Percolation model of axon guidance

Gaetano L. Aiello and Valentino Romano

Universita' di Palermo - Dipartimento di Fisica
Viale delle Scienze, Ed. 18, 90128, Palermo - Italy

Abstract. In the developing brain neurons interconnect via the action of molecules that guide the axon to its targets, thus allowing the proper wiring scheme to emerge. It is not fully understood whether the underlying mechanism is wholly deterministic or not. The existence of "choice-points" and "decision-regions" suggests that options are available to the growth cone. The guidance mechanism is here simulated by equating the axonal trajectory to that of a trickle of ground water sipping through a bed of sand. Decision regions are implemented by assigning each site of the percolation lattice a set of probabilities ruling the possible moves.

1 Introduction

In the fully developed brain of vertebrates the number of connections among neurons are immensely complicated. What we see is the end-product of multiple genes acting in concert, along with intense neural activity. Functional specificity, however, is evident when the neuronal structure is in the making. In the embryonic brain connections are influenced by cellular and extra-cellular substrata [1] and guidance cues [2], the latter being special molecules strategically located in the environment, which tell the growth cone whether to extend or to retract, to veer or to split. Primitive glia processes pave the road for the axon of the first neurons - the "pioneers"- so that other neurons – the "followers" - can join the path. In insects, pioneers are clearly identifiable as their axons always originate from the very same cells. A rigid blueprint is typical of neural structures involving a limited number of neurons, or whenever the guidance cues are abundant, the distances between cells are short, and the options for path-finding are scarce. In vertebrates, however, what is actually identifiable is a *set* of neurons projecting their axons to a corresponding set. In our model the focus is on the genesis and maturation of a network of pioneer neurons.

The density of guidance cues are higher in the embryo, where a more accurate guidance is necessary for the safe development of the basic structures. There is no room for recovery in the embryonic brain: accuracy is mandatory. Necessity, however, does not rule out chance: despite the complexity of the cytoskeleton dynamics, the growth cone is blind as for where to go. It can only probe blind-folded the environment with its filipodia in search of the right path, much like a blind person with a cane. Wrong decisions do occur, and they are undone through axonal retraction – a physical re-uptaking of biological material into the growth cone [3] – and through "pruning" [4] of unused, stagnating branches. Right decisions are embedded in the environment under the form of navigational cues. The shape of the axon – stereotyped as it can be – is the result of guidance cues, casuality, and pruning altogether.

Although the genetic blueprint is still obscure, we know at least the essentials of the cytoskeleton dynamics leading to the basic network. The reason why an axon splits at an obstacle [5], however, is hardly explained in terms of guidance cues alone.

Branching has a pivotal role in determining the network connectivity, inasmuch as it provides multiple targets to a pioneer neuron. Branching, like pruning, is likely to be *functional*. Both pruning and branching lie at the ends of allegedly similar process: pruning results from a loss of functionality, branching would be the response to an excess of "traffic", like a shunt detouring the activity along a different pathway. Both processes would occur at a later stage, when functionality takes over the genetic blueprint. How "late" branching would occur is beyond the scope of the model. We venture on assuming an evolutionary-type mechanism where axons are continuously generated and then selected/pruned based on the network demands.

The percolation model is proposed as a suggestive metaphor aimed to cast further insight into the relevant mechanisms underlying the genesis and maturation of a neuronal network.

2 *Percolating* axon

The trajectory of a trickle of ground water sipping through a bed of sands, with all its deflections and branching, looks as much stereotyped and reproducible as the trajectory of the growth cone in its erratic motion toward a target. In this percolation model, pioneer neurons play the "sources", their targets the "sinks". Sources and sinks lie, respectively, on the upper and lower edges of a 2D percolation lattice (Fig. 1). Obstacles (*filled in black*) act as guidance molecules, placed at random through the lattice. The direction of percolation is downwards, simulating a chemical gradient that pushes the axon down to the targets.
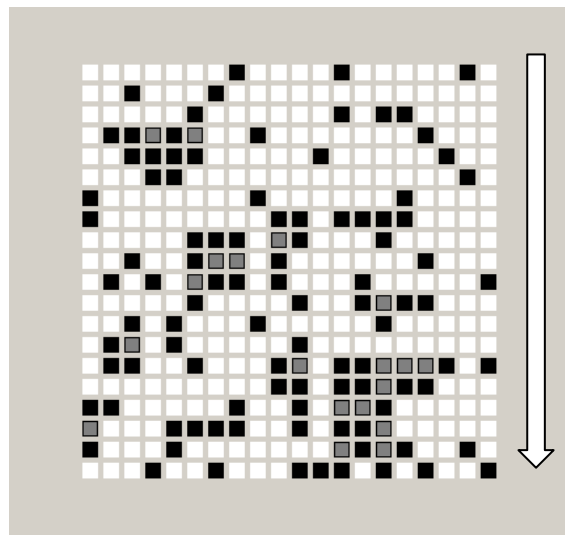

Fig. 1: Screen image of a 20×20 percolation lattice with 300 holes. Sources and sinks lay on the first and last line of the array. Points of stagnation are filled in gray.

The percolation lattice in this model is somewhat different from those found in cluster theory [6]. In general, a 2D lattice is said to "percolate" if there exist a cluster of empty sites spanning all *four* edges of the lattice. In our case, the condition is less stringent, as only the upper and lower edges matter. Paths that percolate elsewhere are considered stagnating.

Although the percolation model closely mimic the motion of the growth cone, substantial differences in the guidance mechanism exist. Unlike a trickle of water, the growth cone is effectively guided via specific navigational cues. Some non-mechanical interaction between neuron and "guide-post" cells must exist, with "choice points" responsible for deflections. What determines a choice, however, is still unclear. Thus, guide-post cells cannot be equated *tout-court* to grains of sand, no more than an axon can be equated to a trickle of water. To better emulate the guidance mechanism, each site of the lattice is loaded with a set of probabilities about the next move. The probabilities reflect the local morphology (the landscape). Thus, each location becomes a "decision region" about whether to move (grow) or to retract (re-uptake), to stop growing or to veer. The decision regions are a unique algebraic add-on to a percolation cluster, inasmuch as it provides specific guidance cues to the axon.

3   Methods and procedures

A 20×20 lattice is initially filled solid with obstacles, then a number $N_0 \leq 20$ of obstacles, chosen at random, are removed. As a result, N_0 holes – randomly distributed – are created, yielding a *porosity* $\rho = N_0/400$. The probability of finding a percolating clusters of holes increases with ρ. Lattices with $\rho = 25\%$ show no percolating paths, while at $\rho = 75\%$ (Fig. 1) there are many percolating paths. Our interest is focused in lattices with relatively large porosity, say, 75%, for it allows many pioneers to express percolating paths. This makes it possible to find the *distribution* of percolating paths among pioneers, which – in turn – allows us to measure the *strength* of the pioneer-target "junction".

Navigation through the lattice requires a "nautical chart" and a set of rules for handling the "wheel". Table I shows the possible actions, each with its probability.

z=1+Random(6)	1	2	3	4	5	6	k
Right/Down	R	R	D	D	D	D	3
Left/Down	L	L	D	D	D	D	5
Left/ Right	R	R	R	L	L	L	6
Left/Right/ Down	R	L	D	D	D	D	7

Table I : How the probabilities in the decision regions are implemented (See text).

For each of the four options, a number z from 1 to 6 is sorted. Thus, in the case of Right/Down, if $z < 3$ is sorted then R is chosen, else Down is chosen. "Down" (D) has the highest probability (4/6), which accounts for the direction of the chemical

gradient. A number k from 0 to 7 is associated to each options. A value k=0 means no-option, k=1 refers to Down Only, k=2 to Right Only, k=4 to Left Only.

4   Quasi-random navigation

Given a pioneer and its potential targets, the actual axonal trajectory and exact destination are unknown *a priori*. It all depends on the decisions taken "at the wheel" during navigation, each decision coming with its own probability. Fig. 2 shows the nautical chart for the lattice of Fig.1. All information about a safe cruising are in here.

```
1 1 0  1 1 1 0  -  1 1 1 1  -  1 1 1 1 1  -  1
3 5 -   3 7 4  -  3  7 7 7 7 6 7 6 6 7 7 7 5
3 6 6  7 4  - 3 7  6 7 7 5  - 1 -  - 2 7 7 5
1 -  -  0  -  2 7 5  -  3 7 6 7 7 7 5  -  2 7 5
3 5 -  -  -  - 3 7 7  7 5  -  3 7 7 7 5  -  2 5
2 7 5 -  -  3 7 7 6 7 7 7  7 7 7 6 7 5  -  1
-  3 7 7 7  7 7 5  -  2 6 7  6 6 4  - 3 7 7 5
-  3 7 7 7  6 6 6 5  -  -  1  -  -  -  - 3 7 7 5
3 7 6 7 5  -  -  - 3 4  -  3 7 5  -  3 6 7 7 5
3 4  -  2 5  -  2 6 5  -  3  7 7 6 7 5  - 3 7 4
1 -  0  - 3  4  -  - 1  -  2  7  5  - 3 6 6 7 5  -
3 7 6 7 4  -  3 7 6 5  -  3  5  - 0  -  -  - 3 7 5
3 4  - 1  - 3 7  5  - 3 6  7 7 5  -  3 7 7 7 5
1 -  2 5  -  2 7 7 7 4  -   3 6 6 7 7 7  6 7 4
1 -  - 3 5  -  3 7 5  -  2  5  -  - 3 6 4  - 1 -
2 6 7 7 7 7 7 6 5  -  -   1 -  - 0  -  -  3 7 5
-  - 3 7 6 6 4  - 3 5  -   3 6 4  -  3 7 7 7 5
2 7 7 5 -  -  -  - 3 5  -   1 -  -  3 6 7 7 6 5
-  3 7 5  - 3 6 7 7 7 6  6 4  -  0  -  2  5  - 0
0 0 0 -  0 0  -  0 0 0  -   -  -  0  -  0  -  0 0 -
```

Fig. 2: Nautical chart for the lattice of Fig. 1 according to the values of k.

Pioneers neurons (line #1) are thought to be *oriented*, with their "hillocks" facing down. Thus, if the site immediately down is blocked, that pioneer is prevented from growing an axon, and its site will be labeled with k=0, otherwise with k=1.

No such option as "splitting" is included in the nautical chart. Splitting, however, can be simulated by *iterating* the path-finding procedure so that other available routes may emerge. Late paths will partially overlap with early ones, then separate in "branches". The mechanism recalls an evolutionary process where branches are continuously generated and later selected, or "pruned", leaving only those paths that best "fit" the network's demands. Any possible path has a chance to be expressed, given sufficient time. Thus, "time" arises in conjunction with "branching". This view is in tune with a scenario of a steadily increasing neuropil leading to a neuronal network [7]. In the model, the "time" allotted for "evolution" equals the number of iterations of the navigation program.

Fig. 3 shows the paths originated from pioneer (9,1) in 40 independent trials. Thirty paths were found percolating − which yields a probability of percolation *from pioneer #9*, $P_9=30/40$ − and so distributed: 12 to target #3, 14 to target #10, 2 to target #2, and 2 to target #9. The strength of the connections of pioneer #9 with targets #2,3,9,10 are: $p_{9,2} = 2/40$ (i.e., $p_{9,2} = P_9\ 2/30$), $p_{9,3}=12/40$, $p_{9,9}=2/40$, $p_{9,10}=14/40$.
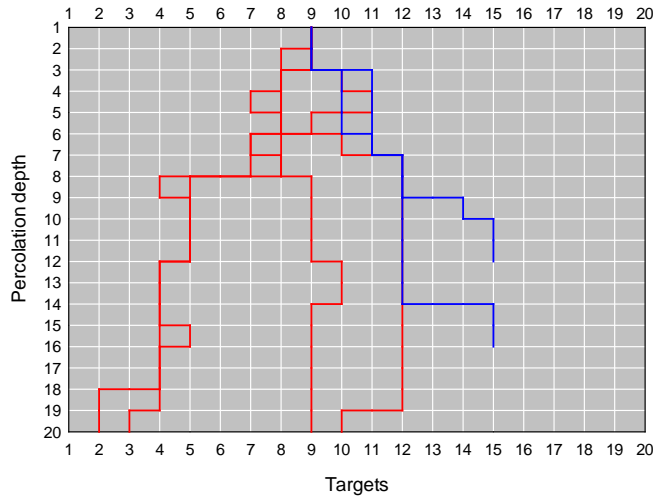

Fig.3: Percolating and stagnating paths from pioneer (9,1). All paths are "pruned".

Targets

	2	3	8	9	10	18	C
1	.120	.620					2
2	.125	.525					2
4	.050	.050					2
5	.050	.050					2
6		.050					1
9	.050	.300		.050	.350		4
10	.025	.175		.075	.350		4
11	.025		.025	.075	.600		4
12		.075	.075	.075	.400		4
14		.025		.150	.425	.025	4
15	.025			.025	.350	.175	4
16		.050		.050	.150	.325	4
17		.025		.025		.375	3
18					.025	.300	2
20						.450	1
σ	.470	1.945	.100	.525	2.650	1.650	43

(Pioneers label on the left side)

Table II: Table of the connections with weights of pioneer-target junctions. C is the number of targets actually reached by a pioneer. Only pioneers with C≠0 are shown.

Table II shows the results for all pioneers. The last row is the "synaptic vector" [8], namely, the sum of all the synaptic weights of a cell. Only 15 out of 20 pioneers exhibit percolating paths. The probability of percolation of the whole lattice is thus $\approx 15/20 = 0.75$.

Careful analysis of the data reveals a typical feature associated to the spanning cluster. For example, pioneer # 18 is strongly "self-excitatory" as 12 out of 13 paths end to itself. However, we noticed that 14 non-percolating paths end to site (20,19), i.e., just *one* step short of percolating. If obstacle at (20,20) in Fig. 1 were removed, then all those paths would be counted as percolating, which would add a target #20 and a weight $p_{18,20} = 0.325$ (14/40) to Table II. Thus, while removing *one* obstacle out of 100 has almost no effect on the porosity, it might dramatically change the network dynamics, possibly introducing singularities, like phase-transitions [6] and bifurcations [8], typically associated with the fractal nature of the spanning cluster.

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