such interactions

could provide a mechanism for forming maps. The first more quantitative proposal in this literature was the "mass action" model of Nakamoto et al. (1996). These authors proposed that axons stop growing across the tectum when they encounter a standard value of a negative signal p from a receptor, and that the amount of p is related to receptor R and ligand L concentrations by $RL = kR.L$ where k is a constant, the standard law of mass action (e.g., Gutfreund 1995). This is purely a type I model, much simpler than those discussed above, and has a number of problems. It specifies only when axons should stop growing and does not address how they seek out appropriate targets. It is unable to account for most of the map plasticity experiments reviewed earlier without proposing changes in gradient profiles in these cases. It makes incorrect predictions for the results of Eph and ephrin misexpression experiments. It also imposes strong constraints on possible gradient shapes in retina and tectum, since for a map of constant magnification factor to form, it is required that $R \propto 1/L$. Constraints on gradient shapes imposed by this and related models were quantitatively analysed for mass action models in Goodhill (1998) and Goodhill and Richards (1999).

This type of mass action model was subsequently developed further by Honda (1998, 2003), in his "servomechanism" model (see also Loschinger et al. 2000). This again assumed that each retinal axon is searching for the same standard signal strength $S = R.L$. However, a difference signal d is now included to provide directional growth, where $d = \|R.L - S\|$. At each timestep, a retinal axon measures d at its current position, selects a neighbouring position it might move to, and calculates $d = d'$ again at the putative new position. If $d' < d$, the move is selected with a certain probability. This is determined by random numbers drawn from a gaussian function, $p(d)$, such that the probability of moving is $p(d')/(p(d) + p(d'))$. Thus, if $d = d'$, the move is accepted with probability 1/2, and this probability increases towards 1 as d' becomes greater than d. This is similar to the movement rule of the multiple constraint model (Fraser & Perkel 1990), though it does not exploit the abilities of the simulated annealing algorithm to find global optima (Kirkpatrick et al. 1983). The initial selection of a possible neighbouring position is probabilistically biased towards moving forwards through the tectum rather than backwards. Besides one-dimensional simulations, Honda (1998) presented two-dimensional simulations of this model, assuming the movement rules operate independently along the two axes in response to two different pairs of retinal and tectal gradients. The retina and tectum were each discrete with a size of 100 by 100, and R and L values both varied between 1 and 100. The retinal gradient was linear, and a variety of tectal gradient shapes were considered. There were no interactions between retinal axons, and no constraints preventing multiple retinal axons from occupying the same tectal position. Honda showed that this model was capable of generating maps under normal conditions, and as expected (Goodhill 1998), the magnification factor varied across the map depending on the shape of the tectal gradient. For the first time in the theoretical literature, Honda (1998) also simulated stripe assay experiments involving gradients (Baier & Bonhoeffer 1992). A parameter regime was presented where the axons displayed a transition in growth as a function of retinal position, from growing uniformly on both lanes to growing just on lanes from rostral tectum.

Since this is a type I matching scheme, its explanatory power is limited. Honda (2003) therefore introduced competition into the model as follows. First, an "initial mapping" is set up by applying the rules of the original servomechanism model until the map has stabilized. Second, neighbouring tectal sites are chosen at random, and if the axon density at the site with the larger density exceeds a critical density, the axon at that site whose d' value were it to move the neighbouring site would be smallest then migrates to the neighbouring site. This process is iterated to stability. A competitive process that is temporally dissociated from, rather than simultaneous with, the chemoaffinity matching process is unique to this model. Direct biological evidence for such a two-stage process is lacking, though it is

conceivable that the model might function equally well with a simultaneous process. Using this "servomechanism-competition" model, Honda (2003) addressed the EphA knock-in experiment of Brown et al. (2000). He found that it was possible to reproduce the homozygous case (two separate maps), as long as the most rostral part of the tectum was assumed to have a smaller effective area for innervation than the rest of the tectum. For the heterozygous case, it was stated that this "... showed a discrepancy ... from the experimental result... . The exact reason for this discrepancy cannot be elucidated at present". Honda (2003) went on to consider the ephrin-A knockout data. A parameter regime was found where these could be reproduced in the model, though this regime was not the same one used for the EphA3 knock-in experiments. The ephrin-A2 gradient shape assumed had a very shallow increase moving to caudal tectum and then declined again. The infiuence of ephrin-A2 gradients in the retina was also considered.

Overall, this model is one of the most detailed attempts yet to address recent EphA and ephrin-A misexpression data. However, some of its assumptions are rather arbitrary, and its explanatory power is limited.

Markov chain model (2004)

Koulakov and Tsigankov (2004) proposed a model based on stochastic interchange between neighbouring axon terminations in the tectum, with some similarities to the arrow (Hope et al. 1976) and servomechanism (Honda 1998) models. Given receptor levels R_1 and R_2 for axons with neighbouring terminations in the tectum, and corresponding ligand levels L_1 and L_2, the probability of interchange P at each timestep is

$$P = \frac{1}{2} + \alpha[(R_1 - R_2)(L_1 - L_2)],$$

where α is a constant >0. That is, exchange between neighbouring sites is likely when, for instance, the axon at site 1 expresses more receptor than the axon at site 2, and also the ligand level is higher at site 1 than site 2. This implements the idea of repellent countergradients, i.e., that retinal regions with low levels of receptor map to tectal regions with high levels of ligand. Attractive gradients are modelled in this scheme by changing the sign in the probability to $P = \frac{1}{2} - \alpha \ldots$. The initial starting condition is purely random. This model is similar to the arrow model except for the explicit inclusion of ligand levels, and for the way in which stochasticity is introduced, which in the arrow model was by the addition of a random walk component. An important difference with the servomechanism model is that the Markov chain model considers relative rather than absolute ligand levels. It is thus a type II model, and competition is implicit, since each tectal site supports only one axon.

The main experimental result addressed in Koulakov and Tsigankov (2004) is the EphA knock-in experiment of Brown et al. (2000), which is modelled by assuming that alternating retinal sites have elevated EphA levels. Now when axons from neighbouring retinal sites are adjacent in the tectum, there is a large probability of them being exchanged: two separated maps form, modelling the homozygous case. The more interesting heterozygous case was modelled by assuming an elevation in EphA levels of half the magnitude to before for alternating retinal sites. Now, as in the experimental data, a fusing of the two maps in rostral tectum occurs. This was explained to be because the signal-to-noise ratio is lower in rostral than in caudal tectum: the noise is the probabilistic switching, which is unvarying over the tectum, and the signal is the EphA level, which is lower in rostral tectum. According to this explanation, the position of fusing of the two maps should depend on the magnitude and steepness assumed for the retinal EphA gradients levels, and Koulakov and Tsigankov

(2004) confirmed this to be the case. Thus, in this model, the fusion point depends on absolute rather than relative EphA levels. These authors also made the prediction that an analogous experiment knocking in EphBs along the dorsal–ventral axis of the retina should lead to a dorsal–ventral map in tectum with two bifurcations, a prediction that remains to be tested experimentally.

Branching model (2004)

Motivated by experimental data such as that of Yates et al. (2001), Yates et al. (2004) proposed a model in which the development of topographic specificity is based purely on axonal branching. Three hundred retinal axons from a one-dimensional array of 100 retinal sites project across a one-dimensional array of 100 tectal sites. Each axon is visualized as a line spanning the whole tectum, i.e., in the initial unbranched pattern, there is no specificity. As the simulation proceeds, branches form laterally from particular positions along each axon shaft, eventually generating one or more "terminal arbors". In this model, countergradients of both branch-promoting and branch-inhibiting molecules are required in the tectum to generate topographic specificity, and Yates et al. (2004) argue that these can be identified with the gradients of ephrin-As and EphAs known to exist in SC.

Branching in the model occurs probabilistically. The expression for the probability depends in a complex way on several parameters, including receptor and ligand levels in retina and tectum, and repulsive interactions between nearby arbors in the tectum. Branches may extend or retract, and form secondary branches if sufficiently long according to the same probability expression. There is thus a synergistic effect, whereby initial branching in one spot is likely to lead to more branching. However, it was found that to generate the degree of arbor refinement seen experimentally, this synergistic bias should be superlinear. The branching probability was therefore multiplied by a term taking into account the branch density already existing at that point. Yates et al. (2004) presented simulations reproducing both normal development, and appropriate maps when ephrinA levels are decreased by misexpression. The EphA knockin experiments of Brown et al. (2000) were also addressed. However, unlike in Honda (2003) or Koulakov and Tsigankov (2004), a plot of retinal versus tectal location was not presented, and it is thus hard to assess how quantitatively these simulations matched the data of Brown et al. (2000). Overall, this is mostly a type I model, with some additional flexibility due to the ability of axons to interact. Uniquely among the models discussed, it considers differences between mouse and chick development by using slightly different parameter values to model each of these species.

Relative signalling model (2004)

Reber et al. (2004) presented a quantitative version of the relative signalling argument of Brown et al. (2000), and used it to predict the collapse points for duplicated maps when EphA3 is expressed in a subset of retinal axons. They argued that relative signalling would mean that the EphA gradient should be of exponential form, so that a constant increment of distance in the retina would cause a constant relative increase in EphA concentration. This equation proved to be a good match to measured mRNA levels. The effect of the EphA knock-in could then be modelled by an appropriate additional offset to the wildtype equation. Dividing these two equations, and taking into account where the collapse point occurred in the heterozygote (Brown et al. 2000), allowed a value of 1.36 to be determined as the "discrimination limit", the ratio of Eph concentrations for neighbouring retinal cells

below which their difference could not be distinguished. Reber et al. (2004) then performed experiments to determine collapse points when, besides expressing EphA3 in a subset of cells, EphA4 was also knocked out. Using the equations already derived, and the critical value of 1.36, allowed quantitatively accurate predictions for when collapse occurred in these maps. For instance, maps for mice that had EphA3 knocked in and EphA4 levels reduced by 50% were predicted to collapse at 88% of the distance to the temporal pole, quantitatively matching the experimental result. To explain the lack of collapse in the wildtype, where the difference in summed EphA levels between neighbouring retinal axons is much less than 1.36, Reber et al. (2004) argued that in this case, retinal axons use the highest EphA level in the population as a reference value.

This model is somewhat more abstract than the others described above, since it does not offer rules for actual movement of axons in the tectum. Rather, through simple quantitative reasoning, it does a very good job of explaining when and where a particular event, i.e., collapse of a double map, will occur. It will be interesting to see if similar reasoning can be used to address the other phenomena we have discussed in retinotectal map development.

Summary of modelling assumptions and their relation to experimental data

Overall architecture

Most models treat the retina and tectum as discrete, regular arrays. While this is a reasonable assumption for ganglion cells in the retina, it may also be reasonable to treat the tectum as a continuous structure (Overton and Arbib 1982; Gierer 1987; Fraser and Perkel 1990; Reber et al. 2004) since retinal arbors are not in reality constrained to discrete locations. Many models have analysed only one-dimensional simulations, corresponding to the mapping from the nasal–temporal axis of the retina to the rostral–caudal axis of the tectum. This is a useful simplification but does prevent more subtle analyses of gradient detection (see below), branching, and competition, for instance.

Initial conditions

Many models assume that each retinal axon initially contacts an entirely random subset of tectal cells. Depending on the specific model, the size of this subset varies from one cell to the entire tectal array. However, in reality retinal axons invade the tectum from one end. Even in cases where branching is crucial (cf. Yates et al. 2001, 2004), it seems unlikely that every retinal axon invades the whole tectum before any topographic refinement occurs. The model of Honda (1998) is unique in explicitly modelling initial invasion from one end of the tectum. When initial invasion is not modelled, a more plausible starting condition might be that each retinal axon makes a diffuse but spatially limited projection, i.e., neither to only one tectal cell nor to the entire tectal array. This was implemented in several earlier models (Prestige & Willshaw 1975; Willshaw & von der Malsburg 1979; Overton & Arbib 1982; Fraser & Perkel 1990) but has not been a feature of more recent models.

Mechanisms of movement

Several models, particularly those considering only a 1–1 map between retinal and tectal locations, assume that axons move in the tectum by exchanging positions with their neighbours. It seems unlikely biologically that movement of an axon terminal would always be accompanied by reciprocal movement of otherwise unrelated terminals. However, this can

perhaps be regarded as a crude approximation to the more plausible scenario that axon terminals move gradually across the tectum exerting a more graded competitive force on other axon terminals in their way, as implemented in Willshaw & von der Malsburg (1979), Overton & Arbib (1982), and Fraser and Perkel (1990), for instance.

None of the models we have discussed address gradient detection, i.e., how a static growth cone determines an appropriate direction in which to move (cf. Goodhill and Urbach 1999; Guan and Rao 2003; Goodhill et al. 2004; Xu et al. 2005). Instead, many models assume that axon terminals have the ability to determine if a new location would be appropriate before actually committing to move to that location. A notable feature of the Tea Trade model (Willshaw & von der Malsburg 1979) is that it explicitly considers sprouting of new branches from each axonal tree as the mechanism by which terminals migrate to explore new territory.

Gradients/matching

Essentially all models can be classified as type I (direct or rigid matching), type II (relative matching), or mixed type I/type II. The Eph/ephrin misexpression data reinforce the conclusion already gained from earlier systems level data, that type I or type II alone do not adequately describe the data. The models vary somewhat in how they implement type I or type II mechanisms. Mass action models (e.g., Honda 1998) implement type I by assuming one retinal and one tectal gradient, and a "set point" level of reaction product. Gierer (1987) implemented type I via countergradients in the tectum. The simplest form of type II matching is to consider one retinal and one tectal gradient, with candidate movements such as flips up or down the gradient (e.g., Hope et al. 1976; Koulakov & Tsigankov 2004). A more realistic version is to explore territory by branching (e.g., Willshaw & von der Malsburg 1979).

Earlier models were expressed purely in terms of attractive gradients. Now that the repulsive nature of Eph/ephrin interaction is known, more recent models have been expressed in these terms. However, it seems likely that earlier models could be implemented straightforwardly with repulsive rather than attractive gradient interactions without significantly changing the results they produce, though this has not generally been explicitly demonstrated.

Competition and fibre–fibre interactions

Competition seems essential for explaining much of the systems-level data, though it was not included in Gierer (1987) or in mass action models (e.g., Honda 1998) until recently (Honda 2003). It can be implemented implicitly, by assuming that a purely 1–1 mapping always exists. Explicit implementation has been done using hard limits on the total number of axons a tectal site can support (e.g., normalization) or with soft limits merely encouraging a uniform density of terminations (e.g., Fraser & Perkel 1990). The latter seems the most plausible biologically, though in Fraser & Perkel (1990), it was implemented rather abstractly. There is some direct experimental evidence for at least postsynaptic normalization (Hayes & Meyer 1988a).

Fibre–fibre interactions, i.e., positive influences of axons on other axons originating from nearby sites in the retina, seem important for explaining certain aspects of the systems level data (e.g., Cowan & Friedman 1991). However they have not featured in more recent models. An obvious biological interpretation is in terms of fasciculation effects (e.g., Tessier-Lavigne & Goodman 1996).

Data addressed

Different models have had different goals regarding the data they have tried to address. Gierer (1987) and Honda (1998) considered essentially only how a normal map is established. Earlier models such as Willshaw and von der Malsburg (1979), Whitelaw and Cowan (1981), Overton and Arbib (1982), Fraser and Perkel (1990), and Cowan & Friedman (1991) tried to account for the largest proportion possible of the systems-level data then available. More recently, there has been a trend towards more "special purpose" models which address only specific phenomena without considering the larger picture (e.g., Honda 2003; Koulakov & Tsigankov 2004; Reber et al. 2004; Yates et al. 2004). These more limited approaches can still yield useful insights into mechanisms that might account for the particular data they address. However, since in isolation these individual phenomena often provide relatively few constraints on mechanisms, it is perhaps not surprising that apparently quite different approaches can all account for the same data, such as the results of Brown et al. (2000) by Honda (2003), Koulakov and Tsigankov (2004), and Yates et al. (2004). Until more is understood about how each of these mechanisms performs on a wider set of data, it is hard to choose between them. It may be that individual phenomena that appear to yield to a relatively simple explanation in isolation are in fact the result of a delicate interplay of several competing constraints, all of which are required to explain the full range of data available.

One notable set of data that, with the exception of Honda (1998), has not been considered in the modelling literature are the *in vitro* results, for instance using the stripe assay. This is largely because most models do not really consider how isolated axons move forward; usually, their movement is imagined to be just the result of constant jockeying for position with other axons. On a uniform carpet of ligand concentration, axons in purely type I models would never stop moving forwards, since they would never find their optimal position, while axons in purely type II models would never start moving forwards, since there is no vector signal available. Clearly, some of the assumptions common to nearly all models need to be revised to address these types of data.

Suggestions for future modelling

Many models have been proposed, each of which is more or less successful at accounting for a subet of the data available, but none of which has ever yet attempted to address it all. In addition, as discussed above, some of the underlying assumptions common to many models clearly need to be revised. We conclude with the suggestion that a model that is truly successful at accounting for both the systems-level and Eph/ephrin misexpression data will probably need to include all of the following ingredients:

- An explicit mechanism for gradient detection by growth cones, making realistic assumptions about the noise inherent in the sensing process (cf. Goodhill and Urbach 1999; Goodhill et al. 2004; Xu et al. 2005), rather than this being added arbitrarily.
- A mechanism specifying how isolated axons grow, which is essential for addressing the stripe assay results.
- A continuous rather than discrete tectum.
- Consideration of two-dimensional rather than just one-dimensional mapping. It is hard to produce a plausible rule for movement of growth cones if they are constrained to only one dimension.
- Rules specifying branching of axons in specific circumstances.
- Competition between retinal axons for tectal space, ideally implemented as a soft rather than hard constraint.

- A tendency for retinal axons to stick together as a function of retinal position.
- A fairly complete set of the known Eph and ephrin gradients in both retina and tectum.

We also suggest that researchers with primarily experimental backgrounds interested in building a new model might benefit by first implementing and exploring some of the previous models, a straightforward job for a competent programmer. This would directly highlight both the abilities and limitations of those models, and may provide useful guidance in how best to present one's own model so that it can be implemented by someone else.

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