Optimal axonal and dendritic branching strategies during the development of neural circuitry

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INTRODUCTION

Neural development is a dynamic process that leads to the establishment of precise connectivity (Ruthazer and Cline, 2004). In vivo time lapse imaging has shown that the formation of axonal and dendritic arbors involves the simultaneous creation and elimination of neuronal branches and synapses (Alsina et al., 2001; Niell et al., 2004; Haas et al., 2006; Meyer and Smith, 2006; Ruthazer et al., 2006; Sanchez et al., 2006). The high rate of branch turnover results in the formation of a number of branches that substantially exceeds the number maintained in the mature brain (Rajan et al., 1999; Meyer and Smith, 2006). These observations suggest that a form of ‘trial-and-error’ search algorithm is implemented by axons and dendrites (Hua and Smith, 2004).

The branching of axons and dendrites depends upon the synapses they form. First, branch survival depends on the presence and strength of the synapses it bears (Niell et al., 2004; Meyer and Smith, 2006; Ruthazer et al., 2006). Second, a spatial bias of the locations of branch points towards synapses has been reported (Alsina et al., 2001; Meyer and Smith, 2006), suggesting that new branches are formed preferentially in the vicinity of synapses. Finally, it has been shown that the rates of branch additions and relocations are affected by neuronal electric activity. These rates increase for retinal axons and decrease for tectal dendrites after an NMDAR antagonist is applied to a developing *Xenopus laevis* retinotectal system (Rajan et al., 1999; Sin et al., 2002). The branching rules, therefore, are different for axons and dendrites. The functional significance of the asymmetry between axons and dendrites is not clear.

Here, we theoretically investigate the role of branching in the formation of neural connectivity. We ask three questions stemming from the experimental findings mentioned above. First, we ask: what is the functional significance of branching, from the standpoint of neural development? Second, we ask why axons and dendrites preferentially form branches in the vicinity of synapses. Third, we address the asymmetry in the branching rules between axons and dendrites that has been revealed in experiments on NMDA receptor blockade. To answer these questions, we have developed a computational model that allows us to compare different branching strategies, based upon the speed of development of target circuitry and the number of erroneous branches formed. We show that three prominent features of axon and dendrite dynamics can be viewed as evolutionary adaptations that save time and minimize the number of errors. We propose experimental tests that can differentiate the various branching strategies used by axons and dendrites.

MATERIALS AND METHODS

We propose a mathematical description of the dynamics of axonal and dendritic arbors, using the theoretical model of stochastic growth. In this model, new branches are created, eliminated, elongated and retracted randomly, with probabilities dependent upon how the energy of the system changes after a segment of a branch is added or removed. The neural connections are formed in the model by creating synapses between the branches of spatially overlapping axons and dendrites. Similarly to branches, the synapses can be created, maintained, or retracted, in a stochastic manner, depending on the energy change that results from these actions. We simulate the developmental process using the Metropolis Monte Carlo algorithm. On each Monte Carlo step, one of the six changes is attempted: formation, elimination, extension or retraction of branches, or creation or elimination of synapses. The attempts for every possible configuration change are equally likely. Thus we attempt to form a synapse between every pair of overlapping axonal and dendritic branch segments with the same probability but the acceptance probabilities for these attempts are different. Similarly, the attempts to eliminate every existing synapse are equally likely but their survival probabilities differ. The acceptance probabilities for every configuration change depend upon the change in the energy function that occurs during these processes, ΔE, and are given by:

\[ p = \frac{1}{2} + \frac{1}{2} \tanh(-2\Delta E). \]
Acceptance probability is smaller/larger than 1/2 if the underlying change in the energy function is positive/negative. As a result, the system performs the stochastic minimalization of its energy. The exact form of the energy function defines both the dynamics of the arbors and the final connectivity configuration (Tsigankov and Koulakov, 2006).

The energy function incorporates the affinity that exists between connected cells and the configuration of the arbors. It contains additive contributions from axonal and dendritic branches and synaptic connections:

\[ E = E_{\text{ax.arb}} + E_{\text{den.arb}} + E_{\text{syn}}. \]

The contribution from arbor branches to the energy function is positive, meaning that there is a cost associated with the formation of branches. We also suggest that the synaptic contribution is negative, reflecting the tendency of neurons to form synapses. This contribution is different in magnitude for every synapse, and depends upon interactions between the connected cells. Combined together, these contributions reflect the synaptotropic hypothesis (Hua and Smith, 2004; Meyer and Smith, 2006), since the cost of a branch bearing a synapse is reduced, and such a branch is more stable than a branch without synapses.

The synaptic part of the energy function depends on the connectivity between axons and dendrites, given by the weight matrix \( W \), which is step-wise updated according to the evolution of axonal and dendritic arborizations during the simulation. We previously have studied the form of the synaptic energy function for the system of point-like dendrites and a single synapse per axon (Tsigankov and Koulakov, 2006). Here, we reformulate it for the system of axons and dendrites with spatially distributed arbors that have multiple synaptic connections. The weight matrix \( W \) consists of the integer numbers representing the number of synapses made between \( p \) tectal dendrite and \( j \) retinal axon anywhere on their arbors. There are three additive terms in the synaptic part of energy, representing different contributions:

\[ E_{\text{syn}} = E_{\text{chem}} + E_{\text{act}} + E_{\text{comp}}. \]

The chemoaffinity term depends upon the interactions between the chemical labels expressed on axons and dendrites. For the retinocollicular system, this is given by the expression levels of EphA and EphB receptors on axons, and of ephrinA and ephrinB ligands on dendrites:

\[ E_{\text{chem}} = \sum_{\alpha \beta} M_{\alpha \beta} \sum_{ij} l_{ij} W_{ij}^\alpha R_{ij}^\beta. \]

Here, indices \( \alpha \) and \( \beta \) denote the chemical labels; the matrix \( M_{\alpha \beta} \) defines the affinities for receptor/ligand pairs; and \( l_{ij} \), \( R_{ij}^\beta \) are the concentrations of ligand \( \alpha \) and receptor \( \beta \) on the \( p \) \( \text{th} \) dendrite and the \( j \) \( \text{th} \) axon, respectively. Throughout the paper, we have adopted the simplest description, where we distinguish only two types of receptor and ligand expressed in the gradients in perpendicular directions in both the target and retina; for details see (Koulakov and Tsigankov, 2004; Tsigankov and Koulakov, 2006).

The activity-dependent term is obtained from the Hebbian learning rule and has the form:

\[ E_{\text{act}} = -\frac{1}{2} \sum_{ij} W_{ij} D_{ij}. \]

Here, \( D_{ij} \) is the correlation of electrical activity between tectal dendrite \( i \) and retinal axon \( j \). The correlations \( D_{ij} \) change over the course of development and depend on the weight matrix \( W \). They arise from the correlations of activity between retinal axons that are driving the activity of tectal dendrites, through the following expression:

\[ D_{ij} = \sum_{lm} W_{im} U_{i} C_{jm}. \]

\( C_{jm} \) is the correlation of activity between retinal axons \( j \) and \( m \) that emerges from the spontaneous retinal waves of activity or early visual experience, and is assumed to be unvaried during the development. \( U_{i} \) is the strength of the lateral connections between tectal cells \( i \) and \( l \) and is also assumed to be constant. Both these functions are assumed to depend only upon the spatial separation that exists between the origins of axons \( j \) and \( m \) in retina and dendrites \( i \) and \( l \) in tectum, respectively and are given by (Tsigankov and Koulakov, 2006):

\[ C_{jm} = \exp \left(-\frac{|j - m|}{a}\right), \quad U_{ij} = \gamma \exp \left(-\frac{|i - j|^2}{2R^2}\right). \]

The last term \( E_{\text{comp}} \) in the synaptic part of the energy function describes axonal and dendritic competition and ensures the tendency of neurons to form synapses. This term is negative and depends upon the number of synapses made by each neuron, similarly to what was proposed for the system of neuromuscular junctions (Barber and Lichtman, 1999). If the energy gain decreases with an increase in the total number of synapses per cell, then cells with fewer synapses have a competitive advantage to form new synapses. As a result, every axon and every dendrite maintains approximately the same number of synapses. In our model, we used the following form of energy contribution with this property that has the least number of parameters:

\[ E_{\text{comp}} = -b \sum_{j} \left( \sum_{l} W_{ij} \right)^{1/2} + b_{2} \sum_{j} \left( \sum_{l} W_{ij} \right)^2. \]

The sums in the brackets give the number of synapses made by axons and dendrites respectively; \( b_{1} > 0 \) and \( b_{2} > 0 \) are the constants defining the average number of synapses per cell and overall strength of competition.

The arbor parts of the energy function that describe the costs for axonal and dendritic branching are given by:

\[ E_{\text{ax.arb}} = \sum_{\alpha \beta} \mu_{\alpha \beta} l + \sum_{\alpha \beta} \mu_{\alpha \beta}^{\alpha \beta}, \quad E_{\text{den.arb}} = \sum_{\alpha \beta} \mu_{\alpha \beta} l + \sum_{\alpha \beta} \mu_{\alpha \beta}^{\alpha \beta}. \]

Here the first sum over axonal and dendritic branches yields the cost for the branch with length \( l \), and the second sum represents the additional cost for the formation of the branch points. We assume that the costs of the branches per unit length \( \mu_{\alpha \beta} \) and \( \mu_{\alpha \beta}^{\alpha \beta} \) are constant and are taken to be the same for axons and dendrites, in order to ensure symmetry between axons and dendrites.

In contrast, we vary the costs of branch points \( \mu_{\alpha \beta} \) and \( \mu_{\alpha \beta}^{\alpha \beta} \) and use different forms for different branching strategies. If axons or dendrites use synapse-independent branching Strategy 1, we use the same branching cost everywhere on the arbor:

\[ \mu_{\alpha \beta} = \mu_{\alpha \beta}^{\alpha \beta} = \text{const}. \]
For synaptotropic branching Strategy 2, we use

\[ \mu_{bp} = \frac{\mu_0}{n_s}, \]

where \( n_s \) is the number of synapses on the arbor in the same unit square with a branch point. Thus it is easier (less costly) to create branch points at locations that contain several synapses.

Finally, for Hebbian branching Strategy 3, the cost has the form

\[ \mu_{bp} = \sum_{i,j} \frac{\mu_0}{D_{ij(i,j)}}. \]

Here, the sum is taken over synapses made on branches in the same unit square with a branch point, and \( D_{ij} \) is the correlation of the electrical activity between dendrite \( i \) and axon \( j \) connected with these synapses. This form makes it less costly to create branch points at synapses with correlated activity.

In this description, for every branching strategy used, we vary the overall amount of branching by changing the single parameter \( \mu_0 \). If it equals to zero then there is no additional cost for formation of new branches and the branching is the most elaborate. If it tends to infinity there is essentially no branching and each arbor has only one branch tip. We then change parameter \( \mu_0 \) to investigate the role of branching on the performance of developmental algorithm for every branching strategy.

To compare the performance of different branching strategies we vary every parameter in the branching part of the energy function and keep every parameter in the synaptic part of the energy function constant. For every set of parameters in the energy function we have averaged over 100 random initial conditions. More precisely we start with axons entering the target from the anterior edge, randomly arranged along dorsal ventral axis with a single branch tip representing the point like initial arbors on the edge of the target. The initial conditions for dendritic arbors are point like precursors of new branches and the branching is the most elaborate. If it tends to infinity there is essentially no branching and each arbor has only one branch tip. We then change parameter \( \mu_0 \) to investigate the role of branching on the performance of developmental algorithm for every branching strategy.

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For all 9 combinations of branching strategies we used 10 different values for both axonal and dendritic branching cost, thus 10 × 10 sets of 100 simulations with different initial conditions. Thus the comparison of different branching strategies is obtained from almost 100,000 simulation runs each taking about 4 h each on a high-performance computing cluster.

RESULTS

FORMATION OF RETINOTECTAL CONNECTIVITY IS INFLUENCED BY SEVERAL FACTORS

The projections from the retina to optic tectum often are used as a model system to study the development of neural circuitry. While establishing this projection, the axons of retinal ganglion cells (RGC) arrive at the optic tectum and make topographically-ordered connections with dendrites in the target. This implies that axons originated from neighboring points in retina terminate at proximal tectal dendrites, thus preserving a topographic representation of the visual world. This form of connectivity is often called a ‘topographic map’.

Several factors contribute to the formation of topographic maps. A set of chemical labels is thought to encode coordinates in the retina and tectum (McLaughlin and O’Leary, 2005). Thus, the nasal–temporal (NT) axis in the retina is encoded by the graded expression of EphA receptor tyrosine kinases on RGC axons (Flanagan and Vanderhaeghen, 1998). The recipient anterior–posterior coordinate in the tectum is established by graded expression of ephrin-A, which can bind to and activate EphA receptors, and transmit to RGC axons information about their position in the target. A similar chemical labeling system, involving an EphB/ephrin-B receptor/ligand pair, exists for the mapping of the dorso-ventral (DV) axis of the retina to the medial-lateral (ML) direction of the optic tectum. The two approximately perpendicular expression profiles appear to be in place to bias axonal branching in the direction of the correct termination site (Lemke and Reber, 2005).

The precision of axonal projections is further enhanced through mechanisms based upon correlated neural activity (Ruthazer and Cline, 2004). Due to correlations in the visual stimuli or the presence of retinal waves during development, electrical activity is similar in neighboring RGC axons in the retina (McLaughlin et al., 2003). Correlated activity, therefore, provides additional information about relative positions of axonal origins in retina, and contributes to the precision of topographic projection (McLaughlin et al., 2003; Peifferberger et al., 2005). Finally, competition between axons in the target is thought to be an important factor in the formation of the map (Hua et al., 2005). The interplay of chemo-specificity, activity-dependent factors, and competition results in the formation of connectivity that sometimes can achieve single-cell precision (Hamos et al., 1987).

Precise connectivity requires spatial overlap between an axonal arbor and the arbors of appropriate dendrites. This is because the synapses can be made only between segments of axonal and dendritic branches that are in close proximity; i.e., have the potential to form connectivity (Stepanyants and Chklovskii, 2005). Thus, before appropriate axons and dendrites are connected, they must solve the search problem, which implies that axons have to arrive in the area of appropriate dendrites. This task is achieved by creating and eliminating new axon and dendrite branches (Alsina et al., 2001; Ruthazer et al., 2003; Meyer and Smith, 2006). The exact rules by which axonal and dendritic branching occurs and their functional significance are not known. Here, we identify the axonal and dendritic branching rules that implement the optimal search strategy, based upon the conservation of material and time.

BRANCHING ALLOWS FOR FASTER FORMATION OF TARGET CONNECTIVITY

To compare various search strategies, we have developed a computational model for the stochastic growth of axonal and dendritic arbors. This model describes the behavior of RGC axons that form synapses with a matching set of tectal dendrites (Figure 1). Both axons and dendrites can create, eliminate, extend, and retract their branches. In addition, an axon and a dendrite with overlapping arbors can form a new synapse or eliminate the existing one. All
these events occur stochastically, with probabilities biased towards the formation of a topographic map. A conventional method to describe such a bias is to introduce an energy function (Fraser and Perkel, 1990; Koulakov and Tsigankov, 2004; Tsigankov and Koulakov, 2006). With this approach, the stochastic events of creation and elimination of new branches and synapses are biased in the direction of an overall decrease in energy function. The energy function includes both contributions from the binding and activation of chemical labels, such as Eph receptors, and the contribution arising from the correlations in electric activity that exist between retinal axons (see Materials and Methods for details). The exact form of the energy function defines both the dynamics of the arbor formation and the structure of the ultimately established connectivity.

Using this approach, we investigated different branching strategies available to axons and dendrites. One possibility is that formation of new branches occurs everywhere on the arbor with the same probability, independent of the locations of synapses. We call this type of branching strategy synapse-independent or Strategy 1 (Figure 2). Another option is to preferentially form new branches in the vicinity of existing synapses. This strategy is called synaptotropic or Strategy 2. Finally, we considered the possibility that branches are formed preferentially in the vicinity of synapses with correlated pre- and post-synaptic activity. This form of branching rules is called Hebbian or Strategy 3. To implement these branching rules, we introduced the cost of the formation of a branch point that differs for the different strategies. This cost was included in the cost function, as described in Materials and Methods. Thus for strategies 2 and 3 we set the probability of branching at non-synaptic sites to zero. We show below that every branching strategy is capable of producing the required connectivity, but their efficiencies differ.

As measures of the efficiency of different branching strategies, we used the time and the total number of branches formed (dendritic and axonal) that are required to achieve target mapping precision. The mapping precision is determined by the average mapping error of every synapse as compared to the perfect topographic map. Thus for every synaptic connection we calculate the mismatch between the position of the axonal origin (RGC body) and the position of post-synaptic cell body in the target. We propose that a more efficient developmental mechanism should allow for the formation of required connectivity using less physical time and less material for creating and elongating neuronal branches. These two separate criteria are not independent and cannot be minimized simultaneously. In fact, we show that there is a trade-off between time and the number of branches: if connectivity is formed faster, it uses a greater number of branches, and vice versa.

To illustrate the trade-off between time and the number of branches formed, we consider the case in which both axons and dendrites implement synapse-independent branching (Strategy 1). One of the parameters that can be varied in the model is the probability of forming a new branch point on an axon. If this probability is small, axon arbors have a simple structure with few branch points (see inset on Figure 3A). Nevertheless, the mapping error is decreased over time and can always reach the target value (Figure 3A), even if virtually no branches are formed. If the
branching probability is increased, the arbor structure becomes more complex with more branch tips. This results in a faster convergence of map precision, because multiple branches are searching for the correct partners in parallel. At the same time, higher branching frequency results in a greater number of transient branches formed when a 15% level of mapping precision is reached. A mapping precision level of 15% implies that the standard deviation of synapse location is 15% of the map size. Each circle in (B) corresponds to a circle in (A) and shows the time and the number of branches formed when a 15% level of mapping precision is reached. A set of curves similar to that shown in (B) is obtained when both axonal and dendritic branching probabilities are varied. Points corresponding to the same axon/dendrite branching probabilities are connected by solid/dashed lines. The lower boundary of the collection of these points (blue line in (C)) gives the performance boundary for this combination of branching strategies used by axons and dendrites. These findings suggest a possible functional role for axonal branching, as an effective parallel search algorithm that allows for the conservation of time during development.

### SYNAPTOTROPIC BRANCHING MINIMIZES THE TOTAL NUMBER OF BRANCHES FORMED

We next optimized the total number of transient branches formed for varying frequencies of both axonal and dendritic branching if they use synapse-independent branching Strategy 1. To this end, we obtained a series of curves similar to those shown in Figure 3B for different values of dendrite branching frequency. The lower boundary (blue in Figure 3C) of the collection of these curves defines the optimal performance of this combination of branching strategies (Strategy 1 for axons and Strategy 1 for dendrites). This performance boundary depicts the minimal number of branches that are required to establish the connectivity with given level of precision after a given period of physical time.

To compare the efficiency of different branching strategies, we obtained the performance boundaries for all 9 combinations of strategies used by axons and dendrites; i.e., strategies 1 through 3 for axons and 1 through 3 for dendrites (Figure 4). The combination of branching strategies with the lowest boundary allows for the most effective formation of circuitry.

One of the findings evident from Figure 4 is that both synaptotropic strategies (activity-dependent and -independent) generally outperform the synapse-independent strategy. Thus, if both axons and dendrites implement synapse-independent branching (Figure 4, top left panel), the performance boundary represents the worst solution. This is because the performance boundary for this case is higher than all eight other performance boundaries. The same conclusion follows from examining the number of branches averaged along the performance boundary (Figure 5). The three bars on the left, representing the synapse-independent strategy implemented by axons, are higher than all others, reflecting the inefficiency of the synapse-independent branching rule. A similar conclusion is reached comparing the dendritic strategies (Figure 5). Therefore, for both axons and dendrites, synaptotropic branching improves the performance of the search algorithm over synapse-independent rules. This finding suggests a functional role for the spatial correlations between the branch points and synapses observed among axons (Alsina et al., 2001; Meyer and Smith, 2006). According to our
results, the increased probability to form a branch point at an existing synapse (synaptotropic branching) allows for the establishment of required connectivity using fewer transient branches.

**THE OPTIMAL BRANCHING RULES ARE DIFFERENT FOR AXONS AND DENDRITES**

What is the optimal synaptotropic branching strategy? In our simulations (Figures 4 and 5) the most efficient combination of branching rules is achieved when axons implement Strategy 2 (synaptotropic), while dendrites implement Strategy 3 (Hebbian). The performance boundary for this combination of branching rules (red in Figure 4) is lower than all other eight curves. This implies that the optimal branching rules are different for axons and dendrites. To minimize the total amount of material spent on transient branches, axons branch in the vicinity of existing synapses. But the frequency of such branching does not depend upon the correlations in patterned pre- and post-synaptic activity. At the same time, optimal dendritic branching is achieved when new branches are formed more likely in the vicinity of synapses with higher levels of correlated activity.

If axons and dendrites implement different branching strategies, they can react differently to activity blockade. Consequently, our findings could explain the differences in the reaction to the blockade of NMDA receptors observed in developing retinotectal projections of *Xenopus laevis* (Rajan et al., 1999). To mimic the blockade of NMDA receptors in the model, we set the activity correlations to zero during simulations. We used the optimal combination of synaptotropic branching strategies (Strategy 2 for axons and...
Strategy 3 for dendrites). We observed that, for axons, both the rate of addition and retraction of branches increase after activity blockage (Figure 6). This is because, while the frequency of axonal branching does not change at any location on the arbor if axons implement activity-independent branching rules, the area occupied by the axonal arbor increases due to the loss of map precision induced by the activity block. Hence, larger arbors produce an increased rate of branch turnover.

At the same time, the rates of formation and elimination of dendritic branches are decreased after the levels of activity are reduced. This is a consequence of the activity-dependent branching rule (Strategy 3) implemented by dendrites, because the frequency of branching in the vicinity of the synapses is reduced. Therefore, in our model, the behavior of axons and dendrites is different, due to the differences in the optimal branching strategies. The experimentally-observed asymmetry in the reaction of axons and dendrites to NMDA receptor blockade could be a manifestation of different branching strategies being implemented by axons and dendrites in developing brain.

DISCUSSION

During neural development, axons solve the problem of locating the dendrites of appropriate cells and creating synapses with them. Finding appropriate synaptic partners occurs in the presence of other axons and dendrites, and is influenced by several factors, such as molecular labels and correlations in electric activity. How can precise connectivity be formed in the developing brain under the constraints of limited resources, like time and material? It is common to benchmark different algorithms based upon the number of steps that they require to solve particular problems. The algorithm that solves a given problem with the smallest number of iterations usually is implemented. In this study, we benchmarked various algorithms for axonal and dendritic branching, and derived the branching rule that solves the problem of forming connectivity with the smallest number of steps. We assumed that the elementary step in the development of brain circuitry is the formation or elimination of an axonal or dendritic branch. We, thus, compared different branching rules, in terms of the total number of branches needed to form target circuitry. We assumed that the search strategy that allows for the location of targets using the fewest number of transient branches is implemented in the developing brain. This point is similar to the wiring optimization argument (Chklovskii and Koulakov, 2004).

We centered our studies on the role of synapses in the development of connectivity. In the developing retinotectal projection, synapses are formed and eliminated, as axons (Alsina et al., 2001; Meyer and Smith, 2006; Ruthazer et al., 2006) and dendrites (Niell et al., 2004; Haas et al., 2006; Sanchez et al., 2006) refine their connectivity. The role of synapses in this process may be diverse: they stabilize existing axon branches (Meyer and Smith, 2006) in a way that is dependent upon synaptic maturation (Ruthazer et al., 2006) and may contribute to the process of forming new branches (Meyer and Smith, 2006). The latter possibility is highlighted by strong correlations between the locations of synaptic puncta and the branch points observed for both axons and dendrites (Alsina et al., 2001). The effect of synapses on branch formation and elimination sets the basis for the synaptotropic hypothesis, according to which the formation of axonal and dendritic arbors is instructed by synapses. Here, we investigated the functional significance of the instructive role of synapses in the formation of new branches. To this end, we compared the branching rule that does not take into account the
The hypothesis that axons and dendrites use different branching strategies is consistent with existing experiments on the blockade of NMDA receptors (Rajan et al., 1999). Our modeling shows that axons accelerate the formation and elimination of new branches, while the branching of dendrites slows down under conditions of reduced correlated activity (Figure 6). The latter finding is a direct result of the instructive role of activity in dendritic, but not axonal branching. In our model, acceleration of axonal branching is a result of removing the activity-dependent stabilization of synapses that exists in the condition of NMDA receptor blockade, which ultimately leads to more dynamic axons. Our results permit us to interpret the asymmetry that transpires in the changes occurring in the dynamics of branch formation, under the conditions of NMDA receptor blockade (Rajan et al., 1999).
We now propose ways in which this asymmetry in branching strategy can be further tested experimentally. We suggest that, if an NMDA antagonist is applied to developing optic tectum, the spatial correlations between axonal branch points and synapses should remain the same as in the control case. In contrast, the correlations between the locations of dendritic branch points and synapses should be reduced after NMDA blockade. We illustrate this prediction in Figure 8, where we measure the fraction of synapses that are located in the vicinity of axonal and dendritic branch points before and after activity block in the model. Such observations recently were made in *Xenopus* for both axons (Meyer and Smith, 2006; Ruthazer et al., 2006) and dendrites (Niell et al., 2004; Sanchez et al., 2006) without the application of NMDA antagonists.

We propose the functional role of axonal and dendritic branching from a developmental point of view. With this approach, branching is required to speed up the developmental process. Acceleration in the location of correct targets due to branching is accomplished via the use of a parallel search algorithm. Another possibility is that branching is required to optimize the functionality of the mature circuit; for example, to improve the signal transmission properties of the network by minimizing the path length and attenuation of the signal between connected neurons (Wen and Chklovskii, 2005), or to perform nonlinear computation of the inputs in the dendritic arbor (Poirazi et al., 2003).

In conclusion, we studied computationally-different branching rules for axons and dendrites within a developing retinotectal projection. Our studies suggest that branching serves to accelerate the formation of neuronal circuitry through the use of the parallel search of targets. We argue that the observed abundance of synapses on branch points for both axons and dendrites serves to minimize the number of erroneous transient branches. We also explain the asymmetry that is observed experimentally in the reaction to NMDA receptor blockade between axons and dendrites. We suggest that this asymmetry stems from the branching of dendrites, but not axons, being directly instructed by correlations in electric activity. Finally, we propose experimental tests that could verify that optimal branching rules, indeed, are being implemented in developing brain.

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**REFERENCES**

Alisina, B., Vu, T., and Cohen-Cory, S. (2001). Visualizing synapse formation in arboring optic axons in vivo: dynamics and modulation by BDNF. *Nat. Neurosci.* 4, 1093–1101.

Barber, M. J., and Lichtman, J. W. (1999). Activity-driven synapse elimination leads paradoxically to domination by inactive neurons. *J. Neurosci.* 19, 9975–9985.

Chklovskii, D. B., and Koulakov, A. A. (2004). Maps in the brain: what can we learn from them? *Annu. Rev. Neurosci.* 27, 369–392.

Ewald, R. C., Van Keuren-Jensen, K. R., Aizenman, C. D., and Cline, H. T. (2008). Roles of NR2A and NR2B in the development of dendritic arbor morphology *in vivo*. *J. Neurosci.* 28, 850–861.

Flanagan, J. G., and Vanderhaeghen, P. (1998). The ephrins and Eph receptors in neural development. *Annu. Rev. Neurosci.* 21, 309–345.

Fraser, S. E., and Perkel, D. H. (1990). Competitive and positional cues in the patterning of nerve connections. *J. Neurobiol.* 21, 51–72.

Haas, K., Li, J., and Cline, H. T. (2006). AMPA receptors regulate experience-dependent dendritic arbor growth *in vivo*. *Proc. Natl. Acad. Sci. U.S.A.* 103, 12127–12131.

Hamos, J. E., Van Horn, S. C., Raczkowski, D., and Sherman, S. M. (1987). Synaptic circuits involving an individual retinogeniculate axon in the cat. *J. Comp. Neurol.* 259, 165–192.

Hua, J. Y., Smear, M. C., Baier, H., and Smith, S. J. (2005). Regulation of axon growth *in vivo* by activity-based competition. *Nature* 434, 1022–1026.

Hua, J. Y., and Smith, S. J. (2004). Neural activity and the dynamics of central nervous system development. *Nat. Neurosci.* 7, 327–332.

Koulakov, A. A., and Tsigankov, D. N. (2004). A stochastic model for retinocollicular map development. *BMC Neurosci.* 5, 30.

Lemke, G., and Reber, M. (2005). Retinotopic mapping: new insights from molecular genetics. *Annu. Rev. Cell Dev. Biol.* 21, 531–580.

McLaughlin, T., and O’Leary, D. D. (2005). Molecular gradients and development of retinotopic maps. *Annu. Rev. Neurosci.* 28, 327–355.

McLaughlin, T., Torborg, C. L., Feller, M. B., and O’Leary, D. D. (2003). Retinotopic map refinement requires spontaneous retinal waves during a brief critical period of development. *Neuron* 40, 1147–1160.

Meyer, M. P., and Smith, S. J. (2006). Evidence from *in vivo* imaging that synaptogenesis guides the growth.
and branching of axonal arbors by two distinct mechanisms. *J. Neurosci.* 26, 3604–3614.

Niell, C. M., Meyer, M. P., and Smith, S. J. (2004). *In vivo* imaging of synapse formation on a growing dendritic arbor. *Nat. Neurosci.* 7, 254–260.

Pfeifferberger, C., Cutforth, T., Woods, G., Yamada, J., Renteria, R. C., Copenhagen, D. R., Flanagan, J. G., and Feldheim, D. A. (2005). Ephrin-As and neural activity are required for eye-specific patterning during retinogeniculate mapping. *Nat. Neurosci.* 8, 1022–1027.

Poirazi, P., Brannon, T., and Mel, B. W. (2003). Arithmetic of subthreshold synaptic summation in a model CA1 pyramidal cell. *Neuron* 37, 977–987.

Rajan, I., Witte, S., and Cline, H. T. (1999). NMDA receptor activity stabilizes presynaptic retinotectal axons and postsynaptic optic tectal cell dendrites *in vivo*. *J. Neurobiol.* 38, 357–368.

Ruthazer, E. S., Akerman, C. I., and Cline, H. T. (2003). Control of axon branch dynamics by correlated activity *in vivo*. *Science (New York, NY)* 301, 66–70.

Ruthazer, E. S., and Cline, H. T. (2004). Insights into activity-dependent map formation from the retinotectal system: a middle-of-the-brain perspective. *J. Neurobiol.* 59, 134–146.

Ruthazer, E. S., Li, J., and Cline, H. T. (2006). Stabilization of axon branch dynamics by synaptic maturation. *J. Neurosci.* 26, 3594–3603.

Sanchez, A. L., Matthews, B. J., Meynard, M. M., Hu, B., Javed, S., and Cohen Cory, S. (2006). BDNF increases synapse density in dendrites of developing tectal neurons *in vivo*. *Development* 133, 2477–2486.

Sin, W. C., Haas, K., Ruthazer, E. S., and Cline, H. T. (2002). Dendrite growth increased by visual activity requires NMDA receptor and Rho GTPases. *Nature* 419, 475–480.

Stepanyants, A., and Chklovskii, D. B. (2005). Neurogeometry and potential synaptic connectivity. *Trends Neurosci.* 28, 387–394.

Tsigankov, D. N., and Koulakov, A. A. (2006). A unifying model for activity-dependent and activity-independent mechanisms predicts complete structure of topographic maps in ephrin-A deficient mice. *J. Comput. Neurosci.* 21, 101–114.

Wen, Q., and Chklovskii, D. B. (2003). Segregation of the brain into gray and white matter: a design minimizing conduction delays. *PLoS Comput. Biol.* 1, e78.

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