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View of mathematicians on biological data: Modeling axon growth using CTRW

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> In the theory of Brownian motion the first concern has always been the calculation of the mean square displacement of the particle, because this could be immediately observed.
>
> *George Uhlenbeck and Leonard Ornstein (1930)*

1 Description and analysis of the model

The main goal of this note is to propose a mathematical model that describes an ensemble of axon growth cones and shows the difference in the behavior of normal and mutant axons. We use here experimental microscopic data provided by the Morphem team (INRIA). An essential part of our analysis is to find the crucial characteristics of axon paths which indicates whether the family of axons is normal or mutant.

We introduce a probabilistic model for axon growing such that each family of axons is described as an ensemble of trajectories of a continuous time random walk (CTRW). We describe different regimes in the model and conclude how the behavior of axons depends on the parameters of the model. Biological observations of the axonal growth process show that axons are guided towards their targets by chemical signals from the cellular environment. To represent this control mechanism in mathematical terms we propose the CTRW model, where a random waiting time reflects a reaction time of the growth cones on the neighboring chemical environment. We observed that the distributions of the waiting time in the model for the normal axons and for the mutant ones differ a lot.

Continuous-time random walks (CTRW) are a natural generalization of a usual random walk. Mathematical analysis can be dated back to the pioneering work of Montroll and Weiss in the sixties [1]. At present they are extensively used in applications to physics, chemistry, and other sciences, see e.g. [2], [3].

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We are working with three families of (static) trajectories associated with the axon growth cones. One of the family is for normal axons, the other two are for two different axon mutations. We don't have dynamical data, and each trajectory presents positions of an axon tip during the observation time. The observation time is the same for all axons, but we don't have information about the intermediate stopping places for development of each axon. On figure 1 we present three sets of trajectories of axon growth cones. In fact, axons represented on real data images have different starting positions, but we shifted all of them to have the same starting point.

Now our main question is how to determine whether the family of axons on Fig. 1 is normal or mutant? We give the answer on this question below.

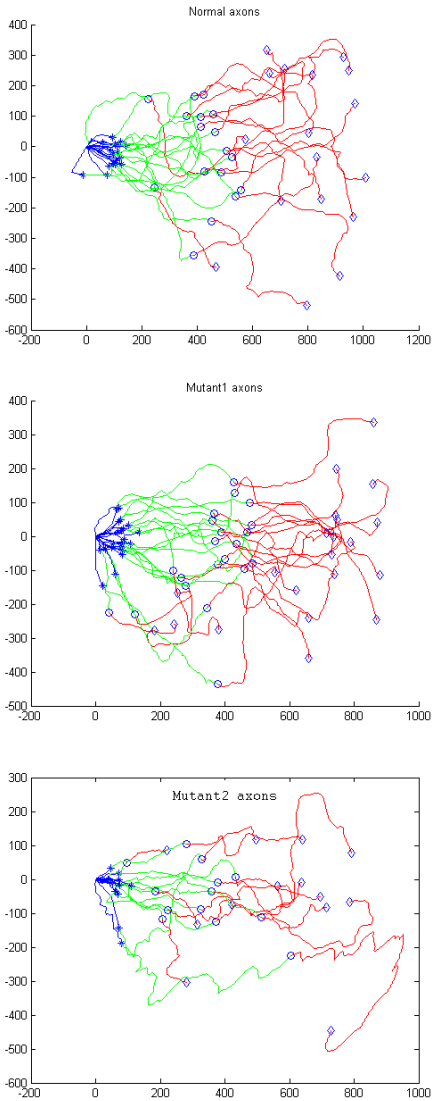

Fig. 1.1: Axonal trajectories

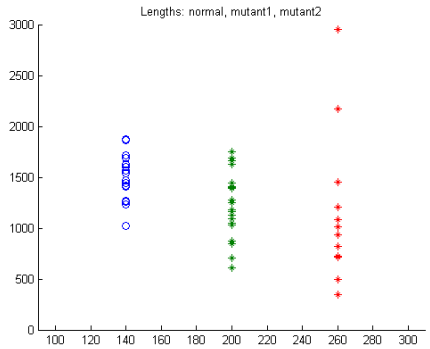

Fig. 1.2: Length distributions

The first observation is about length of axons. On fig. 2 we present the values of the lengths for the normal and mutant axons. One can see that the average length for the mutant axons is less than for the normal ones.

The second observation concerns the value of the average deviation of trajectories from the origin. We propose a model of axon growing based on a CTRW model. A CTRW model is a symmetrical random walk subordinated to a renewal process. It is defined by two probability distributions: a distribution $p(x \to y),\ x, y \in \mathbb{Z}^d$ for a spacial random walk and a distribution $f(t),\ t \geq 0$ for a waiting time. Then CTRW can be described as follows: a particle wait at position x a random time distributed by $f(t)$, then it jumps from x to y according to the distribution $p(x-y)$, and so on. Then a longer waiting time implies reducing of trajectories lengths.

Since we don't have any dynamical data for axon growing, we couldn't control absolute time and should introduce in our model an artificial time. We study here three cases, which are reasonable from our point of view.

The first case (A uniform partition). Assuming an equal absolute time T for growing of all axons and the existence of the average speed for any trajectory of the CTRW $X(t) \in \mathbb{Z}^d,\ t \in [0, T]$ (depending on the length of the trajectory) we can consider uniform partitions of trajectories proportional to the length L of axons: $X(0) = 0,\ X(T) = x_{end},\ X(\frac{k}{10}T) = x_k,\ k = 0, 1, \ldots, 10$, where x_{end} is a position of the end of the trajectory of the length L, and $x_k,\ k = 0, 1, \ldots, 10$ are points on the trajectory corresponding to the length $\frac{k}{10}L,\ k = 0, 1, \ldots, 10$.

The second case (A uniform partition after elongation). In this case we assume different time for axon growing but the same evolving time T for all axons. For long axons we consider again an equal absolute growing/evolving time as above, assuming different average speeds of the growth dependent on the length L. For short axons we say that the growing process stops at some moment of time, and after that the short axons just keep their final position in evolution process. Let L_n be an average length of trajectories of normal axons, then we put $L_n = T$ as the absolute evolving time and consider the following elongation in time for all short axons with a length L less than $L_n = T$: we take

the last part of the trajectory (from "time" L to time T) coinciding with the end point of axons. Thus we obtain that all short trajectories evolve during the same time $T = L_n$ with a constant speed 1, and we assume that it is the same absolute growing/evolving time $T = L_n$ for long trajectories. Finally, we construct the uniform partitions depending on the length of axons L, which is the same as in the first case.

The third case (A non uniform partition). Assuming again the same absolute time for growing of all axons and using observations from biological experiments that a speed of axon growing is decreasing in time (especially for mutant axons), we consider a non uniform partitions of trajectories corresponding to the following lengths $l(k)$:

$$l(k) \;=\; \frac{\alpha L}{1-e^{-\alpha}} \int_0^{t_k} e^{-\alpha t}\, dt, \quad t_k = \frac{k}{10}, \quad k \;= 0, 1, \dots 10$$

with $\alpha = 2$.

Since the axon growth cones in real growing processes develop along the main canal, we consider in our model a permanent drift along the X-axis, and study the deviation only along the Y-axis. Thus we can take the X direction as a direction of an artificial time. We formulate the following well-known result for the mean squared deviation $\langle Y^2(t)\rangle$, where $Y(t)$ is the position of the Y-coordinate of the 1-D CTRW when time t is large enough, see e.g. [1, 3].

Proposition 1.1. *Let $p(u) = p(-u)$ is a distribution of a symmetrical random walk on Z^1, and we consider two cases:*

1) *diffusive behaviour: $\langle\tau\rangle = \int_0^\infty t\ f(t)dt < \infty$,*

2) *anomalous diffusion: $\langle\tau\rangle = \infty$ and $f(t) \sim \dfrac{1}{t^{\alpha+1}}$ as $t \to \infty$ with $\alpha \in (0,1)$.*

Then for large enough t we have for the mean squared displacement

$$\langle Y^2(t)\rangle \;\approx\; \frac{2a}{\langle\tau\rangle} t \quad \textit{in the first case} \tag{1.1}$$

and

$$\langle Y^2(t)\rangle \;\approx\; t^\alpha \quad \textit{in the second case with } \alpha \in (0,1). \tag{1.2}$$

Here a is the dispersion of the symmetrical random walk.

The proof of the Proposition is based on the Fourier–Laplace transform of the characteristic function of the random walk and on the formula

$$\hat{Y}^2(s) \;=\; \int \langle Y^2(t)\rangle\ e^{-st}\ dt \;=\; -\frac{\partial^2 \hat{\theta}(\lambda, s)}{\partial \lambda^2}\Big|_{\lambda=0},$$

where $\hat{\theta}(\lambda, s) \;=\; \int_0^\infty e^{-st} \langle e^{i\lambda Y(t)}\rangle\ dt$.

The main idea of our analysis is to compare statistical characteristics of the trajectories from different families (for normal and mutant axons separately) with the mean squared displacements for CTRW given by (1.1)–(1.2).

We use the empirical law for $\langle Y^2(t)\rangle$ to construct the graph of $\langle Y^2(t)\rangle$ as a function of t. Then we compare these functions with the linear or sub-linear growth given by (1.1)–(1.2) and conclude which parameters of the CTRW model imply the similar law for $\langle Y^2(t)\rangle$. For example, if $\langle Y^2(t)\rangle$ increases as a linear function: $y(t) = rt$, then by (1.1) we get that in this case the growth rate r of the function $y(t) = \langle Y^2(t)\rangle$ is connected with parameters a and $\langle\tau\rangle$ as follows:

$$r = \frac{2a}{\langle\tau\rangle}.$$

On Fig. 3–8 we present our calculations of $\langle Y^2(t)\rangle$ and $\left\langle (Y(t) - \langle Y(t)\rangle)^2 \right\rangle$ using the statistical data and construct corresponding interpolation curves in each of three cases under our consideration. Here $\langle\cdot\rangle$ is the empirical average.

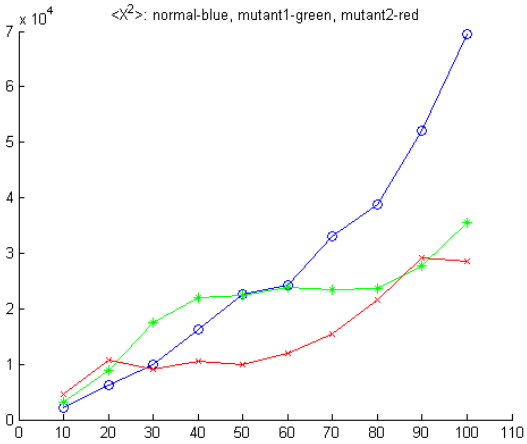

Fig. 1.3: The first case: second moments as a function of time (% of length)

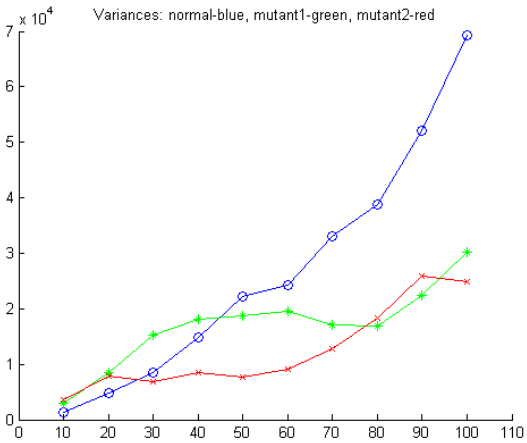

Fig. 1.4: The first case: variances as a function of time (% of length)

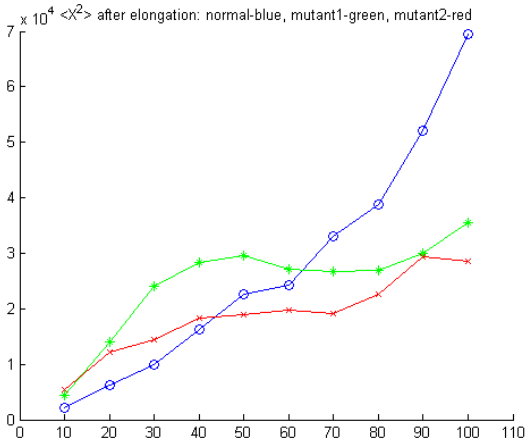

Fig. 1.5: The second case (elongation of short axons): second moments as a function of time (% of length)

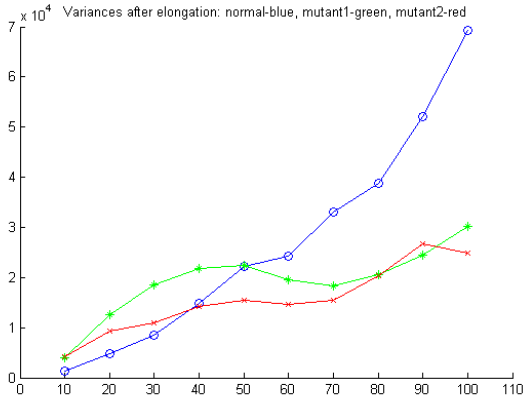

Fig. 1.6: The second case (elongation of short axons): variances as a function of time (% of length)

2 Conclusions

The analysis of the graph of the functions $y(t) = \langle Y^2(t)\rangle$ and $\big\langle (Y(t) - \langle Y(t)\rangle)^2\big\rangle$ allows one to conclude whether the family of corresponding axons is normal or mutant.

I. The difference in the behavior of the graph of $y(t) = \langle Y^2(t)\rangle$ and $\big\langle (Y(t) - \langle Y(t)\rangle)^2\big\rangle$ on Fig. 3–8 in the case of normal and mutant axons is evident: for normal axons the graph increases linearly whereas for mutant axons the increasing is sub-linear (or linear but with essentially smaller growth rate then in the normal case: $r_m < r_n$). Consequently, by the proposition the distributions of the waiting time $f(t)$ for normal and mutant axons are different, and by the formula (1.1) the average waiting time for mutant axons is longer

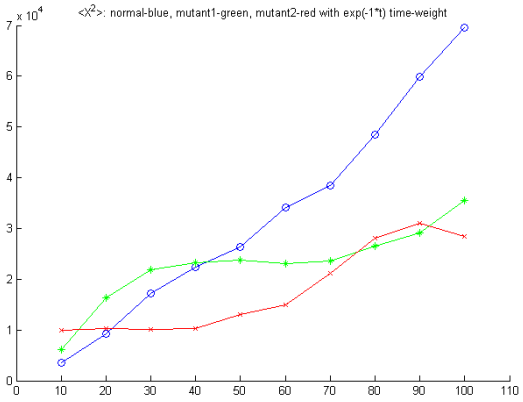

Fig. 1.7: The third case: second moments as a function of time (% of length with weights)

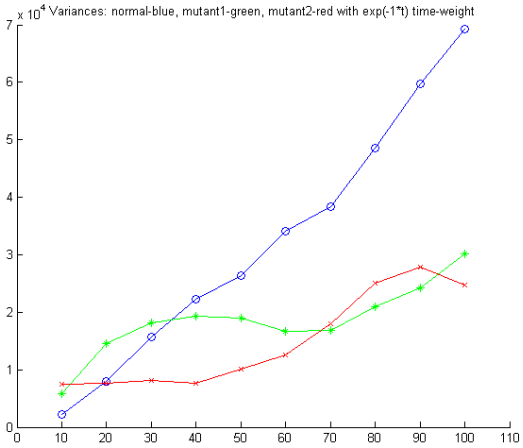

Fig. 1.8: The third case: variances as a function of time (% of length with weights)

(greater) than for normal axons:

$$\langle \tau_m \rangle \ > \ \langle \tau_n \rangle.$$

Using the constructions of the graphs of $\langle Y^2(t) \rangle$ and $\left\langle (Y(t) - \langle Y(t) \rangle)^2 \right\rangle$ for mutant axons we can formulate a hypothesis that for normal axons the time between renewals has a finite mean, whereas for mutant axons the time between renewals is greater in average or even can have an infinite mean. In the latter case, the scaling limit for the CTRW is an operator of the Levy motion subordinated to the hitting time process of a classical stable subordinator, see e.g. [4]. In this case, for large enough t we have $\langle Y^2(t) \rangle \ \approx \ t^\alpha$ with $0 < \alpha < 1$. That means that the hitting time for this CTRW to reach distant compact sets is much more greater for mutant axons than for normal ones.

II. We can observe two different regimes during evolution of axon growth cones. In the second regime, which is started approximately after 0.6 L, the coefficient $\dfrac{2a}{\langle\tau\rangle}$ increases, see formula (1.1). That can be the result of decreasing averaged waiting time $\langle\tau\rangle$ or increasing dispersion of the spacial random walk a on the second phase of the evolution.

We present in this note our observations on the statistical behavior of three families of axons, and the corresponding explanations of this behavior from a biological point of view is an open question.

We believe that modeling and analysis of the axon shape for different populations (normal/mutant) of axons is an important step of better understanding pathologies and degenerative diseases.

References

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