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Computational Developmental Neuroscience: Exploring the Interactions Between Genetics and Neural Activity

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Abstract—**Both activity-dependent (AD) and activity-independent (AI) processes play important roles in neural development. For example, in the development of the vertebrate visual system, molecular guidance cues that are largely activity-independent provide a rough topography of early projections, while activity-dependent refinement of termination zones occurs later on through correlated retinal activity. A key question concerns the nature of the interaction between these processes. Recent knockout experiments involving the β2 subunit of nicotinic acetylcholine receptors and bone morphogenic protein (BMP) suggest that these two processes make genuinely separate contributions – but leave open the precise nature of their interaction. In this article we show how a novel, computational framework (dubbed INTEGRATE) can illuminate the scope and limits of the AI-AD interaction, including facts about critical periods and timing.**

I. Introduction

In the coming decades, one of the most pressing challenges in the field of developmental neuroscience is to understand the interactions between activity-dependent (AD) and activity-independent (AI) mechanisms of development While both AI and AD factors play a role in neural development, the interactions between these processes remain elusive [1], and is at the core of our understanding of the interaction between genes and the environment. We argue here that computational approaches can further our understanding of these fundamental interactions.

Our specific empirical focus here is on the development of a paradigmatic system, the retinotopic map. The genetic and neural principles that influence its formation have been extensively studied (for a review, see [2]), and it has been the object of numerous theoretical accounts (for a review, see [3-4]). However, as explained in further detail below, AI-AD interaction remains poorly understood, with a host of open questions. Are the respective contributions of AI and AD factors completely independent from one another, occurring at different stages of development? Further, assuming these different stages, can initial deficiencies in the AI process be corrected through AD processes at later stages? Or are there critical periods for map formation beyond which a certain aberrant organization is not fully reversible?

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II. Understanding the Interaction Between Activity-Dependent and Activity-Independent Developmental Processes: A Computational Approach

One way to address these questions is computational (for a review, see [5]); *in silico* experiments can often be run more quickly and reliably than *in vivo* experiments. Moreover, there are already extant models for understanding both AD and AI contributions, though as yet relatively little work directly characterizing the nature of their interaction.

There are several reasons why the interaction between molecular and AD mechanisms has not yet been clearly established. First, the time course of axonal guidance includes an initial stage of map formation that is strongly influenced by chemotropic gradients, followed by pre-critical and critical periods; few models have even attempted to capture this dynamic. Second, most extant models have not addressed many of the benchmark details associated with retinotopic map formation, including cell-cell interactions [5], interstitial branching [6-8], and stochastic exploration [9].

A few models (e.g., [1][10]) demonstrate how different starting conditions for the AD process can have consequences in later development., as part of an important investigation into the influence of one stage on another. However, most models contain no AI mechanism, so it is difficult to relate the proposed initial conditions to genetic mechanisms (e.g., relating topographical biases to certain expressions of chemotropic gradients). An additional concern with most extant computational models derives from the logic of their operation. They work by adjusting connection weights according to some pre-defined rules for synaptic plasticity. On this assumption, the output of activity-independent processes would presumably have to cache out as some sort of bias on initial conditions that constrains later activity-dependence; although this is not impossible in principle, it is a non-trivial problem that has not been directly tackled.

Here, we propose a model, INTEGRATE, with the explicit aim of understanding the interactions between AI and AD processes. The starting point of the model is the generally held assumption that retinotopic development follows two distinct phases, with only small overlap, namely an initial AI phase followed by an AD phase. We instantiate AI as servomechanism guidance [5] and AD as Hebbian

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learning [11], explained in the next two sections; Section V explains how they are combined; VI describes a test case, and VII preliminary results.

III. Activity-independent development

Development of the vertebrate visual system is characterized by an extension of projections from the retina (retinal ganglion cells; RGCs) to topographically faithful termination zones (TZs) in the superior colliculus (SC) or tectum in the midbrain. Early topography is heavily influenced by AI processes that rely on genetically expressed molecular guidance cues (Eph/ephrins; [12]). Later on in the course of development, the initial projections are refined by processes that depend on the flow of ions across cell membranes triggering biochemical and electrical activity in cells. These AD factors are known to play a role both during a pre-critical and a critical period of development. In many species including the mouse, the pre-critical period occurs prior to eye opening, and is characterized by spontaneous waves of locally correlated activity on the RGCs [13]. The critical period follows eye opening, and involves refinement through interactions with the environment [14-17]. In both pre-critical and critical stages, activity is a necessary condition for synaptic plasticity and morphological changes in axonal projections [18].

Recent studies in mice have highlighted the distinct contributions of AD and AI mechanisms [13,19,20]. Results of these studies argue that AD and AI processes play distinct roles in retinotopic map formation, and likely occur in distinct stages in the course of development.

The particular role of AI mechanisms is shown in experiments involving transgenic mice with misexpressed bone morphogenetic protein (BMP). In these animals, ventral RGCs initially projected to inappropriate locations lateral to their normal TZs, leading to a miswired map [19]. The impact of this disruption is sustained despite later AD refinement. These results argue for a central role of AI mechanisms in shaping the initial projections from RGCs to the SC. These initial connections form a bias that cannot be fully transformed through AD mechanisms.

The role of AI mechanisms in map formation is also highlighted in experiments involving a genetically-induced knockout of a component of the machinery for mediating AD, the β2 subunit of neuronal nicotinic receptors. In these animals, even lacking a reliable means for AD, AI mechanisms are sufficient for an initial rough map established (although axons lacking robust AD fail to refine their final TZs). With the influence of AD mechanisms drastically diminished, the degree of remaining map organization is presumably due to AI mechanisms.

In sum, AI development is characterized by an early stage of map formation where a rough map is formed which influences all subsequent AD phases of development.

IV. Activity-dependent development

Experiments involving genetically modified mice highlight the role of AD mechanisms in map formation, and form the empirical basis of our study. In BMP transgenic mice, ventral RGCs project to inappropriate locations lateral to their normal TZs on the SC, leading to a miswired map [3]. Given this mistargetted map laid down by AI processes, AD processes will refine the diffuse TZs and prune out extranumerary connections, but are unable to correct the faulty TZs. As a result, activity refines the faulty TZs in a manner that leads to focused yet mistargetted projections. These findings argue for a limited role of AD processes in map formation. Rather than being able to produce topographically correct organizations regardless of initial conditions, AD mechanisms are in fact quite sensitive to initial (AI) conditions.

The role of AD in refining initially diffuse TZs is also highlighted in β2 knockouts. The β2 subunit of the nicotinic receptors is especially important for lateral communication in retinal circuits; their removal leads to a drastic reduction in the influence of AD processes. In β2 knockouts, drastically reducing the influence of AD mechanisms leads to a map that is unrefined, compared to normal (wild-type) animal.

V. Interactions between activity-dependent and independent development

Experiments combining both β2 knockout and BMP manipulations have argued for independent contributions of intrinsic and AD mechanisms of map formation. Indeed, there is a cumulative effect of disrupting both the initial map through BMP, and the AD process, through β2 knockout. As a result, maps are not only mistargetted, but also diffuse and unfocussed.

The above results on β2 knockouts and BMP manipulations are compatible with a staged approach to modeling the development of the retinotopic system. The idea of critical stages implies that, if one stage is skipped or incorrectly performed, consequences are irreversible for later development. In these critical stages, each stage builds on the previous, and each possesses inherent limited capacities: early development can only provide a gross map, and later development can only perform some refinement of the existing map. These two stages complement each other well, but do not allow a lot of room for later stages overcoming problems in early ones (as is the case in BMP transgenic mice).

An account of retinotopic development based on distinct stages suggests that, despite the fact that activity may be present early in the retinotopic system (e.g., as early as prenatal day E16 in mice; [13]), its role in map formation remains limited until a later time [but see 18]. Further research suggests that spontaneous activity can only refine projections during a brief critical period prior to eye opening [13].

VI. INTEGRATE: A FRAMEWORK FOR MOLECULAR AND AD MECHANISMS

The goal of INTEGRATE is to act as an interface between chemotropic models and AD models. Within this framework, both can be manipulated independently. In this way, AI processes can be set off in an early stage of development, and AD processes can be triggered in a later stage. The proposed account is based on the assumption of two stages of development, one that involves the formation of an initial map mainly under the influence of AI processes, and another that involves map refinement mainly under AD processes.

An important challenge here is to grow axons through an AI process, and then extract connection weights that will serve as initial conditions to an AD model. The proposed account should be general enough to allow for any AI model [3], as well as any AD model (e.g., self-organizing map; [21]; spike-time-dependent plasticity; [10]; etc.), to be employed.

As discussed earlier, obtaining trainable connection weights from axonal projections is a difficult problem that has not received much attention in computational approaches. One way of addressing it, which we adopt here, is to treat axons as progressively migrating across the target surface. We then have a matrix that keeps track of the termination position of axons, based on an index of their start position (i), and an index of each axon starting from there (j).

A matrix transformation is performed to obtain trainable connection weights based on the stop locations s obtained through the AI process (Appendix 1; [1]). To do so, a matrix of weights $w_{i,j}$ is initialized to zeros. Iterating through all i,j,k,

$$w_{i,j} = w_{i,j} + 1 \qquad \text{if } s_{i,k}=j, \qquad (1)$$

$$w_{i,j} = 0 \qquad \text{otherwise.}$$

It is possible to generate an AI distribution of axonal projections through the servomechanism model (see Appendix 1, [9]). Such a distribution is shown in Fig.1a. Through Eq.1, it is then possible to transform this distribution into trainable weights (Fig.1b). These weights are characterized by a rough bias towards topography (topographic weights are mapped on the diagonal).

Eq.1 is reversible but this transformation has no unique solution. Nonetheless, it is possible to use it as basis for applying synaptic plasticity through AD mechanisms, and then revert back to an AI matrix of stop locations that can be used to resume axonal migration. To do so, a matrix $s_{i,j}$ is initialized to zeros, and j=1. Then, iterating for all i,k,

While $w_{i,k} > 0$.

$s_{i,j} = i$,

$w_{i,k} = w_{i,k} - 1$.

j=j+1;

End While.

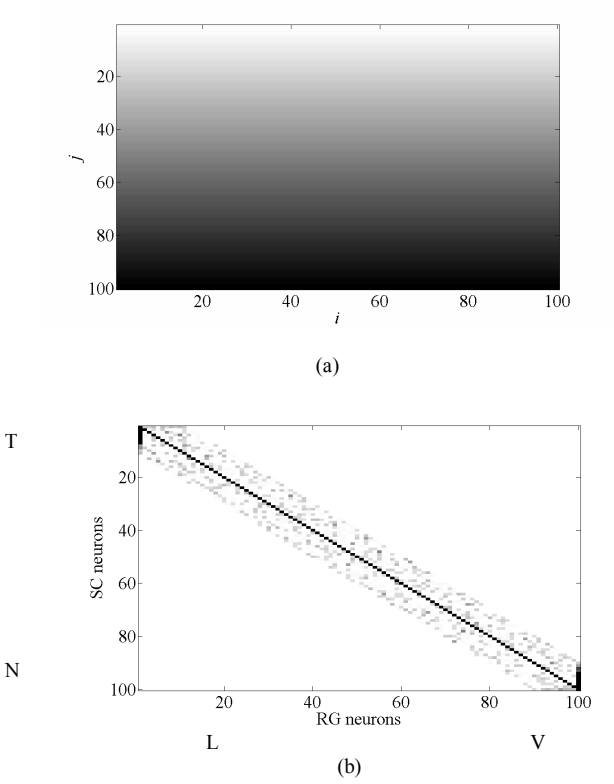

Fig. 1: Translating axonal arborisation to connection weights. (a) a matrix s of stop locations obtained from AI axonal guidance. (b) the translation of the s matrix into a distribution of trainable connection weights that provide a rough bias towards topography (see Equation 1). N=nasal; T=temporal, L=lateral; V=ventral.

The fact that the initial TZs of projecting RGC axons are determined through AI mechanisms alone is compatible with the idea that these mechanisms provide an initial bias towards certain TZs that are then refined through AD processes. In the proposed model, a bias towards a perfect point-to-point topography would be achieved if the highest weights w_{ij} per row i are found along the diagonal of the matrix:

$$\max_j (w_i) = w_{ii} .$$

An advantage of INTEGRATE is that it is flexible enough to allow for various types of AI and AD processes to be incorporated under a single umbrella. Possible AI processes include not only molecular gradients, but also cell-cell competitive interactions [5], interstitial branching along the main axonal shaft [6-8], and stochastic exploration [9]. Possible AD mechanisms include competition for neurotropic factors [22], plasticity through modulations in synaptic efficacy [23], and morphological changes in axonal arborisation [18].

VII. COMPUTATIONAL INSTANTIATION OF INTEGRATE

In order to test some of the proposed ideas on critical stages of development, we combine both AI and AD mechanisms in INTEGRATE. Here, AI axonal guidance is modeled through the servomechanism model with cell-cell competitivity [5]. The AD process is modeled through

Hebbian learning [11]. The proposed account is based on the assumption of two stages of development, one that involves the formation of an initial map mainly under the influence of AI processes, and another that involves map refinement mainly under AD processes.

A. Servomechanism Axonal Guidance

The servomechanism model [5,9] offers an account of how axons gradually extend projections through a target surface (Appendix 1). In the model, migration of the growth cone is determined mainly by chemotropic factors, but also by stochastic exploration and cell-cell competitive interactions (the model contains no backbranching along the main axonal shaft, c.f., [7]). The result of these processes on migration is a "guided stochastic" walk through the target surface (Fig.2).

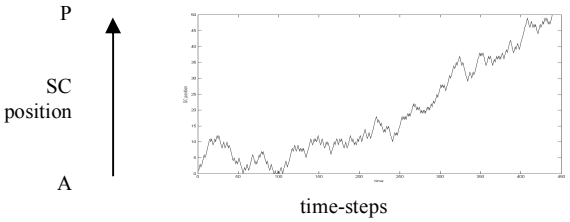

Fig. 2: Migration of a single projecting retinal growth cone through one dimension of the target surface (SC). $R(i)$=50. A=anterior; P=posterior. Arrow shows the direction of migration.

B. Hebbian Synaptic Weight Modification

Following the AI process, an AD process is introduced based on Hebbian learning with a Gaussian neighborhood activation [1]. This learning scheme adjusts connection strengths between the RGCs and SC, thus refining the projections obtained through servomechanism guidance. Such principle reflects the known influence of AD mechanisms in stages of development following the initial guidance of axons through molecular gradient cues.

The learning rule for connection strengths w_{ij} linking the RGCs to the SC cells is:

$$\Delta w_{ij} = \frac{1}{N}\sum_i \sum_j v_j^s \left(x_i^s - w_{ij}\right), \qquad (2)$$

where v is the activity of tectal neurons j given input pattern s, represented by logistic units, and N is the total number of cells in each layer. Retinal input patterns x are presented as waves with random centers expanding throughout the retina in a radial fashion (see [1], for details; [13]). These spontaneous waves of activity are characteristic of the pre-critical period of development that precedes eye opening. The synaptic plasticity rule of Eq.2 seeks to maximize the connection weights from RGC to SC cells that fire together, and minimize the connection weights from cells that do not.

VIII. RESULTS

A. BMP transgenic projections

In the wild-type (WT; normal) condition, initial projections obtained through AI mechanisms are characterized by a rough topography, where TZs are centered appropriately but are diffuse (Fig.3a). AD plasticity refines these TZs, resulting in the elimination of many non-topographic connections (Fig.3b).

The BMP condition is modeled by applying the AI mechanism as in the WT condition, but shifting over the ventral RGC projections to inappropriate locations laterally. With this manipulation, projections are initially miswired (Fig.3c). If activity is not introduced, TZs remain not only inappropriately wired, but also lack refinement, thus replicating the cumulative influences of disrupting AI and AD processes [19]. If activity is introduced in the BMP condition, spontaneous waves can refine their TZs, despite being miswired (Fig.3d).

These results replicate the empirical findings reported in Section V, and suggest that the idea of critical stages of development can indeed by captured by the INTEGRATE framework. The simulations show how each stage plays a specialized role in retinotopic map formation, with a rough topography established early in development, and refinement of TZs occurring in a later stage. The model captures well the limited capacity of the AD mechanism; indeed, mistargetted TZs through the BMP manipulation make it impossible for Hebbian learning to produce a correctly wired map. To our knowledge, no other existent model captures this range of results.

B. Role of AI conditions on map refinement

Our results suggest that AI conditions play a determining role in map formation, and thereby influence the scope of refinement that is later on possible through AD processes. Hebbian learning by itself, without some initial bias, cannot produce a topographically faithful map. For instance, given an initial map with weights of 0.0, Hebbian learning fails to adapt the map in any way (i.e., weights remain at 0.0). If the result of the AI process is a random map, the result of the AD process will also be a random map. Absent some prior topographical bias induced by AI process(es), AD processes have limited effect.

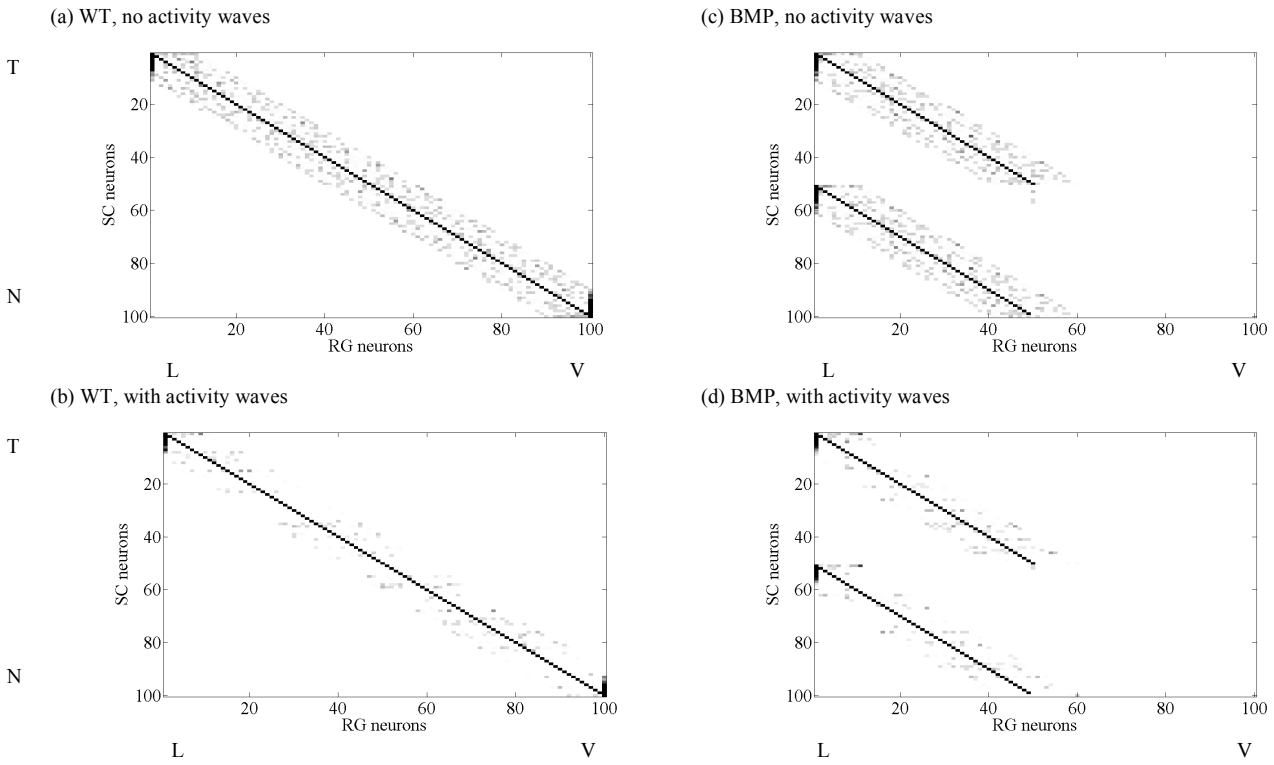

Fig. 3: Effect of spontaneous activity and BMP on retinotopic map refinement (figure shows weights w_{ij}, ranging from 0.0 to N_c). (a) WT without activity waves; (b) WT with activity waves; (c) BMP without activity waves; (d) BMP with activity waves. L=lateral, V=ventral, T=temporal, N=nasal.

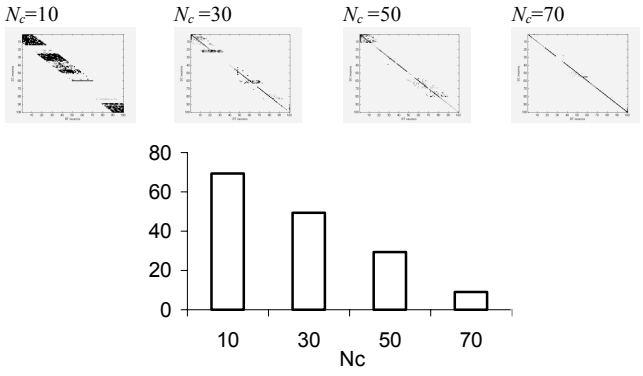

Fig. 4: Influence of axonal density (Nc) on STDP map refinement. below: average over 10 runs, non-topographic weights.

How much prior bias is required remains unknown, and is clearly parametrically-dependent. As a preliminary investigation of this issue, we manipulated the density of arborisation at topographically faithful TZs, i.e., the N_c parameter in the servomechanism model. These follow up simulations suggested a monotonically decreasing function, with the upper limits on activity-dependence declining as initial topography ordering decreases. Conversely, a stronger bias promotes topography (Fig.4).

In more general terms, the proposed account predicts that AD processes will always refine TZs by increasing arborisation in a projecting region of highest density, and eliminate it in all other regions. Any AI bias that shifts the region of highest density to a non-topographic location will lead to a mistargetted map that cannot be overcome by AD processes.

Given the set of parameters we used, activity was sufficient to rescue maps with an initial a density of N_c =30 (i.e., 30% of the model's default density), but not initial maps with less density. Although these specific number must be taken with a grain of salt (until further empirical data that allow us to more precisely set parameters), the overall lesson seems clear: the power of activity-dependence very much depends on the power of prior activity-independent processes. To paraphrase an ancient but well-known saying, activity helps those who help themselves.

IX. REMAINING ISSUES

Models such as INTEGRATE that explore the interaction between activity-dependent and activity-independent processes can be used to investigate many of the most important questions in development. If it is a truism that nature and nurture interact, understanding *how* they interact is a necessity. In the particular case of retinotopic development, one can explore questions such as what factors (environmental and genetic) mediate the progression through developmental stages; what is the precise time-course of influence of genetic and biophysical processes on development; how small genetic disruptions affect map formation; what influence can enriched or deprived environments exhort on neural organization. More broadly,

any account of neural development may profit from a precise exploration of activity-dependent and AI processes.

The whole in this case can only be as good as the sum of the parts: investigations into the interactions of these two key components depend on solid models of their individual contributions. In each component, many important challenges remain. With respect to activity-independent processes, one immediate challenge consists in quantifying the precise shapes of molecular gradients on the retina and SC. Some efforts towards this goal (e.g., [24]) have successfully fitted functions to some of the molecules involved; however, there are many more whose shapes are unknown. Further, the interaction between these molecules and the growth cone receptors are not fully understood. Some avenues of exploration with computational models [8] have shown how basic biokinetic forces of attraction and repulsion can be used to account for recent experimental evidence on the role of Eph/ephrin gradients.

In AD mechanisms, an important issue concerns their possible instructive versus permissive roles in map formation [25]. One the one hand, activity can be conferred an instructive role if found necessary to obtain topographic projections, and if these projections are directly affected by features of the activity. On the other hand, activity is said to be permissive if topographic projections can be obtained as long as there is a sufficient level of activity present. Current empirical evidence argues for an instructive role of activity [25]. However, an understanding of what features of activity in particular influence development of the retinotopic system remains to be investigated. In particular, computational models could investigate the influence of certain features of spontaneous activity waves in early development. Biophysical models of these waves have so far been successful at replicating recorded RGC activity, but not its influence on synaptic plasticity [26]. An investigation of retinal waves on synaptic plasticity will require a more sophisticated model than the one proposed here, one that will likely involve precise membrane potentials and time-dependent learning rules [23].

Returning to the combination of activity-independent and activity dependent processes, much more remains to be investigated. For example, under what activity-independent conditions can activity-dependent processes perform a refinement to correct TZs? The answer to this question should be in part influenced by the known limited capacity of activity-dependent processes to overcome a faulty initial map – as demonstrated in BMP manipulations (Section V), where activity was not able to reverse a mistargetted map [19] and modeled in our studies But current computational approaches to map formation may actually be too powerful to capture such limited capacity. Indeed, many algorithms for unsupervised learning (e.g., self-organizing maps [21]) can learn difficult distributions from scratch. Despite this capacity to perform powerful learning, it is also possible that topographic map formation may require a bias, because it is one of many possible solutions, all equi-probable from a statistical standpoint, to achieve a one-to-one connectivity between two layers of neurons. This potential limitation of learning algorithms would not apply to models that combine both AD and AI processes.

Future developments using the INTEGRATE framework will include the shaping of axonal morphology through AD mechanisms [18], as well as the incorporation of molecular mechanisms that orchestrate the beginning and ending of different developmental stages (e.g., BDNF, [27]).

X. CONCLUSION

The proposed model of retinotopic map formation incorporates both AI and AD mechanisms in a way that allows them to be manipulated separately, as in recent experimental work [19]. Simulations support the view that chemotropic and AD processes may provide independent sources of influence during retinocollicular map formation, and occur at different critical stages. As a consequence, there is a cumulative effect of disrupting these processes (e.g., see Fig.3). One implication of these results is that AD processes possess a limited instructive power; they can refine maps by eliminating extranumerary connections, but cannot correct mistargetted TZs. Finally, through simulations, the amount of topographic bias provided by the AI process has been argued to play a critical role in retinotopic map formation.

The challenges proposed in the study of retinotopic map formation will likely require the collaboration of scientists across many disciplines, and foster links between molecular biology and computational neuroscience. The field of developmental neuroscience will likely benefit from these efforts, as principles that are found in retinotopic map formation are also pervasive in other brain centers involved in sensory processing. Indeed, the Eph/ephrin molecular gradients discussed here also influence topographic map formation in the somatosensory system [28]; projections from the thalamus to the somatosensory neocortex), and tonotopic system [29], and vomeronasal system [30]. In addition to shaping projections along sensory pathways, Eph/ephrins are also responsible for map formation in hippocampus-entorhinal connections [31,32], hippocampus-septum connections [33], patch-matrix connections of the striosome [34], dopaminergic striatal neuron-midbrain connections (nucleus accumbens; [35]), and cortical columns of layers 2/3 [36] . A proper understanding of the interaction between AD and AI mechanisms is likely to cast light on all of these processes.

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APPENDIX 1: SERVOMECHANISM MODEL

In the model, RGC axons send out projections that travel through discrete positions[1] in the SC, through a number of time-steps (for pseudo-code, see Table I). Through its interactions with the target surface, the growth cone will

[1] Although the SC is a continuous surface, it can only be sampled discretely by traveling axons.

naturally aim towards a position where all its receptors are occupied (referred to as the point of maximum receptor saturation [8].

For simplicity, and because migration can be modeled independently along the dorsal-ventral and anterior-posterior axis [9], a single dimension of migration is modeled here (i.e., the anterior-posterior axis of the SC).

TABLE I: PSEUDO-CODE FOR SERVOMECHANISM MIGRATION

```
Set the default number of positions and axons N=100
Set the default number of time-steps T=100
For each retinal position i to N, and each axon j to N
   Set M_i =[R(u_i)]^2
   Set v(1)=1
   For each time-step t,
         Set G(t) = u_i * v(t)
         Set d(t) = |G(t) – M_i|
         If d(t)<1
            s_i,j = v(t)
            Goto next axon j
         End If
         Else
            Set v(t+1) = v(t)+1
            Set G(t+1) = u_i * v(t+1)
            Set d(t+1) = |G(t+1) – M_i|
            If d(t+1) > d(t)
               v(t+1)=v(t)-1
            End If
   End For
End For
```

The model assumes a linear simplification of receptor and ligand gradients (more precise models have been proposed, e.g., [23], and account for nonlinearities in these gradients). In the proposed model, the number of available receptors on the RGC growth cones varies according to position on the retina, in a high nasal – low temporal fashion [8,37].

TABLE II : PSEUDO-CODE FOR SERVOMECHANISM COMPETITION

```
Set the default density tolerance N_c = 50
Set the default travel distance q =10
For each location i
   Set density(i) = 0
   While density(i)<N_c
      For axon j to N
         If s_i,j=i
            Set density(i)=density(i)+1
         End If
      End For
      While s_i,j ≠ i
         Set j = ceil(random(0,1) * N)
         If s_i,j = i
            Set s_i,j = s_i,j ± ceil(random(0,1) * travel)
      Bind s_i,j between a range of [1, N_c]
         End If
      End While
   End While
End For
```

The model forces all axons to enter from the same SC position. This insures that axons gain no information as to where they belong simply by where they enter (biologically plausible to a large extend).

The precise mechanisms involved in axonal guidance are still under debate in the literature. Part of this debate centers around the type of stop signal produced (i.e., setpoint versus local optimum rules; see [38]), as well as the type of molecular signaling that provides guidance (i.e., absolute versus relative; [24,39]. The proposed account steers clear of these debates, and is theoretically compatible with all accounts; a detailed discussion on the topic is beyond the scope of this paper, and can be found elsewhere [8].

Chemotropic factors influence migration through their interaction with the growth cone receptors, as captured through the law of mass action (i.e., second-order kinetics). Under the assumption that the ligand function employed is already taken to be a summation over all ligand molecules, there is no requirement to sum this equation over multiple receptor and ligand interactions.

Axons travel in small steps of fixed size, and try to approach the point of maximum receptor saturation, where they will stop. If a new travel location decreases maximum receptor saturation, the axon retracts one step.

Once all axons have migrated, a process of axonal competition is introduced [5]. The goal of this competition is to discourage axons from terminating in a region of the target surface where the density of projecting axons is high (Table II).

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