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Gradients for retinotectal mapping

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Abstract

The initial activity-independent formation of a topographic map in the retinotectal system has long been thought to rely on the matching of molecular cues expressed in gradients in the retina and the tectum. However, direct experimental evidence for the existence of such gradients has only emerged in the past two years. The new data has provoked the discussion of a new set of models in the experimental literature. Here, these models are subjected to a rigourous theoretical analysis.

1 INTRODUCTION

During the early development of the visual system in for instance rats, mice, fish and chickens, retinal axons grow across the surface of the optic tectum and establish connections so as to form an ordered map. Although later neural activity refines the map, it is not required to set up the initial topography (for review see Udin & Fawcett (1988)). A long-standing idea is that the initial topography is formed by matching gradients of receptor expression in the retina with gradients of ligand expression in the tectum (Sperry, 1963). Particular versions of this idea have been formalized in theoretical models such as Prestige & Willshaw (1975), Willshaw & von der Malsburg (1979), and Gierer (1983;1987). However, these models were developed in the absence of any direct experimental evidence for the existence of the necessary gradients. In the past two years, major breakthroughs have occurred in this regard in the experimental literature. These center around the Eph (Erythropoetin-producing hepatocellular) subfamily of receptor tyrosine kinases. Members of this family such as Cek4 and Cek8 are expressed

in gradients in the retina[1], and ligands of these receptors such as Elf-1 and RAGS (Repulsive Axon Guidance Signal, also known as AL-1) are expressed in gradients in the tectum (Cheng et al, 1995; Drescher et al 1995; for reviews see Tessier-Lavigne (1995); Friedman & O'Leary (1996); Tessier-Lavigne & Goodman (1996)). Eph receptors and their ligands have also recently been implicated in the formation of topographic projections between the hippocampus and the septum (Gao et al, 1996).

These exciting new developments have led experimentalists to discuss theoretical models different from those prevoously proposed (e.g. Tessier-Lavigne (1995); Tessier-Lavigne & Goodman (1996); Nakamoto et al, (1996)). However, the mathematical consequences of these new models, for instance the precise gradient shapes they require, have not been analysed. This is the purpose of the current paper. I show that only certain combinations of gradients produce appropriate maps in these models, and that the validity of these models is therefore experimentally testable.

2 RECENT EXPERIMENTAL DATA

Recent studies have shown the following (see e.g. Friedman & O'Leary (1996) and Tessier-Lavigne & Goodman (1996) for more details, and figure 1 for terminology).

- Cek4, and its homologues Mek4, Tyro4 and Hek, are expressed in an increasing nasal to temporal gradient in the retina.
- Cek8, and its homologues Sek1, Tyro1 and Hek8, are expressed uniformly in the retina.
- Elf-1, a ligand of all the receptors above, is expressed in an increasing rostral to caudal gradient in the tectum.
- RAGS/AL1, a ligand of all the receptors above, is expressed in an increasing rostral to caudal gradient in the tectum, but at very low levels (if at all) in the rostral half of the tectum.

Cek5 and its ligands Lerk2 and Lerk5 are expressed in gradients along the dorsal-ventral axis of the retina and the lateral-medial axis of the tectum respectively; however for the purposes of this paper only the mapping from the nasal-temporal to the rostral-caudal axis will be considered. Gradient shapes have not yet been quantified. I will assume certain gradients are linear, and derive the consequences for the other gradients.

3 MATHEMATICAL MODELS

Let R be the concentration of a receptor expressed on a growth cone or axon, and L the concentration of a ligand present in the tectum. Refer to position along the nasal-temporal axis of the retina as x, and position along the rostral-caudal axis of

[1]Receptor terminology: a general rule is that Ceks are expressed in the Chicken, Meks and Seks in Mouse, Heks in Humans, and Reks and Tyros in rats.

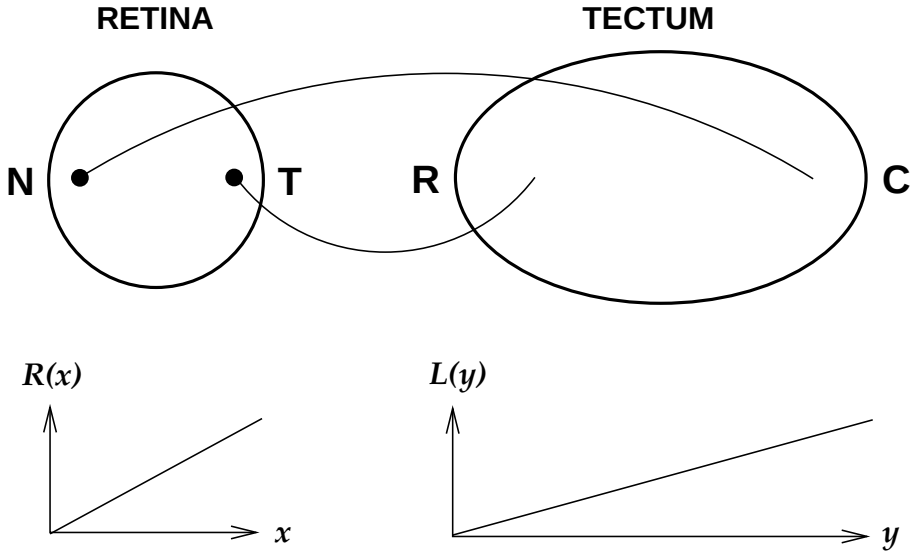

Figure 1: This shows the mapping that is normally set up from the retina to the tectum. Distance along the nasal-temporal axis of the retina is referred to as x and receptor concentration as $R(x)$. Distance along the rostral-caudal axis of the tectum is referred to as y and ligand concentration as $L(y)$.

the tectum as y, so that $R = R(x)$ and $L = L(y)$ (see figure 1). Gierer (1983; 1987) discusses how topographic information could be signalled by interactions between ligands and receptors. A particular type of interaction, proposed by Nakamoto et al (1996), is that the concentration of a "topographic signal", the signal that tells axons where to stop, is related to the concentration of receptor and ligand by the law of mass action:

$$G(x, y) = kR(x)L(y) \tag{1}$$

where $G(x, y)$ is the concentration of topographic signal produced within an axon originating from position x in the retina when it is at position y in the tectum, and k is a constant. In the general case of multiple receptors and ligands, with promiscuous interactions between them, this equation becomes

$$G(x, y) = \sum_{i,j} k_{ij} R_i(x) L_j(y) \tag{2}$$

Whether each receptor-ligand interaction is attractive or repulsive is taken care of by the sign of the relevant k_{ij}.

Two possibilities for how $G(x, y)$ might produce a stop (or branch) signal in the growth cone (or axon) are that this occurs when (1) a "set point" is reached (Tessier-Lavigne and Goodman, 1996; Nakamoto et al, 1996) , i.e. $G(x, y) = c$ where c is a constant, or (2) attraction (or repulsion) reaches a local maximum (or minimum), i.e. $\frac{\partial G(x,y)}{\partial y} = 0$ (Gierer, 1983; 1987). For a smooth, uniform mapping, one of these conditions must hold along a line $y \propto x$. For simplicity I will assume the constant of proportionality is one.

3.1 Set point rule

For one gradient in the retina and one gradient in the tectum (i.e. equation 1), this requires that the ligand gradient be inversely proportional to the receptor gradient:

$$L(x) = \frac{c}{R(x)}$$

If $R(x)$ is linear (c.f. the gradient of Cek4 in the chicken retina), the ligand concentration is required to go to infinity at one end of the tectum (see figure 2). One way round this is to assume $R(x)$ does not go to zero at $x = 0$: the experimental data is not precise enough to decide on this point. However, the addition of a second receptor gradient gives

$$L(x) = \frac{c}{k_1 R_1(x) + k_2 R_2(x)}$$

If $R_1(x)$ is linear and $R_2(x)$ is flat (c.f. the gradient of Cek8 in chicken retina), then $L(y)$ is no longer required to go to infinity (see figure 2). For two receptor and two ligand gradients many combinations of gradient shapes are possible. As a special case, consider $R_1(x)$ linear, $R_2(x)$ flat, and $L_1(y)$ linear (c.f. the gradient of Elf1 in the tectum). Then L_2 is required to have the shape

$$L_2(y) = \frac{ay^2 + by}{dy + e}$$

where a, b, d, e are constants. This shape depends on the values of the constants, which depend on the relative strengths of binding between the different receptor and ligand combinations. An interesting case is where R_1 binds only to L_1 and R_2 binds only to L_2, i.e. there is no promiscuity. In this case we have

$$L_2(y) \propto y^2$$

(see figure 2). This function somewhat resembles the shape of the gradient that has been reported for the repulsive factor RAGS in the tectum, though this model requires the linear gradient to be attractive, whereas Elf1 is repulsive.

3.2 Local optimum rule

For one retinal and one tectal gradient we have the requirement

$$R(x)\frac{\partial L(y)}{\partial y} = 0$$

This is not generally true along the line $y = x$, therefore there is no map. The same problem arises with two receptor gradients, whatever their shapes. For two receptor and two ligand gradients many combinations of gradient shapes are possible. (Gierer (1983; 1987) investigated this case, but for a more complicated reaction law for generating the topographic signal than mass action.) For the special case introduced above, $L_2(y)$ is required to have the shape

$$L_2(y) = ay + b\log(dy + e) + f$$

where a, b, d, e, and f are constants as before. Considering the case of no promiscuity, we again obtain

$$L_2(y) \propto y^2$$

i.e. the same shape for $L_2(y)$ as that specified by the set point rule.

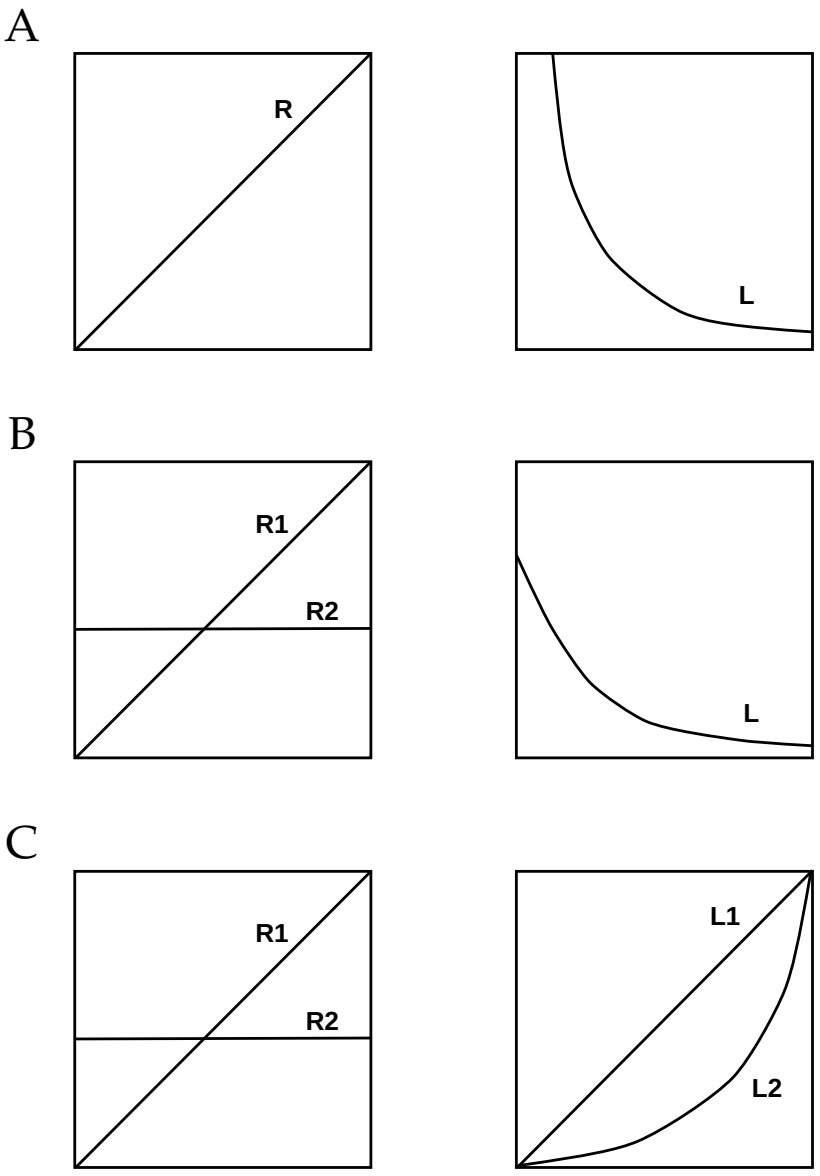

Figure 2: Three combinations of gradient shapes that are sufficient to produce a smooth mapping with the mass action rule. In the left column the horizontal axis is position in the retina while the vertical axis is the concentration of receptor. In the right column the horizontal axis is position in the tectum while the vertical axis is the concentration of ligand. Models A and B work with the set point but not the local optimum rule, while model C works with both rules. For models B and C, one gradient is negative and the other positive.

4 DISCUSSION AND CONCLUSIONS

For both rules, there is a set of gradient shapes for the mass-action model that is consistent with the experimental data, except for the fact that they require one gradient in the tectum to be attractive. Both Elf-1 and RAGS/AL-1 are repulsive, which is clearly a problem for these models.

The local optimum rule is more restrictive than the set point rule, since it requires at least two ligand gradients in the tectum. However, unlike the set point rule, it supplies directional information (in terms of an appropriate gradient for the topographic signal) when the axon is not at the optimal location.

In conclusion, models based on the mass action assumption in conjunction with either a "set point" or "local optimum" rule can be true only if the relevant gradients satisfy the quantitative relationships described above. Advances in experimental technique should enable a more quantitative analysis of the gradients in situ to be performed shortly, allowing the predictions above to be tested.

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