

# Neuro-Percolation as a Superposition of Random-Walks

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**Abstract.** Axons of pioneer neurons are actively directed towards their targets by signaling molecules. The result is a highly stereotyped axonal trajectory. The tip of the axon appears to proceed erratically, which has favored models of axon guidance as random-walk processes. In reality, axon guidance is basically a deterministic process, although largely unknown. Random-walk models assume noise as a representation of what is actually unknown. Wadsworth's guidance gives an experimental account of the axonal bending as induced by addition/subtraction of specific guidance agents. The axonal trajectory, however, is not a simple random-walk but a series of Wiener-Lévy stochastic processes.

## 1 Introduction

Axon guidance has been drawing the attention of researchers for almost half a century [1-4]. The wonders of cytoskeleton dynamics and its exquisite mechanism of control have been revealed in all details, from the discovery of the signaling mechanism to the gene's controlled response of the growth cone. Table 1 summarizes the most studied molecules, known as "the canonical four".

Name / Type	Action	Receptors / Type
Semaphorins / Proteins	Deflective	Plexins/Transmembrane
Netrins / Secreted proteins	Attractive	DCC / Gene
Slits / proteins	Repulsive	Transmembrane
Ephrins / bound proteins	Repulsive	Eph / Membrane-bound

Table 1: Signaling Molecules Family

Signaling molecules interact with the growth cone, directing axonal growth. The action of a molecule, however, may differ from that listed, e.g., an attractive one may become unresponsive, or even change its action to repulsive, depending on "where" the growth cone happens to be and "when". Table 1 lists the most likely action. In reality signaling molecules are *multifunctional*. The mechanism underlying this behavior is still obscure, to the point the outcome of a signaling event is essentially unpredictable [2]. The growth cone is like a vessel navigating across a landscape set with conspicuous points, which appear "out of the box", and with uncertain directional cues. A relatively small number of molecules with fixed action would also be capable of directing a large number of axons to their selected partners, but the result would be a sort of rigid scaffold of connections with a relatively few synapses,

because destinations outside the scaffold would not be allowed. In contrast, few multifunctional cues, cooperating in time, would yield an almost infinite possible destinations. That's exactly what happens in an infant's brain [5]: by age 2 a child's brain has a staggering number of synapses, about one hundred trillion. Half of them will be pared back and the remaining reinforced as age progresses. Hyperconnectivity allows plenty of distinct ways of pruning that one-half, each way uniquely shaping the brain. Multi-functionality is thus at the very base of our own uniqueness. A percolation model of axon guidance is able to mimic the complexity of multi-functionality by portraying the growth cone as navigating across a time-varying landscape, with guidance cues that potentially allow for an almost unrestricted number of destinations.

## 2 Percolation on a time-varying landscape

The term "percolation" refers to classical models in cluster theory [6-7] referring to the seeping of a fluid through soils of different permeability. A percolation-based model deals with a discrete-type system, featuring "allowed" and "forbidden" sites randomly distributed, yet a system that can be harnessed to a point it can be controlled by a single parameter, the site occupational probability. In a 2-dimensional case the occupational probability determines the formation of clusters. At a critical value of probability a single, weakly connected cluster remains - the "spanning cluster"- one that barely touches the edges of the lattice. Percolating paths within the spanning cluster are reduced to a minimum. The spanning cluster is prone to disruption: a minimal change in the spatial configuration can lead to its disappearance. The critical probability is thus evaluated through repeated trials, each dealing with different configurations of "allowed" (or "forbidden") sites. The procedure is then iterated for different values of the occupational probability until the critical value is found. In conclusion, a percolation model becomes useful provided that a large number of distinct distributions of "allowed" (or "forbidden") sites are tested. Spanning trajectories are by no means unique in shape. In our model, a time-varying landscape is the premise. The landscape is framed in a 2D rectangular lattice of height  $h$  and indefinite width, set with guidance cues allowing any possible percolating trajectory. At each site the growth cone is given the same options about the next move, namely: to go to Right (with probability  $p_R$ ), or Left (with probability  $p_L$ ), or Down (with probability  $p_D$ ). Upwards moves are negated. The growth cone moves as in response to signals from a multifunctional cue nearby, which may tell to "turn-Right", but also

the opposite, to "turn-Left", or let it free to follow the natural bias, in which case the growth cone proceeds undisturbed Down.

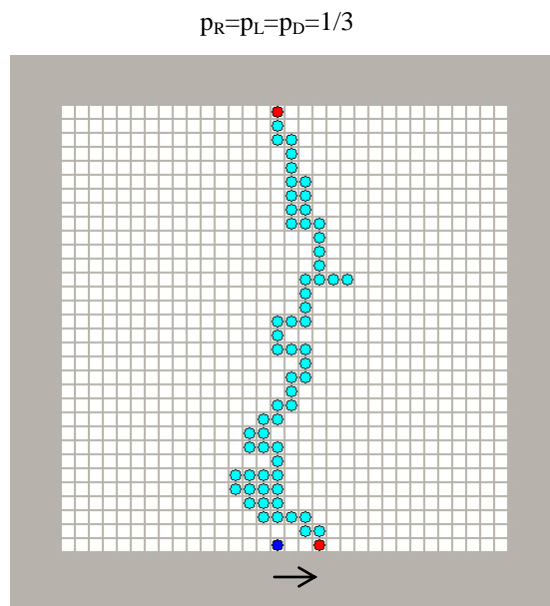


Fig. 1. Percolating trajectory. Time-length  $T=74$ , net displacement  $x=+3$ .

Fig. 1 shows a computer-generated trajectory "percolating" to the bottom line. The trajectory may be thought as the result of precise, specific sequence of commands, like "DDRDDDRLDRL...", the size of the string being the "spanning time"  $T$ . One may even imagine to actually reveal the guidance cues responsible for the sequence, for example, by iterating the navigation from the same departing point, as it would mimic the sprouting of new axons travelling across an unchanged medium. The result would be a bundle of trajectories, ending to different points. That's because signaling events are not necessarily the same in each trial, but vary according with some hidden dynamics. Given the fractal nature of the medium, a small, local variation would make the ending point unpredictable. Such behavior is typical of *deterministic chaos*, the initial conditions of the landscape being the states of all the cues at a given time.

### 3 Law of motion and probability

The motion of the growth cone is a combination of a monotonic descent (D) interrupted by stops (R, L), and a succession of random lateral moves (R, L) intertwined with stops (D). The spanning time  $T$  is the sum of all the moves. There will be the same number of D's in any percolating trajectory, in our case 31. The sum

of all sideways moves depends on the trajectory. At any  $t$  the net displacement is the difference between all R's and all L's, i.e.,  $x(t)=m_R-m_L$ . Fig 2 (*left*) is a plot of  $x(t)$  for the trajectory in Fig.1. The stops do not affect the displacement, thus they can be eliminated. Fig.2 (*right*) is the plot of  $x(t)$  without stops.

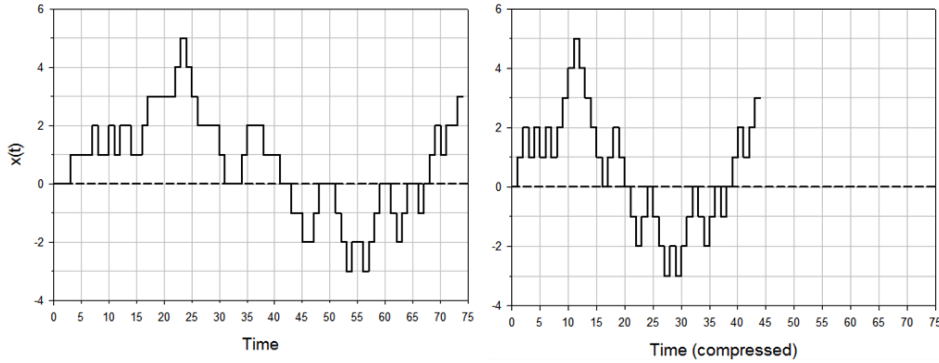


Fig. 2.  $x$ -axis notion for the trajectory in Fig.1, with (*left*) and without (*right*).stops.

The reduced spanning time is  $M=43$ , sum of 23 R's and 20 L's, the net final displacement is  $x(M)=m_R-m_L=23-20=3$ . The probability of a trajectory's percolating at exactly  $x(M)=3$ , can be calculated with the binomial formula on account that any sequence of 23 R's and 20 L's, in whatever order, will yield the same net displacement. In the binomial formula, however, there are only *two* events, with probabilities  $p$  and  $q=1-p$ , while in our case there are three. Elimination of D's does not affect  $x(M)$ , but it affects the probabilistic space. The values of  $p_R, p_L, p_D$  must be adjusted in order to comply with the change as follows:

$$p_R \Rightarrow \frac{p_R}{p_R + p_L} = p; \quad p_L \Rightarrow \frac{p_L}{p_R + p_L} = q$$

where  $p+q=1$ ,  $p_R/p_L=p/q=r$ . With  $p_R$  and  $p_L$  so transformed, the binomial formula yields  $P\{x(M)=3\}=0.1092$ . Any other trajectory with the *same*  $M$  is described by the *same* probability distribution. It follows that all trajectories with the same  $M$  are samples of the same stochastic process, namely, a *Wiener-Lévi's*. After replacing  $x$  with  $\xi=x/2$ , and  $M$  with  $K=M/2$ , the probability of a trajectory ending to  $\xi$  can be written in a more convenient form as:

$$P_k(\xi) = \frac{(2k)!}{(k+\xi)!(k-\xi)!} q^{2k} r^{k+\xi}; \quad \xi = -K, -K+1, \dots, k-1, K$$

## 4 Method and Results

Navigation in a time-varying landscape was implemented with a computer program where  $p_R$  and  $p_L$  are entered as parameters.. An interval was partitioned in three

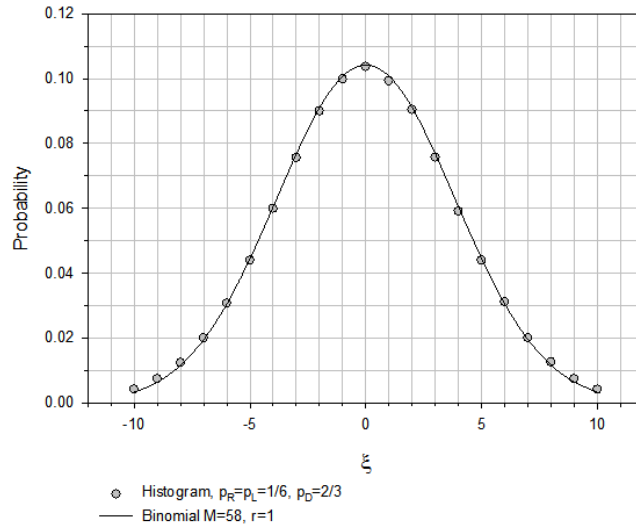


Fig. 3 - Experimental results (*bullets*) for  $p_R=p_L=1/6$ ,  $p_D=2/3$ . The histogram is peaked at  $\xi=0$ , with a value 0.1037. For comparison, a binomial distribution (*solid line*) with  $M=58$ ,  $r=1$  is superimposed, the binomial peak at  $\xi=0$  being 0.1043.

segments, the relative length of each was taken as a probability. Another program was also created for implementing a binomial distribution, with  $M$  and  $r=p/q$  as parameters. Navigation was iterated one million times, each trial yielding a trajectory departing from the same point and ending somewhere on the  $\xi$ -axis.

Fig.3 shows the probability distribution  $H(\xi)$  in the case  $p_R=p_L=1/6$ ,  $p_D=2/3$ . In order to compare  $H(\xi)$  with a binomial distribution, the value of  $M$  was sought by equating the peaks of both distribution, which yields  $M \approx 58$ . As shown in Fig. 3 a Binomial with  $M=58$ ,  $r=1$  is indeed a close fit to the histogram.

## 5 Analysis

The close matching shown in Fig. 3 is somewhat surprising as the spanning times of the trajectories are not all the same.  $M$  is itself distributed among the trajectories with values  $M_1, M_2, \dots, M_n$ ,  $N_1$  trajectories with the same  $M_1$ ,  $N_2$  with the same  $M_2$ , and so on. Each group of  $N_k$  trajectories with the same  $M_k$  belong to the same Binomial, therefore there are  $n$  different binomial distributions (with the same  $r=1$ ) hidden in  $H(\xi)$ . The probability of finding  $M=M_k$  is  $N_k/N$ . Thus, the contribution on the  $n$  Binomials to the histogram is:

$$H(\xi) = \sum_{k=1}^n \alpha_k P_{M_k}(\xi) ; \sum_{k=1}^n \alpha_k = 1$$

with  $\alpha_k = N_k/N$ . All Binomials are peaked at  $\xi=0$ , as  $r=1$  for all of them. They are "coherent", all peaked at  $\xi=0$ , thus the sum is also a Binomial peaked at  $\xi=0$ .

Coherence explains the close match in Fig. 3. When  $r \neq 1$ , however, the sum can no longer be equated to a *single* Binomial. All the binomial components have the same  $r$ , but they are peaked at different values of  $\xi$ . They are "incoherent". Thus,  $\xi(t)$  is not a single random-walk but a *superposition* of random-walks:

$$\underline{\xi}(t) = \sum_{k,1}^n a_k \underline{\xi}_k(t)$$

The range of  $t$  in  $\underline{\xi}(t)$  extends up to the maximum value of  $M$ , as it includes all subranges of the stochastic components. Thus, depending on  $t$ , some components can be out of range, therefore their contributions are null. Thus, the mean  $\langle \underline{\xi}(t) \rangle$  depends on  $t$ . Even though a superposition of stationary processes  $\underline{\xi}(t)$  is *non-stationary* in strict-sense, which is another way to say  $\underline{\xi}(t)$  is *not* a Wiener-Lévy process.

## 6 Conclusions

Neuro-percolation is in perfect tune with Wadsworth's findings [4]. The directional bias induced by the loss of specific cues is modelled by a change in the ratio  $r = p_R/p_L$ , where  $r=1$  means all directional cues compensate for each other, and no directional bias results. The trajectory of the growth cone is indeed "a succession of randomly directed movements" - as in the percolation model - but it is not a random-walk. The note is more than mere mathematical finesse. A superposition of random-walks is closer to the actual motion of the growth cone than a single random-walk. In the percolation model, the spanning time is considered essentially unpredictable. There is no biological evidence the growth cone should complete its trajectories all in the same time, as this would imply a variable rate of outgrowth: the more tortuous the trajectory the higher the outgrowing, which is hard to sustain. Rather, it is more realistic to assume the outgrowth's *rate* to be a constant, as result of an identical underlying biological process.

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