Modeling biological tissue growth: Discrete to continuum representations

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There is much interest in building deterministic continuum models from discrete agent-based models governed by local stochastic rules where an agent represents a biological cell. In developmental biology, cells are able to move and undergo cell division on and within growing tissues. A growing tissue is itself made up of cells which undergo cell division, thereby providing a significant transport mechanism for other cells within it. We develop a discrete agent-based model where domain agents represent tissue cells. Each agent has the ability to undergo a proliferation event whereby an additional domain agent is incorporated into the lattice. If a probability distribution describes the waiting times between proliferation events for an individual agent, then the total length of the domain is a random variable. The average behavior of these stochastically proliferating agents defining the growing lattice is determined in terms of a Fokker-Planck equation, with an advection and diffusion term. The diffusion term differs from the one obtained Landman and Binder [J. Theor. Biol. **259**, 541 (2009)] when the rate of growth of the domain is specified, but the choice of agents is random. This discrepancy is reconciled by determining a discrete-time master equation for this process and an associated asymmetric nonexclusion random walk, together with consideration of synchronous and asynchronous updating schemes. All theoretical results are confirmed with numerical simulations. This study furthers our understanding of the relationship between agent-based rules, their implementation, and their associated partial differential equations. Since tissue growth is a significant cellular transport mechanism during embryonic growth, it is important to use the correct partial differential equation description when combining with other cellular functions.

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I. INTRODUCTION

Biological tissues undergo dramatic expansion due to cell division during embryonic development. For example, the mesenchymal cells which make up the intestine of amniote vertebrates (e.g., birds, rodents, humans) undergo a massive increase in cell number by cell division. Since the cell density within the tissue remains constant, the intestine grows dramatically in length (and relatively little in the radial direction). The intestinal tissue growth has been quantified to be growing exponentially in time [1].

Any tissue growth will alter the spatial distribution of cells and signaling molecules within the developing tissue. For example, intestinal elongation is a major contributing factor to the success or otherwise of neural crest cell invasion and colonization within an elongating intestinal tissue to form the nervous system in the intestine. Consequently, a deeper understanding of the additional transport mechanisms which arise from tissue growth are key to better models of cell and morphogen transport in developmental biology.

Deterministic continuum models for pattern formation, cell invasion, and morphogen movement within growing domains have been in use for nearly two decades [2–9]. More recently, focus has shifted to discrete models of domain growth, including fungal hypthal growth [10–12], neural crest cell colonization of the enteric nervous system [1,13], and general theoretical considerations [14,15].

Agent-based models are often favored by biologists because the agent rules can incorporate local cellular behavior as well as the stochastic variability between cells. However, it is important to understand the movement of the population as a whole, where pattern can emerge from stochastic rules. Therefore, there is much interest in being able to predict population-scale behavior from information about individuals on a local level [16–21]. A way to do this quantitatively is to derive partial differential equations (PDEs), using the discrete agent-based rules as the starting point. We will develop such PDEs here using the formalism of the Fokker-Planck equation, as well as the master equation approach.

Binder *et al*. [1] and Binder and Landman [22] developed a discrete model for tissue growth based on a discrete lattice model, where the lattice has unit spacing and is made up of domain agents which represent cells of the tissue. In that work the total length of the lattice (or equivalently the number of domain agents) is a prescribed increasing function of time.

We extend this work to a stochastically growing lattice in continuous time and derive the PDE describing the spatiotemporal evolution of the domain agents. The diffusion term for the stochastically growing lattice is larger than the one determined for the deterministically growing lattice in discrete time [22]. This interesting discrepancy is reconciled here by formulating a discrete-time master equation for the deterministically growing lattice. This provides an alternative viewpoint. The process is observed to be equivalent to a totally asymmetric random walk for noninteracting walkers. The type of updating scheme used affects the simulation outcomes; we explore synchronous updating and random sequential updating, a type of asynchronous updating [23,24]. Our theoretical results are confirmed with numerical simulation. These considerations further highlight the subtleties which arise in producing PDEs from agent-based probabilistic rules.

Cell division is a complex biological process, where a cell does not instantaneously divide into two fully sized cells and the cycle times between cell division events vary. Here we study an idealized lattice system which produces the type of growth (exponential) observed [1].

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II. SPATIALLY DISCRETE TISSUE GROWTH MODEL

We consider a one-dimensional semi-infinite lattice, with lattice spacing Δ. Let $i \in \mathbb{N}$ denote the number of the lattice site, so that the position of the site is given by $x = i\Delta$. Consider the lattice being occupied by contiguous domain agents, representing a biological tissue. Each lattice site can be occupied by at most a single domain agent. Let N_t be the number of domain agents at time t, with the domain agents occupying lattice sites $i = 1,2,\ldots,N_t$, giving $L_t = \Delta N_t$ as the length of the occupied domain. Initially N_0 and L_0 are set.

A domain agent has the ability to undergo a proliferation event (equivalent to a cell division event), whereby an additional domain agent is incorporated into the lattice, increasing the total number of agents by unity. If the domain agent at site i proliferates, this domain agent moves to site $i+1$, pushing all domain agents to the right of i (i.e. agents occupying $i+1$ to N_t before the proliferation event), one site to the right. This process makes room for the new domain agent, which occupies site i.

Figure 1 illustrates a single realization of three proliferation events, where a subset of the domain agents are marked in green. Whenever a domain agent is selected to proliferate, whether it is a marked or an unmarked agent, the new agent inserted into the lattice is an unmarked agent. The figure clearly illustrates how proliferation events cause domain agents to move.

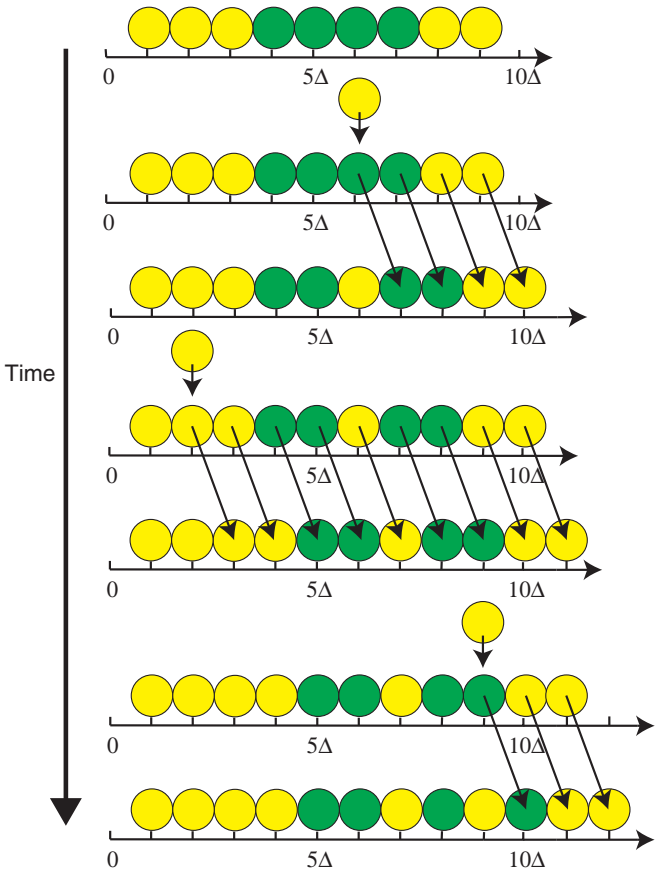

FIG. 1. (Color online) Schematic representation of a growing lattice made up of domain agents, some of which are marked (green [dark gray]). Starting with nine domain agents, the domain agents occupying sites 4–7 are marked (green [dark gray]), and the remaining domain agents are unmarked (yellow [light gray]). Three sequential random proliferation events are shown from top to bottom (sites 6, 2, 9, respectively). Short arrows indicate the movements of respective domain agents.

Alternatives to this model, for example, (1) where agents are placed to the right of the agent undergoing the proliferation event or (2) where agents are placed with equal probability either to the left or right of the agent undergoing the proliferation event, give the same results as presented here. We therefore consider only new agents placed to the left of the proliferating agent, producing a lattice growing to the right.

A mathematical description for the population-level behavior of the domain agents can be obtained by considering such a marked subset of the domain agents and determining how they move with time. The behavior of the marked agents averaged over many realizations can be easily computed. Our aim is to build a PDE to describe this average behavior and compare the two descriptions.

III. STOCHASTICALLY GROWING LATTICE: CONTINUOUS-TIME ONE-DIMENSIONAL MODEL

Here we consider a lattice growing stochastically in continuous time.

A. Population size

Suppose the waiting times between proliferation events for individual domain agents are exponentially distributed with rate parameter λ. Since each agent proliferates at a rate that is independent of the other agents and N_t counts the total number of agents, the random process N_t is equivalent to a standard birth process [25]. Therefore the expected value of N_t is $\mathbb{E}[N_t] = N_0 e^{\lambda t}$. The expected length of the lattice is defined as

$$\mathcal{L}(t) = \mathbb{E}[L_t] = L_0 e^{\lambda t}. \tag{1}$$

B. Equivalence to a totally asymmetric random walk

Define $\gamma_i(t)$ to be an indicator random variable, indicating whether site i is occupied by a marked agent at time t, such that

$$\gamma_i(t) = \begin{cases} 1 & \text{if site } i \text{ occupied by } \textit{marked} \text{ agent at time } t, \\ 0 & \text{otherwise.} \end{cases} \tag{2}$$

We denote the expected occupancy of site i at time t with

$$C_i(t) = \mathbb{E}[\gamma_i(t)] = \mathbb{P}(\gamma_i(t) = 1). \tag{3}$$

We are interested in the time evolution of $C_i(t)$ for all i in terms of its continuous approximation given by $C(x,t)$.

To develop a PDE for $C(x,t)$ we utilize the Fokker-Planck equation, which describes the evolution of the transition probability density function or concentrations for a diffusion process [26,27]. While the continuous-time model for the growing tissue is not continuous in x, using the Fokker-Planck equation gives a highly accurate approximation.

From the formulation of the Fokker-Planck equation, the particles must move independently of one another. Clearly the movements of agents, as illustrated in Fig. 1, are dependent

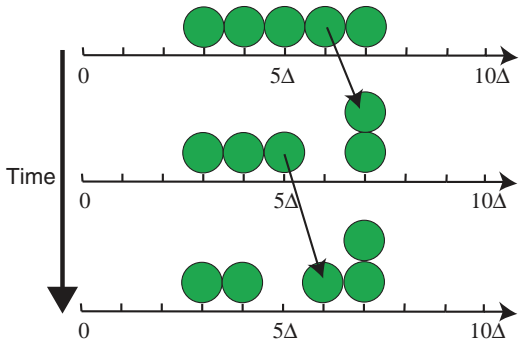

FIG. 2. (Color online) Typical examples of two moves by agents undergoing a totally asymmetric walk in continuous time. Whether an agent moves or not is determined independently of other agents. Short arrows indicate the movement of agents.

on the movement of other agents. However, the Fokker-Planck equation framework will be justified once we establish that our growing lattice process is equivalent to another process where the agents move independently.

We define a new process consisting of noninteracting agents conducting independent continuous-time random walks on a one-dimensional semi-infinite lattice. Now a site can be occupied by multiple agents, and the movement of agents is not influenced in any way by neighboring agents. Let each agent be governed by the following probabilistic rules: agents cannot hop to the left, but they can hop to the right one site at a time. This defines a totally asymmetric random walk. If an agent occupies some site i at time t, then let the time until the agent's next hop follow an exponential distribution with parameter $i\lambda$. Figure 2 illustrates two such moves by the noninteracting agents. The process is a Markov process.

To establish that our growing tissue model is equivalent to this asymmetric random walk process, consider a marked domain agent in the growing tissue model at site i at some time t. Then this agent moves one site to the right if it or any of the $i-1$ domain agents to its left undergoes a proliferation event. Since the time until the next proliferation event for each of these i domain agents is exponentially distributed with parameter λ, the waiting times between hoping events for an agent at site i to hop one site to the right are exponentially distributed with parameter $i\lambda$. This is exactly the same distribution as in the continuous-time totally asymmetric random walk process defined above.

So if we define $p(m,y,t)$ to be the probability that a marked domain agent in the growing tissue model, initially occupying site m, occupies site y at time t, and define $p_{\mathrm{arw}}(m,y,t)$ to be the same quantity but for an agent in the totally asymmetric random walk, then it follows that

$$p(m,y,t) = p_{\mathrm{arw}}(m,y,t). \tag{4}$$

In addition, let $\{X_t\}_{t\geqslant 0}$ and $\{X_t^{\mathrm{arw}}\}_{t\geqslant 0}$ be stochastic processes such that X_t and and X_t^{arw} denote the position at time t occupied by an individual marked domain agent in the growing tissue model and an individual agent in the continuous-time asymmetric random walk process, respectively. Consider an initial distribution of agents undergoing the asymmetric random walk to be identical with the initial distribution of marked domain agents in the growing tissue model. Then if we consider a marked domain agent and a random walker agent such that $X_0 = X_0^{\mathrm{arw}}$, Eq. (4) says that the two stochastic processes have identical probability distributions. Hence, by considering all the agents and their individual evolutions, it can be shown (Appendix A) that the expected lattice site occupancy for the two processes is the same. This is perhaps surprising, given that the two processes can have significant differences in individual evolutions of the processes (compare Figs. 1 and 2).

Since X_t is equivalent to the X_t^{arw}, we are justified in using the Fokker-Planck equation to describe the evolution of the marked domain agents in the growing lattice model.

C. The Fokker-Planck PDE

The equivalence between X_t and and X_t^{arw} means that we can continue to use the Fokker-Planck equation for either process. For notational ease we use X_t. The Fokker-Planck PDE describing the evolution of $C(x,t)$, the continuous function approximating the expected occupancy $C_i(t)$ of marked domain agents, is given by [26–28]

$$\frac{\partial C}{\partial t} = -\frac{\partial}{\partial x}[\mu(x,t)C(x,t)] + \frac{\partial^2}{\partial x^2}\left[\frac{1}{2}\sigma^2(x,t)C(x,t)\right], \tag{5}$$

where $\mu(x,t)$ and $\sigma^2(x,t)$ are the infinitesimal mean and variance of the stochastic process X_t:

$$\mu(x,t) = \lim_{h\to 0}\frac{1}{h}\mathbb{E}[X_{t+h} - X_t | X_t = x] \tag{6}$$

and

$$\sigma^2(x,t) = \lim_{h\to 0}\frac{1}{h}\mathrm{Var}(X_{t+h} - X_t | X_t = x). \tag{7}$$

The functions μ and σ^2 are also referred to as the drift and diffusivity coefficient, respectively [26,27]. (Note that X_t will always be a multiple of Δ.)

Our aim now is to determine the infinitesimal moments of X_t. The marked domain agent at X_t will move only if there is a proliferation event at X_t or to the left of X_t; proliferations occurring to the right of X_t do not influence its position or its propensity to change position.

For the birth process described, the probability mass function for k proliferation events during time interval $[t,t+h)$ (for $k = 0,1,2,\ldots$) is

$$\begin{aligned}&\mathbb{P}[X_{t+h} - X_t = k\Delta | X_t = x]\\ &\quad = \binom{x/\Delta + k - 1}{k}(1 - e^{-\lambda h})^k e^{-x\lambda h/\Delta}.\end{aligned} \tag{8}$$

From this we can determine expressions for the infinitesimal mean and variance [Eqs. (6) and (7)]. Taking the mean and limit as $h \to 0$, gives

$$\lim_{h\to 0}\frac{1}{h}\mathbb{E}[X_{t+h} - X_t | X_t = x] = \lim_{h\to 0}\frac{1}{h}x(e^{h\lambda} - 1) = x\lambda. \tag{9}$$

Furthermore

$$\begin{aligned}&\mathrm{Var}(X_{t+h} - X_t | X_t = x)\\ &\quad = \mathbb{E}[(X_{t+h} - X_t)^2 | X_t = x] - \mathbb{E}[X_{t+h} - X_t | X_t = x]^2\\ &\quad = \mathbb{E}[(X_{t+h} - X_t)^2 | X_t = x] + o(h).\end{aligned} \tag{10}$$

Here the variance for the displacement reduces to the second moment in the limit $h \to 0$:

$$\begin{aligned}\lim_{h\to 0}\frac{1}{h}&\mathrm{Var}(X_{t+h}-X_t|X_t=x)\\ &=\lim_{h\to 0}\frac{1}{h}\mathbb{E}[(X_{t+h}-X_t)^2|X_t=x]\\ &=\lim_{h\to 0}\frac{1}{h}\Delta^2\frac{x}{\Delta}(e^{h\lambda}-1)e^{h\lambda}=\Delta x\lambda. \end{aligned}\tag{11}$$

Therefore, Eqs. (6) and (7) become

$$\mu(x,t)=x\lambda,\quad \sigma^2(x,t)=\Delta x\lambda. \tag{12}$$

Using these expressions in Eq. (5) gives

$$\frac{\partial C}{\partial t}=-\lambda\frac{\partial}{\partial x}[xC(x,t)]+\frac{\Delta\lambda}{2}\frac{\partial^2}{\partial x^2}[xC(x,t)]. \tag{13}$$

Note that the proliferation rate λ can be replaced with $\mathcal{L}'(t)/\mathcal{L}(t)$ from Eq. (1), allowing us to rewrite Eq. (13) as

$$\begin{aligned}\frac{\partial C}{\partial t}=&-\mathcal{L}'(t)\frac{\partial}{\partial x}\left[\frac{x}{\mathcal{L}(t)}C(x,t)\right]\\ &+\mathcal{L}'(t)\frac{\Delta}{2}\frac{\partial^2}{\partial x^2}\left[\frac{x}{\mathcal{L}(t)}C(x,t)\right]. \end{aligned}\tag{14}$$

This equation [and Eq. (13)] is valid for $0\leqslant x\leqslant\mathcal{L}(t)$, with a moving right-hand boundary. Here the rightmost domain agent is not deterministic, but rather stochastic, with its expected continuous position at time t given by $\mathcal{L}(t)$, the expected length of the lattice $\mathbb{E}[L_t]$.

We solve Eq. (14) with appropriate boundary and initial conditions (Appendix B), setting the parameter Δ equal to the lattice spacing used in the simulations. Figure 3 compares the PDE solution of Eq. (13) with simulation results averaged over 1000 simulations for two values of Δ. The fit is excellent for both values of Δ. The fit is surprisingly accurate even for the relatively large value of Δ, namely, $\Delta=1$. Therefore, we deduce that the lattice spacing Δ does not need to be small for this analysis.

Equation (13) has a different diffusion term from the one derived in Binder and Landman [22] for a discrete-time growing domain, where the total number of domain agents was deterministic [so that the position of the rightmost agent is a specified function, namely, $L(t)$, an analog to $\mathcal{L}(t)$], and a predetermined number of agents were chosen randomly to proliferate at each discrete fixed time step. For the deterministic model the diffusivity was proportional to $[x/L(t)][1-x/L(t)]$ and therefore is smaller than the continuous-time model. When the length is deterministic, the variance must be zero at $x=\mathcal{L}(t)$. By way of contrast, the variance for the stochastically growing model has its maximum at $x=\mathcal{L}(t)$. Binder and Landman [22] considered only the case $\Delta=1$. We revisit, recast, and extend this deterministic process for other values of Δ in order to understand the difference in the two approaches and theoretical results.

IV. DETERMINISTICALLY GROWING LATTICE: DISCRETE-TIME ONE-DIMENSIONAL MODEL

We next consider an alternative model of a lattice growing in discrete time as a specified function of time.

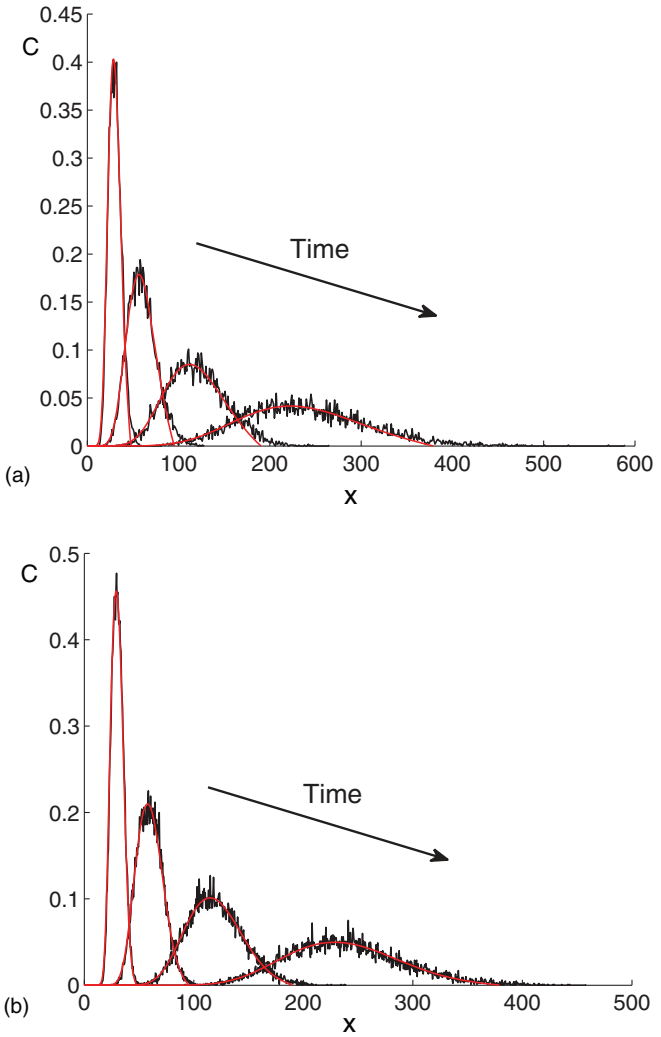

FIG. 3. (Color online) Solutions to Eq. (13) [red (light gray) curve] and expected occupancy averaged over 1000 realizations (black curve) with $L_0=24$ and $\lambda=0.69$ for $t=1,2,3,4$. Initially, the marked agents are in $12\leqslant x\leqslant 18$. (a) $\Delta=1$, (b) $\Delta=1/2$. Note the different axes scales.

Binder and Landman [22] used the Fokker-Planck approach, where the Pólya distribution describes the number of moves of a marked agent (Appendix C). Here a different approach is used. The discrete-time master equation approach is a common approach used to derive PDEs to approximate the expected behavior of interacting random walkers [14,20,29–31].

To start, some notation is introduced. A deterministic continuous increasing function $L(t)$ gives the length approximately spanned by the contiguous domain agents at time t. The step function $N(t)=\lfloor L(t)/\Delta\rfloor$ gives the number of domain agents occupying the lattice at time t. As such the true length spanned by the agents at time t is $\Delta N(t)\approx L(t)$, and as $\Delta\to 0$, $\Delta N(t)\to L(t)$.

The jumps in $N(t)$ indicate the times at which proliferation events occur, so that $M(t)=N(t)-N(0)$ gives the number of proliferation events that have occurred in the time interval $[0,t]$. Proliferation events again refer to the addition of a single domain agent to the lattice as illustrated in Fig. 1. However,

now the times at which the proliferation events occur are set deterministically by $L(t)$ and Δ. At each time step, a domain agent is chosen at random from all the existing domain agents, with each domain agent equally likely to be selected; this chosen agent proliferates.

Define T_j as the time at which the jth proliferation event occurs, giving $T_j = \min\{t : M(t) = j\}$. Now let τ_j be the value of the time interval between the jth and $(j+1)$-th proliferation events, $\tau_j = T_{j+1} - T_j$. From these definitions it is clear that $\tau_{M(t)}$ gives the value of the time interval between the time steps that occur before and after t. Furthermore, $\tau_{M(t)}$ is not independent of Δ. Rather, $\tau_{M(t)}$ is dependent on $L(t)$ and Δ and as $\Delta \to 0$, we have $\tau_{M(t)} \to 0$ for all t.

A. PDE from the master equation approach

To determine the change of the expected occupancy of all sites over the time steps, we determine a difference equation for $C_i(T_j + \tau_j)$. For notational ease we let $t = T_j$ for some j, allowing us to replace $C_i(T_j + \tau_j)$ with $C_i(t + \tau_{M(t)})$. We wish to calculate $C_i(t + \tau_{M(t)})$ from $C_i(t)$. Careful arguments involving conditional probabilities are presented.

Consider the ways that a single agent proliferation can change the marked agent occupancy status of site i:

(1) Suppose $\gamma_{i-1}(t) = 1$ and $\gamma_i(t) = 1$. Then site i will only be unoccupied at time $t + \tau_{M(t)}$ if the marked domain agent at site i is selected to proliferate.Thus $\mathbb{P}(\gamma_i(t + \tau_{M(t)}) = 1|\gamma_{i-1}(t) = 1, \gamma_i(t) = 1) = 1 - 1/N(t)$.

(2) Suppose $\gamma_{i-1}(t) = 1$ and $\gamma_i(t) = 0$. Then site i will only be occupied at time $t + \tau_{M(t)}$ if the domain agent selected to proliferate occurs at some site k, with $k \leqslant i - 1$.Thus $\mathbb{P}(\gamma_i(t + \tau_{M(t)}) = 1|\gamma_{i-1}(t) = 1, \gamma_i(t) = 0) = (i-1)/N(t)$.

(3) Suppose $\gamma_{i-1}(t) = 0$ and $\gamma_i(t) = 1$. Then site i will only be occupied at time $t + \tau_{M(t)}$ if the domain agent selected to proliferate occurs at some site k, with $k > i$.Thus $\mathbb{P}(\gamma_i(t + \tau_{M(t)}) = 1|\gamma_{i-1}(t) = 0, \gamma_i(t) = 1) = 1 - i/N(t)$

We note that the case when $i - 1$ and i are unoccupied cannot produce an occupied site at i at time $t + \tau_{M(t)}$, and so its associated conditional probability is zero.

In terms of $C_i(t)$, this gives

$$\begin{aligned} C_i(t + \tau_{M(t)}) &= C_{i-1}(t)C_i(t)\left[1 - \frac{1}{N(t)}\right] \\ &\quad + C_{i-1}(t)[1 - C_i(t)]\left[\frac{i-1}{N(t)}\right] \\ &\quad + [1 - C_{i-1}(t)]C_i(t)\left[1 - \frac{i}{N(t)}\right] \\ &= C_{i-1}(t)\left[\frac{i-1}{N(t)}\right] + C_i(t)\left[1 - \frac{i}{N(t)}\right]. \end{aligned} \tag{15}$$

Transforming from discrete to continuous variables and functions: $i \mapsto x/\Delta$ and $C_i(t) \mapsto C(x,t)$, taking the Taylor expansions about x gives

$$\begin{aligned} &\frac{C(x,t + \tau_{M(t)}) - C(x,t)}{\tau_{M(t)}} \\ &= -\frac{1}{\tau_{M(t)}N(t)}\frac{\partial}{\partial x}[xC(x,t)] \\ &\quad + \frac{\Delta}{2\tau_{M(t)}N(t)}\frac{\partial^2}{\partial x^2}[xC(x,t)] + O(\Delta^3/\tau_{M(t)}). \end{aligned} \tag{16}$$

Taking $\Delta \to 0$, recalling that $\tau_{M(t)} \to 0$ as $\Delta \to 0$, and noting that $\lim_{\Delta\to 0} \Delta N(t) = \lim_{\Delta\to 0} \Delta\lfloor L(t)/\Delta \rfloor = L(t)$, Eq. (16) can be written as

$$\begin{aligned} \frac{\partial C}{\partial t} &= -V_{\Delta,\tau_{M(t)}}\frac{\partial}{\partial x}\left[\frac{x}{L(t)}C(x,t)\right] \\ &\quad + \frac{D_{\Delta,\tau_{M(t)}}}{2}\frac{\partial^2}{\partial x^2}\left[\frac{x}{L(t)}C(x,t)\right], \end{aligned} \tag{17}$$

where

$$V_{\Delta,\tau_{M(t)}} = \lim_{\Delta\to 0}\frac{\Delta}{\tau_{M(t)}}, \quad D_{\Delta,\tau_{M(t)}} = \lim_{\Delta\to 0}\frac{\Delta^2}{\tau_{M(t)}}. \tag{18}$$

Here we are assuming that $V_{\Delta,\tau_{M(t)}}$ and $D_{\Delta,\tau_{M(t)}}$ exist as nonzero constants. However, it is clear that these two limits cannot hold simultaneously, as is possible for biased random walks where the bias can be chosen to be $O(\Delta)$ [32]). However, Simpson *et al.* [30] found that the continuum limits were valid even when the bias was as large as 0.75.

For discrete-time random walks on lattices, Δ and τ_j are typically taken to be independent. Furthermore, τ_j is almost exclusively taken to be constant for all j, such that all time steps are taken to be of length τ. Thus, in the continuum limit, with $\Delta, \tau \to 0$, the ratio at which they decrease can be chosen so that well-defined limits hold [20,30]. In contrast, as previously stated, here for our growing lattice, Δ and τ_j are inextricable linked.

Furthermore,

$$L(t + \tau_{M(t)}) - L(t) = \Delta,$$

and so

$$\frac{L(t + \tau_{M(t)}) - L(t)}{\tau_{M(t)}} = \frac{\Delta}{\tau_{M(t)}}. \tag{19}$$

Hence we have the following limit:

$$V_{\Delta,\tau_{M(t)}} = \lim_{\Delta\to 0}\frac{\Delta}{\tau_{M(t)}} = L'(t), \tag{20}$$

and therefore

$$D_{\Delta,\tau_{M(t)}} = \lim_{\Delta\to 0}\frac{\Delta^2}{\tau_{M(t)}} = \lim_{\Delta\to 0}\Delta L'(t). \tag{21}$$

In the limit as $\Delta \to 0$, the diffusivity of course goes to zero, and we have a pure advection equation given by the first two terms of Eq. (13) (removing the diffusive term). However, since we are producing simulations with finite values of Δ (and even ones with size $\Delta = 1$), we notice that if we write $D_{\Delta,\tau_{M(t)}} = \Delta L'(t)$, then we obtain exactly the diffusion-advection equation (13), where the mean length $\mathcal{L}(t)$ is replaced by deterministic length. In this section $L(t)$ can be any predetermined function (e.g., exponentially or linearly growing in time), whereas in the stochastic model, $\mathcal{L}(t) = e^{\lambda t}$. Substituting the approximations

$$V_{\Delta,\tau_{M(t)}} = L'(t), \quad D_{\Delta,\tau_{M(t)}} \approx L'(t)\Delta. \tag{22}$$

into the PDE (17) gives

$$\begin{aligned} \frac{\partial C}{\partial t} &= -L'(t)\frac{\partial}{\partial x}\left[\frac{x}{L(t)}C(x,t)\right] \\ &\quad + \Delta\frac{L'(t)}{2}\frac{\partial^2}{\partial x^2}\left[\frac{x}{L(t)}C(x,t)\right]. \end{aligned} \tag{23}$$

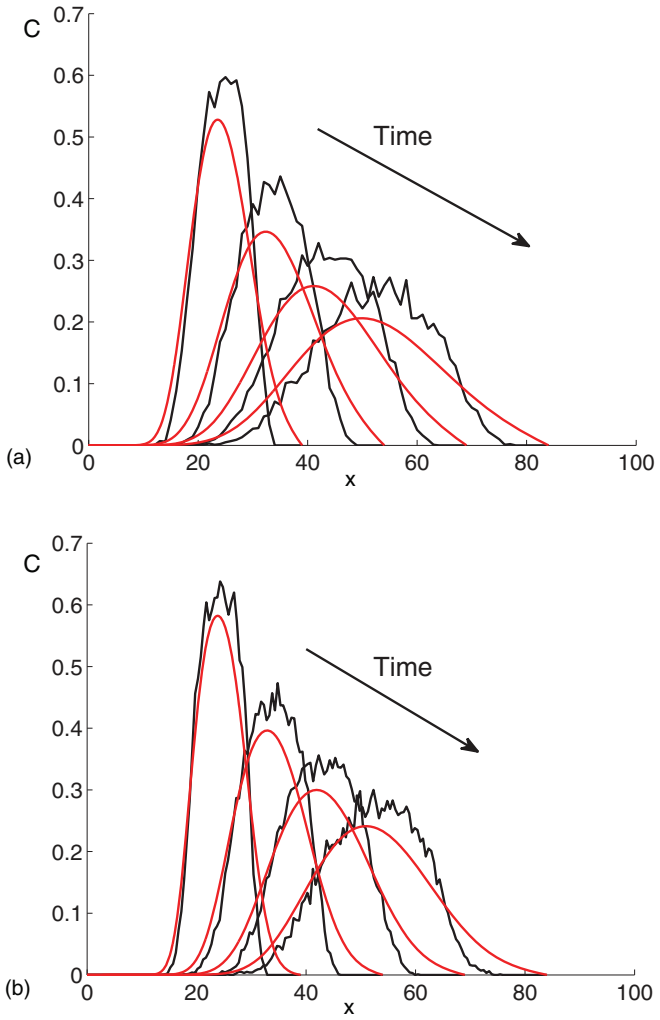

FIG. 4. (Color online) Solutions to Eq. (23) [red (light gray) curve] and expected occupancy averaged over 1000 realizations (black curve) with $L(t) = 24 + t$, for $t = 15, 30, 45, 60$. Initially, the marked agents are in $12 \leqslant x \leqslant 18$. (a) $\Delta = 1$, (b) $\Delta = 1/2$.

We solve Eq. (23) with appropriate boundary and initial conditions (Appendix B), setting the parameter Δ equal to the lattice spacing used in the simulations.

We anticipate the fit will be poor, as we know that the Binder and Landman [22] PDE, which has a diffusivity proportional to $[1 - x/L(t)]x/L(t)$, gives an excellent fit to simulations of the deterministic process. Indeed, Fig. 4 shows that the PDE solution is too spread out for all times for both $\Delta = 1$ and $\Delta = 1/2$.

Why is the master equation approach giving the wrong PDE? Is it because the approximations $V_{\Delta,\tau_{M(t)}}$ and $D_{\Delta,\tau_{M(t)}}$ are invalid or because the domains agents do not move independently of each other? Neither of these proves to be the reason. Indeed, we next show that the discrete-time master equation does not take into account an important feature of the process.

B. Equivalence to a totally asymmetric random walk

As for the continuous-time model for tissue growth discussed in Sec. II, the model for growing tissue with deterministic length is equivalent to a noninteracting random walk in terms of expected site occupancy. But now this is occurring in discrete time.

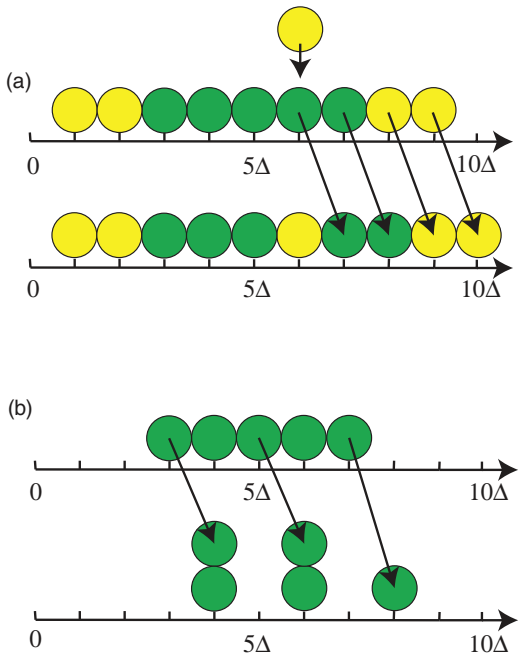

FIG. 5. (Color online) Typical example of movements resulting from a single time step. (a) The growing lattice process with nine domain agents, containing marked agents at sites 3–7. The domain agent at site 6 is selected to proliferate. (b) The totally asymmetric random walk process with sites 3–7 occupied by agents. Whether an agent moves or not is determined independently of other agents. A movement probability is assigned to each agent, and movements are implemented synchronously. In both, arrows indicate the movement of domain agents.

The probabilistic rules that govern the behavior of the agents are the following: at each discrete time step, each agent moves to the right with hopping probability $p_i^{\mathrm{R}}(t)$, and does not move with probability $1 - p_i^{\mathrm{R}}(t)$, where $p_i^{\mathrm{R}}(t)$ is dependent on the current site i occupied by the agent and time t. We set $p_i^{\mathrm{R}}(t) = \frac{i}{N(t)}$. The probability of hopping to the left is $p_i^{\mathrm{L}}(t) = 0$. Therefore we have defined a totally asymmetric random walk with noninteracting agents. Let the discrete time steps occur at times T_j for $j = 0,1,2,\ldots$, where T_j were defined as the times of individual proliferation events in the growing tissue case (at the beginning of this section).

Note that the movement probabilities are the same as for the growing tissue model, but one has agent interaction while the other has none. The results of the two simulation processes (with identical initial conditions) can look very different even after a few discrete time steps. For example, Fig. 5(a) illustrates a typical single proliferation event in the growing tissue model. This causes four agents to simultaneously move. By way of contrast, starting with the same initial distribution of green agents Fig. 5(b) shows a typical set of movements within a single time step: three agents have been randomly chosen to move while two remain at rest. A synchronous updating scheme is the most natural and efficient for non-interacting systems, where each agent is selected to move

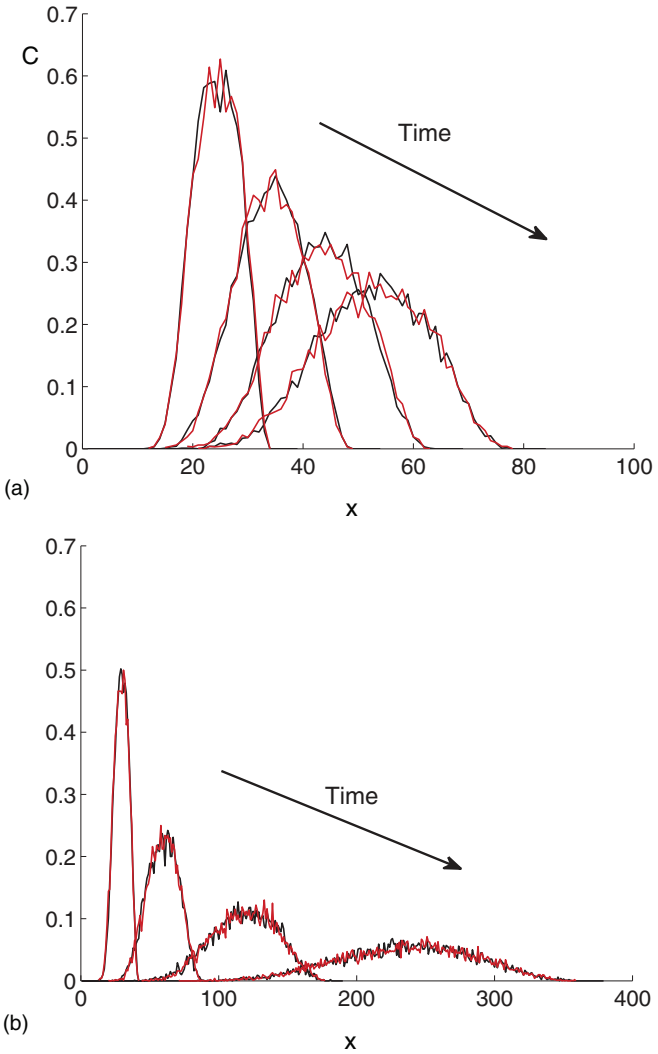

FIG. 6. (Color online) Expected occupancy averaged over 1000 realizations for the deterministic growing lattice model [red (light gray) curve] and the asymmetric random walk with synchronous updating (black curve) with $\Delta = 1$. Initially, the marked agents are in $12 \leqslant x \leqslant 18$. (a) Profiles at times $t = 15, 30, 45, 60$, where $L(t) = 24 + t$. (b) Profiles at times $t = 1, 2, 3, 4$, where $L(t) = 24e^{0.69t}$. Note the different axes scales.

exactly once each time step and all moves are implemented simultaneously.

However, despite the differences that arise in individual evolutions of these processes, the expected site occupancy for both processes is the same, given identical initial conditions (the arguments in Appendix A can be made appropriate to this discrete case and are therefore not repeated). This implies that the two processes are equivalent in terms of expected site occupancy. This equivalence is independent of $L(t)$. This is verified through the comparison of simulations for both processes for different growth functions, as shown in Fig. 6.

The Fokker-Plank formalism described earlier has been applied to a general noninteracting asymmetric random walkers [33] for different simulation updating schemes. For a synchronous updating scheme, the infinitesimal mean and variance defined in Eqs. (6) and (7) needed for Eq. (5) are

$$\mu(x,t) = V_{\Delta,\tau_{M(t)}}[p^{\mathrm{R}}(x,t) - p^{\mathrm{L}}(x,t)], \tag{24}$$

$$\sigma^2(x,t) = D_{\Delta,\tau_{M(t)}}\{p^{\mathrm{R}}(x,t) + p^{\mathrm{L}}(x,t) - [p^{\mathrm{R}}(x,t) - p^{\mathrm{L}}(x,t)]^2\}. \tag{25}$$

Using our approximations for $V_{\Delta,\tau_{M(t)}}$ and $D_{\Delta,\tau_{M(t)}}$ given in Eq. (20) and the continuous variable transformation of the hopping probabilities $p^{\mathrm{L}}(x,t) = 0$ and $p^{\mathrm{R}}(x,t) = x/L(t)$, the Fokker-Planck equation for the noninteracting random walk with synchronous update scheme is

$$\frac{\partial C}{\partial t} = -L'(t)\frac{\partial}{\partial x}\left[\frac{x}{L(t)}C\right] + \Delta\frac{L'(t)}{2}\frac{\partial^2}{\partial x^2}\left\{\frac{x}{L(t)}\left[1 - \frac{x}{L(t)}\right]C\right\}. \tag{26}$$

This PDE is (almost) the same as that derived by Binder and Landman [22] for the case $\Delta = 1$. However, PDE (26)

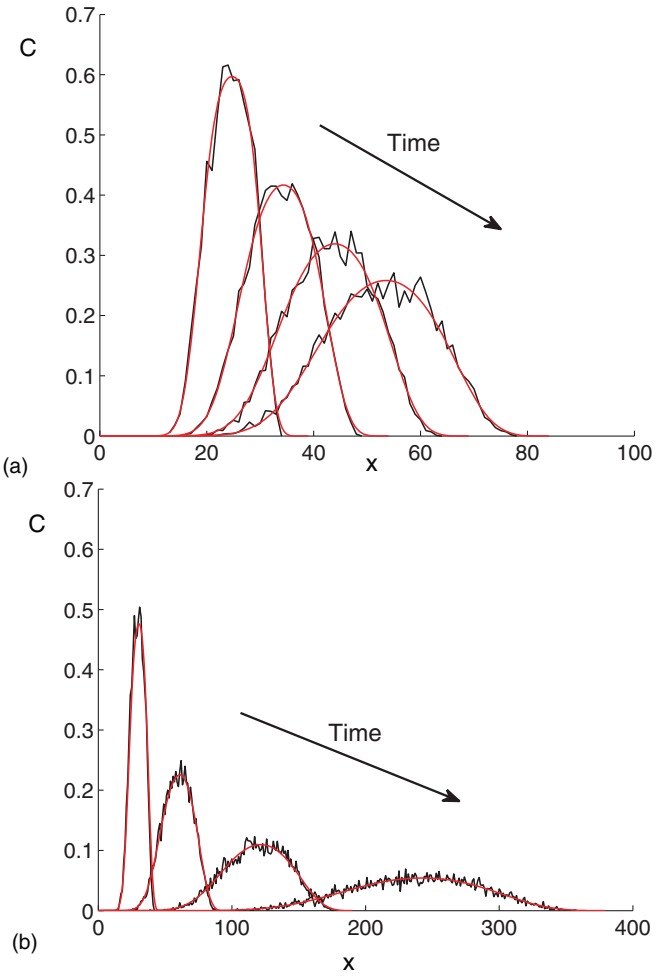

FIG. 7. (Color online) Solutions to Eq. (26) [red (light gray) curve] and expected occupancy averaged over 1000 realizations (black curve) for the asymmetric random walk with synchronous updating (blue curve) with $\Delta = 1$. Initially, the marked agents are in $12 \leqslant x \leqslant 18$. (a) Profiles at times $t = 15, 30, 45, 60$, where $L(t) = 24 + t$. (b) Profiles at times $t = 1, 2, 3, 4$, where $L(t) = 24e^{0.69t}$. Note the different axes scales.

generalizes that previous result for all cases of Δ. [Note that it satisfyingly does not contain the factor $1/(L(t)+\Delta)$ term, which occurs in Binder and Landman [22] with $\Delta = 1$, which is correct since $\Delta \ll L(t)$. See Appendix C.] It is physically correct that the variance should be zero at both ends, as these are both deterministically specified. Figure 7 compares the solution to Eq. (26) with average simulation data from the asymmetric random walk with synchronous updating scheme; the PDE solution describes the expected occupancy very well indeed.

The two PDE descriptions can be reconciled by considering a different simulation update scheme for the general asymmetric noninteracting random walk [33]. The simulation updating scheme effects the probability distributions related to the stochastic process and therefore affects the infinitesimal means and variance. Suppose instead an asynchronous updating scheme is used, such as a random sequential updating scheme [24]. In this case, if there are Q agents, then at each time step Q sequential independent random choices of an agent are made, and each agent is immediately updated on selection. Of course, sometimes an agent will be selected to update more than once, or in fact not at all. For the random sequential updating scheme the infinitesimal mean is given by Eq. (24), but the variance is larger:

$$\sigma^2(x,t) = D_{\Delta,\tau_{M(t)}}[p^{\mathrm{R}}(x,t) + p^{\mathrm{L}}(x,t)]. \tag{27}$$

Substitution of these expressions into Eq. (20) then gives the PDE already encountered, namely, Eq. (23).

V. DISCUSSION

Partial differential equations have been derived that are highly accurate at approximating the evolution of expected site occupancy for a stochastic growing tissue and a deterministically growing tissue.

The stochastic growing tissue, where agents (cells) have exponential waiting times between proliferation events and proliferation events between cells are independent, gives rise to a total length which is a random variable with mean $\mathcal{L}(t)$ given by exponential growth. Such growth occurs naturally in embryonic tissue [1]. The time evolution of a subset of the tissue cells is well described by PDE (14). In contrast, if the length of the tissue is deterministic, but the agents which proliferate are selected randomly, then the appropriate PDE is given by Eq. (26), where $L(t)$ can be any prescribed increasing function.

When a discrete-time master equation is used to derive a PDE for the deterministic growing lattice, we obtain Eq. (23). This equation has the same form as PDE (14), but now $L(t)$ is not limited to being exponential. This gives rise to an apparent contradiction with Eq. (26). However, the master equation approach is equivalent to a noninteracting random walk which is implemented with a random sequential update scheme. This computational method produces a larger variance, because leading agents can be chosen more frequently to move (and always asymmetrically to the right here). It is well known that the random sequential update scheme is the discrete-time analog of a continuous-time process [24]. This is the reason that it gives rise to the same PDE as the continuous-time stochastically growing lattice.

These models can be easily extended to include actively moving, proliferating or differentiating population of cells (active agents) on the growing lattice, with volume exclusion assumptions, as discussed in Binder and Landman [22]. A PDE description of the active agents must incorporate the advection and diffusion contributions arising from domain growth, alongside any other transport and kinetic mechanisms exhibited by the active agents [22]. It is therefore important to choose the correct PDE description arising from domain growth since these terms are used for the active agents too [22]. Here we have analyzed models of domain growth and explained the issues giving rise to different descriptions, so that the choice of PDE is understood.

ACKNOWLEDGMENT

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APPENDIX A: EQUIVALENCY OF EXPECTED SITE OCCUPANCY PROOF: CONTINUOUS TIME

First, consider the continuous-time model for tissue growth. Let the number of domain agents initially be N_0, and let the positions of the leftmost and rightmost marked domain agents be M_l and M_r respectively, with $M_l \leqslant M_r < N_0$, and let all domain agents between these positions also be marked.

Now, let us consider some arbitrary site $y \geqslant 0$. Let Y_t give the occupancy of site y at time t. Let $\xi(m,y,t)$ be an indicator random variable such that $\xi(m,y,t) = 1$ if, at time t, site y is occupied by the marked domain agent initially at position m, and 0 otherwise. At any time t, each site on the lattice can only be occupied by at most one marked domain agent. Hence, Y_t can be expressed as $Y_t = \sum_{m=M_l}^{M_r} \xi(m,y,t)$. Thus the expectation of Y_t can be expressed as

$$\mathbb{E}[Y_t] = \sum_{m=M_l}^{M_r} \mathbb{E}[\xi(m,y,t)] = \sum_{m=M_l}^{M_r} p(m,y,t), \tag{A1}$$

where $p(m,y,t)$ is the probability that a domain agent that initially starts at position m occupies site y at time t.

Next consider the continuous-time nonexclusion random walk. For this case, $Y_t = \sum_{m=M_l}^{M_r} \xi_{\mathrm{arw}}(m,x,t)$, where $\xi_{\mathrm{arw}}(m,x,t)$ is the indicator random variable such that $\xi_{\mathrm{arw}}(m,x,t) = 1$ if, at time t, site y is occupied by the marked domain agent initially at position m, and 0 otherwise. Again, it follows that $\mathbb{E}[Y_t] = \sum_{m=M_l}^{M_r} \mathbb{E}[\xi_{\mathrm{arw}}(m,x,t)] = \sum_{m=M_l}^{M_r} p_{\mathrm{arw}}(m,x,t)$, where $p_{\mathrm{arw}}(m,y,t)$ is the probability that a random walker that initially starts at position m occupies site y at time t.

From Eq. (4), we have $p(m,y,t) = p_{\mathrm{arw}}(m,y,t)$ for all m, y, and t, and hence both processes have the same expected site occupancy.

APPENDIX B: SIMULATION METHODS

Data from averaged simulation results are compared with solutions to the relevant PDEs. Each lattice site between $M_l \leqslant x \leqslant M_r$ (for some chosen M_l and M_r) is initially

occupied with a single agent, while the remaining lattice sites are empty.

For the PDEs, the boundary conditions are chosen as $C(0,t) = 0$ and $C(\mathcal{L}(t),t) = 0$ or $C(L(t),t) = 0$ for the stochastic and deterministic cases, respectively. [Marked domain agents cannot occur beyond the rightmost domain agent, so setting $C(x,t) = 0$ for $x > \mathcal{L}(t)$ is valid. The rightmost agent is not marked.]

APPENDIX C: BINDER AND LANDMAN METHODS

Binder *et al*. [1] established that the probability distribution for the position of a single marked lattice agent is equivalent to the Pólya distribution. In 1923 the Pólya distribution was used to describe random drawings of colored balls from an urn [34]. In terms of our variables, initially there are X_0 white balls and $N(0) - X - 0$ black balls. One ball is drawn at random, and then replaced along with one additional ball of the same color. Counting the number of white balls out of the total of $N(t)$ balls can be shown to be equivalent to the position of a single marked agent.

The Fokker-Plank approach was used to determine infinitesimal moments. However, since the lattice size was set to unity, the correct limits as lattice width $\Delta \to 0$ such that $\Delta N(t) \to L(t)$ was not rigorous. We have repeated the work in Binder and Landman [22] with a general Δ using the Pólya probability distribution (rather than the totally asymmetric random walk described in the main paper), taking rigorous limits in a similar way as performed in the body of this work. The resulting PDE is exactly Eq. (26).

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