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**COMMENTARY**

# Retinocollicular mapping explained?

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**Abstract**

We review and comment on the recent model of Grimbert and Cang of the development of topographically ordered maps from the retina to the superior colliculus. This model posits a phase in which arbors are created in zones permitted by Eph and ephrin signaling, followed by a phase in which activity-dependent synaptic plasticity refines the map. We show that it is not possible to generate the arborization probability functions used in the simulations of Grimbert and Cang using gradients of Ephs and ephrins and the interaction mechanism that Grimbert and Cang propose in their results. Furthermore, the arborization probabilities we do generate are far less sharp than we imagine truly "permissive" ones would be. It remains to be seen if maps can be generated from the nonpermissive arborization probabilities generated from gradients.

**Keywords:** Visual system, Topography, Computational modeling, Chemoaffinity, Retinal waves

The extensive experimental and theoretical investigation of the development of topographically ordered maps from the retina to its targets (Fig. 1A) has led to two important theories of map development: molecular signaling and activity-dependent synaptic plasticity (Goodhill & Xu, 2005). In theories of molecular signaling, retinal ganglion cell (RGC) growth cones bear receptors in different densities depending on the location of the RGC soma in the retina, and these receptors are activated by ligands expressed in cells in the superior colliculus (SC) at levels depending on their location. This confers on each RGC a preferred location in the SC, which, depending on the pattern of receptor and ligand expression, is not necessarily its correct topographical position. Activity-dependent synaptic plasticity of RGC-SC synapses along with correlated activity in the retina can also, in theory, lead to map formation, though extra cues are needed to ensure that the orientation of the map is correct (Willshaw & von der Malsburg, 1976). In both theories, other mechanisms, such as competition, may be required for a normal topographic map to form.

There is experimental evidence that both molecular signaling and activity-dependent synaptic plasticity are involved in map formation. In support of molecular signaling, the Eph and ephrin families of molecules are expressed in gradients along the axes of the retina and colliculus, and their disruption genetically leads to disrupted maps (Feldheim & O'Leary, 2010; Cang & Feldheim, 2013). In support of activity-dependent synaptic plasticity, correlated activity exists in the retina in the form of retinal waves, and its disruption leads to impaired map precision (Torborg & Feller, 2005). Thus, the two theories are complementary, and the questions center around the exact form and role of each mechanism and how they interact.

Grimbert and Cang (2012) use a computational model to address the roles of activity-dependent synaptic plasticity and molecular signaling in the development of topographically ordered maps from the retina to the SC. In contrast to previous models where molecular signaling and activity act simultaneously (Whitelaw & Cowan, 1981; Fraser & Perkel, 1990; Triplett et al., 2011), in the model of Grimbert and Cang, molecular signaling and activity act in two phases, similar to Godfrey et al. (2009). (i) In the arborization phase, RGC arbors, represented as points, are placed on the SC according to a probability distribution determined by molecular signaling, assumed to be mediated by gradients of Ephs and ephrins. Grimbert and Cang explore the hypothesis that molecular signaling imparts *permissive* rather than *instructive* information. Permissive signaling restricts the space in the SC within which RGC axons are permitted to arborize, but within the allowed space, axons have little or no preference for any one location (Fig. 1B). In contrast, an instructive mechanism gives each RGC a preferred location in the SC that coincides with its topographically appropriate location in the final map (Fig. 1C). After the arbors have been placed, those in the least favorable locations are pruned. (ii) In the dynamic phase, the arbors move around under the influence of spatially correlated neural activity and competition. The development of wild-type (WT) maps is simulated in this model and, by manipulating the probability distribution

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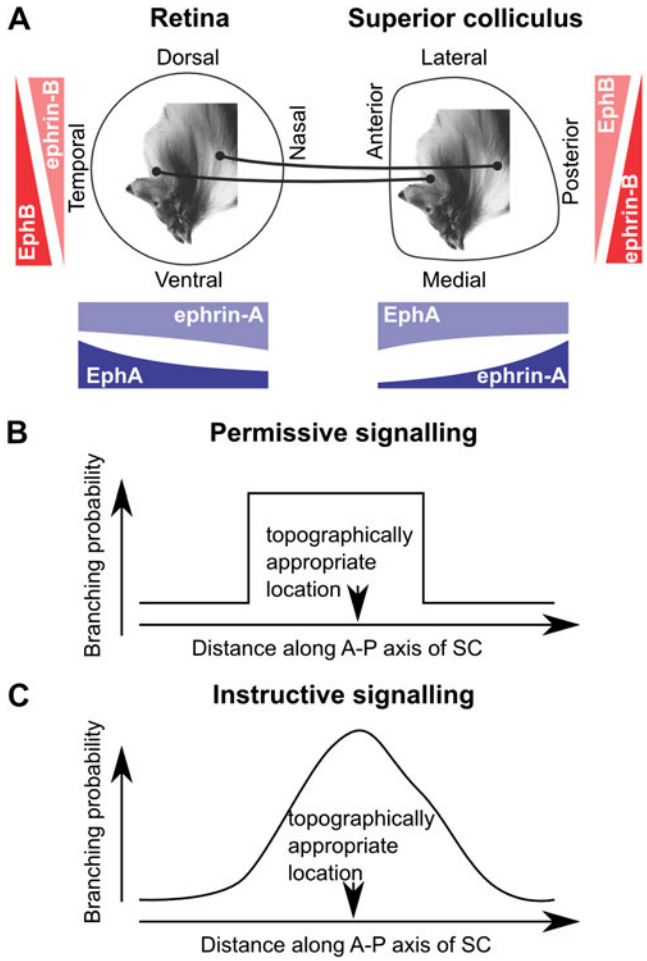



**Fig. 1.** Retinocollicular mapping and permissive *versus* instructive molecular signaling. (**A**) Schematic diagram of retinocollicular mapping and forward and reverse gradients. Along the nasotemporal and anterior–posterior axes, the forward signaling system is made up of EphA in retina and ephrin-A in the SC and the reverse system comprises ephrin-A in the retina and EphA in the SC. The size of gradients is proportional to those used in the simulations shown in Fig. 2. Along the retinal dorsoventral axis and the mediolateral axis of the SC, EphB and ephrin-B make up the forward and reverse systems; they are not modeled explicitly in Grimbert and Cang (2012), so the gradients shown are purely schematic. (**B**) Permissive cues restrict the region in which an axon can arborize but do not favor any position within the permitted region. (**C**) Instructive cues give the maximum arborization probability at the topographically appropriate location.

representing molecular signaling information, the model can also produce maps resembling those found in the Isl2-EphA3 knock-in phenotype (Brown et al., 2000), the EphA7 KO phenotype (Rashid et al., 2005), and the p75NTR KO phenotype (Lim et al., 2008).

Grimbert and Cang focus on the nasotemporal to anterior–posterior projection; for dorsoventral to mediolateral mapping, they assume that axons enter the SC at approximately the correct mediolateral position. They model the forward and reverse signaling pathways by means of two arborization probability functions (Fig. 2A and 2B) that, when multiplied together (Fig. 2C), permit growth of each RGC in a region around its topographically appropriate location. However, Grimbert and Cang face the challenge of showing how known gradients of Ephs and ephrins can lead to this permissive signal. In the Results, they make the reasonable assumption that "permission to arborize is inversely proportional to both receptor and ligand concentrations." Because measured concentration gradients are approximated by a constant plus an exponential (Reber et al., 2004), they deduce correctly that each arborization probability function should have a sigmoidal dependence on distance along the anterior–posterior axis. However, when we computed a probability to arborize that is inversely proportional to the gradients measured by Reber et al. (2004), we found that the dependence of the arborization probability on distance along the nasotemporal axis (Fig. 2H) is far less sharp than in the functions used by Grimbert and Cang (Fig. 2D). This problem might be alleviated by invoking cooperative binding between Ephs and ephrins, which would sharpen the resulting probability distributions.

Grimbert and Cang criticize, rightly in our view, the notion that gradients in the forward and reverse pathways need to be precisely matched to give an instructive mechanism in which each axon prefers to connect to its topographically appropriate location (Gierer, 1983; Yates et al., 2004). However, the parameters of their arborization probability functions are such that the permitted area of any RGC is centered on its final location, which is analogous to having matching gradients.

To explore this, we put deliberately unmatched but plausible gradients into the prescription of Grimbert and Cang for the branching probabilities (Fig. 2E and 2F). This resulted in a probability map (Fig. 2G) that did not have a stripe along the correct map and is akin to a Type II affinity mechanism (Prestige & Willshaw, 1975) that requires additional mechanisms for a map to form. Furthermore, the linear contours evident in their forward and reverse signaling functions (Fig. 2A and 2B) are not found in the plots created by the product of inverse gradients (Fig. 2E and 2F); it can be verified that the curved contours observed are a mathematical property of a product of sigmoids. It remains to be shown whether the second phase of development would be able to form a WT map from this starting point. With the branching probabilities formed by the product of the inverse gradients, for any location along the nasotemporal axis, the probability will be a scaled version of the same function along the anterior–posterior axis. Given the strategy of Grimbert and Cang for resampling rejected positions on the anterior–posterior axis, the scaled versions of the probability distribution should all give the same final distribution of positions, regardless of the RGC position. This is illustrated in Fig. 2G, which shows, for one nasal and one temporal axon, arbor locations along the anterior–posterior axis generated by sampling randomly from the arborization distribution. The distributions overlap considerably along the anterior–posterior axis, in contrast to the distribution of points chosen using the arborization probability of Grimbert and Cang (Fig. 2C).

In the dynamic phase, the molecular signaling is inactive and the arbor points move solely under the influence of correlated activity and competition. The correlated activity moves arbors toward the mean locations of arbors emanating from nearby locations on the retina. The competition causes arbors in areas of the SC with higher densities of arbors to move to areas containing lower densities (Fraser & Perkel, 1990; Simpson & Goodhill, 2011), which tends to smooth out the distribution over the colliculus. As demonstrated in the ephrin-A triple knock-out (TKO) simulations (Figure 6 in Grimbert & Cang), in which molecular signaling along the nasotemporal axis is abolished, the net effect of activity and competition is to create local order without global order. This type of order is obtained when chemical cues are removed in previous models with correlated activity and synaptic plasticity (Willshaw & von der Malsburg, 1976). In the WT simulations (Figure 4 in Grimbert & Cang), the

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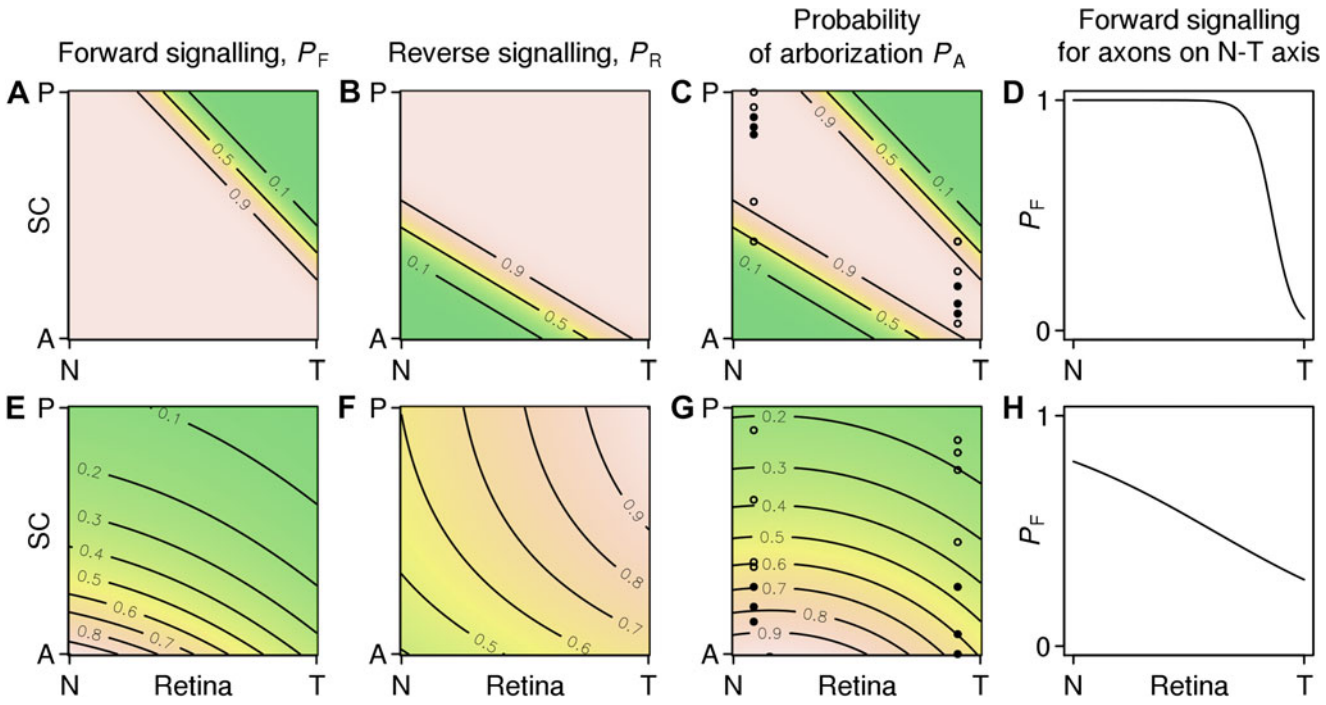



**Fig. 2.** Arborization probabilities of axons from the retinal nasotemporal axis along the anterior–posterior axis of the SC. (**A**–**D**) The arborization probabilities plotted from equations in the methods section of Grimbert and Cang (2012) and displayed in their Fig. 2A–2C. (**A**) The forward arborization probability $P_F$, which restricts arborizations from temporal axons in the posterior SC. (**B**) The reverse arborization probability $P_R$. (**C**) The combined arborization probability $P_A$, which is the product of $P_F$ and $P_R$. Note that each axon is permitted to arborize in a region around its topographically appropriate location. The filled and open circles indicate the locations in the SC of arborizations from nasal and temporal axons generated by sampling from $P_A$. There are seven points in total; in the simulations of Grimbert and Cang, the arborizations with the four lowest values of $P_A$ (open circles) would be pruned leaving the three arborizations with the highest values of $P_A$ (filled circles). (**D**) A nasotemporal slice of the forward arborization probability in (**A**). (**E**–**H**) Arborization probabilities computed by substituting plausible but unmatched gradients into the prescription in the results section of Grimbert and Cang (2012). (**E**) The forward arborization probability $P_F = 1/R_F L_F$, where $R_F$ is the concentration of EphA receptor borne by an arbor and $L_F$ is the concentration of ephrin-A ligand it encounters at a location in the SC. Gradients are $R_F(x) = (1.05 + 0.26\exp(2.3x))/1.05$, where $x = 0$ is nasal and $x = 1$ is temporal (Reber et al., 2004), and $L_F(y) = \exp(2.1(y - 1))$, where $y = 0$ is anterior and $y = 1$ is posterior. (**F**) The reverse arborization probability $P_R$ and the concentrations $R_R$ and $L_R$ of ephrin-A and EphA are related similarly, with gradients $R_R(x) = 1 + 1.7\exp(-x)$ and $L_R(y) = 1 + 0.6\exp(-2.6y)$. (**G**) The arborization probability computed from the product of $P_F$ and $P_R$ (**E**, **F**) and arborizations generated from the probability distribution as described in (**C**). (**H**) A nasotemporal slice of the plausible forward arborization probability, which is equal to $1/R_F(x)$. Code to reproduce this figure is available in the Supplemental Information.

activity and competition serve to refine the coarse mapping created by the gradients.

Grimbert and Cang go on to apply the model to the Isl2-EphA3 knock-in phenotypes (Brown et al., 2000). To do this, they modify the shape of the probability maps. In contrast to other models (Willshaw, 2006; Tsigankov & Koulakov, 2010), the new probability maps are not derived from the levels of EphA borne by the WT and Isl2 cells, but are "chosen for their simple convex shape." With these modified probability maps, the authors get the model to produce double maps.

Leaving aside the justification for the changes in the branching probability distributions, the model makes an interesting prediction. Retrograde tracing with injections in the *center* of the SC (Brown et al., 2000) shows that nasal axons projecting there express Isl2-EphA3 but temporal ones do not. The model of Grimbert and Cang and other models are consistent with this finding. However, the model of Grimbert and Cang predicts that *anterior* injections will label *both* Isl2-EphA3$^+$ and Isl2-EphA3$^-$ RGCs. Other models (Willshaw, 2006; Tsigankov & Koulakov, 2010) predict otherwise. Brown et al. (2000) did not report anterior injections, and so this prediction is yet to be tested.

The EphA7 knock-out (Rashid et al., 2005) is modeled by complete removal of the reverse signaling pathway. This is a stronger manipulation than in the phenotype, where there is still a gradient of EphA4 in the SC. Nevertheless, activity and competition are shown to be able to bunch together neurons at the anterior edge of the SC, in line with experimental results. It would be interesting to explore this mechanism in other models.

In order for Grimbert and Cang to reproduce the p75NTR KO phenotype, they reduce the inhibitory effect of the reverse signaling and also weaken the competition by 30%. The reduction in reverse signaling allows nasal axons to branch in inappropriate (anterior) parts of the SC. Were the competition to be at full strength, the map would be more ordered than the phenotype; the effect of weakening the competition is to reduce its ability to create order.

In summary, Grimbert and Cang argue that molecular signaling provides permissive rather than instructive cues, and in their model, activity and competition can refine a crude initial map. They reason that models should not depend on precise matching of parameters, but their explanation of how molecular signaling gives rise to permissive cues that can be refined by activity does seem to depend on matching of parameter values. Their model proposes "an alternative to the usual

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view that retinotopic order is shaped through chemoaffinity while activity-dependent processes only serve to refine the map." However in the WT, each RGC's permissive region is centered on its topographically appropriate location; thus, activity only needs to refine the projection. To offer a true alternative, and demonstrate how activity can remodel the map deeply, they need to apply their competition and activity mechanism to probability maps produced by nonmatched chemical gradients that have not shaped the topography so strongly. In its favor, their model is applied to a wide range of experimental maps and provides a novel prediction that can be tested in Isl2-EphA3 mice.

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### Supplementary Materials

Supplemental materials can be viewed in this issue of VNS by visiting http://journals.cambridge.org/VNS.

R Code to reproduce Figure 2

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