

# Computational modeling of neuronal map development: insights into disease

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The study of the formation of neuronal maps in the brain has greatly increased our understanding of how the brain develops and, in some cases, regenerates. Computational modeling of neuronal map development has been invaluable in integrating complex biological phenomena and synthesizing them into quantitative and predictive frameworks. These models allow us to investigate how neuronal map development is perturbed under conditions of altered development, disease and regeneration. In this article, we use examples of activity-dependent and activity-independent models of retinotopic map formation to illustrate how they can aid our understanding of developmental and acquired disease processes. We note that fully extending these models to specific clinically relevant problems is a largely unexplored domain and suggest future work in this direction. We argue that this type of modeling will be necessary in furthering our understanding of the pathophysiology of neurological diseases and in developing treatments for them. Furthermore, we discuss how the nature of computational and theoretical approaches uniquely places them to bridge the gap between the bench and the clinic.

The development of connections within the human brain is perhaps the most complex feat of self-organization known to science. Billions of neurons must be carefully and specifically connected up in order for us to function properly. Each neuron forms up to tens of thousands of connections to other neurons, and these connections may span distances of micrometers up to several centimeters. The precise targeting of individual connections is finely tuned, and the consequences of errors in this targeting are profound, with many important neurological and psychiatric conditions now linked to defects in this neural wiring [1,2]. It is imperative that we understand how normal wiring develops, so that we might learn more about how miswiring contributes to developmental brain disease and, eventually, how we might go about designing interventions to prevent or treat these diseases.

Neuroscience has moved on from the dogma that no new neurons are created in the adult mammalian brain and accepted that new neurons are constantly being created in the hippocampus and olfactory bulb of mammals and potentially elsewhere in the CNS as well [3]. Similarly, the idea that neurological repair after CNS injury – whether acute or degenerative – is not possible is being challenged by novel therapeutic approaches in the field of regenerative medicine [4]. Stem cell transplantation methods

and the recruitment of endogenous precursors and endogenous repair mechanisms are examples of such approaches. While any significant discussion of current approaches in stem cell and regenerative medicine is beyond the scope of this article, we note the following:

- These methods have been trialed in a number of neurological diseases, such as stroke, Parkinson's disease and Huntington's disease, and in some cases, they have been found to be safe and effective [3,5];
- These methods offer avenues for replacing cells that are lost during neurological disease processes [6,7];
- Little is known about factors influencing how replacement neurons might form their connections [5,8].

Indeed, replacing damaged or lost cells is only part of the problem; these replacement cells must also integrate into their environment, extend axons and dendrites, sometimes over long distances, and form functional synaptic connections. A better understanding of the development of brain wiring could significantly improve treatment strategies in this area. For example, a quantitative understanding of how replaced neurons respond to their new, and most likely abnormal, environment

## Keywords

- computational modeling
- developmental neuroscience
- neural map
- neurology
- neurosurgery

could allow us to manipulate aspects of treatment that would maximize cell survival and proper connectivity.

#### What can computers tell us about disease?

Computational modeling of the development of neural wiring is a powerful tool in gaining a quantitative understanding of these complex processes. This is particularly true when employed in concert with experimental strategies where the interaction has proved synergistic. From a general scientific point of view, computational and theoretical techniques offer a number of advantages, including making hidden assumptions explicit, the ability to rapidly test a large number of hypotheses and making specific and precise predictions. But what can computers tell us about disease? We consider this question more generally first, before addressing it within the context of specific examples in computational modeling.

Understanding many neurological diseases is made more challenging than in other organ systems, simply because of the sheer complexity of the nervous system. Because of this, a quantitative understanding of the pathophysiology of neurological disease is important, and mandates the use of mathematical and computational techniques. Computational models are often referred to as phenomenological if they model systems of interest in a relatively abstract way (i.e., capturing general properties or trends of a system) and biophysical if they model specific mechanisms in a direct way (i.e., if the model variables correspond closely to real quantities). Although we generally aim to move from the former to the latter, this does not always reveal new insights, and detailed biophysical modeling can quickly become practically and computationally difficult in complex systems.

By modeling specific mechanisms of interest, including how they are modulated in pathological processes, we can tightly relate particular mechanisms to particular outcomes in disease states. In this way, models can potentially inform us about disease processes, and hence also optimal avenues for treatment. Using computational models of disease, we can probe mechanisms and responses to treatment without invasive experiments. This not only reduces the burden on animal models to advance our understanding, but also provides a stepping stone between the bench and the clinic as an additional testing ground prior to human trials. We can develop models based on *in vitro* and *in vivo* experiments and then tune these models for conditions that

are relevant to human disease and treatment, allowing us to optimize and tailor our therapies. Indeed, some illnesses (e.g., psychiatric) cannot be adequately studied in animal models, due to the need to read out cognitive and affective changes, and some relevant experiments cannot be done in humans for biological and ethical reasons. In these instances, appropriate computational models can provide insights that would be otherwise unavailable, and in some cases may be the only technique available to ask and answer certain questions.

#### The visual system

One of the most fruitful model systems for studying the development of brain wiring is the visual system. The connections between the eye and the brain are often referred to as visual ‘maps’ because they map features of visual space from the retina to particular areas of the brain. Retinotopic maps are neuronal connections that map points in visual space to points in a 2D sheet of neurons in the brain. Neighboring points in visual space are monitored by neighboring cells in the retina, and these retinal cells project to neighboring points in the target sheet (either directly or via intermediate structures). In this way, a facsimile of visual space is delivered to a particular part of the brain, faithfully representing the image of the world presented to the retina. Just as this map conveys information about what point in space a given retinal neuron best responds to, other maps, called feature maps, form ordered projections consisting of higher-order stimulus properties, such as ocular dominance and orientation preference (discussed in a later section).

The retinal ganglion cell (RGC) layer is the output structure of the eye. RGC bodies send out axons during development that exit the eye, travel along the optic nerve and tract and then to their eventual targets. There are a number of such projections from the retina to target structures in the brain, but two of the most important are the retinohalamocortical projection and the retinotectal/retinocollicular projection. The retinohalamocortical projection connects the eye to the visual cortex via a synaptic relay in the thalamus, and is the primary visual system in humans and other mammals. The retinotectal/retinocollicular projection connects the eye to a midbrain structure known as the optic tectum in lower vertebrates such as fish, frogs and chicks, and as the superior colliculus in mammals. In the retinotectal case, it is the primary visual system, whereas in the retinocollicular case, it is secondary to the retinohalamocortical system.

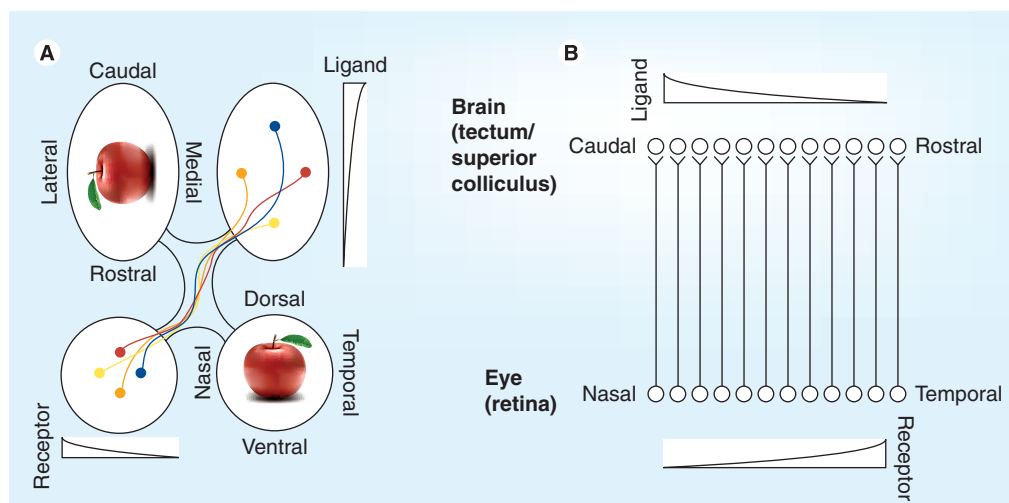
For both midbrain and cortical maps, initial map formation is determined by axons using molecular markers to find their targets, while neuronal activity further refines and patterns the projection [9–11]. Maps from the eye to the midbrain (which we will refer to hereafter as retinotectal maps) are simpler and have been mostly used to study the role of guidance by gradients of marker molecules, whereas visual cortical maps have been used to study map development based on patterned visual activity. Although these are simplifications, we will consider the contributions of computational modeling of neuronal map development in these two broad categories – activity-independent and activity-dependent, respectively – and use examples in each category to show what these models can tell us about disease and, perhaps, approaches to therapy.

### Modeling guidance by gradients: insights into anatomical lesions & developmental disease

The retinotectal map is one of the most well-studied examples of retinotopic map development (FIGURE 1A). The dependence of this map on molecular gradients for its formation has allowed us to probe the fundamental mechanisms involved in how growing axons respond to molecular gradients and find their targets appropriately. It has been postulated that gradients of molecular markers could be used to specify position within

a structure, with the amount of molecular marker being used as a surrogate for position. If such gradients are present both in an area where a projection originates (e.g., the eye) and also in the target area for that projection (e.g., the midbrain), then when coupled with a mechanism for matching the gradients, these features are sufficient to allow for a map to form between the input and output structures. One pair of gradients can form a 1D map, two pairs of gradients can form a 2D map, and so on (FIGURE 1B). This was first formalized by Roger Sperry [12], and is known as the chemoaffinity hypothesis. It has been widely supported by experimental and theoretical studies, and a number of molecular species that could play this role have been found [11,13]. Examples of these molecules include the Eph receptors and their ephrin ligands, Wnt3, Ryk, RGM, semaphorins and others [11,14]. Mutations in the genes encoding these proteins can have profound effects on map development, and a number of experiments have been designed to investigate these effects (for a review, see [15]).

We will examine two approaches to computational modeling of retinotectal map formation, and use these to illustrate how each approach has informed us about disease processes and how other models of retinotectal map development might be able to perform this better in the future. The first approach is that taken in the extended branch arrow model (XBAM) of Overton and Arbib [16], and in



**Figure 1. The retinotectal map and chemoaffinity. (A)** Schematic representation of the retinotectal map. Retinal ganglion cells form the output layer of the eye and extend their axons along the optic nerve and tract to their midbrain target. Neighboring retinal ganglion cells (and hence neighboring parts of visual space) are mapped to neighboring points in the tectum. This preservation of neighbor spatial relationships is the hallmark of topographic maps. **(B)** A 1D schematic of the retinotectal map, showing gradients corresponding to Sperry's hypothesis. Here, a 1D line of cells in the retina is labeled by a gradient of receptors, while a 1D line of cells in the target is labeled with corresponding ligands. High receptor maps to low ligand, and *vice versa*, so that a map can form between the two areas.

an updated version of this model by Simpson and Goodhill [17]. The second approach we examine is that taken in the retinal induction model [18,19] (for reviews of the many computational models of retinotectal map formation created from the 1970s onward, see [20–23]).

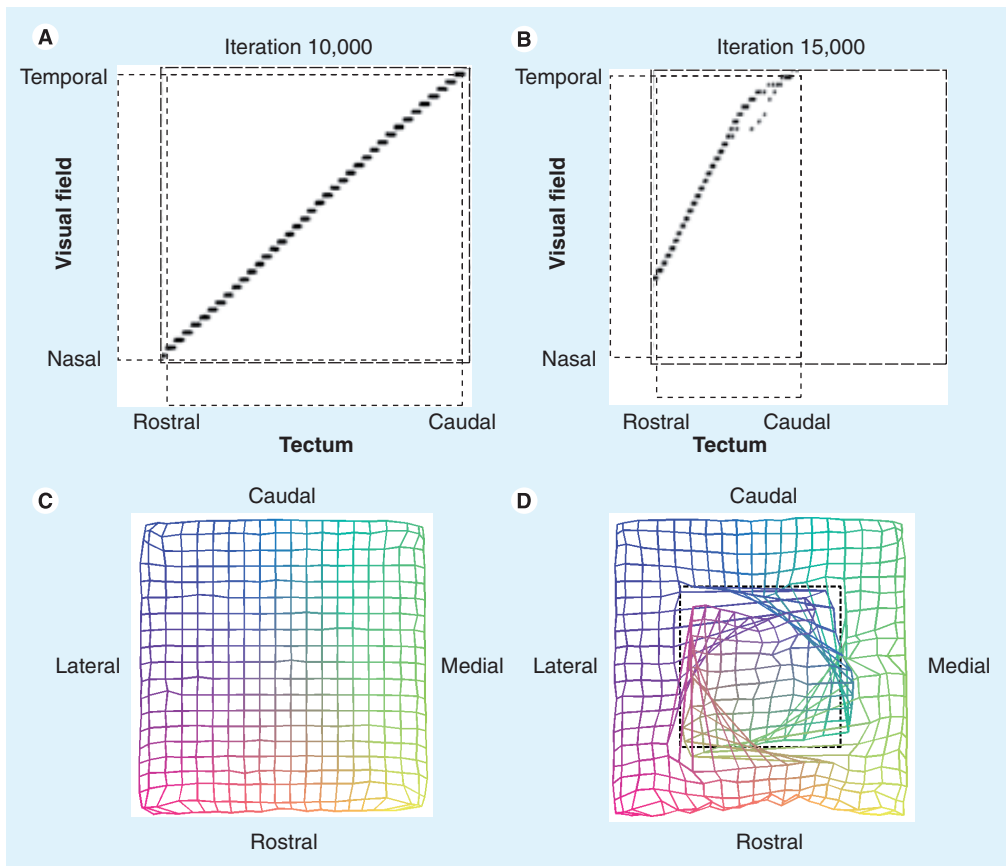
The XBAM model was developed to model the motion of growth cones (the sensory and motile structures at the tips of growing axons) moving over their target and their responses to each other and to molecular gradients. Motivating this approach were a number of experiments performed on the retinotectal system that suggested that the chemoaffinity hypothesis alone was not sufficient to account for certain experimental observations. These experiments were typically surgical manipulations of either the origin (retina) or target (tectum), which generally involved rearranging parts of either/both or surgically removing parts of either/both [24]. For example, in one such experiment, the caudal half of the tectum was removed and the optic nerve was cut and allowed to regrow [25]. (This experiment was performed in goldfish, whose optic nerves can regenerate.) When the projection was measured, instead of only the remaining hemitectum responding to its usual half of the visual field, it responded to the whole visual field, so that the retinotopic map was effectively compressed along one axis in the tectum (FIGURE 2A & B). Based on these results, it appeared that fibers were able to partially ignore their chemoaffinity cues, and that other mechanisms must be involved in map development [26]. However, being a 1D model, XBAM was unable to fully explore the effects of another type of surgical manipulation, the graft experiments. In an example of this type of experiment, a central part of goldfish tectum was removed, rotated 90° and then the optic nerve was allowed to regrow [27]. The visual map was found to be similarly rotated. Simpson and Goodhill investigated this and a wide range of other surgical manipulations in 2D (FIGURE 2C & D) [17].

The XBAM model considered an array, or lattice, of discrete RGCs and modeled their motion on the tectum subject to a number of influences or ‘forces’. These forces were: guidance by molecular gradients; the effect of ‘edges’ (surgical grafts, joins and/or tectal boundaries); an interaction term enacted when growth cones encounter each other (based on a sorting mechanism explored earlier in a simpler model [28]); and an averaging influence that growth cones from the same axon exert on each other. Each of these forces contributed a vector ‘push’ to growth cones, and an overall movement vector was calculated

based on a weighted sum of each of the influences. The model considered a 1D retina – a row of cells – projecting to a continuous 1D tectal line (similar to that shown in FIGURE 1B). Simpson and Goodhill considered a similar framework, but updated it to 2D, removed the edge and averaging term and separated out the interaction/sorting term into competition and axon–axon interaction terms [17]. Recently quantified molecular gradients were also modeled implicitly [29], so that experiments involving genetic manipulations of these gradients [29,30] could be addressed. The axons and structure of their arbors were not specifically modeled in either model. Instead, each growth cone was represented as a small circle that could interact with any other of these circles/edges that it touched. As previously described, movement vectors were calculated for each growth cone, and all were moved simultaneously according to the calculated vectors. The growth cone movements were iterated in this way in computer simulations, and the resulting maps were analyzed when certain patterns emerged.

Using this approach, these models successfully replicated many of the surgical-type experiments, such as map compression and graft rotations (FIGURE 2), and were relatively realistic in modeling movement of growth cones across the target. Overton and Arbib further observed that the boundaries of surgical grafts caused problems for in-growing fibers and that fibers could become trapped in these areas [16]. Simpson and Goodhill showed that the effects of molecular guidance by gradients, competition for space and guidance receptor-based interactions between RGC axons were all required to explain the range of surgical and genetic manipulation results to date [17].

This kind of approach to modeling and these kinds of experiments constitute an ideal paradigm for analyzing how traumatic CNS injuries might affect future treatment strategies designed to regenerate parts of the damaged brain and/or spinal cord. They suggest that in addition to the significant challenges involved in either regenerating endogenous neurons or transplanting exogenous neuronal stem cells, there are important issues to consider from a guidance point of view. Specifically, models such as XBAM suggest that aspects of the pathologically altered environment (retinal/tectal geometry and lesion edges, among others) can have a significant effect on shaping projections. The model highlights that interactions between RGC axons need to be carefully considered [17], as they can cause striking disruptions to map formation under certain conditions. Both models suggest that patterns such as



**Figure 2. Experimental and modeling results in normal development and surgical manipulations. (A & B)** Simulation results from the 1D extended branch arrow model of Overton and Arbib [16]. Individual fiber positions are indicated by a black dot, which gives the 1D retinal position of origin and the 1D position in the tectum. **(A)** Normal development. A smooth retinotopic map is demonstrated: the nasal to temporal axis of the visual field is mapped to the rostral to caudal axis of the tectum. **(B)** Tectal ablation, or map compression experiment. The caudal tectum is ablated and the fibers are forced to innervate the remaining tectum. A topographic map of the entire visual field still forms, so that the projection is compressed along the rostrocaudal tectal axis. **(C & D)** Simulation results from the 2D model of Simpson and Goodhill [17]. Here, a topographic grid represents the current location of retinal ganglion cells on the (right) tectum. Grid intersection points represent the current position of a retinal ganglion cell axon arbor, and lines are drawn between them if their cell bodies are neighboring in the retina. Gridline colors correspond to positions of retinal origin, so that nasal retinal positions are blue and green, and temporal positions range from red to yellow. The grids shown are averaged over ten simulation runs of the model. **(C)** Simulation of normal development. A normal retinotopic map forms. **(D)** Simulation of graft rotation experiments. In these experiments, a central piece of tectum is excised, rotated 90° and replaced in the tectum; the nerve is then allowed to regrow. In the simulation results, the central part of the map is rotated, similar to that observed experimentally. **(A & B)** are reproduced from [16] with permission from Springer Science+Business Media.

retinotopy may be robust to certain disruptions, and reinforce that molecular gradients are important tools in maintaining or encouraging these patterns. These issues appear to be somewhat unique to regenerative medicine applied to the nervous system; for instance, in cardiac myocyte replacement, bone marrow replacement and some other systems, there appears to be no obvious need for further intervention other than just cell replacement. However, in repairing neural systems, unless the rewiring is effective and precise, the benefit of the treatment may be limited (e.g., [8]).

Another approach taken to understand the development of retinotectal maps is the retinal induction model [18,19]. This model also employed guidance of in-growing fibers by molecular markers, but in contrast to the implicit modeling of the effects of molecular markers explored by Simpson and Goodhill [17], gradients were represented explicitly. In addition, the central mechanism of the retinal induction model was quite different, and assumed that in-growing fibers could up- or down-regulate the same molecules that they were guided by. This model

employed the molecular gradients quantified by Reber *et al.* [29], and has examined the effects of gain- and loss-of-function assays involving these molecules. The retinal induction model considered the projection of a discrete array of RGC axons onto a discrete tectum or tectal array. Each RGC axon was marked with an individual level of a particular molecule and was able to up- or down-regulate corresponding molecules labeling the tectal cell on which the RGC axon currently terminated. This regulation always acted to make the pre- and post-synaptic markers more similar, and did so in proportion to the synaptic strength between those two and the similarity of markers. Neighboring tectal cells were able to influence each other similarly. In this way, the mechanism effected the neighbor-matching property that is central to retinotopic maps.

The retinal induction model established the effectiveness of using a precise neighbor-matching scheme in retinotectal map development. Analogous to the first modeling approach discussed previously, the retinal induction model also demonstrated how interactions between axons (although in this case indirect interactions) were important in determining the mapping. Modeling molecular gradients also allowed the authors to model various misexpression studies involving molecular gradients known to be involved in setting up the map, such as the aforementioned examples. These misexpression experiments resulted in a variety of different map phenotypes; some important examples include the creation of duplicate termination zones in some cases, duplicated maps in others, and other more complicated phenomena [29–32]. The retinal induction model was able to account for some important examples of these results.

The explicit use of molecular gradients and the modeling of studies of misexpression of those gradients allows this kind of model to be used to gain insight into developmental brain disease, in the same way as XBAM-type models could be used to examine diseases involving gross anatomical disturbances. Wiring deficits underlying neurological and psychiatric diseases have been associated with mutations in genes encoding guidance molecules. Examples include the ephrins, semaphorins, slits and many others, and associated diseases include Parkinson's disease and epilepsy [1,2]. In addition, this type of model gives us part of the framework we need for estimating the efficacy of therapeutic strategies for preventing or treating developmental brain disorders, highlighting in particular that careful attention must be paid to expression of developmental gradients.

We have presented the mechanisms and potential applications of XBAM-type models and the retinal induction model separately, in that we have suggested that the more physical modeling of XBAM lends itself best to considering acquired CNS lesions, whereas the molecular–genetic focus of the retinal induction model is more relevant to developmental disease. Of course, this is a simplification, and it would be an advantage to be able to combine both approaches, as this would allow models to address a wider range of phenomena. For example, the molecular regulatory effects of ingrowing axons from cell therapies in CNS injury need to be considered, particularly given that axons must traverse an abnormal environment. Similarly, the physical modeling of XBAM may reveal new insights into the potential barriers to, and influences on, growth cone motion in altered CNS environments during development. The Simpson and Goodhill model is a step in this direction as it has been used to model both surgical and genetic manipulations using the same model framework and parameter set [17]. Of course, there are other important aspects of retinotectal map formation not considered by the models discussed here, two important examples being the role of axonal branching in axon guidance (e.g., see the models in [33,34]) and correlated neural activity (e.g., see the models in [35,36]).

Models and experiments in the retinotectal system can help us understand disease processes, and potential therapies for them, on a number of levels. Models of retinotopic map development are perhaps most immediately applicable to diseases such as glaucoma, which involve the loss of RGCs, and how regenerating RGC axons might behave under these circumstances. In glaucoma, XBAM-type models could potentially tell us how the loss of RGC axon density in the tectum can affect the visual map, and hence vision. If regeneration or replacement of lost RGCs can be achieved, modeling could potentially provide an estimate of what sort of RGC density is required to achieve particular outcomes. Although cell replacement strategies for glaucoma are still a long way off, there is promising initial work on generating cell lines that could be used for these purposes [37,38]. As previously mentioned, obtaining replacement cells is only part of the solution; these cells must survive, extend axons and form functional connections as well. Encouragingly, it has been shown that taking hippocampal precursor cells and transplanting them into the retina of

RGC-depleted adult rats resulted in significant numbers of these cells residing in the ganglion cell layer, while others extended processes into the optic nerve [39].

Moving laterally into other visual systems, these models may also be relevant to visual retinotopic map formation in the cortex. Hence, cortical map development and/or cortical map regeneration in response to cortical lesions could potentially also be analyzed and modeled in similar ways. This may prove useful in understanding the responses of the brain to stroke, neoplastic conditions and traumatic injuries, particularly if combined with other work utilizing activity-dependent models of cortical lesions (e.g., [40]). More generally, models such as those discussed in this article could be adapted to the formation of other types of neuronal maps, so that by varying aspects of the underlying algorithms, we may gain insight into how other stereotyped neural connections respond to injury and how they might be amenable to therapy.

Although these may seem ambitious goals, they have already been partially achieved in the work by Sarah Dunlop and colleagues. Using insights gained from the positive effects of training on the scrambled regenerated visual maps in lizards [41], and applying similar methods to damaged whisker maps in rats [42], Dunlop and colleagues have provided the basis for part of an intensive therapy program for patients with spinal cord injury – Spinal Cord Injury and Physical Activity (SCIPA) [101] – currently undergoing clinical trials (e.g., [43]). Although at an early stage and based largely on experimental rather than modeling work, this research provides optimism that the types of models discussed in this article can also be generalized in such a way as to be clinically relevant.

#### Modeling map plasticity: insights into environmental impacts on development

Map development is not entirely determined by a genetic program; patterns of activity, dictated by the environment, are critical to a later stage of map development, after the broad initial architecture of connections is established. To mimic the biological situation, models of this stage of map development generally start with a fixed architecture, assumed to have been established by activity-independent mechanisms (such as those described in the previous section) and changing synaptic strengths or weights. Models in this class give ‘learning rules’ that dictate how these weights change in response to particular input activity. They aim to generate a network with

properties that reflect those observed in biology, such as topographic maps of space, orientation and ocular dominance.

Retinotopic maps are an example of a type of neural patterning that can arise from activity-independent mechanisms (as discussed in the previous sections) or activity-dependent mechanisms. Activity-dependent models of retinotopic map development generally use unsupervised learning rules. These depend only on pre- and post-synaptic activity, without any feedback based on the output to help the network learn. Without feedback, the set of weights that develops only depends on the statistical structure of the input activity and the learning rule describing how the environment influences development.

The learning rules are broadly inspired by Hebb’s hypothesis that connections between neurons strengthen if their firing is correlated [44]. This hypothesis was subsequently verified by biophysical observation (reviewed in [45]). Different models of map development use slightly different mathematical instantiations of this rule to describe how weights change. In this article, we consider competitive models, since these in particular have been used to model and understand how abnormal experience during development changes brain wiring [23,46,47].

Two successful competitive learning models are the Kohonen and elastic net models. These models come in several variants, as described in detail elsewhere [47–51]. All formulations map an input space containing stimuli with various features (e.g., position and orientation) onto a 2D sheet of neurons representing the primary visual cortex. They do this in such a way that all combinations of features are represented in the cortex (good coverage) and neighboring cortical neurons have similar receptive fields (good continuity), two properties of real cortical maps.

The Kohonen and elastic net models have been used to simulate several grossly abnormal rearing conditions including monocular deprivation [52,53], strabismus [54] and stripe-rearing [53,55]. The topographic maps of retinotopy, ocular dominance and orientation generated by these models match experimental maps in their individual overall structure and the relationships between maps in normal and abnormal rearing conditions [46,47,56]. Modeling studies of abnormal developmental conditions have given insight into the variables that create or mitigate changes in the primary visual cortex (and presumably functional vision) [52–55].

In the models, the most dramatic changes in cortical structure occur when there is a mismatch in input to the two eyes. We will briefly discuss

the changes in map structure owing to these mismatches in three cases, and the implications for functional vision.

Of the different rearing conditions examined with models, monocular deprivation is probably the closest to a human developmental disease or disorder: that of deprivation amblyopia. Monocular deprivation in computational models causes the input from the deprived eye to the cortex to weaken, causing the deprived eye's ocular dominance columns to shrink and allowing the open eye's ocular dominance columns to expand (FIGURE 3A & B) [52,53], as seen in monkeys and cats [57,58]. This weakens visual acuity through the deprived eye in a manner similar to that experienced by human deprivation amblyopia (reviewed in [59]). A detailed investigation of the onset and duration of deprivation suggests that even brief detrimental environmental input at the incorrect time in development can have large consequences for the structure of multiple maps [53].

Another common human disorder, strabismus, is modeled as a decorrelation in the input to the two eyes. In the models, it results in wider ocular dominance columns and fewer binocular cells (FIGURE 3A & C) [54]. Unfortunately, attempts to experimentally validate these predictions have been inconclusive because large inter-individual variability in ocular dominance column widths makes it impossible to definitively correlate changes in column spacing with strabismus [60,61]. (An advantage of models is the ability to see how a map develops with and without a perturbation, while keeping all other parameters the same.) The direct effect of ocular dominance column width on functional vision is unclear. There is some evidence that this causes a loss in stereoscopic vision (reviewed in [59]). On the

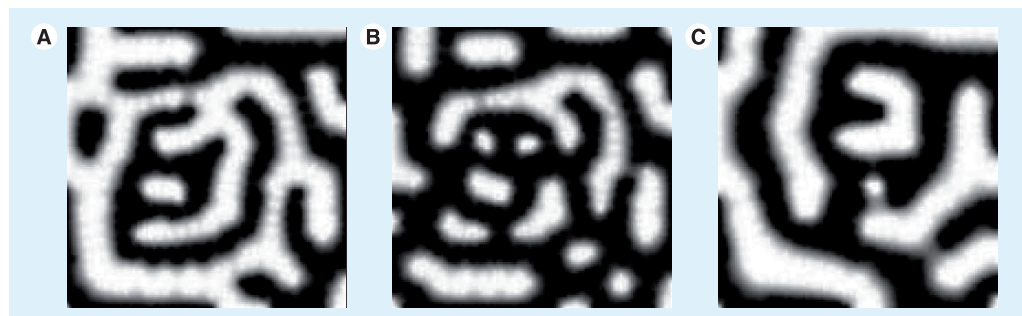
other hand, column spacing is variable between species and even within species without any detectable correlation to functional vision [62,63].

Overall, the activity-dependent models indicate that normal environmental input is critical to the development of normal vision. Abnormal visual experience during development can have profound consequences on the anatomical structure of the visual system. In the cases of deprivation amblyopia and strabismus, computational models shed light on specific pathophysiological rearrangements of neural circuitry that occur in these states and how these may in turn influence functional vision. This emphasizes the importance of early intervention on developmental disorders. Promisingly, it also suggests that if the period of high plasticity can be extended or induced, then a period of normal visual experience may be able to correct the problems resulting from abnormal experience [64].

#### Conclusion & future perspective

If we are indeed aiming to bridge the gap from the laboratory to the clinic with the aid of computational modeling, what needs to be done and what can be achieved?

The first challenge is to engage more closely with clinically relevant conditions. This could be done by routinely incorporating more disease-specific components into models, and ideally also incorporating treatments and responses to treatment. This would essentially involve tailoring models to specific diseases and directly modeling the effects of various potential treatments. For example, in the case of stroke, models of retinotectal map formation could be used to investigate the response to treatment by endogenous regeneration or cell transplantation. This could be done by incorporating the altered geometry of the post-stroke



**Figure 3. Elastic net model of visual cortical map development with abnormal visual experience. (A)** Simulation of a normal ocular dominance map. **(B)** Simulating monocular deprivation with all other model parameters the same as **(A)**. This causes the deprived eye's ocular dominance columns (white) to shrink and the open eye's ocular dominance columns (black) to expand [52,53]. **(C)** Modeling strabismus by reducing the correlation in input to the two eyes models with all other model parameters the same as **(A)**. This increases the width of ocular dominance columns [54].



brain region, any altered molecular gradients and by using neurons with characteristics of regenerated/transplanted cells (e.g., morphology and receptor expression profiles, among others) instead of RGCs. Another important step is having a more closely enmeshed research community, such that computational modeling is familiar for more traditional clinical researchers and that computational neuroscientists are also comfortable interacting with the medical community. This type of interaction can be enhanced by actions such as facilitating access to neuroinformatics, computational modeling tools and code to more experimentally focused researchers, and also by making available more quantitative data for modelers. In this article, we take heed of the lessons learned within the developmental neuroscience community, where it quickly became apparent that computational and theoretical techniques tended to carry little weight unless very closely tied with biological and experimental data.

Currently, predictions and results from computational models of neuronal map development can, for the most part, only be qualitatively compared with experimental results, rather than the more quantitative comparisons that computational neuroscience has the potential to make. This is in part due to many of the models discussed in this article being phenomenological, rather than more detailed biophysical models. Developing these more detailed biophysical models is made more complicated because of the multiscale nature of neural systems and their innate complexity, but also by a lack of the quantitative experimental data that are required

to specify certain parameter values and to tune models. An example of this is the lack of quantitative data on protein levels in molecular gradients that in part determine retinotectal map formation. It would be very useful to be able to model map development under conditions where protein levels are altered by mutations in the genes coding for these proteins; however, this is difficult without measurements of protein copy numbers. On the other hand, more detailed biophysical models that incorporate growth cone advance, axon branching and synapse formation, for example, are desirable. These models could then analyze how gain and loss of function of genes underlying these processes (e.g., *TrkB/BDNF* for branching) affect map development. In phenomenological models, this can only be done coarsely by changing parameter values such as growth cone velocity or branching probabilities. The gathering of more quantitative data and the development of more biophysically based models are important challenges for future work.

Apart from general themes of forwarding our understanding in its own right and augmenting other avenues of scientific enquiry, computational methods can also achieve some unique outcomes. In human studies, there are some experiments that cannot be performed or cannot be performed in the same way as experiments in animal models. However, taking a computational model derived from animal models and equipping it with parameters relevant for humans could provide a method for the final stages of preclinical testing, where the risks of treatment inefficacy are much higher. Computational models also

## Executive summary

### Introduction

- Studying the development of neuronal maps can help us to understand general strategies for how the brain wires itself up.
- Computational modeling is useful in dealing with the scale and complexity of brain development, while allowing accurate predictions to be made when normal development is perturbed.

### Modeling guidance by gradients

- Modeling surgical manipulations in retinotectal maps may inform us as to how gross anatomical disturbances, such as CNS lesions, might affect development, and also strategies for regeneration.
- Modeling genetic manipulations in retinotectal maps offers insight into how developmental disorders might arise from the gain or loss of function of specific genes.

### Modeling map plasticity

- Models of activity-dependent visual map formation have shown how altered environmental conditions during development may lead to reorganization of cortical functional anatomy.

### Future perspective

- Applying computational models of these processes to more specific clinical situations could significantly enhance our understanding of neurological disease.
- When extended to include modeling of responses of disease to treatments such as cell therapy, this could allow otherwise difficult optimization and tailoring of therapies.
- Computational models could provide an important method of performing preclinical studies, as well as for optimizing and individualizing treatment.

offer a way of optimizing and individualizing or tailoring therapies by incorporating individual differences into models and running a number of different scenarios to determine which strategy offers optimal response.

In summary, computational methods are a valuable primary research tool in their own right, but have been hitherto underutilized in many fields, so that the potential for synergism with other fields is only beginning to be tapped. Computational approaches foster mutual productivity with both laboratory and clinical medicine, and may well also provide a critical bridge between the two.

### Bibliography

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▪ of interest

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