A Probabilistic Model for Establishment of Neuron Polarity

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The main aim of this paper is to present a simple probabilistic model for the early stage of neuron growth: the specification on an axon out of several initially similar neurites. The model is a Markov process with competition between the growing neurites, wherein longer objects have more chances to grow, and parameter a determines the intensity of the competition. For $a > 1$ the model provides results which are qualitatively similar to the experimental ones, i.e. selection of one rapidly elongating axon out of several neurites while other less successful neurites stop growing at some random time. Rigorous mathematical proofs are given.

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A probabilistic model for establishment of neuron polarity

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Abstract

The main aim of this paper is to present a simple probabilistic model for the early stage of neuron growth: the specification on an axon out of several initially similar neurites. The model is a Markov process with competition between the growing neurites, wherein longer objects have more chances to grow, and parameter α determines the intensity of the competition. For $\alpha > 1$ the model provides results which are qualitatively similar to the experimental ones, i.e. selection of one rapidly elongating axon out of several neurites while other less successful neurites stop growing at some random time. Rigorous mathematical proofs are given.

1 Introduction

There are many open questions concerning biophysical mechanisms of the establishment of neuron polarity, which is a crucial early step in neuron development. In particular, it is not known how the axon is first specified from a number of similar neurites.

When neurites first form, they cannot be distinguished as either axons or dendrites (Dotti and Banker, 1987; Dotti et al, 1988). The neurites exhibit periods of growth and

retraction until one rapidly elongates to eventually become an axon. Until the length of a successful neurite exceeds the length of others by $10 - 15\ \mu m$ (Goslin and Banker, 1989), it is morphologically and molecularly the same as its other less successful counterparts.

In experiments with hippocampal neurons it was observed that transecting the neurites (which are also called "minor processes") early in the development can cause an alteration of polarity; a neurite that would have become a dendrite instead becomes an axon (Dotti and Banker, 1987). It is impossible to predict with any certainty which neurite (out of several) will become an axon unless it was originally longer than other neurites by more than a threshold length ($10\mu m$) (Goslin and Banker, 1989). If the neurites were transected at the same length, a competition (or dynamical equilibrium) between them was observed until one neurite exceeded the others by a critical length and rapidly elongated to eventually become an axon. Other neurites subsequently become dendrites.

Goslin and Banker (1989) hypothesised that specification of axon depends on its length relative to other minor processes. Recent experimental evidence shows that the axon specification can be directed by growth-promoting molecules which are applied locally (Esch *et al*, 1999).

This experimental data suggests that there is a probabilistic aspect of the phenomenon which involves interaction among the neurites wherein any of the neurites is capable of becoming an axon while the others stop growing and eventually become dendrites.

The main aim of this paper is to present a simple probabilistic model for the early stage of the neuron growth: the specification of an axon out of several initially similar neurites. In the next section we describe the model and then proceed with a probabilistic analysis of it. Rigorous proofs are given in the last section, followed by the discussion of the model.

2 Probabilistic model

Consider k growing objects, neurites. Denote their length at time t by $a_1(t), a_2(t)..., a_k(t)$, and their initial lengths at time $t = 0$ by $a_s(0) > 0, 1 \leq s \leq k$. Let us consider a discrete model, where time takes integer values. Suppose also, that for each interval of time $[t, t+1]$ a unit of length, l, is added to one of the neurites, while others remain unchanged. Thus, at time $t + 1$ there exist a neurite with number j, $1 \leq j \leq k$ such that

$$a_j(t+1) = a_j + l. \tag{1}$$

For all other neurites, wherein $s \neq j$, $a_s(t+1) = a_s(t)$. Clearly, the total length of all neurites at time t is given by

$$L(t) = \sum_{j=1}^{k} a_j(t) = L(0) + l\ t, \quad \text{where} \quad L(0) = \sum_{j=1}^{k} a_j(0). \tag{2}$$

Let us now define the transitional probabilities. The probability that a neurite a_j grows at time t depends on the current length of this neurite and the lengths of all other neurites.

It is clear from the experimental data (Goslin and Banker, 1989) that the longer the neurite, the higher the probability it will grow the next moment of time. Suppose that the probability that neurite j will grow at time $t+1$ is proportional to its length a_j at time t to the power α:

$$P[a_j(t+1) = a_j(t) + l] \sim a_j^\alpha(t). \tag{3}$$

This is a natural way to quantitate the experimentally observed advantage of being long. Since at every moment of time t one neurite grows with probability 1, the sum of all probabilities equals to one and we obtain the formula for the transitional probability

$$P[a_j(t+1) = a_j(t) + l] = \frac{a_j^\alpha(t)}{\sum\limits_{s=1}^{k} a_s^\alpha(t)}, \quad \alpha > 0. \tag{4}$$

Equations (1)-(4) describe a Markov process with competition between the growing neurites. Longer objects have more chances to grow and parameter α determines the intensity of the competition between them.

3 Analysis of the model

The above model turns out to have three different regimes depending on parameter α: the *critical regime* $\alpha = 1$, the regime of *ballistic growth* $\alpha > 1$ and the *subcritical* regime $\alpha < 1$. In this section we present results with explanation for all three cases. Rigorous proofs which are based on Rubin's representations (Davis, 1990) are given in the next section. Without loss of generality, we set $l = 1$.

3.1 Critical regime: $\alpha = 1$

In this case, each neurite grows linearly with time so that

$$\frac{a_s(t)}{t} \to \gamma_s, \quad t \to \infty. \tag{5}$$

Here the growth speeds γ_s are random variables whose distribution depends on the initial lengths of the neurites $a_s(0)$, $1 \le s \le k$. It follows from (5) that there exists one neurite which is longer than the others for sufficiently large times. Namely, it is a neurite which corresponds to a largest value of γ_s. However, the advantage of being long is not strong enough to stop other neurites from growing. Thus, the case $\alpha = 1$ does not adequately describe the phenomenon of the axon specification. All neurites continue to grow contrary to the experimental findings, where only one neurite significantly elongates. Fig. 1 shows a representative example of the growth of several initially similar neurites. As is seen, all five neurites grow linearly in time although with different speeds γ_s.

The case $\alpha = 1$ corresponds to the Polya urn scheme. In its classical formulation this scheme is described as follows. There is a certain number of black and white balls in an urn.

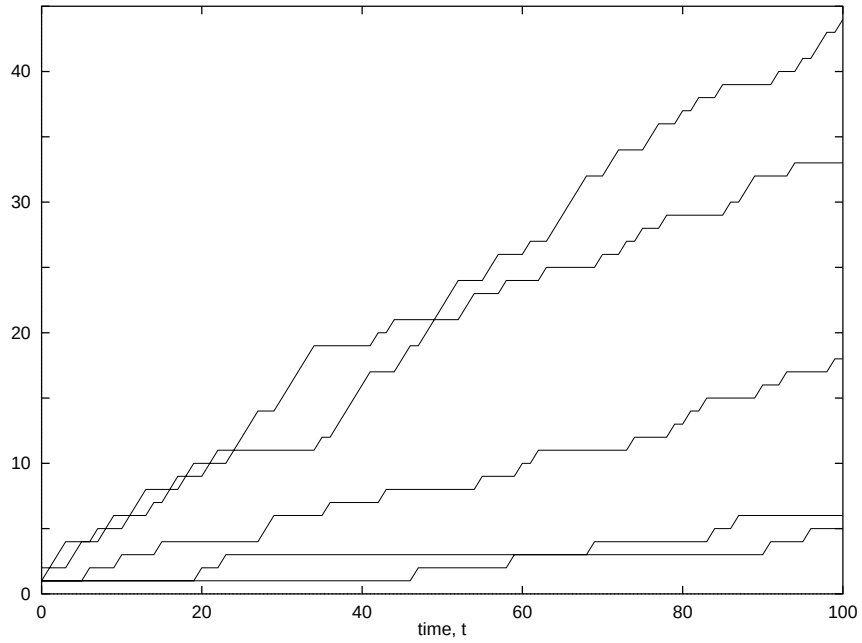

Figure 1: A representative example of the simulation of the growth model $(1)-(4)$ for $\alpha = 1$. Lengths, $a_s(t)$, of five neurites are given as functions of time, t. Initially all neurites have the same length: $a_s(0) = 1, 1 \leq s \leq 5$, $l = 1$

At each moment of time an observer randomly picks one ball from the urn and then puts it back together with an additional ball of the same colour. This model has an exact solution (Feller, Vol.I, 1966). The numbers of white and black balls grow linearly with time and the ratio between them tends to a finite limit as $t \to \infty$.

3.2 Regime of ballistic growth: $\alpha > 1$

The cases $\alpha > 1$ and $\alpha < 1$ correspond to a generalised Polya scheme. In the case $\alpha > 1$, after a random moment of time only one neurite will grow. More precisely, with probability 1 there exists a number s, $1 \leq s \leq k$ and random time T^* such that

$$a_s(t+1) = a_s(t) + 1, \quad \text{for all} \quad t > T^*, \tag{6}$$

while for all $j \neq s$

$$a_j(t+1) = a_j(t), \quad \text{for all} \quad t > T^*. \tag{7}$$

In terms of the biological model this means that with probability 1 competition leads to selection of just one neurite, which rapidly elongates and eventually forms an axon. If all neurites initially have the same lengths as appears to be the case in some of the experiments (Goslin and Banker, 1989), the neurite s that wins the competition to become an axon is selected randomly with a uniform probability distribution. In other words, if P_s denotes the probability that the axon is formed from the neurite s, then $P_s = 1/k$. In general, P_s has a

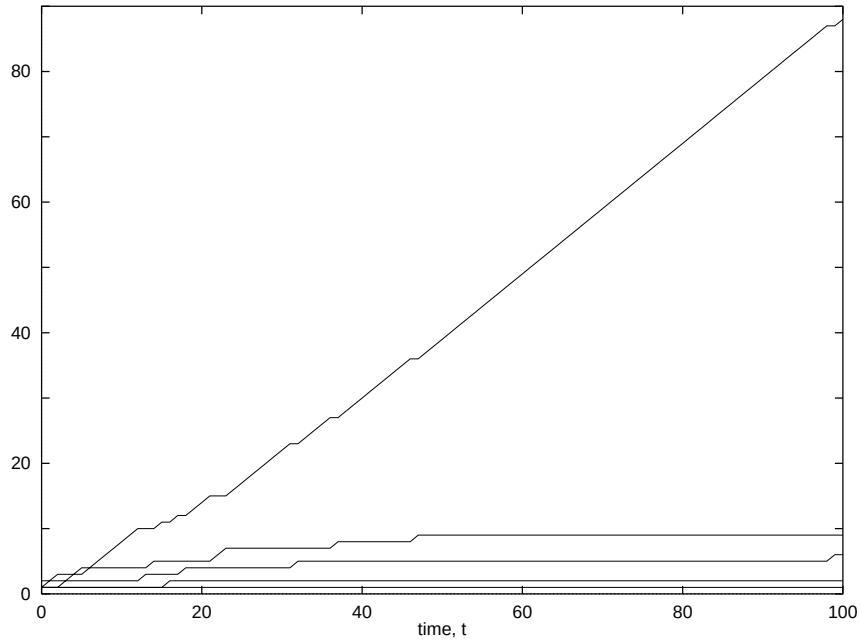

Figure 2: A representative example of the simulation of the growth model $(1)-(4)$ for $\alpha = 2$. Lengths of five neurites are given as functions of time, t. All five neurites are initially the same length: $a_s(0) = 1, 1 \leq s \leq 5$, $l = 1$

probability distribution that depends on the original lengths of the minor processes, $a_s(0)$, $1 \leq s \leq k$. Obviously, the longer is the neurite the more chances it has to win the race and to become an axon.

Clearly, this model gives results qualitatively similar to the experimental ones. Fig. 2 shows a representative graph for the case $\alpha = 2$ for a neuron with five minor processes of initially the same length. In this case only one neurite takes over and rapidly grows while other four stop growing.

3.3 Subcritical regime: $\alpha < 1$

In the subcritical regime all neurites have the lengths of the same order. More precisely, the ratios of lengths for any two neurites tend to 1 as t tends to infinity:

$$\frac{a_{s_1}(t)}{a_{s_2}(t)} \to 1 \quad as \quad t \to \infty, \ 1 \leq s_1, s_2 \leq k. \tag{8}$$

It follows from (8) that

$$a_s(t) = \frac{t}{k} + \hat{a}_s(t), \tag{9}$$

where $\hat{a}_s = o(t)$ are fluctuations of the lengths. Asymptotic behaviour of $\hat{a}_s$ depends on α. If $1/2 < \alpha < 1$ then there exist nonzero random constants c_s, $1 \le s \le k$, such that

$$\frac{\hat{a}_s(t)}{t^\alpha} \to c_s \text{ as } t \to \infty,\ 1 \le s \le k. \tag{10}$$

Although fluctuations $\hat{a}_s$ are much smaller then $a_s(t)$, still there exists a neurite which is longer than all others for all large enough t. As in the critical case, it is a neurite which corresponds to the largest value of c_s.

In the second subcase, $0 < \alpha \le 1/2$, no neurite grows faster than any of the other neurites. In other words, for any neurite there exists a sequence $t_n \to \infty$ such that this neurite is the longest at time t_n. Fluctuations $\hat{a}_s(t)$ from eqn. (9) are of the order $\sqrt{t}$ if $0 < \alpha < 1/2$ and of the order $\sqrt{t\ \log t}$ if $\alpha = 1/2$. However, if we normalise $\hat{a}_s(t)$ by dividing on $\sqrt{t}$ or $\sqrt{t\ \log t}$ respectively, the normalised fluctuations have no limit as $t \to \infty$, but only a limiting probability distribution. More precisely, if $0 < \alpha < 1/2$ then

$$\text{Dist}(\frac{\hat{a}_s(t)}{\sqrt{t}}) \to N(0, \sigma_\alpha^2), \quad \text{as } t \to \infty, \tag{11}$$

where

$$\sigma_\alpha^2 = \frac{(k-1)}{k^{1+2\alpha}(1-2\alpha)}$$

and $N(0, \sigma^2)$ is a Gaussian distribution with mean value zero, and variance σ^2. If $\alpha = 1/2$ then

$$\text{Dist}(\frac{\hat{a}_s(t)}{\sqrt{t\ \log\ t}}) \to N(0, \bar{\sigma}^2) \ \text{ as } t \to \infty, \tag{12}$$

where $\bar{\sigma}^2 = (k-1)/k^2$.

4 Precise statements and proofs

Let us give give rigorous proofs for the assertions made in the previous section. We consider 3 cases corresponding to critical, ballistic and subcritical regimes.

I. The results for the case $\alpha = 1$ are classical (see Feller, Vol.I,II, 1966). We present them here only for completeness of exposition. Consider random variables

$$\xi_s(t) = \frac{a_s(t)}{L(t)},\ 1 \le s \le k,\ \text{where } L(t) = \sum_{j=1}^{k} a_j(t) = L(0) + t. \tag{13}$$

Proposition 1. 1. There exist random constants $0 < \hat{\xi}_s < 1, 1 \le s \le k$, such that with probability 1

$$\lim_{t\to\infty} \xi_s(t) = \hat{\xi}_s. \tag{14}$$

2. For every $1 \leq s \leq k$ random variable $\hat{\xi}_s$ has a probability distribution with a density $\beta_{a(s),b(s)}(\hat{\xi}_s)$:

$$\beta_{a(s),b(s)}(\hat{\xi}_s) = \frac{\Gamma(a(s)+b(s))}{\Gamma(a(s))\Gamma(b(s))}\hat{\xi}_s^{a(s)-1}(1-\hat{\xi}_s)^{b(s)-1}, \tag{15}$$

where Γ is the gamma function, $a(s) = a_s(0), b(s) = L(0) - a_s(0)$.

Proof. It is easy to see that for each s random process $\xi_s(t)$ is a martingale. Indeed, a conditional expectation of $\xi_s(t)$ is given by

$$E(\xi_s(t+1) \mid \xi_s(t)) = \frac{(a_s(t)+1)}{(L(t)+1)}\frac{a_s(t)}{L(t)} + \frac{a_s(t)}{(L(t)+1)}\frac{(L(t)-a_s(t))}{L(t)} = \frac{a_s(t)}{L(t)} = \xi_s(t) \tag{16}$$

Since $0 \leq \xi_s(t) \leq 1$ it follows from the martingale convergence theorem (Feller, Vol.II, 1966) that with probability 1 there exists a limit

$$\lim_{t\to\infty} \xi_s(t) = \hat{\xi}_s, \tag{17}$$

which proves the first part of Proposition 1. To prove the second part, consider the probability distribution for $a_s(t)$. It can be shown (see Feller, Vol.I, 1966) that

$$P(a_s(t) = a) = C_t^{a-a(s)}\frac{[a(s)(a(s)+1)...(a-1)][b(s)(b(s)+1)...(b(s)+a(s)+t-a-1)]}{(a(s)+b(s))(a(s)+b(s)+1)...(a(s)+b(s)+t-1)}$$
$$= \frac{t!}{(a-a(s))!(t-a+a(s))!}\frac{(a-1)!}{(a(s)-1)!}\frac{(t-a+a(s)+b(s)-1)!}{(b(s)-1)!}\frac{(a(s)+b(s)-1)!}{(a(s)+b(s)+t-1)!}$$

Take $a_s = \xi t$. Then, asymptotically as $t \to \infty$,

$$P(a_s(t) = \xi t) \sim \frac{1}{t}\frac{(a(s)+b(s)-1)!}{(a(s)-1)!(b(s)-1)!}\xi^{a(s)-1}(1-\xi)^{b(s)-1}, \tag{18}$$

where $\sim$ stands for asymptotic equivalence. Namely, $G(t) \sim H(t)$ if $G(t)/H(t) \to 1$ as $t \to \infty$. It immediately follows from (18) that $\hat{\xi}_s = \lim_{t\to\infty}\frac{a_s(t)}{L(t)}$ has a density given by $\beta_{a(s),b(s)}(\hat{\xi}_s)$. □

II. Consider now the case of ballistic growth, $\alpha > 1$. Analysis of the growth for this case is based on remarkable representation found by (Davis, 1990).

Consider the following random process. Let

$$\{\eta_i^{(s)}\}, \quad 1 \leq s \leq k, i \geq 1 \tag{19}$$

be independent random variables with exponential distribution with exponent $\delta_i = i^\alpha$, i.e.

$$P(\eta_i^{(s)} > x) = \delta_i \int_x^\infty e^{-\delta_i y}dy, \quad x \geq 0. \tag{20}$$

Define the following sums

$$\Sigma_i{}^{(s)} = \sum_{j=a_s(0)}^{i} \eta_j^{(s)}, \quad i \geq a_s(0) \tag{21}$$

which form a positive monotone increasing sequence for each given s. Consider now all $\{\Sigma_i^{(s)}, i \geq a_s(0), 1 \leq s \leq k\}$ together in increasing order; denote random elements in the resulting sequence by $A_1, A_2, ..., A_n, ...$ We can now describe the growth process corresponding to the sequence $\{A_i\}$. If A_1 belongs to $\{\Sigma_i^{(s_1)}\}$ then on the first step we add one unit of length to the s_1-th neurite. If A_2 belongs to the $\{\Sigma_i^{(s_2)}\}$ then on the second step we add one unit of length to the s_2-th neurite and so on.

Theorem [Rubin]. The growth process corresponding to the sequence $\{A_i\}$ is equivalent to our original growth model, i.e. the probability distributions of the two processes are the same.

Although, the second construction of the growth process looks more artificial and less transparent than the original one, it is much easier to analyse it mathematically. This simplicity is due to the independence of random variables $\eta_j^{(s)}$.

Proposition 2. Let $\alpha > 1$. Then, there exists a random time T^* such that for all $t > T^*$ only one neurite grows.

Proof. The proof is an easy consequence from Rubin's Theorem. Consider $\Sigma_\infty^{(s)} = \sum_{j=a_0(s)}^{\infty} \eta_j^{(s)}$. It easily follows from the classical Kolmogorov's "three series theorem" (Feller, 1966, Vol.II) that the series above is convergent with probability 1. Moreover, $\Sigma_\infty^{(s)}$ has an absolutely continuous distribution with characteristic function

$$\phi(\lambda) = Ee^{i\lambda\Sigma_\infty^{(s)}} = [\prod_{j=a_0(s)}^{\infty}(1 - i\frac{\lambda}{j^\alpha})]^{-1}. \tag{22}$$

Let $\Sigma_\infty^{(s_0)} = \min_{1\leq s\leq k} \Sigma_\infty^{(s)}$. It follows that $\Sigma_\infty^{(s)} > \Sigma_\infty^{(s_0)}$, for all $s \neq s_0$. Then, there exists I such that $\Sigma_i^{(s)} > \Sigma_\infty^{(s_0)}$ for all $s \neq s_0$ and $i > I$. It follows from the Rubin's construction that for all $s \neq s_0$ and all t, $a_s(t) \leq a_s(0) + I$. Hence, there exists time T^* after which only neurite s_0 will grow. □

III. Suppose now $0 < \alpha < 1$. Let $\hat{a}_s(t) = a_s(t) - t/k$ be the fluctuations of the lengthes defined in (9).

Proposition 3. 1. If $1/2 < \alpha < 1$, then there exist nonzero random constants c_s such that with probability 1

$$\frac{\hat{a}_s(t)}{t^\alpha} \to c_s \text{ as } t \to \infty,\ 1 \leq s \leq k. \tag{23}$$

2. If $0 < \alpha < 1/2$, then for all $1 \leq s \leq k$ the probability distribution of $\frac{\hat{a}_s(t)}{\sqrt{t}}$ converges weakly to a Gaussian distribution $N(0, \sigma_\alpha^2)$, where

$$\sigma_\alpha^2 = \frac{(k-1)}{k^{1+2\alpha}(1-2\alpha)}.$$

3. If $\alpha = \frac{1}{2}$ then for all $1 \leq s \leq k$ the probability distribution of $\frac{\hat{a}_s(t)}{\sqrt{t\log t}}$ converges weakly to a Gaussian distribution $N(0, \bar{\sigma}^2)$, where $\bar{\sigma}^2 = \frac{k-1}{k^2}$.

Proof. The proof is again based on Rubin's construction. Define independent random variables with zero mean value by $\xi_j^{(s)} = \eta_j^{(s)} - < \eta_j^{(s)} >= \eta_j^{(s)} - 1/j^\alpha$. We can write $\Sigma_i^{(s)}$ in the following form:

$$\Sigma_i^{(s)} = A_i + \zeta_i^{(s)}, \tag{24}$$

where

$$A_i = \sum_{j=1}^{i} \frac{1}{j^\alpha}\ \zeta_i^{(s)} = \sum_{j=1}^{i} \xi_j^{(s)} - \sum_{j=1}^{a_0(s)-1} \eta_j^{(s)}. \tag{25}$$

Consider arbitrary $1 \le s_1, s_2 \le k$. It follows from Rubin's construction that if $\sum_{a_{s_2}(t)}^{(s_2)} \le \sum_{a_{s_1}(t)}^{(s_1)}$, then

$$\sum\nolimits_{a_{s_2}(t)}^{(s_2)} \le \sum\nolimits_{a_{s_1}(t)}^{(s_1)} \le \sum\nolimits_{a_{s_2}(t)+1}^{(s_2)}. \tag{26}$$

Since $\sum_i^{(s)}$ diverges as $i \to \infty$, for all $1 \le s \le k$, $a_s(t) \to \infty$ as $t \to \infty$. Hence, using inequalities (26), we obtain

$$|\sum\nolimits_{a_{s_1}(t)}^{(s_1)} - \sum\nolimits_{a_{s_2}(t)}^{(s_2)}| \to 0 \text{ as } t \to \infty. \tag{27}$$

We next study asymptotic behaviour of $\zeta_i^{(s)}$. In the case $1/2 < \alpha < 1$ the series $\zeta_i^{(s)}$ is convergent, i.e. $\zeta_i^{(s)} \to \zeta_\infty^{(s)}$ as $i \to \infty$ for all $1 \le s \le k$. Here again we have used Kolmogorov's three series theorem. Notice that $\zeta_\infty^{(s)}$ has an absolutely continuous distribution. In the case $0 < \alpha \le 1/2$ the series for $\zeta_i^{(s)}$ is divergent. It is easy to check that one can apply Lindeberg's Central Limit Theorem (see Feller, II). Since

$$\mathrm{Var}(\zeta_i^{(s)}) \sim \sum_{j=1}^{i} \frac{1}{j^{2\alpha}} \sim V_\alpha(i) = \begin{cases} \frac{1}{1-2\alpha}\ i^{(1-2\alpha)}, & 0 < \alpha \le \frac{1}{2}, \\ \log i\ , & \alpha = \frac{1}{2}. \end{cases} \tag{28}$$

we have

$$\mathrm{Dist}\left(\frac{\zeta_i^{(s)}}{\sqrt{V_\alpha(i)}}\right) \to \mathrm{N}(0,1) \tag{29}$$

Notice that

$$A_i = \sum_{j=1}^{i} \frac{1}{j^\alpha} \sim \frac{1}{1-\alpha}\ i^{1-\alpha}. \tag{30}$$

It follows from equation (31) together with equations (26-29) that

$$|a_{s_1}(t) - a_{s_2}(t)| = \mathrm{o}(\min(a_{s_1}(t), a_{s_2}(t))) \tag{31}$$

Hence, $a_s(t) = t/k + \hat{a}_s(t)$, where $\hat{a}_s(t) = \mathrm{o}(t)$.

We are ready now to study asymptotic behaviour of fluctuations $\hat{a}_s(t)$. Without loss of generality assume that $a_{s_1}(t) < a_{s_2}(t)$. Then,

$$\sum\nolimits_{j=a_{s_1}(t)+1}^{a_{s_2}(t)} \frac{1}{j^\alpha} = \zeta_{a_{s_1}(t)}^{(s_1)} - \zeta_{a_{s_2}(t)}^{(s_2)} + \mathrm{o}(1). \tag{32}$$

Hence,

$$\frac{1}{1-\alpha}(a_{s_2}^{1-\alpha}(t) - a_{s_1}^{1-\alpha}(t)) = \zeta_{a_{s_1}(t)}^{(s_1)} - \zeta_{a_{s_2}(t)}^{(s_2)} + \mathrm{o}(1), \tag{33}$$

which implies

$$\frac{1}{1-\alpha}(a_{s_2}^{1-\alpha}(t) - a_{s_1}^{1-\alpha}(t)) = \frac{1}{1-\alpha}a_{s_1}^{1-\alpha}(t)\left(\left(1 + \frac{a_{s_2}(t) - a_{s_1}(t)}{a_{s_1}(t)}\right)^{1-\alpha} - 1\right) =$$

$$\frac{1}{1-\alpha}a_{s_1}^{1-\alpha}(t)(1-\alpha)\frac{a_{s_2}(t) - a_{s_1}(t)}{a_{s_1}(t)}(1 + \mathrm{o}(1)) = \frac{a_{s_2}(t) - a_{s_1}(t)}{a_{s_1}^{\alpha}(t)}(1 + \mathrm{o}(1)) =$$

$$\zeta_{a_{s_1}(t)}^{(s_1)} - \zeta_{a_{s_2}(t)}^{(s_1)} + \mathrm{o}(1).$$

Since $a_s(t) \sim t/k$ for all s, it follows that

$$\hat{a}_{s_2}(t) - \hat{a}_{s_1}(t) = a_{s_2}(t) - a_{s_1}(t) = \left(\frac{t}{k}\right)^{\alpha}\left(\zeta_{a_{s_1}(t)}^{(s_1)} - \zeta_{a_{s_2}(t)}^{(s_2)} + \mathrm{o}(1)\right)(1 + \mathrm{o}(1)). \tag{34}$$

In the case $1/2 < \alpha < 1$,

$$\zeta_{a_s(t)}^{(s)} = \zeta_{\infty}^{(s)} + \mathrm{o}(1) \ \text{ as } t \to \infty$$

Using equation (34) we have

$$\hat{a}_{s_2}(t) - \hat{a}_{s_1}(t) = \left(\frac{t}{k}\right)^{\alpha}(\zeta_{\infty}^{(s_1)} - \zeta_{\infty}^{(s_2)})(1 + \mathrm{o}(1)). \tag{35}$$

Since $\sum_{s=1}^{k} \hat{a}_s(t) = L(0)$ equation (35) easily implies

$$\hat{a}_s(t) = \left(\frac{t}{k}\right)^{\alpha}(B - \zeta_{\infty}^{(s)})(1 + \mathrm{o}(1)), \tag{36}$$

where

$$B = \frac{1}{k}\sum_{s=1}^{k} \xi_{\infty}^{(s)}.$$

Notice that in (35), (36) we have used the following fact: with probability 1, $\zeta_{\infty}^{(s_1)} \neq \zeta_{\infty}^{(s_2)}$, $s_1 \neq s_2$, and $\zeta_{\infty}^{(s)} \neq B$, $1 \leq s \leq k$. The first statement of Proposition 3 immediately follows from (36).

In the case $0 < \alpha \leq 1/2$ we have to strengthen estimates (31) and (34). Denote

$$\zeta^{(s)}(t) = \zeta_{[\frac{t}{k}]}^{(s)}, \ B(t) = \frac{1}{k}\sum_{s=1}^{k} \xi^{(s)}(t).$$

It is easy to show that for any $\epsilon > 0$ there exists $I(\epsilon)$ such that for all $i > I(\epsilon)$

$$|\zeta_i^{(s)}| \leq V_{\alpha}^{\frac{1}{2}}(i) i^{\epsilon}, \quad |\eta_i^{(s)}| \leq \frac{1}{i^{\alpha-\epsilon}} \tag{37}$$

Using (24)-(26) one immediately obtains from (37) that there exists $T(\epsilon)$ such that for all $t > T(\epsilon)$

$$|\hat{a}_{s_1}(t) - \hat{a}_{s_2}(t)| \leq t^{\frac{1}{2}+2\epsilon}. \tag{38}$$

Since $\sum_{s=1}^{k} \hat{a}_s(t) = L(0)$, equation (38) implies that

$$|\hat{a}_s(t)| \leq t^{\frac{1}{2}+2\epsilon}, \quad |\zeta^{(s)}_{a_s(t)} - \zeta^{(s)}(t)| \leq \frac{1}{t^{\alpha}} t^{\frac{1}{4}+2\epsilon}, \quad 1 \leq s \leq k, \tag{39}$$

for t large enough. Notice that $\zeta^s(t)$ are of the order of $V_{\alpha}^{\frac{1}{2}}(t)$, where

$$V_{\alpha}^{\frac{1}{2}}(t) = \begin{cases} \frac{1}{\sqrt{1-2\alpha}} t^{1/2-\alpha}, & 0 < \alpha < \frac{1}{2}, \\ \sqrt{\log t}, & \alpha = \frac{1}{2}. \end{cases} \tag{40}$$

It follows easily from equations (28, 29) that there exist $\beta(t) \to 0$ as $t \to \infty$ such that with probability greater than $1 - \beta(t)$:

$$\min_{1 \leq s, s_1, s_2 \leq k} (|\zeta^{(s)}(t)|, |\zeta^{(s_1)}(t) - \zeta^{(s_2)}(t)|, |\zeta^{(s)}(t) - B(t)|) \geq \frac{V_{\alpha}^{\frac{1}{2}}(t)}{\mathrm{loglog} t} \tag{41}$$

and

$$\max_{1 \leq s, s_1, s_2 \leq k} (|\zeta^{(s)}(t)|, |\zeta^{(s_1)}(t) - \zeta^{(s_2)}(t)|, |\zeta^{(s)}(t) - B(t)|) \leq V_{\alpha}^{\frac{1}{2}}(t) \mathrm{loglog} t. \tag{42}$$

If equations (37)-(42) hold and $a_{s_1}(t) < a_{s_2}(t)$ then

$$\sum_{i=a_{s_1}(t)+1}^{a_{s_2}(t)} \frac{1}{j^{\alpha}} = \zeta^{(s_1)}(t) - \zeta^{(s_2)}(t) + \mathrm{O}(t^{\frac{1}{4}+2\epsilon-\alpha}). \tag{43}$$

Hence,

$$\frac{1}{1-\alpha}(a_{s_2}^{1-\alpha}(t) - a_{s_1}^{1-\alpha}(t)) = \zeta^{(s_1)}(t) - \zeta^{(s_2)}(t) + \mathrm{O}(t^{\frac{1}{4}+2\epsilon-\alpha}) =$$

$$(\zeta^{(s_1)}(t) - \zeta^{(s_2)}(t)) \left(1 + \mathrm{O}\left(\frac{t^{\frac{1}{4}+2\epsilon-\alpha} \mathrm{loglog}\ t}{V_{\alpha}^{\frac{1}{2}}(t)}\right)\right).$$

Since

$$\frac{1}{1-\alpha}(a_{s_2}^{1-\alpha}(t) - a_{s_1}^{1-\alpha}(t)) = \frac{a_{s_2}(t) - a_{s_1}(t)}{\frac{t}{k}^{\alpha}} \left(1 + \mathrm{O}\left(\frac{t^{\frac{1}{2}+2\epsilon}}{t}\right)\right), \tag{44}$$

we have

$$\hat{a}_{s_2}(t) - \hat{a}_{s_1}(t) = a_{s_2}(t) - a_{s_1}(t) =$$

$$\left(\frac{t}{k}\right)^{\alpha} \left(\zeta^{(s_1)}(t) - \zeta^{(s_2)}(t)\right) \left(1 + \mathrm{O}\left(\frac{t^{\frac{1}{2}+2\epsilon}}{t}\right) + \mathrm{O}\left(\frac{t^{\frac{1}{4}+2\epsilon-\alpha} \mathrm{log\ log} t}{V_{\alpha}^{\frac{1}{2}}(t)}\right)\right) =$$

$$\left(\frac{t}{k}\right)^{\alpha} (\zeta^{(s_1)}(t) - \zeta^{(s_2)}(t))(1 + \mathrm{o}(t^{3\epsilon-\frac{1}{4}})).$$

Taking $\epsilon < 1/12$ we obtain

$$\hat{a}_{s_2}(t) - \hat{a}_{s_1}(t) = \left(\frac{t}{k}\right)^{\alpha} (\zeta^{(s_1)}(t) - \zeta^{(s_2)}(t))(1 + \mathrm{o}(t^{-\nu})) \tag{45}$$

for some $\nu > 0$. Using (41), (42) and $\sum_{s=1}^{k} \hat{a}_s(t) = L(0)$, we obtain from (45):

$$\hat{a}_s(t) = \left(\frac{t}{k}\right)^{\alpha} (B(t) - \zeta^{(s)}(t))(1 + \mathrm{o}(t^{-\nu/2})), \quad 1 \le s \le k. \tag{46}$$

Notice that (46) holds with probability greater than $(1 - \beta(t))$ for all t large enough. Dividing on $\sqrt{t}$ for $0 < \alpha < 1/2$ and on $\sqrt{t \log t}$ for $\alpha = 1/2$ and using eqs. (28, 29) and independence of $\zeta^{(s)}(t)$ for different s, we immediately obtain statements 2 and 3 of Proposition 3. □

In fact, limit theorem holds for a distribution of a whole vector $(\hat{a}_1(t), \hat{a}_2(t), ..., \hat{a}_k(t))$. Denote

$$\vec{a}\ (t) = \begin{cases} \frac{1}{\sqrt{t}}(\hat{a}_1(t), \ldots, \hat{a}_k(t)), & 0 < \alpha < 1/2, \\ \frac{1}{\sqrt{t \log t}}(\hat{a}_1(t), \ldots, \hat{a}_k(t)), & \alpha = 1/2 \end{cases} \tag{47}$$

and

$$\tilde{\sigma}_{\alpha}^2 = \begin{cases} \frac{1}{(1-2\alpha)k^{2+2\alpha}}, & 0 < \alpha < 1/2, \\ \frac{1}{k^3}, & \alpha = 1/2. \end{cases} \tag{48}$$

Then the following proposition easily follows from (46).

Proposition 4. Probability distribution of the vector $\vec{a}\ (t)$ converges weakly as $t \to \infty$ to the probability distribution of the vector $\vec{\chi} = (\chi_1, \ldots, \chi_k)$, where $\chi_s = \sum_{i \ne s}(\zeta^{(i)} - \zeta^{(s)}), 1 \le s \le k$, and $\zeta^{(s)}$, $1 \le s \le k$, are independent $N(0, \tilde{\sigma}_{\alpha}^2)$ random variables.

5 Summary and Discussion

We present a phenomenological probabilistic model for neurite competition leading to the specification of an axon at the early stages of neuron development. The main aim of our model is to show that quite dramatic effect of only one neurite elongation out of several initially identical can be explained by a simple mechanism of stochastic preference.

The model captures the main features of the experiments: (1) for neurites of the same length it is impossible to predict which will become an axon, (2) the probability that a neurite becomes an axon depends on its relative length, and (3) longer neurites have more chances to win. For $\alpha > 1$ the behaviour of this model is qualitatively very similar to the one observed experimentally (see Fig. 2) (Dotti and Banker, 1987; Goslin and Banker, 1989; Esch *et al*, 1999). The model also demonstrates sharp transition in asymptotic behaviour depending on parameter α. Indeed, in the case $\alpha \le 1$ there is no axon specification and all dendrites asymptotically have lengths of the same order.

We have chosen the discrete model purely for simplicity of presentation. In fact, the same phenomena will be observed for a continuous time Markov process or for a model wherein the

length increments are random. Once again, if stochastic preferences mechanism has enough strength ($\alpha > 1$), then only one neurite wins the race. A choice of the power-law dependence of probability P_j on the length of the neurite (eqs. 3-4) is the simplest and quite natural assumption based on the experimental fact that the length is crucial in the competition of the neurites (Goslin and Banker, 1989).

A competition time T^* which is defined as the time needed for an axon to exceed the others by some threshold length depends on two factors: (1) the initial distribution of lengths, and (2) the value of α (> 1). Here we take the length increment l as a unit of length. If there is a neurite which is much longer than other four neurites, it has more chances to win. Thus, for example if one neurite is 10% percent longer than the others, for $\alpha = 2$ it wins with an estimated probability 0.74, and it wins almost always (with an estimated probability 0.99) if it is initially 20% longer than the others. The bigger the initial difference in the lengths, the shorter is the competition time. Competition time dramatically decreases with increase of α, which measures the advantage of being long. At present experimental data does not provide reliable conditional probabilities for the process of axon specification. In future, however, probabilities calculated on a basis of extensive experimental studies might be used in order to determine possible values of the power-law constant α.

The phenomenon of axon formation has been previously modelled by Samuels et al (1996). Their deterministic model is based upon the assumption of the existence of a determinant chemical whose concentration inside the neuron influences the growth rate of the neurite. Although this model predicts that it is the length that is more crucial than the initial concentration of the yet unknown chemical, it fails to account for the main feature of the experiment: the randomness of the choice for the axon. According to Samuels *et al* (1996) model, even small differences in initial neurite lengths will almost invariably lead to the longer neurite forming the axon. This contradicts with the experimental data according to which only if a neurite is longer than the others by a threshold length will it become an axon. Otherwise, according to the experimental data the longest neurite only has more chances of becoming the axon, depending on its relative length. Our phenomenological probabilistic model provides the "one-win" result on the probabilistic grounds.

The molecular mechanisms of the selective elongation are not yet well understood. As was already mentioned above, recent experimental evidence shows that the axon specification can be directed by locally applied growth-promoting molecules (Esch *al*, 1999). It was then suggested that the specification process is probably signal-mediated, involving binding substrate molecules to receptors on the neurite surfaces. Some important extracellular molecules that regulate dendritic development have recently been identified and their signalling pathways have also been elucidated (Higgins *et al*, 1997).

According to a hypothesis by Esch *et al* (1999), the longer the neurite, the more receptors are located on its surface, and the chance of extracellular molecules to bind to those receptors is greater, causing the neurite to elongate even further. Let us elaborate on this hypothesis. The extracellular growth-promoting molecules, S, bind to the cell surface receptors, R. The surface density ρ of these receptors along the neurite length is assumed to be the same for all competing neurites. Thus, the i-th neurite has $R_i = \rho L_i$ receptors on its surface. As axon

specification process is triggered by binding of a substrate S to receptor R_i, forming a complex C_i, the chances of formation of such a complex depend on the number of available receptors (and on the configuration of the neurite). If just one receptor is needed for formation of a complex, which increase chances for neurite to elongate, then

$$P[L_i(t+\triangle t) = L_i(t) + l] \sim R_i \sim L_i$$

This case corresponds to $\alpha = 1$ of our model. As we have seen above, this leads to growth of all neurites. It is plausible, however, to assume that $n > 1$ receptors are needed to form a growth-promoting complex C_i:

$$nR_i + S \rightleftharpoons C_i$$

Then, $P[L_i(t+1) = L_i(t) + l] \sim R_i^n \sim L_i^n$. This, obviously brings us to a model where $\alpha = n > 1$.

Esch *et al*, (1999) proposed several hypotheses of how the growth-promoting molecules initiate a series of events leading to selective elongation. These include redistribution of actin that may allow forward extension of the microtubule network within the growth cone (Burden-Gulley and Lemmon, 1996), or a movement of organelles into the periphery of the growth cone (Futerman and Banker, 1996), possibly associated with the insertion of new plasma membrane either at specific growth sites (e.g. distal end only) or all along the axon (Khanin *et al*, 1998). The initial stages of the axon specification probably involve competition for the growth bulk material.

Future mathematical models of the axon specification should elaborate on the issues of ligand-binding mediated events, competition for the growth material and the reduction in the growth rate of neurites who failed to win the race to be an axon. These models should be stochastic. It is quite obvious that purely deterministic models would always predict that the longest axon will win, no matter how small the initial differences in length are. In addition, to the random component of the ligand-receptor binding, other signal-mediated events (like interaction between cell surface receptors and actin cytoskeleton, Davis and Bennet (1994)) might contribute to the probabilistic mechanism of the axon specification. It is important to study the relative importance of the various factors in this process.

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