

Survival probability for a diffusive process on a growing domainMatthew J. Simpson,^{1,2} Jesse A. Sharp,¹ and Ruth E. Baker³¹*School of Mathematical Sciences, Queensland University of Technology, Brisbane, Australia*²*Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia*³*Wolfson Centre for Mathematical Biology, Mathematical Institute, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, United Kingdom*

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We consider the motion of a diffusive population on a growing domain, $0 < x < L(t)$, which is motivated by various applications in developmental biology. Individuals in the diffusing population, which could represent molecules or cells in a developmental scenario, undergo two different kinds of motion: (i) undirected movement, characterized by a diffusion coefficient, D , and (ii) directed movement, associated with the underlying domain growth. For a general class of problems with a reflecting boundary at $x = 0$, and an absorbing boundary at $x = L(t)$, we provide an exact solution to the partial differential equation describing the evolution of the population density function, $C(x, t)$. Using this solution, we derive an exact expression for the survival probability, $S(t)$, and an accurate approximation for the long-time limit, $\mathcal{S} = \lim_{t \rightarrow \infty} S(t)$. Unlike traditional analyses on a nongrowing domain, where $\mathcal{S} \equiv 0$, we show that domain growth leads to a very different situation where \mathcal{S} can be positive. The theoretical tools developed and validated in this study allow us to distinguish between situations where the diffusive population reaches the moving boundary at $x = L(t)$ from other situations where the diffusive population never reaches the moving boundary at $x = L(t)$. Making this distinction is relevant to certain applications in developmental biology, such as the development of the enteric nervous system (ENS). All theoretical predictions are verified by implementing a discrete stochastic model.

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I. INTRODUCTION

A canonical problem relevant to several developmental biology processes is to consider the diffusion of a population of molecules or cells on a growing tissue [1–5]. An example of a developmental process involving the diffusion of a population of molecules within a growing tissue is the development of the wing disk in the *Drosophila* embryo [6,7]. Wing disk development is thought to be regulated by morphogen gradients, which are produced by molecular diffusion within the growing wing disk tissues [8,9]. An example of a developmental process involving the diffusion of a population of cells within a growing tissue is the development of the enteric nervous system (ENS) during vertebrate embryogenesis [10–14]. ENS development involves the diffusion of population of precursor cells that are initially confined toward the oral end of the developing gut. As development proceeds, the population of precursor cells spreads, by diffusion, toward the anal end of the gut. The diffusion of the precursor cells through the developing gut tissue occurs simultaneously as the gut tissues elongate [15–17].

In these types of problems the population density profile is thought to evolve according to an advection-diffusion mechanism [18–24]. The diffusion mechanism is associated with individual cells or molecules in the population undergoing an undirected random walk, and the advection mechanism describes the directed motion of individuals driven by the underlying tissue growth. Since the rate of advection is spatially dependent [18–24], the advection process also gives rise to a dilution effect. Here, we consider a diffusion process on a one-dimensional growing domain, $0 < x < L(t)$, where $L(t)$ is the increasing length of the domain. Inspired by previous numerical simulations of ENS development [18,19] we consider a general class of problems where the diffusing

population is initially located near the boundary at $x = 0$, and we ask the question whether the diffusing population is ever able to reach the moving boundary at $x = L(t)$. Broadly speaking we anticipate two different types of behavior: (i) when the rate of tissue growth is sufficiently large compared to the diffusivity of the spreading population the initial profile will never reach the moving boundary at $x = L(t)$; and (ii) when rate of tissue growth is sufficiently small compared to the diffusivity of the spreading population the initial profile will reach $x = L(t)$, at some finite time. Developing analytical methods that distinguish between these two outcomes is important since, in certain applications such as ENS development, normal outcomes are associated with the spreading profile reaching the moving boundary at $x = L(t)$, whereas abnormal outcomes are associated with situations where the spreading profile fails to reach $x = L(t)$ [15–17].

In this work we distinguish between these two situations using the concept of survival probability [25,26]. To achieve our aim we first solve the relevant continuum partial differential equation to give the evolution of the density profile, $C(x, t)$, that describes the density of diffusing individuals at location x and time t . Using our solution for $C(x, t)$, we derive exact expressions for the survival probability, $S(t)$, for exponentially and linearly growing domains, and we note that our approach is general and can be applied to other forms of $L(t)$ if required. Employing a leading eigenvalue approximation [27], we derive a straightforward mathematical expression for the long-time survival probability, $\mathcal{S} = \lim_{t \rightarrow \infty} S(t)$. This expression succinctly shows how the details of the initial condition, diffusivity, and the tissue growth rate influences the survival probability. This approximation provides a straightforward criteria to distinguish between cases where the diffusing population can reach $x = L(t)$ from other

cases where the diffusing population can not reach $x = L(t)$. To provide a physical interpretation of our analysis, we also present results from a stochastic model, from which we estimate survival probabilities for a diffusion process on a growing domain, and show that the discrete and continuum results compare very well.

II. MATHEMATICAL MODELS

A. Continuum mathematical model

Domain growth is associated with a velocity field in the elongating tissue [18,19,21–23]. This velocity field causes a point within the growing tissue at location x to translate to $x + v(x,t)\tau$ during a small time period of duration τ . By considering the expansion of an element of initial width Δx , we can derive an expression relating $L(t)$ and $v(x,t)$, which can be written as

$$\frac{dL(t)}{dt} = \int_0^{L(t)} \frac{\partial v}{\partial x} dx. \quad (1)$$

For uniform growth conditions, where $\partial v/\partial x$ is independent of position, we have $\partial v/\partial x = \sigma(t)$ [2–4,18,21]. Combining this with Eq. (1) gives

$$\frac{\partial v}{\partial x} = \sigma(t) = \frac{1}{L(t)} \frac{dL(t)}{dt}. \quad (2)$$

Without loss of generality, we assume that the domain elongates in the positive x direction with $v(0,t) = 0$. Integrating Eq. (2) gives

$$v(x,t) = \frac{x}{L(t)} \frac{dL(t)}{dt}. \quad (3)$$

We now consider a conservation statement for a density function, $C(x,t)$, describing the density of diffusing individuals at location x and time t . Assuming that the density function evolves according to a linear diffusion process on the growing domain, the associated conservation statement can be written as

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} - \frac{\partial(Cv)}{\partial x}, \quad 0 < x < L(t), \quad (4)$$

where D is the diffusivity and v is the velocity associated with the domain growth, given by Eq. (3). Expanding the advection term on the right of Eq. (4) gives two terms: (i) $-v\partial C/\partial x$, which is a standard advection term [27], and (ii) $-C\partial v/\partial x$, which, since $\partial v/\partial x > 0$, is a domain growth-induced dilution term [2–4,18,21]. Inspired by Landman’s previous numerical simulations of ENS development [18], we focus on the initial condition

$$C(x,0) = \begin{cases} 1 & 0 \leq x < \gamma, \\ 0 & \gamma \leq x \leq L(0), \end{cases} \quad (5)$$

which corresponds to some initial length of the domain, $0 \leq x < \gamma$, uniformly occupied at a maximum density, and the remaining portion of the domain is vacant. This initial condition is relevant to ENS development since the initial condition is confined toward the $x = 0$ (oral) end of the tissue [18]. Varying γ allows us to alter the width of the initial population and we will later make a comment about how the survival probability

depends on the width of the initial condition. At $x = 0$ we impose a no-flux boundary condition, $\partial C/\partial x = 0$, which is consistent with the idea that the diffusing cells or molecules cannot leave the end of the tissue at $x = 0$. At $x = L(t)$ we impose an absorbing boundary condition, $C[L(t),t] = 0$. We interpret the absorbing boundary as indicating that individual cells or molecules in the diffusing population will leave the domain when they reach $x = L(t)$. Although all our analysis corresponds to this set of initial conditions and boundary conditions, it is possible to repeat all of our analysis for different forms of $C(x,0)$ and other types of boundary conditions, if required.

To solve Eq. (4) for $C(x,t)$, we use a boundary fixing transformation, $\xi = x/L(t)$, which, with $v = \xi dL(t)/dt$, gives

$$\frac{\partial C}{\partial t} = \frac{D}{L^2(t)} \frac{\partial^2 C}{\partial \xi^2} - \sigma(t)C, \quad 0 < \xi < 1. \quad (6)$$

Rescaling time, $T(t) = \int_0^t D/L^2(s) ds$ [28], gives

$$\frac{\partial C}{\partial T} = \frac{\partial^2 C}{\partial \xi^2} + f(T)C, \quad 0 < \xi < 1, \quad (7)$$

where $f(T) = -L^2(t)\sigma(t)/D$. The solution of Eq. (7) is given by

$$C(\xi,T) = \sum_{n=1}^{\infty} A_n \cos(\lambda_n \xi) \exp \left[\int_0^T f(T^*) dT^* - \lambda_n^2 T \right], \quad (8)$$

where $\lambda_n = (2n-1)\pi/2$ and n is a positive integer. The exact solution for $C(\xi,T)$ can be rewritten in terms of the original coordinates, giving $C(x,t)$, and the Fourier coefficients, A_n , can be chosen to ensure that the exact solution satisfies Eq. (5) at $t = 0$ [27].

Following Redner [25,26] we define the survival probability as

$$S(t) = \frac{\int_0^{L(t)} C(x,t) dx}{\int_0^{L(0)} C(x,0) dx}, \quad (9)$$

and our aim now is to develop an exact expression for $S(t)$, and to examine the properties of this function. While the framework developed here is valid for general $L(t)$, we focus on two cases.

B. Exponentially growing domains

For $L(t) = L(0)e^{\alpha t}$, with $\alpha > 0$, we have $T(t) = D(1 - e^{-2\alpha t})/2\alpha L^2(0)$, and the solution of Eq. (4) is

$$C(x,t) = \sum_{n=1}^{\infty} A_n \cos \left[\frac{\lambda_n x}{L(t)} \right] \exp(-T\lambda_n^2 - \alpha t), \quad (10)$$

where $A_n = 2 \sin[\lambda_n \gamma / L(0)] / \lambda_n$. With this solution we calculate the survival probability, given by Eq. (9), as

$$S(t) = \frac{L(0)}{\gamma} \sum_{n=1}^{\infty} \frac{A_n}{\lambda_n} \sin(\lambda_n) \exp(-T\lambda_n^2). \quad (11)$$

While our expression for $S(t)$ is valid for all $t > 0$, it is also useful to calculate the long-time survival probability. To do this we note that $\lim_{t \rightarrow \infty} T(t) = D/[2\alpha L^2(0)]$, and we employ a leading eigenvalue approximation since we anticipate that the

long-time behavior of $S(t)$ will be dominated by the first term in the infinite series [27]. This gives

$$S \approx \frac{8L(0)}{\gamma\pi^2} \sin\left[\frac{\pi\gamma}{2L(0)}\right] \exp\left[-\frac{D\pi^2}{8\alpha L^2(0)}\right], \quad (12)$$

where $S = \lim_{t \rightarrow \infty} S(t)$. This expression gives a very simple relationship describing how the effects of the diffusivity, D , the growth rate, α , and the details of the initial condition, $L(0)$ and γ , control the long term survival probability. For example, we see that the long-time survival probability decays exponentially with D , and is inversely proportional to $\gamma/L(0)$, which is the proportion of the domain that is initially occupied by the diffusive population. These relationships are consistent with our intuitive expectations since we anticipate that larger D would lead to a reduction in $S(t)$, and that a wider initial condition would also lead to reduced $S(t)$. However, instead of relying on intuition or numerical simulation alone, our analysis is exact and gives us quantitative insight into the interactions between the diffusivity, domain growth rate, and the details of the initial condition in terms of the survival probability.

C. Linearly growing domains

For $L(t) = L(0) + \beta t$, with $\beta > 0$, we have $T(t) = Dt/[L(0)L(t)]$, and the solution of Eq. (4) is

$$C(x,t) = \sum_{n=1}^{\infty} \frac{A_n L(0)}{L(t)} \cos\left[\frac{\lambda_n x}{L(t)}\right] \exp(-T\lambda_n^2), \quad (13)$$

where $A_n = 2 \sin[\lambda_n \gamma / L(0)] / \lambda_n$. The survival probability, Eq. (9), simplifies to

$$S(t) = \frac{L(0)}{\gamma} \sum_{n=1}^{\infty} \frac{A_n}{\lambda_n} \sin(\lambda_n) \exp(-T\lambda_n^2). \quad (14)$$

Again, it is useful to calculate the the long-time survival probability. Here we have $\lim_{t \rightarrow \infty} T(t) = D/[L(0)\beta]$, and a leading eigenvalue approximation gives

$$S \approx \frac{8L(0)}{\gamma\pi^2} \sin\left[\frac{\pi\gamma}{2L(0)}\right] \exp\left[-\frac{D\pi^2}{4\beta L(0)}\right], \quad (15)$$

which shows approximately how the long-time survival probability depends on the diffusivity, D , the growth rate, β , and the details of the initial condition, $L(0)$ and γ . Before presenting specific results from our analysis, we also provide a physical interpretation of these predictions by implementing a discrete, stochastic model.

D. Discrete mathematical model

To initiate our stochastic model we consider a one-dimensional lattice, with unit lattice spacing, of initial length $L(0)$. Each site is indexed $i \in [0, L(t)]$. The initial condition, Eq. (5), is represented by initially populating all sites with $x < \gamma$ with $N \gg 1$ agents and all sites with $x \geq \gamma$ with zero agents. Time is discretized into uniform time steps, each of unit duration. To advance from time t to $t + 1$ we use an operator splitting algorithm by implementing the following two steps sequentially [29]:

(1) To model the domain growth we specify $L(t)$ and calculate $j = \lfloor L(t + 1) - L(t) \rfloor$, the nearest integer value

of $L(t + 1) - L(t)$. The domain grows by inserting j new lattice sites per time step. To insert each new lattice site we randomly choose an existing site, at location i^* , and translate each existing site with $i > i^*$ in the direction of increasing i . This leaves all existing sites with $i \leq i^*$ unchanged and we insert the new lattice site at location $i^* + 1$. We implement the simplest possible growth mechanism which means that the newly inserted lattice site, at $i^* + 1$, contains zero agents immediately after insertion.

(2) After j new lattice sites have been randomly inserted, we allow agents on the lattice to undergo an unbiased random walk. A random sequential update method is implemented in the following way. If there are $Q(t)$ agents on the lattice at time t , we select $Q(t)$ agents, with replacement, at random, one at a time, and give each agent an opportunity to move with probability $P \in [0, 1]$ [30]. Since the random walk is unbiased, an agent at $0 < i < L(t)$ will step to $i \pm 1$, with each potential target site chosen with equal probability of $1/2$. Agents located at $i = 0$ step to $i = 1$ with probability $1/2$. Any agent that steps to $i = L(t)$ is removed and $Q(t)$ is adjusted. Since we have unit lattice spacing and time steps of unit duration we have $D = P/2$.

We implement the initial condition, given by Eq. (5), with the restriction that γ is a positive integer. This gives $N\gamma$ agents on the lattice at $t = 0$, and we estimate the survival probability by calculating $S(t) = Q(t)/(N\gamma)$.

III. RESULTS

Continuum and discrete results for an exponentially elongating domain are given in Fig. 1(a). For the exponential growth case with $\alpha = 10^{-5}$, we see that $S(t)$ decays with time, indicating that the domain growth is sufficiently slow that most of the initial density profile is eventually absorbed at $x = L(t)$. The comparison between our continuum and discrete results is excellent, and our long-time approximation of the survival probability, given by Eq. (12), is $S \approx 0.00$, indicating that approximately 100% of the initial density profile is eventually absorbed at $x = L(t)$. This is very similar to the nongrowing case, $\alpha = 0$, where it is well-known that precisely 100% of the initial density profile is absorbed at $x = L$ as $t \rightarrow \infty$ [25]. A very different result is observed when we have $\alpha = 5 \times 10^{-5}$, where again we have an excellent match between our theoretical prediction, Eq. (11), and results from the discrete model. However, in this case we have $S \approx 0.36$, indicating that approximately 64% of the initial density profile is absorbed at $x = L(t)$, whereas approximately 36% of the initial density profile remains on the growing domain as $t \rightarrow \infty$. Comparing our estimate of $S \approx 0.36$ with the exact results in Fig. 1(a) indicates that both our continuum prediction of $S(t)$ and our discrete simulations match this prediction very closely by approximately $t = 5 \times 10^4$. Similarly, for $\alpha = 10^{-4}$, we have $S \approx 0.67$, which matches both our discrete results and our continuum prediction very well. Of particular interest are the results for $\alpha = 5 \times 10^{-4}$, for which our approximation gives $S \approx 1.0$, indicating that the domain growth is sufficiently fast that the initial density profile is never absorbed at $x = L(t)$. This result, which is in agreement with Eq. (11) and our discrete simulations, gives us a straightforward means of distinguishing between those cases where the domain growth

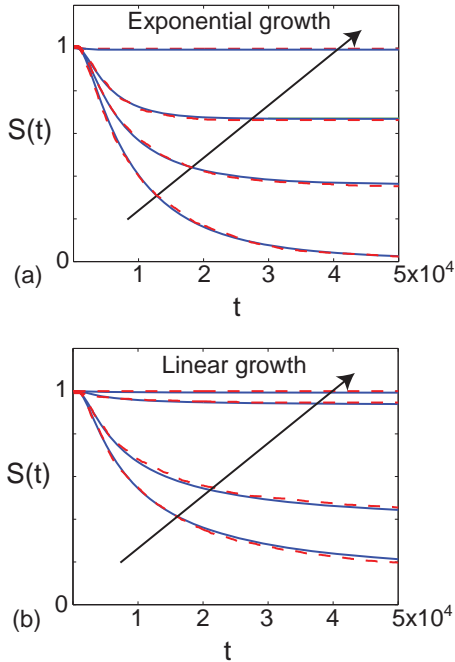


FIG. 1. (Color online) Comparison of continuum predictions (solid blue) and discrete estimates (red dashed) of $S(t)$ for (a) exponential domain growth $L(t) = L(0)e^{\alpha t}$, and (b) linear domain growth $L(t) = L(0) + \beta t$. In all cases we have $L(0) = 100$, and the initial condition is given by Eq. (5) with $\gamma = 25$. Results in (a) correspond to $\alpha = 10^{-5}, 5 \times 10^{-5}, 10^{-4}$, and 5×10^{-4} , with the arrow showing the direction of increasing α . Results in (b) correspond to $\beta = 5 \times 10^{-3}, 10^{-2}, 5 \times 10^{-2}$, and 10^{-1} , with the arrow showing the direction of increasing β . To evaluate the exact continuum expressions for $S(t)$, given by Eqs. (11) and (14), we truncated the infinite series after 100 terms and checked that these results were insensitive to this choice of truncation. To generate the discrete results we set $N = 80$ and $P = 1$, giving $D = 1/2$.

is sufficiently slow that the density profile reaches $x = L(t)$ from those cases where the domain growth is sufficiently rapid that the density profile never reaches $x = L(t)$. Our ability to distinguish between situations where the initial density profile is partially or completely absorbed ($0 \leq S < 1$) from cases where the initial density profile is never absorbed ($S \equiv 1$) is particularly important in certain processes in developmental biology, such as ENS development [15,18], and we will elaborate more on this in the Discussion and Conclusion section.

Continuum and discrete results for a linearly growing domain are given in Fig. 1(b). Similar to the exponentially growing results, we see that the comparison between $S(t)$, predicted by Eq. (14), and the results from the discrete model are good. Results are presented for $\beta = 5 \times 10^{-3}, 10^{-2}, 5 \times 10^{-2}$, and 10^{-1} and we see that when β is sufficiently small the survival probability asymptotes to give $S > 0$, indicating that a certain proportion of the initial population eventually reaches $x = L(t)$, whereas the remainder of the population remains on the growing domain indefinitely. For cases where β is sufficiently large we have $S \approx 1$, indicating that the initial density profile never reaches $x = L(t)$.

Although all results in Fig. 1 correspond to fixed values of $L(0)$, γ , and D , we also performed similar comparisons

between our theoretical prediction of $S(t)$ and results from our discrete model for different choices of $L(0)$, γ , and D . For all cases considered we observed a similar quality of match between the theoretical prediction of $S(t)$ and the results from the discrete model as those presented in Fig. 1.

IV. DISCUSSION AND CONCLUSION

In this work we have presented exact solutions for the survival probability of a diffusing population on a one-dimensional growing domain. Our results are significantly different from previous results in two ways. First, previous results for similar problems on nongrowing domains have shown that $S(t)$ decays to zero, exponentially fast, as $t \rightarrow \infty$ [25], whereas here we have $S(t) > 0$ in the long-time limit. Second, our results are superficially similar to, but significantly different from previous analyses of survival probability in expanding cages, receding cliffs [25,31], and parabolic geometries [32,33]. In these previous studies the motion of individual agents in the diffusing population is uncoupled from the expansion of the domain, whereas in the problems we consider, the motion of individuals in the population is coupled to the domain growth.

The physical motivation for our analysis is the development of the ENS [10–14]. This developmental process involves a population of precursor cells that are initially confined toward the oral end of the gut. Individual precursor cells undergo an unbiased random walk [14], which results in a moving front of precursor cells spreading toward the anal end of the developing gut. This process is complicated by the fact that the gut tissues elongate simultaneously as the cell population spreads along the growing tissues [15,16,20]. Normal development requires that the moving front of precursor cells reaches the anal end of the developing tissue. Abnormal development, which is associated with Hirschsprung’s disease and other related birth defects [11–13], is thought to occur in situations where the moving front of cells fails to completely colonize the growing gut tissue. Developing analytical methods that can distinguish between complete or incomplete colonization provides us with information about how the combination of cell diffusivity, tissue growth, and the initial distribution of cells controls the outcome of the developmental process. Our model can be used to distinguish between complete and incomplete colonization in terms of survival probability since complete colonization corresponds to $S < 1$, whereas incomplete colonization corresponds to $S \equiv 1$.

We note that our analytical framework for calculating $S(t)$ is sufficiently general that it can be applied to other uniform domain growth functions by specifying different forms of $\partial v / \partial x$ [or equivalently, by specifying a different form of $L(t)$ in Eq. (1)]. Further generalizations are also possible. For example, although we presented all results using Eq. (5) as the initial condition, it is straightforward to consider for other initial conditions by reevaluating the Fourier coefficients in Eq. (8).

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