Dynamics of path aggregation in the presence of turnover

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Abstract – We investigate the slow time scales that arise from aging of the paths during the process of path aggregation. This is studied using Monte Carlo simulations of a model aiming to describe the formation of fascicles of axons mediated by contact axon-axon interactions. The growing axons are represented as interacting directed random walks in two spatial dimensions. To mimic axonal turnover, random walkers are injected and whole paths of individual walkers are removed at specified rates. We identify several distinct time scales that emerge from the system dynamics and can exceed the average axonal lifetime by orders of magnitude. In the dynamical steady state, the position-dependent distribution of fascicle sizes obeys a scaling law. We discuss our findings in terms of an analytically tractable, effective model of fascicle dynamics.

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Introduction. – The process of path aggregation is a ubiquitous phenomenon in nature. Some examples of such phenomena are river basin formation [1,2], aggregation of trails of liquid droplets moving down a window pane, formation of insect pheromone trails [3–5], and of pedestrian trail systems [6,7].

Path aggregation has been mathematically studied mainly in two classes of models. One of them is known as the active-walker models [7] in which each walker in course of its passage through the system changes the surrounding environment locally, which in turn influences the later walkers. An example of such a process is the ant trail formation [3,4]. While walking, an ant leaves a chemical trail of pheromones which other ants can sense and follow. The mechanism of human and animal trail formation is mediated by the deformation of vegetation that generates an interaction between earlier and later walkers [7]. A mathematical formalism to study the formation of such trails has been developed in refs. [6,7]. The other class of models showing path aggregation deals with non-interacting random walkers moving through a fluctuating environment. In ref. [8], condensation of trails of particles moving in an environment with Gaussian spatial and temporal correlation is demonstrated analytically. Another example of this model class is the Scheidegger river model [1] (and related models [2]) which describes the formation of a stream network by aggregation of streams flowing downhill on a slope with local random elevations.

In this letter we analyze the dynamics of path aggregation using a simple model that belongs to the class of active walker systems discussed above. The model is similar to the one used to study path localization in ref. [9]. In our model, however, we take into account the aging of the paths, an important aspect of the active walker models. For instance, in ant trail systems, the pheromone trails age due to evaporation. In the mammalian trail formation, the deformation of the vegetation due to the movement of a mammal decays continuously with time [7]. In our model, the individual paths do not age gradually, but rather maintain their full identity until they are abruptly removed from the system. This particular rule for path aging is chosen to allow application of our model to the process of axon fasciculation (formation of axon bundles1), which we discuss next.

1Throughout the text we use the term “axon fasciculation” rather than “axon bundling” as the term “axon fasciculation” is standard in biological literature.
During the development of an organism, neurons located at peripheral tissues (e.g. the retina or the nasal epithelium) establish connections to the brain via growing axons. The growth cone structure at the tip of the axon interacts with other axons or external chemical signals and can bias the direction of growth when spatially distributed chemical signals are present [10]. In the absence of directional signals, the growth cone maintains an approximately constant average growth direction, while exploring stochastically the environment in the transverse direction [11]. The interaction of growth cones with the shafts of other axons commonly leads to fasciculation of axon shafts [12]. During development, a significant portion of fully grown neurons die and get replaced by newborn neurons with newly growing axons. For certain types of neurons (such as the sensory neurons of the mammalian olfactory system) the turnover persists throughout the lifespan of an animal. In mice, the average lifetime of an olfactory sensory neuron is 1–2 months [13], which is less than one tenth of the mouse lifespan. The mature connectivity pattern is fully established only after several turnover periods [14,15].

The model we propose in this letter captures the basic ingredients of the process of axon fascilitation, i.e. attractive interaction of growth cones with axon shafts, as well as neuronal turnover. The main contribution of this letter is a detailed discussion of the slow time scales that emerge from the dynamics of our model. Using Monte Carlo simulations we characterize the time scale for the approach to steady state and the correlation time within the steady state, and show that they can exceed the average axonal lifetime by orders of magnitude. To understand these results we formulate an analytically tractable effective single-fascicle dynamics. This allows us to relate the observed slow time scales to the dynamics of the basins of the fascicles. From the effective fascicle dynamics we derive three time scales which we compare to the time scales extracted from the Monte Carlo simulation of the full system.

For clarity, we stress that the dynamics of our model differs substantially from one-dimensional coalescence ($A + A \rightarrow A$) [16] or aggregation ($mA + nA \rightarrow (m + n)A$) [17]. In our model, there is no direct inter-walker interaction; rather, each random walker interacts locally with the trails of other walkers. While the stationary properties of the system (such as the fascicle size distribution in the steady state) may be approximately understood using an analogy to one-dimensional diffusion with aggregation, the dynamical properties (such as the time scale of approach to the steady state, and the correlation time in the steady state) are undefined in the one-dimensional analogy, and require understanding based on the full two-dimensional model. This is in contrast to the situation for path aggregation models without turnover: e.g., the Scheidegger river network model can be mapped onto the Takayasu model of diffusion-aggregation in the presence of injection of mass in one dimension [18].

Fig. 1: (Color online) (a) Interacting directed random walks on a tilted square lattice. A random walker (+) represents a growth cone. For one walker, the possible future sites (filled ⌂) and their nearest neighbours (○) are marked. The trail of a walker (line) models an axon shaft. (b) Typical late-time configuration ($t = 25T$) in a system with $L = 800$ and $N_0 = 100$. For the fascicle identified at $y = 6000$ (arrow), $D$ indicates its basin, i.e. the interval at the level $y = 0$ between the right-most and left-most axons belonging to the fascicle. The gap $E$ is the inter-basin free space at $y = 0$. Note that the $y$-coordinate cannot be understood as equivalent to time (see the main text).

Model and numerical implementation. – Each growing axon is represented as a directed random walk in two spatial dimensions (fig. 1(a)). The random walkers (representing the growth cones) are initiated at the periphery ($y = 0$, random $x$) with a birth rate $\alpha$, and move towards the target area (large $y$) with constant velocity $v_0 = 1$. In the numerical implementation on a tilted square lattice, at each time step the growth cone at ($x, y$) can move to ($x - 1, y + 1$) (left) or ($x + 1, y + 1$) (right). (Note that the sites are labeled alternatively by even $x$ and odd $x$ at successive $y$-levels.) The probability $p_{L,R}$ to move left/right is evaluated based on the axon occupancy at the ($x - 1, y + 1$) and ($x + 1, y + 1$) sites and their nearest neighbours (see fig. 1(a)). In the simplest version of the model, the interaction is governed by the “always attach, never detach” rule: $p_{L} = 1$ when among the sites ($x \pm 1, y + 1$), ($x \pm 3, y + 1$) only ($x - 3, y + 1$) is already occupied; $p_R = 1$ when only ($x + 3, y + 1$) is occupied; $p_{L} = p_{R} = 1/2$ in all other cases. Periodic boundary conditions are used in the x-direction.

To capture the effect of neuronal turnover, each random walker is assigned a lifetime from an exponential distribution with mean $T$. When the lifetime expires, the random walker and its entire trail is removed from the system. The mean number of axons in the system therefore reaches the steady-state value $N(y) = N_0 \exp(-\beta y)$, where $N_0 = \alpha / \beta$, and $\beta = 1/T$ is the death rate per axon. In the simulations, we use $T = 10^5$ time steps, and restrict our attention to $y \leq T/10$. The birth rate $\alpha$ is chosen so as to obtain the desired number of axons $N_0$, or equivalently, the desired axon density $\rho = N_0 / L$ ($\rho = 1/2$ implies an average occupancy of one axon per site), where $L$ is the system size in the $x$-direction. The presence of turnover distinguishes our model from previous theoretical work on axon fascilitation [19,20]. The $y$-coordinate in fig. 1(a) cannot be viewed as equivalent to time, and the dynamics at fixed $y$
(which is the main focus of this letter) has no analogy in one-dimensional models of aggregation or coalescence.

**Mean fascicle size.** – A typical late-time configuration for a system with \( L = 800 \) and \( N_0 = 100 \) is shown in fig. 1(b). With increasing fasciculation distance \( y \), the axons aggregate into a decreasing number \( m(y) \) of fascicles. (At a given \( y \), two axons are considered to be part of the same fascicle if they are not separated by any unoccupied sites.) The number of axons in the fascicle is referred to as the fascicle size \( n \). The mean fascicle size \( \bar{n} \) at level \( y \) may be estimated using the following mean-field argument. Each of the \( m \) fascicles collects axons that were initiated on an interval of length \( D \approx L/m \) at the level \( y = 0 \) (the basin of the fascicle, see fig. 1(b)). The number of collected axons that survive at level \( y \) (i.e., grow to \( y \) before being deleted) is \( D \rho \exp(-\beta y) \). The axons initiated at opposite edges of the basin are expected to meet within \( y \approx (D/2)^2 \) steps of the random walk in the \( x \)-direction. Consequently, \( \bar{n} \approx 2 \rho y^{1/2} \exp(-\beta y) \) for \( y \) up to \( y \approx (L/2)^2 \), where complete fasciculation (\( \bar{n} = N(y) \)) is expected. Thus, for \( y \ll (L/2)^2 \) and \( \beta y \ll 1 \) (which is satisfied in our simulations), the mean-field argument predicts the power law growth \( \bar{n} \approx 2 \rho y^{1/2} \).

**Slow time scales.** – The measured mean fascicle size, obtained by averaging over all the existing fascicles at a given \( y \) (fig. 2), grows with time as \( \bar{n}(t; y) = n_{\infty} - \rho \exp(-\beta t) - q \exp(-t/\tau_{au}) \), where \( \tau_{au}(y) \) defines the time scale of approach to the steady-state value \( n_{\infty}(y) \). We find that \( \tau_{au} \) is an increasing function of \( y \) (up to \( y \approx (L/2)^2 \) where a single fascicle remains and \( \tau_{au} \) drops to \( T \)), and can exceed the axon lifetime \( T \) by orders of magnitude (figs. 2 and 3(b)). Asymptotically in \( y \), we find \( \bar{n}_{\infty} = n_{\infty} + 2 \rho y^{1/2} \exp(-\beta y) \), with \( b \approx 0.48 \) (fig. 2, inset); we expect that the true asymptotic exponent \( b = 1/2 \) would be reached in a simulation with extended range of \( y \). See footnote\(^2\) for a discussion of the offset \( n_{\infty} \) and footnote\(^3\) for the error bars on the growth exponent \( b \).

The dynamics in the steady state is characterized by the auto-correlation function for the mean fascicle size \( \bar{n}(t) \) at a fixed \( y \)-level: \( c(t) = \langle \bar{n}(t)\bar{n}(0) \rangle \) which fits to the form \( p + \exp(-\beta t) + r \exp(-t/\tau_c) \). In fig. 3(a) we plot the subtracted correlation function \( g(t) = [c(t) - p]/(q + r) \). The correlation time \( \tau_c \) increases with \( y \) and significantly exceeds the axon lifetime \( T \) (fig. 3(b)).

**Effective fascicle dynamics at fixed \( y \).** – We next examine the dynamics of individual fascicles. These are typically long lived, but at a given \( y \)-level the fascicles very rarely merge or split (data not shown). Consequently, the number \( n(t) \) of axons in each fascicle may be viewed as given by a stochastic process specified by the rates \( u_+(n, y) \) (for transitions \( n \to n \pm 1 \)). At fixed \( y \), a fascicle can loose an axon only when the axon dies, thus \( u_-(n) = \beta n \), independent of \( y \).

\(^2\)The offset \( n_{\infty} \) arises since even isolated axons are counted as fascicles (of size 1); therefore \( n_{\infty}(y = 0) \geq 1 \). At low system density \( \rho = 1/8 \), we find \( n_{\infty} = 1.11 \). At high density \( \rho = 1/2 \), the offset is higher \( n_{\infty}(y = 4.2) \) as most new axons are injected within one lattice unit distance from existing axons, and are therefore part of a fascicle of size \( > 1 \) already at \( y = 0 \). The higher value of \( n_{\infty} \) in the \( \rho = 1/2 \) system contributes to the stronger deviation of fitted growth exponent \( b \) from the expected asymptotic value \( b = 1/2 \).

\(^3\)The fitting procedures used to extract the values of the growth exponent \( b \) were as follows. At a given fasciculation distance \( y \) we extracted the asymptotic (in time) fascicle size \( n_{\infty}(y) \) as discussed in the main text; the corresponding error bar on \( n_{\infty}(y) \) is \( < 0.5 \% \). We then fit the \( n_{\infty}(y) \) values to the form \( n_{\infty} = n_{\infty} + 2 \rho y^{1/2} \exp(-\beta y) \), yielding the offset \( n_{\infty} \) and the growth exponent \( b \). The least-squares fitting was restricted to the range \( y \gtrsim 80 \). For the two system densities used \( \rho = 1/8 \) and \( \rho = 1/2 \), the fit parameters are \( n_{\infty} = 1.11 \pm 0.01 \) and \( b = 0.486 \pm 0.002 \) (\( L = 800 \)) and \( N_0 = 100 \), and \( n_{\infty} = 1.20 \pm 0.03 \) and \( b = 0.478 \pm 0.001 \) (\( L = 400 \) and \( N_0 = 200 \)). Combined with the 0.5% error on the \( n_{\infty} \) data this yielded a combined error bar on \( b \) of \(< 1 \% \).
with the number of fascicles of size \( n \) and basin size \( D \) for an individual fascicle in a system of \( L=100 \) and \( N_0=50 \) at \( y=400 \). The equal time cross-correlation coefficient averaged over this time-span, \( c(D,n) = \langle (Dn) - \langle D \rangle \langle n \rangle \rangle / \sqrt{\langle D^2 \rangle - \langle D \rangle^2} \langle n^2 \rangle - \langle n \rangle^2 \rangle = 0.74 \). (b) Mean gain and loss rates (in units of \( N_D \)) (averaged over \( 10^3 \) initial conditions and the interval \( 100T \leq t \leq 150T \)) as a function of fascicle size \( n \). The rates are measured at \( y=400 \) in a system with \( L=100 \). The fits (lines) are \( u_+ = n, u_-^{(1)} = 1.92 + 0.974n - 0.002n^2 \) (for \( N_0 = 50 \)), and \( u_-^{(2)} = 1.95 + 0.927n - 0.008n^2 \) (for \( N_0 = 25 \)).

The gain rate \( u_+(n,y) \) is governed by the properties of the fascicle basin (see fig. 1(b)). Under the “always attach, never detach” rule, new axons initiated anywhere within the basin of size \( D \) cannot escape the fascicle. In addition, some of the axons born in the two gaps (of size \( E \)) flanking the basin contribute. Therefore,

\[
\Pi(E,y) = \text{the probability that an axon born within the gap of size } E \text{ survives as a single axon at level } y.
\]

The two stochastic variables that fully characterize the dynamics of a fascicle are the number of axons \( n(t) \) and the basin size \( D(t) \). In fig. 4(a), we plot \( n(t) \) and \( D(t) \) for a specific fascicle followed over 200T. It is seen that \( n \) and \( D \) tend to co-vary (cross-correlation coefficient \( c(D,n) = 0.74 \)). In the following, we treat the dynamics of \( D \) as slaved to the dynamics of \( n \), i.e. we assume that the average separation \( S = D/(n-1) \) between two neighbouring axons within the basin is time-independent. This implies \( u_+(n) = n + b_+ n - c_+ n^2 \) (fig. 4(b)).

The measured average gain rate \( u_+(n) \) in the steady state\(^4\) deviates from linearity at high \( n \), but is well fit by \( u_+(n) = a_+ + b_+ n - c_+ n^2 \) (fig. 4(b)). The quadratic correction may be understood as a saturation effect which reflects that basins of size \( D \) cannot exceed \( 2y \) or \( L \) and that \( D > 2y^{1/2} \) occurs with low probability. The quadratic correction to the linear growth of \( u_+ \) with \( n \) becomes significant at \( n \gtrsim 2y^{1/2} \). Note that the coefficients \( a_+ \), \( b_+ \) and \( c_+ \) are functions of \( y \). The master equation of the effective birth-death process may be written as

\[
\dot{P}(n,t) = u_+(n-1)P(n-1,t) + u_-(n+1)P(n+1,t) - [u_+(n) + u_- (n)]P(n,t),
\]

for \( n > 1 \). For the boundary state \( n=1 \)

\[
\dot{P}(1,t) = J_+(y) + u_- (2)P(2,t) - [u_+(1)+u_-(1)]P(1,t)
\]

where \( J_+(y) \) represents the rate with which new single axons appear between existing fascicles at \( y \). In the steady state, \( J_+(y) \) is balanced by the rate with which existing fascicles disappear from the system, i.e. \( J_+(y) = u_-(1)P_s(1) \). The steady-state condition \( \dot{P}(n,t) = 0 \) then implies pairwise balance, \( u_+(n-1)P_s(n-1) = u_-(n)P_s(n), \) for all \( n \geq 1 \). Thus, the steady-state distribution is given by \( P_s(n) = J_+(y) \sum_{k=0}^{n-1} \frac{u_+(k)}{u_-(k)} \), with the normalization condition \( \sum_{n=0}^{\infty} P_s(n,y) = N(y) \). In order to obtain a closed-form expression for \( P_s(n,y) \), we expand the pairwise balance condition up to linear order in \( 1/N(y) \) and solve to find

\[
\beta P_s(n,y) \approx J_+(y) n^2 \exp[-(n^2 - \kappa n - 1)]
\]

where \( \gamma = a_+ / \beta - 1, \ell = 1 - b_+ / \beta \) and \( \kappa = c_+ / 2 \beta \).

**Time scales.** Three distinct time scales may be extracted from the effective birth-death process. The correlation time \( \tau \) for the fascicle size \( n \), near the macroscopic stationary point \( n_\ast \) \( u_+(n_\ast) = u_-(n_\ast) \), can be expressed [21] as \( \tau = 1/(u'_- (n_\ast)) = 1/(\beta - b_+ + 2c_+ n_\ast) \). With a linear approximation of \( u_+(n) = a_+ + b_+ n \) the approach-to-steady-state time scale for \( n \) is \( \tau_{ap} = 1/(\beta - b_+) \) [21]. We note that the long time scales do not simply arise as a consequence of fascicles containing many axons, but are due to the dynamics of the fascicle basins. To see that, imagine a fascicle with frozen boundary axons, for which \( u_+ \approx (a / L)D \) with \( D \) constant. In this case \( u'_- (n_\ast) = 0 \) and the correlation time \( \tau \approx T \). To obtain \( \tau \gg T, D \) must co-vary with \( n \). At high \( y \), \( u'_- \approx 1/T \) resulting in \( \tau \gg T \). We note that in the full system, the dynamics of the basin size can be viewed as arising from the competition between neighbouring fascicles for basin space.

A third time scale \( \tau_f \) can be defined by \( J_+(y) = m/\tau_f \), and reflects the rate of turnover of fascicles in the full system. Evaluating \( \tau_f = \int P_s(n,y)dn/J_+(y) \) using \( P_s(n,y) \) from eq. (3) (with \( \gamma = 1 \) for consistency with simulation results—see below), we obtain

\[
\tau_f = (T/2\kappa) \left[ 1 - \left( \sqrt{\pi \kappa} \right)^2 (\ell - 2\kappa) \text{erfc}(\ell/2\sqrt{\pi}) / 2\sqrt{\pi} \right].
\]

**Fascicle size distribution in the steady state.** Following the discussion of effective single-fascicle dynamics, we now return to the simulation results for the dynamics of the whole system. The steady state is characterized by the stationary distribution of fascicle
sizes \( P_s(n, y) \), defined as the number of fascicles of size \( n \) at level \( y \). For a system with \( L = 800 \) and \( N_0 = 100 \), \( P_s(n, y) \) is shown at a series of \( y \)-levels in fig. 5. Within the range \( y = 10^3 - 10^4 \) all data collapse onto a single curve after appropriate rescaling (fig. 5). This data collapse implies the scaling law

\[
P_s(n, y) = \langle n(y) \rangle^{-\gamma} \phi(n/\langle n(y) \rangle)
\]

where the scaling function \( \phi(u) = \mathcal{N} u \exp(-\nu u - \lambda u^2) \) and the scaling exponent \( \gamma = 2.1 \).

**Analogy to particle aggregation in one dimension.** – As we have stressed in the introduction, the full dynamics of our system can not be mapped onto the particle dynamics of a one-dimensional reaction-diffusion system. At fixed time \( t \) (within the steady state), however, the aggregation of fascicles with increasing \( y \) may be formally viewed as the evolution of an irreversible aggregation process \( m A + n A \rightarrow (m+n)A \) in one spatial dimension, where the \( y \)-coordinate (fig. 1(b)) takes the meaning of time. This process exhibits analogous scaling properties, but with a different scaling function \( u \exp(-\lambda u^2) \) [17], which lacks the exponential part \( \exp(-\nu u) \). It is interesting to note at this point that to remove the exponential part in the expression of the steady-state distribution (eq. (3)) one would require \( b_+ = \beta \) which in turn implies \( \tau_{ap} = \infty \). In other words, without the exponential part \( \exp(-\nu u) \) the emerging long time scale \( \tau_{ap} \) is lost. This is consistent with the fact that the time scales arising from turnover are undefined in the one-dimensional analogy.

**Scaling of \( y \)-dependent parameters.** – The scaling property of the distribution of fascicle sizes (eq. (5)) implies \( P_s(n, y) = \mathcal{N} \langle n \rangle^{-(r+1)} n \exp(-\nu n \langle n \rangle^{-1} - \lambda n^2 \langle n \rangle^{-2}) \).

The distribution \( P_s(n, y) \) in eq. (5) follows the same normalization as the distribution in eq. (3). The consistency between these two equations requires that \( \gamma = 1 \) and \( J_+ \sim \langle n \rangle^{-(r+1)} \), \( \ell \sim \langle n \rangle^{-1} \), \( \kappa \sim \langle n \rangle^{-2} \). Using the

}\[
\begin{array}{|c|c|c|c|}
\hline
y & a_+ / \beta & b_+ / \beta & c_+ / \beta \\
\hline
20 & 1.96 & 0.862 & 0.0116 \\
40 & 1.94 & 0.909 & 0.0082 \\
100 & 1.96 & 0.947 & 0.0056 \\
400 & 1.92 & 0.974 & 0.0022 \\
\hline
\end{array}
\]

**Conclusion.** – To summarize, we have proposed a simple model for axon fasciculation that shows rich dynamical properties. We identified multiple time scales that grow with the fascication distance \( y \) and become \( \gg T \), the average lifetime of individual axons. The slow time scales do not simply arise as a consequence of fascicles containing many axons, but are due to the
dynamics of the fascicle basins. Our theoretical results have wider relevance for existing related models (*e.g.* insect pheromone trails [3–5] and pedestrian trail formation [6,7]), in which the slow maturation and turnover of the connectivity pattern have not been analyzed in detail.

To conclude, we discuss generalizations of the basic model defined in this article, and the applicability to biological data on axon fasciculation. First, we note that in our discussion of the dynamical properties of the system, it was essential that the random walkers moved in 2 (rather than 3) spatial dimensions, and therefore cannot cross each other without interacting. In contrast, in a 3-dimensional system, the concept of fascicle basins would lose its validity, and the resulting fascicle dynamics would be significantly different. The assumption of 2-dimensionality is satisfied in studies of growth in neuronal cell culture such as [22,23], in which the axons move on the surface of a glass plate. In ref. [23], a fluorescence-based method is proposed for extracting the distribution of fascicle sizes; such data would permit a direct test of our model. To make a quantitative connection, however, it is necessary to examine a generalized version of the basic model, in which there is a non-zero probability for detachment of growth cones from fascicles. With this generalization the concept of the fascicle basins remains relevant, however some aspects of the dynamics are modified [24].

A further generalization of the model is called for in order to describe the sorting of axons by type during fasciculation on the surface of the olfactory bulb. The axons of olfactory sensory neurons expressing distinct odorant receptors [12] are thought to have contact interactions which depend on the receptor [25–27]. In the framework of our model, this corresponds to the introduction of multiple types of random walkers, with type-dependent probabilities for attachment to/detachment from fascicles [24]. In addition, it is necessary to examine to what extent the assumption of 2-dimensionality is satisfied in this system (the depth of the outer nerve layer of the olfactory bulb, in which the axons move, may exceed the radius for contact axon-axon interactions). Ultimately, we aim to address one of the fundamental questions in current olfactory biology: is the convergence of axons into glomeruli [12] achieved predominantly through guidance of individual axons by spatially distributed external cues, or is it the result of a collective process arising from axon-axon interactions?

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