Shape of population interfaces as an indicator of mutational instability in coexisting cell populations

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Abstract
Cellular populations such as avascular tumors and microbial biofilms may ‘invade’ or grow into surrounding populations. The invading population is often comprised of a heterogeneous mixture of cells with varying growth rates. The population may also exhibit mutational instabilities, such as a heavy deleterious mutation load in a cancerous growth. We study the dynamics of a heterogeneous, mutating population competing with a surrounding homogeneous population, as one might find in a cancerous invasion of healthy tissue. We find that the shape of the population interface serves as an indicator for the evolutionary dynamics within the heterogeneous population. In particular, invasion front undulations become enhanced when the invading population is near a mutational meltdown transition or when the surrounding ‘bystander’ population is barely able to reinvade the mutating population. We characterize these interface undulations and the effective fitness of the heterogeneous population in one- and two-dimensional systems.

1. Introduction

Invasion and competitive exclusion is a common phenomenon in biology, with examples spanning a wide range of length and time scales: an invasive land animal species may compete with the species already present in the ecological habitat [1], microbial strains may compete and invade each other within a growing biofilm [2, 3], or virus strains may compete for host resources [4]. Such competitions also exist within the tissues of various organisms, during development and in cancerous growth: a tumor which starts out as a small cluster of rapidly growing and mutating cells must compete with surrounding healthy tissue [5]. In all of these examples, the spatial structure of the population may have a significant impact on the strain competition and evolution.

Spatially-distributed populations are markedly different from their well-mixed counterparts. Because local population sizes are small compared to the population size in, for example, a well-mixed test tube, genetic drift or small number fluctuations become more important: strains within spatially-distributed populations are more likely to locally fix. Also, deleterious mutations more readily accumulate at leading edges of spatially-distributed populations compared to well-mixed populations where natural selection would eliminate such variants [6, 7]. There may be mitigating factors that reduce this mutational load, however, such as the presence of an Allee effect due to strain cooperation, for example [8]. Considering deleterious mutations in a spatial context is particularly important for invading cancerous populations which exhibit genomic instability [9, 10] and are typically spatially heterogeneous, consisting of a wide distribution of strains [11–14]. It is becoming increasingly clear that spatial evolutionary models are necessary to understand the evolutionary dynamics of cancer cell populations [15, 16].

The mutations that drive uncontrolled growth in cancerous populations are the so-called driver mutations. However, the majority of mutations are passenger mutations which have a neutral or slightly deleterious effect on the cancer cells. Such mutations are ubiquitous in cancerous populations, although their importance for cancer progression has only recently been recognized [17]. Weakly deleterious passenger mutations can rapidly accumulate at the edges of spatially-distributed populations, and the combined deleterious effect can lead to a cancer population collapse. Therefore, the elucidation of the impact of the passenger mutations may lead to new cancer therapies and a better understanding of the efficacy of existing therapies [18, 19]. For example, an effective cancer...
treatment may involve increasing the mutation rate such that the passengers overwhelm the drivers or increasing the deleterious effect of the passengers such that the drivers are no longer able to sustain tumor growth. The accumulation of deleterious mutations leading to population collapse is termed ‘mutational meltdown’ [20, 21]. Already there is evidence that cancer therapies may be developed that target passenger mutations to expose vulnerabilities in cancer growth [22] and that cancer cell lines are particularly vulnerable to mutational meltdown [23].

In this paper, we develop a simple spatial model of the invasion of a cellular population (i.e., a ‘bystander’) by another population (i.e., an ‘invader’) that is acquiring deleterious mutations. We show that when the mutating invader is near a mutational meltdown, the interface between the invader and bystander becomes rougher and more undulated. Such interface shapes and physical cues are important as advances in medical imaging allow us to probe the spatial structure of cancerous growth with unprecedented detail [24]. Tumor shape is increasingly being used for diagnostic purposes. For example, the shape of a tumor boundary is used as a diagnostic tool in breast cancers where a rougher tumor edge may indicate a more malignant growth [25]. Spatial heterogeneities also influence the timing of the cancer progression [26]. It is therefore useful to build explicitly spatial models to understand what to look for in clinical images and to better understand the spatial signatures of particular evolutionary dynamics.

Although these spatial evolutionary aspects have only recently been explored in cancerous populations, many of the predictions of spatial models have been borne out in studies of microbial range expansions where a population of microbes grows into virgin territory (e.g., as a colony on a Petri dish). Here, small number fluctuations and local fixation yield a sectoring phenomenon where initially mixed strains demix into uniform sectors containing a single strain over time [27, 28]. The previously mentioned enhancement of deleterious mutations near population edges has been verified via DNA sequencing of bacterial range expansions [7]. Also, the mutational meltdown we will consider in this paper has been demonstrated in yeast cell colonies, where a simple lattice model of the kind employed in this work successfully predicted the effects of the increased genetic drift [29]. Increasingly, results from such microbial populations and simple spatial evolutionary models are yielding insights into what may happen in cancerous populations [15, 30].

In cancerous tissue, current sequencing techniques have a limited ability to probe the spatial structure of the cancer cell population. Adaptation of sequencing techniques to spatially-distributed populations is important as spatial effects have been shown to significantly impact DNA sequencing data of cancerous cell populations [31, 32]. Our study presents a complementary approach where we show that physical cues such as the shape of an interface between competing cellular strains may indicate certain properties of the evolutionary dynamics of the tissue (e.g., the proximity to a mutational meltdown transition). Such heuristic measures are useful in conjunction with DNA sequence information, which is often difficult to interpret and has limited ability to probe the spatial structure of the cancerous growth [31].

In this paper, we build a model for how a mutating strain invades a non-mutating strain in both one- and two-dimensional habitats, which we call \( d = 1 + 1 \) and \( d = 2 + 1 \) evolutions, respectively. The +1 indicates the time dependence. Our focus here is on the competition between multiple strains within a population, so for simplicity we consider flat habitats which do not change shape as the population evolves. For \( d = 1 + 1 \), such a habitat may be a coast, a river bank, or a thin duct. For \( d = 2 + 1 \), the strains may be in a microbial population growing on a flat surface or in an epithelial tissue. Another possibility is that the population in which the strains compete is the leading edge of a range expansion. In this case, we assume that the population growth is confined to a thin region at the edge, which remains flat during the range expansion. This approximation will hold as long as there is a sufficient surface tension keeping the population flat. However, the population edge roughens over time, the roughening will generically change the genetic sector motion [34], an analysis of which is beyond the scope of the current work.

Note that for a cellular population at the edge of a range expansion, the +1 dimension also represents the direction of the range expansion. So, in other words, for \( d = 1 + 1 \), the strains we study may live along a thin, effectively one-dimensional edge of a two-dimensional range expansion (e.g., a thin microbial colony grown on a Petri dish). For \( d = 2 + 1 \) evolution, the population may be the effectively two-dimensional, flat edge of a three-dimensional range expansion. A more realistic scenario is perhaps the \( d = 3 + 1 \)-dimensional case where a population embedded in three dimensions evolves in time with various strains within the population competing for the same space. Although we do not study this case specifically here, the lower dimensional cases provide intuitions for considering this scenario. Also, if the geometry of the three-dimensional population has a large aspect ratio, then our one and two (spatial) dimensional models will describe the behavior of cross sections of the population. A similar kind of dimensional reduction was recently employed for describing bacterial competition in three-dimensional channels [35].

Previous work has shown that range expansions develop frontiers with enhanced roughness when the
population is near a phase transition in its evolutionary dynamics (e.g., at a mutational meltdown transition [34] or near the onset of mutualistic growth [36]). In this work, we consider invasion frontiers which are markedly different as the invader grows into a surrounding population which may rein invade if the invader growth rate decreases. So, the invasion front velocity \( v \) will depend on the relative growth rates of the two populations and may vanish or change signs. In other words, the competition interfaces studied here have a variable velocity, unlike a range expansion in which a population grows into a virgin territory with some particular growth rate. In this sense, the competition interface studied here is more similar to a range shift, in which the population growth is limited by the environment and exhibits variation [37]. We will see that in the case of \( d = 2 + 1 \)-dimensional expansions, the average velocity \( \bar{v} \) of the invasion front will influence the interface roughness.

We will also show here that, like the range expansion, the invasion frontier develops an enhanced roughening at the mutational meltdown transition of the invader population. However, unlike a range expansion frontier, the roughening is more subtle, especially in the \( d = 2 + 1 \)-dimensional case where the invasion front velocity \( v \) influences the roughening dynamics. Moreover, for \( d = 2 + 1 \), the invasion interface does not maintain a compact shape, and isolated pieces of the invading population may pinch off and migrate into the surrounding ‘bystander’ population, especially when the growth rates of the two populations are nearly equal. In this paper we will discuss these issues and connect the shape of the undulating frontier to the evolutionary dynamics of the invading population.

The evolutionary dynamics explored here (e.g., the motion and coarsening of the sectors of strains) has universal properties tying together a large class of systems including tumor growth, reaction–diffusion processes, granular material avalanches, and epidemic spreading [38]. For example, tumor shapes have been shown to have the same fractal boundary properties as films deposited by molecular beam epitaxy [39]. Therefore, many of the techniques originally developed to understand physical phenomena, such as the phase ordering of deposited binary films [40, 41], may be employed to understand the spatial evolutionary dynamics of cellular populations [42]. The universal properties of all of these systems include coarse-grained properties such as the scaling of interface roughness with time [43], a quantity we will explore here for the interface between the bystander and the invader. We may thus reasonably expect our results to hold generally in a wide range of biological and physical contexts.

The paper is organized as follows: in the next section, we present our lattice model for invasion by a mutating population for \( d = 1 + 1 \) and \( d = 2 + 1 \)-dimensional cases. In section 3 we briefly review the nature of the mutational meltdown transition that may occur in the mutating invading population. In section 4 we study the survival probability of the invading strain and construct phase diagrams characterizing whether or not the invasion is successful as a function of the internal mutation rate \( \mu \) and the selective advantage of the various cellular strains. In section 5, we analyze the roughening invasion front near the mutational meltdown transition for the invading population. Finally, we conclude with a discussion of the implications of our results in section 6.

2. Model

We consider a simple lattice model, in the spirit of the Domany–Kinzel cellular automaton [44, 45], of invasion of a stable population by a mutating invader consisting of two species, a fast-growing and a slow-growing strain into which the fast-growing one can mutate. We set the fast-growing strain growth rate to unity \( \Gamma_f = 1 \) without loss of generality, so that time is measured in generation times \( \tau_g \) of the fast-growing strain. The slow-growing strain within the invader population will have growth rate \( \Gamma_s = 1 - s \), where \( 0 \leq s < 1 \) is a measure of the deleterious effect of the mutation. In a tumor or microbial colony, we know that the initial cluster of growing cells may encounter other cells (e.g., surrounding healthy tissue or competing microbial strains). So, we have a third species representing the ‘bystander’ population. The bystander will not mutate, but will be able to displace the mutating population via cell division. We set the bystander growth rate to \( \Gamma_b = 1 + b - s \), with \( b \) the selective advantage of the bystander over the slow-growing invader strain.

The internal dynamics of the invading population (i.e., the mutation rate \( \mu \) and selection parameter \( s \)) will influence how the invader interacts with the bystander strain, with increasing \( \mu \) leading to an overall fitness decrease for the invading population, as might happen in a cancerous tissue during a course of therapy that increases the deleterious mutation rate of the cancerous cells. We focus on the region between the mutating population and the bystander, which we call the invasion front or interface. As we will show, when the invader is close to mutational meltdown, the invasion front develops an enhanced ‘roughness’.

The specific lattice model rules are as follows: in both one- and two-dimensional population scenarios, we consider a three-strain model in which a single ‘bystander’ strain (yellow cells in figure 1) grows in the presence of a fast-growing invading strain (red cells in figure 1) that can mutate to a more slowly growing strain (black cells in figure 1). These cells occupy a single lattice location, as shown in figure 1. During each generation (cell division) time \( \tau_g \), the lattice of cells is regenerated by allowing for adjacent cells to compete and divide into empty sites representing the
in the next generation of cells. In a range expansion context, these empty sites would represent unoccupied territory at the frontier. Alternatively, these updates can represent a turnover of cells due to birth and death within the population. After all empty sites in the next lattice have been filled, the process can be repeated, generating a sequence of successive, non-overlapping generations of the population (or, alternatively, a moving frontier of a range expansion). Note that each time a red (fast-growing) cell is placed in the empty spot, then it in addition has a probability \( \mu \) of mutating to the slower-growing black strain. (b) For a two-dimensional population \((d = 2 + 1)\) the generations are evolved on staggered triangular lattices, as shown. This time, three cells compete to divide into empty lattice sites. Otherwise, the dynamics are the same as the \(d = 1 + 1\) case.

Figure 1. (a) Update rules for the bystander model for a population in \(d = 1 + 1\) dimensions. Each generation is evolved by allowing for two cells from the previous generation to compete for an empty lattice site, as shown by the arrows. The probability of occupation by a cell of a type \(i = s, f, b\) is proportional to its growth rate \(\Gamma_i\), where \(s\) is the slow growing black strain, \(f\) is the fast growing red strain, and \(b\) is the yellow bystander. If a red (fast-growing) cell is placed in the empty spot, then it in addition has a probability \(\mu\) of mutating to the slower-growing black strain. (b) For a two-dimensional population \((d = 2 + 1)\) the generations are evolved on staggered triangular lattices, as shown. This time, three cells compete to divide into empty lattice sites. Otherwise, the dynamics are the same as the \(d = 1 + 1\) case.

Our parameterization allows us to tune the dynamics of the black/red mutating invader population separately. As we will analyze in the next section, the invader has an internal ‘mutational meltdown’ at which the fast-growing red strain is removed from the population due to mutation. This occurs for \(\mu \gtrsim s^2\) in \(d = 1 + 1\) dynamics and \(\mu \gtrsim s \ln s\) in \(d = 2 + 1\) dynamics (\(\mu > s\) in well-mixed populations). Note that an important limitation of our model is that we assume cells divide into adjacent spots on the lattice so that cell motility is essentially absent (apart from the short-range cell rearrangements occurring due to the cell division). This is a reasonable approximation for certain microbial populations such as yeast cell colonies [29] or small, avascular solid tumors where cells primarily proliferate (instead of migrating) [46].

3. Mutational meltdown

Let us first focus on the invading population (ignoring the bystander) and perform a simple analysis of the internal dynamics. The invader consists of two strains: one fast-growing red strain and a second slow-growing black strain into which the fast-growing strain mutates with rate \(\mu\) per cell per generation. In the parameter space \((\mu, s)\), we find two distinct phases [44]: in one phase, the fraction of the fast-growing strain remains positive after many generations, \(p(t \to \infty) > 0\); we call this phase the active phase. In the
other phase, called the *absorbing* or *inactive phase*, the fast-growing strain eventually completely dies out and \( \rho_f(t \to \infty) = 0 \). There is a line of continuous phase transitions \((\mu^*, s^*)\) which defines the boundary between the two phases. Examples of these phases, and the critical region \((\mu \approx \mu^*, s \approx s^*)\), are shown in figure 2 where we have removed the bystander population in order to see the internal dynamics of the invader.

We can understand this transition in a well-mixed population (a mean-field approach). The fraction \( \rho_f \equiv \rho_f(t) \) of the fast-growing strain within the mutating population changes according to:

\[
\frac{d\rho_f}{dt} = s\rho_f(1 - \rho_f) - \mu\rho_f,
\]

which approaches \( \rho_f(t \to \infty) = 1 - \mu/s \) for \( \mu < s \), and \( \rho_f(t \to \infty) = 0 \) for \( \mu > s \). The line \( \mu = s \) is our set of critical points \((\mu^*, s^* = \mu^*)\). For a spatially distributed population, small number fluctuations or “genetic drift” dramatically alters the shape of the phase boundary: the phase transition occurs for \(\mu^* \sim (s^*)^2\) in one-dimensional populations (such as at the edge of a growing biofilm [29]) and \(\mu^* \sim s^* \ln(s^*)\) for two-dimensional populations [47]. This phase transition, called a ‘mutational meltdown,’ is known to belong to the directed percolation (DP) universality class [38]. For the particular lattice model we consider here, this has been explicitly verified [44] by mapping the model to the well-studied Domany–Kinzel cellular automaton [45]. The efficacy of this simple model has been demonstrated in a synthetic yeast strain, for which the parameters \(\mu\) and \(s\) could be tuned over a broad range encompassing the DP phase transition [29].

Note that when the population approaches the mutational meltdown transition, the slow-growing black strain within the population begins to take over. In the active phase in figure 2, the black strain makes finite-sized, small patches within the red population. Then, as we approach the transition, the black strain average patch sizes diverge. In the critical regime, the average patch size becomes infinite. Then, in the ‘inactive’ phase, the red strain will eventually die out completely, leaving behind just the slowly growing black strain. We shall see that it is this divergence of the average black strain patch size near the transition which is responsible for enhanced invasion front roughening.

The two-species model may be generalized to include an arbitrary number of possible mutations, and such models have been shown to exhibit critical behavior that deviates from the DP universality class, but the loss of the fittest mutant in the population is still well-described by DP [47]. The multi-species generalization has many additional phenomena such as multi-critical behavior [48], which would allow for interesting extensions of the work presented here. In this paper, for simplicity, we focus on the fittest mutant in an invading population with just two species. The fitter strain could represent, for example, a driver mutation which has swept through a cancerous tissue with some growth rate \( \Gamma_f = 1 \). The driver strain could then acquire deleterious mutations over time which decrease the growth rate to \( \Gamma_s = 1 - s \) with rate \( \mu \).

### 4. Invasion probabilities

We now return to the bystander and invader competition. In figure 4, we construct a phase diagram for successful invasion of the bystander strain by the mutating invader. We initialize a well-mixed population of equal parts of the mutating red and bystander yellow strains \((\rho_b = \rho_y \equiv 1/2)\) on the lattice, and then calculate the density \(\rho_m = \rho_y + \rho_s\) of the
mutating red/black population at long times \( t \). If \( \rho_m \to 0 \) and the red/black population dies out at long times, then the ‘invasion’ is unsuccessful. Otherwise, \( \rho_m \) approaches a non-zero value and the invasion succeeds. The results are shown in figure 4 for \( d = 1 + 1 \) and \( d = 2 + 1 \), where we see the two distinct phases (the purple and yellow portions of the phase diagram). We also include the phase boundary \( \mu = s - b \) for the well-mixed population (blacked dashed line in figure 4), which we derive in the next subsection. Note how far away the well-mixed population transition line is from the actual transition in a spatial population. The genetic drift associated with the spatial populations suppresses the invasion by the red/black mutating population.

We also know that as we approach the mutational meltdown transition at \( \mu = \mu^* \) for a fixed \( s \) (vertical dashed lines in figure 4), the characteristic sizes \( \xi_{\perp} \) and the characteristic lifetimes \( \xi_i \) of black, slow-growing strain clusters diverge according to \( \xi_{\perp} \sim \Delta^{\nu_{\perp}} \) and \( \xi_i \sim \Delta^{\nu_i} \), where \( 0 < \Delta < 1 \) is the distance from the phase transition in the \((\mu, s)\) plane and \( \nu_{\perp} \) and \( \nu_i \) are critical exponents associated with DP \((\nu_{\perp} \approx 1.097, \nu_i \approx 1.734 \) for \( d = 1 + 1 \) and \( \nu_{\perp} \approx 0.734, \nu_i \approx 1.295 \) for \( d = 2 + 1 \) [38]). We illustrate the sizes \( \xi_{\perp, i} \) in figure 3. The black patches will interact differently with the bystander than with the red patches of the fast-growing strain. As the patch sizes \( \xi_{\perp, i} \) diverge (when \( \Delta \to 0 \)), they would have a more pronounced effect on the invasion dynamics. In particular, there will be larger regions over which either the yellow strain invades a black patch, or a red patch invades the yellow bystander. This will increase the amount of ‘wiggliness’ of the invasion front between the bystander and the mutating red/black population. We will verify this analysis more quantitatively in section 5.

4.1. Mean-field analysis

To understand the behavior of this three-species model, we first briefly describe what happens in a well-mixed (mean-field) context. Consider the time-evolution of the fractions \( \rho_f, \rho_s, \rho_b \) of the fast-growing, slow-growing, and bystander strains, respectively. For a fixed total population size, we have \( \rho_f + \rho_s + \rho_b = 1 \). Given our growth rates \( \Gamma_f = 1, \Gamma_s = 1 - s, \) and \( \Gamma_b = 1 - s - b \), we may define corresponding selection coefficients characterizing the competition between pairs of strains:

\[
\begin{align*}
\xi_{sf} &= \frac{\Gamma_b - \Gamma_s}{(\Gamma_b + \Gamma_s)/2} = \frac{2b}{2 - 2s + b} \\
\xi_{sb} &= \frac{\Gamma_f - \Gamma_b}{(\Gamma_f + \Gamma_b)/2} = \frac{2(s - b)}{2 - s - b} \\
\xi_{fb} &= \frac{\Gamma_f - \Gamma_s}{(\Gamma_f + \Gamma_s)/2} = \frac{2s}{2 - s},
\end{align*}
\]

with selection parameters \( 0 \leq s < 1 \) and \( 0 \leq b \leq s \). In terms of these selection coefficients, the equations for the time-evolution of the bystander and fast-growing strain fractions \( \rho_{b,f} \equiv \rho_{b,f}(t) \) in a well-mixed population are

\[
\begin{align*}
\frac{\partial}{\partial t} \rho_b &= s_f \rho_f \left( 1 - \rho_b - \rho_f \right) - \xi_{sf} \rho_f \rho_b \\
\frac{\partial}{\partial t} \rho_f &= s_b \rho_b \left( 1 - \rho_b - \rho_f \right) + \xi_{fb} \rho_f \rho_b - \mu \rho_f 
\end{align*}
\]

(3)

If \( \rho_b = 0 \), we recover the two-species dynamics of the invader population with a directed percolation-like process between the fast-growing and slow-growing strains. We can also verify that there is no sensible stable fixed point where both the bystander population and the invader coexist. Instead, if \( \mu > s - b \), then the bystander will sweep the total population and \( \rho_b(t) \to 1 \) with increasing time \( t \). Otherwise, if \( \mu < s - b \), the invasion by the mutating population is successful and we find \( \rho_b(t) \to 0 \) over time. Moreover, if \( \mu > s \), then not only is the invasion unsuccessful, but we also get a collapse of the fast-growing strain within the invading population \( \rho_f(t) \to 0 \). So, the mutational meltdown transition of the invader population occurs when \( \mu = s \) in this mean-field analysis.

The mean-field analysis tells us that we should expect a critical surface in the \((s, b, \mu)\) parameter space given by \( \mu = s - b \) separating a region of successful \((\mu < s - b)\) or failed \((\mu > s - b)\) invasion of the bystander strain by the mutating invader (which itself may undergo a mutational meltdown when \( \mu > s \)). As we have already seen, the
spatially-distributed populations also have this critical surface but the enhanced genetic drift suppresses the phase space for successful invasion. To add the effects of genetic drift and the spatial distribution of the population to equation (3), we would have to incorporate a spatial diffusion term $\nabla^2 \rho_{bf}$ in each of the equations and stochastic noise terms describing the birth/death dynamics (see [47] for a more detailed description). These additional terms significantly modify our mean-field equations and introduce different phenomena, such as propagating waves (moving population interfaces) which we will analyze in section 5.

We can get a better approximation to the critical line for the $d = 1 + 1$ case than that given by the mean-field theory by considering a single domain wall. We expect the total length along the domain wall the mean-field theory by considering a single domain equation (4) to predict the critical line in (8) for the mutating invader population. We now can use consistent with previous results [47]. As strain are small and rarely collide, as shown in figure 2. ‘active’ phase, and the patches of black slow-growing strain are near a DP phase transition where $\phi_f \approx A_2 (\mu^* - \mu)^3$, where $A_2$ is an amplitude that will depend on $s$ and $\beta \approx 0.276$ is a DP critical exponent [38]. We may now use equation (4) to make an estimate of the critical value of $b$ for $d = 1 + 1$:

$$b = s (1 - A_1 \mu / \beta) (\mu \ll \mu^*) \quad (5a)$$

$$b = s A_2 (\mu^* - \mu)^3 (\mu \approx \mu^*) \quad (5b)$$

where $A_1$ and $A_2$ can be calculated numerically from separate simulations of the two-species model. These improved estimates are plotted onto the phase diagrams in figure 4(a) (green dashed line for the $\mu \ll \mu^*$ case and white dashed line for the $\mu \approx \mu^*$ case).

For $d = 2 + 1$-dimensional evolutions, the situation is more complicated because the patches of the invader strain no longer have a compact shape describable by a simple random walk [see figure 2(b)]. However, we expect that the bystander population may reinvade the mutating population when $b > s \phi_f$ because, much like in the $d = 1 + 1$ case, the average growth rate of the invader strain is approximately $T \approx \phi_f \Gamma_f + (1 - \phi_f) \Gamma_b = 1 - s + \phi_f s$. The bystander strain has growth rate $\Gamma_b = 1 - s + b$, so we see that the growth rates are equal when $b = \phi_f s$. We now just need estimates for $\phi_f$ for $d = 2 + 1$. When $\mu \ll \mu^*$, previous work [47] has shown that $\phi_f \approx 1 - A_3 \mu \ln (s / \rho_s) / s$, with $A_3 \approx 0.3$ and $\rho_s \approx 40$ some model-dependent parameters. Conversely, when $\mu \approx \mu^*$, we again find a DP transition with $\phi_f \approx A_3 (\mu^* - \mu)^3$ with critical exponent $\beta \approx 0.584$ for $d = 2 + 1$ [38]. The corresponding estimates for $d = 2 + 1$ are:

$$b = s (1 - A_3 \mu \ln (s / \rho_s) / s) (\mu \ll \mu^*) \quad (6a)$$

$$b = s A_3 (\mu^* - \mu)^3 (\mu \approx \mu^*) \quad (6b)$$

These two approximations are plotted in figure 4(b), with $\mu \ll \mu^*$ in the green dashed line and $\mu \approx \mu^*$ in the white dashed line.

The phase diagrams in figure 4 were constructed with simulations using mixed initial conditions; the first generation of cells on the lattice was populated by an even mixture of fast-growing (red) cells and bystander (yellow) cells. These phase diagrams are heat maps corresponding to the density $\rho_m$ of the mutating population (red/black strains) after many generations. Our simulations were performed for $t \approx 10^6$ generations, which yields the steady state solution for the mutating population fraction $\rho_m$ for the vast majority of points on the phase diagram in figure 4, except for points very near the phase transition line. Note that our improved mean-field estimates based on DP and the random walk theory (white and green dashed lines, respectively) do a reasonable job of approximating the shape of the phase boundary, especially when $\mu \approx 0$ and our system reduces to a simple competition between fast-growing red cells and bystander yellow cells. The DP approximation
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Figure 4. Phase diagrams for (a) the $d = 1 + 1$ case and (b) the $d = 2 + 1$ case, calculated by initializing a well-mixed population of the red invader and yellow bystander strains and evolving the whole population for $t \approx 10^6$ generations. The invasion is successful in the darker purple regions of the diagrams and unsuccessful in the lighter yellow regions. In (a) we use a one-dimensional population of $L = 5000$ cells and average over 256 runs of the evolution. In (b) we have a two-dimensional population with $L^2$ cells, where $L = 500$. Here we average over 40 evolution runs. In both cases we set $s = 0.3$. After evolving for $10^6$ generations, we calculate the red/black mutating fraction of the total population: $\rho_m = \rho_f + \rho_s$. In each phase diagram, the black dashed line corresponds to the mean-field prediction $\mu = s - b$. The green and white dashed lines correspond to the improved predictions [see equations (5a), (5b), (6a) and (6b)] for $\mu \ll \mu^*$ and $\mu \approx \mu^*$, respectively, that take into account the spatial structure of the population. We also indicate $\mu = \mu^*$ (gray dashed line) where we find a mutational meltdown transition within the invading red/black population.

works better near $\mu \approx \mu^*$, where we find the mutational meltdown transition of the invader population which is in the directed percolation universality class. Moreover, these approximations generally work better for $d = 2 + 1$ dimensions compared to $d = 1 + 1$ because more cells locally compete in two-dimensional versus one-dimensional habitats. This means that as we increase the dimension of the habitat, we get closer to the well-mixed population dynamics which is fully described by the mean-field equations [equation (3)].

Another biologically interesting quantity to look at is the survival probability $P_{\text{surv}}$ of the progeny of a single red cell invader in a population of yellow bystander cells as $t \to \infty$. Such a survival probability would represent the probability of tumor invasion, for example, from a single mutated cell (i.e., a cell with a newly-acquired driver mutation) within an otherwise healthy population. If the bystander is replaced by the slow-growing strain and we have a two-species evolution, then the evolution will be exactly the same as a DP with a ‘single-seed’ initial condition. We would then have $P_{\text{surv}} \propto \rho_f$ due to the rapidity reversal symmetry of DP [38]. In other words, the survival probability tracks the behavior of the fraction $\rho_f$ of the fast-growing strain in a different simulation where the initial condition is a well-mixed population (or a population of just the mutating, fast-growing strain). In the three-species model we consider, there is no rapidity symmetry due to the presence of the bystander strain. Nevertheless, we expect that the survival probability $P_{\text{surv}}$ vanishes on the same critical surface as the fraction $\rho_m$ (plotted in figure 4) because the invader strain will not be able to invade if the fast-growing strain is lost from the population. We show in figure 5 the survival probability $P_{\text{surv}}$ at long times, which does indeed vanish at approximately the same place as $\rho_m$ in figure 4. So, the approximations we used to estimate where $\rho_m$ vanishes serve as good predictors of the transition of the survival probability, as well. We also show the phase boundary at a smaller values of $s$ ($s = 0.1$) in the right panels of figure 5. Note that our estimates work for the phase boundary in this case, also.
5. Roughening invasion fronts

We now study the shape of the interface between the mutating and bystander populations. When either of the populations is invading the other, the invasion front behaves as a noisy Fisher–Kolmogorov–Petrovsky–Piscounov wave \cite{50, 51}. Most previous studies of such waves have focused on competition between two homogeneous populations or the range expansion of a population into virgin territory. The noise plays a crucial role here \cite{52}, strongly modifying, for example, the wave speed. Also, in the (exactly soluble \cite{53}) $d = 1 + 1$ case, there is a diffusive wandering of the front around its average position. Here we will be interested in analyzing what happens to such a wave when the mutating invader approaches a mutational meltdown at $\mu = \mu^*$. For $d = 2 + 1$, the noisy wave front will have a characteristic roughening. This roughening falls in the Kardar–Parisi–Zhang (KPZ) universality class \cite{54}, although observing the predicted scaling behavior of this class is challenging for noisy Fisher waves \cite{55, 56}. For example, for the KPZ class of interfaces, the characteristic size $\sigma_w$ of the interface should grow as $\sigma_w \propto t^{1/3}$. However, a basic analysis of the noisy Fisher waves \cite{57} is more consistent with $\sigma_w \propto t^{1/2}$, which is also what we observe in our model. Although this apparent discrepancy has been explained, the proper recovery of the KPZ exponents requires a deeper analysis outside the scope of the current paper \cite{55}. So, for our simulations, we will find consistency with previous analyses of noisy Fisher waves and leave the more extensive analysis of the interface shape scaling for future work. Also, as the speed of the invasion goes to zero, we expect a transition to a different, 'voter model' \cite{58} interface coarsening behavior as both the mutating and the bystander populations become stable and do not invade each other (on average). The interface roughens in a different way in this ‘critical’ case, with the characteristic size $\sigma_w$ of the interface increasing diffusively as $\sigma_w \propto t^{1/2}$.

We discuss these issues in more detail below and show that our model exhibits a range of behaviors depending on the invasion velocity $v$ and the proximity of the mutating population to the meltdown transition. These invasion waves are examples of ‘pulled’ wavefronts \cite{59}, which are driven by the growth (invasion) at the leading edge of the wave. Various aspects of such wave fronts are reviewed in, e.g., reference \cite{60}. We shall see in the following that adding mutations to one of the populations significantly modifies the expected pulled-front wave behavior and, in the $d = 1 + 1$ case, introduces a
super-diffusive wandering of the interface. The $d = 2 + 1$ case presents an even richer set of behaviors depending on the mutation rate and relative fitness of the mutating and bystander populations. Our purpose here will not be the particular value of scaling exponents, but rather general features of the roughening dynamics such as a change in roughening due to the internal evolutionary dynamics of the invading strain.

5.1. $d = 1 + 1$-dimensional invasions

In $d = 1 + 1$, domain walls between the bystander and the invading populations can be characterized by a random walk with alternating bias (when $\Gamma_1 < \Gamma_2 < \Gamma_3$) as the bystander will invade the slow-growing species and be invaded by the fast-growing species within the mutating population. As we approach the mutational meltdown transition, the average size of clusters of the slow-growing strain will diverge as expected from the DP transition. In figure 6 we see a comparison of two domain walls for $d = 1 + 1$. At the bottom of the figure, figure 6(b), we see a domain wall where the mutating red/black population is far from the two-species phase transition. In this case, the black patches in the population are small and do not influence the motion of the invasion front much. Conversely, in figure 6(a), we see a domain wall with the mutating population near a mutational meltdown. In this case, there is an enhancement of the ‘roughness’ of the domain wall as the large black patches create more regions of alternating bias in the domain wall between the yellow bystander and the red/black invading population.

To obtain a more quantitative estimate of this roughening effect, we set up a simulation with initial conditions that include a sharp boundary between the bystander and the mutating population: the bystander occupies lattice sites $i \leq L/2$, and all other lattice sites $i > L/2$ are occupied by the mutating population (taken to be all red, fast-growing cells initially). We then track the position $x(t)$ of the invasion front over time. We measure the roughness of the front by calculating the variance of the position:

$$\langle [w(t)]^2 \rangle = \langle [x(t) - \langle x(t) \rangle]^2 \rangle = \langle [x(t)]^2 \rangle - \langle x(t) \rangle^2,$$

where we average over sufficient runs to ensure convergence. In the case of a domain wall between just two strains, perhaps with a difference in growth rates, the domain wall performs a biased random walk [44]. Therefore, we may initially expect that our position $x(t)$ of the interface between the invader and bystander also performs a diffusive motion in time. In this diffusive case, the variance $\sigma_w(t)$ satisfies

$$\sigma_w(t) \approx \sqrt{D_w t},$$

with $D_w$ a diffusion coefficient for the domain wall. Indeed, $x(t)$ itself should perform a biased random walk and we may extract the diffusion constant $D_w$ from a time series of the position $x(t)$ by performing a time average of the squared displacements of the interface [61]. We did this for the simulations shown in figure 6. We see that when the population is near a mutational meltdown at $\mu = \mu^*$ [figure 6(a)], the observed diffusivity is much larger than for a population far away from this transition [figure 6(b)], with $\mu \ll \mu^*$. However, a proper measurement of $D_w$ requires an ensemble averaging over many simulation runs and also a longer time series.

We shall see in the following that a more detailed analysis of the boundary motion will show that $x(t)$ actually performs a super-diffusive motion near the mutational meltdown $\mu \approx \mu^*$, with displacements satisfying $\sigma_w(t) \propto t^{\nu}$, with $\nu > 1/2$. Super-diffusivity is not uncommon in spatial population dynamics: in a range expansion, for example, the roughness of the expansion front may contribute to the motion of sectors of strains, introducing super-diffusivity to the sector boundary motion [27]. However, this super-diffusivity depends on the conditions of the growth, and a diffusive motion often serves as a reasonable approximation [62, 63]. We will find diffusive motion of our sector boundaries everywhere in the $(s, b, \mu)$ parameter space, except near the mutational meltdown $\mu \approx \mu^*$ where the sector motion becomes super-diffusive.
Let us now analyze the dynamics in more detail. For a domain wall or invasion front between our mutating, heterogeneous invader population and the homogeneous bystander, the slow- and fast-growing strain patches of the invader will interact differently with the bystander. We can analyze how this impacts the domain wall motion by studying the standard deviation $\sigma_w(t) = \sqrt{\langle [w(t)]^2 \rangle}$, averaged over an ensemble of simulation runs. We sample our evolved population at times $t = t_i$ and calculate the effective exponent associated with the interface width:

$$\nu(t = t_i) \equiv \frac{\ln[\sigma_w(t_i)/\sigma_w(t_{i-1})]}{\ln[t_i/t_{i-1}]},$$  \hspace{1cm} (9)

where we choose $t_i/t_{i-1} \approx 2$. The effective exponent $\nu(t)$ approaches a limiting value at long times. Moreover, any super-diffusive enhancement to the roughness would be seen as a limiting value $\nu > 1/2$. The exponent is plotted for various values of $(s, b, \mu)$ in figure 7. We find that there is an enhanced, super-diffusive roughness ($\nu > 1/2$) whenever the mutating population is close to the mutational meltdown (DP) transition at $\mu = \mu^*$ [along the vertical line in the phase diagram in figure 4(a)]. The enhanced value of $\nu$ near the DP transition may be understood by considering the limiting case $b = 0$. In this case, the bystander population and slow-growing strain within the mutating population will grow at the same rate, so then an initial condition with a single red fast-growing cell in a population of yellow bystander cells will expand as it would in a standard DP process with a single seed initial condition. Hence, the standard deviation $\sigma_w(t)$ scales with the DP dynamical critical exponent: $\sigma_w(t) \sim t^{\nu_{DP}}$, with $\nu_{DP} = \nu_D = 0.6326$ (upper lines). The phase diagrams were created from simulations with $L = 5000$, $t = 10^5$ generations, and averaged over 256 runs. The exponent curves on the right were created from simulations with $L = 5 \times 10^4$, $t = 10^5$ generations, and 400 runs.

Away from the DP transition, the invasion front has a diffusive behavior, with $\sigma_w(t) \sim t^{\nu_{Diff}}$. The diffusion constant $D_w$ may be measured and serves as a good indicator of the mutational meltdown transition because $D_w$ should diverge as $\mu \to \mu^*$ for fixed $b$ and $s$. This is illustrated in figure 8 for $s = 0.3$ and values of $b$ along the phase transition boundary. In this $d = 1 + 1$-dimensional case, the value of $b$, according to our analysis, does not change the wandering behavior of the domain walls as it only serves to change the domain wall bias. This hypothesis is consistent with the data shown in figure 7, where the red
In any case, we find super-diffusive motion whenever time, limiting value within the simulation time. In red/black population. Moreover, this line can less prominent, but still has an effect. This difference circular interface dissolves. In (a), the dissolution is approximately neutral with respect to the yellow mutating population gets rein-
The angular brackets in equation (11) indicate an ensemble average over many population evolutions. However, we may also use $\sigma_w(t)$ as an indicator of the front roughness for a single snapshot of a population at a particular time, as shown in figure 10. Examples of the calculated $\sigma_w(t)$ (averaged over many simulation runs) for various values of selection parameter $b$ and mutation rate $\mu$ are shown in figure 12. For example, in the case where the invader and bystander populations are relatively neutral and there are no mutations, the roughening of the interface illustrated in figure 10(a) is shown with blue circles (connected by a dashed line) in figure 12. The interface in figure 10(b) approximately corresponds to the red squares in figure 12. Note that, as expected, $\sigma_w(t)$ increases significantly faster in time for the latter case compared to the former.

Note that it is possible to define the interface width $\sigma_w$ in other ways, including estimating the interface position using the location $y_{\min}$ or $y_{\max}$ (see figure 11). Alternatively, one might use the difference $y_{\max} - y_{\min}$ as a measure of the ‘fuzziness’ of the interface, which we might also expect to increase near a mutational meltdown. We have verified that using other definitions of the interface roughness does not change the long-time scaling properties of the interface roughness or the relative enhancement of the roughness near a mutational meltdown. It would be interesting, however, to more systematically study the consequences of using alternative definitions of the roughness.

We will now focus our quantitative analysis on the $v = 0$ case of a stationary (on average) interface, since it is along the critical line where we find a predictable roughening effect. We will then take a closer look at the cases $|v| > 0$ where either the mutating population or the bystander has an overall selective advantage. This introduces complications as the roughening behavior of a moving front is different from a stationary one. Indeed, whenever $|v| > 0$, the invasion becomes a noisy Fisher wave which has its own particular roughening properties. We shall see that a non-zero velocity $v$ suppresses the interface roughness at long times, but signatures of the roughening due to mutational meltdown persist at shorter times.

5.2.1. Voter model coarsening, $v = 0$

Along the 3-species critical surface, where the invader and bystander are relatively neutral, we expect to see an enhancement of the interface roughening as we approach the mutational meltdown transition $\mu \to \mu^*$ for the invader population [the bottom terminal end of the phase boundary in figure 4(b)]. To quantify the roughening, we can calculate the effective exponent $\nu(t)$ [see equation (9)] from the
Figure 11. Schematic for finding an average location of the interface between the yellow bystander and red/black mutating populations. The interface runs along the $x$ direction. We identify columns $x_i$ in the hexagonal lattice as shown with the blue zigzagged line. At each column $x_i$, the average position $\bar{y}$ is calculated by averaging over all red/black cell locations between the red/black cell which is the furthest into the mutating region [at $y_{\text{min}}(x_i)$] and the black/red cell which is the furthest into the bystander population [at $y_{\text{max}}(x_i)$].

Figure 12. The interface width $\sigma_w$, [see equation (11)] in units of cell diameters of a $d = 2 + 1$-dimensional invasion, starting from an initially flat interface between the mutating and bystander population ($\sigma_w = 0$) 4000 cells long and with $s = 0.15$ for various values of selection parameter $b$ and mutation rate $\mu$. [Note that it is helpful to consult the phase diagram in the top panel of figure 13 for identifying the locations of these points in the $(\mu, b)$ plane.] The interface is evolved for $t = 10^4$ generations, and we average over 160 runs. Lines connect the points to guide the eye. Note that the value of $b$ strongly influences the behavior of $\sigma_w$, as seen by comparing the red squares and the purple crosses, both of which have the mutating population near meltdown ($\mu \approx \mu^\ast$). In general, we find a suppressed roughness when the mutating and bystander populations are not relatively neutral (compare blue dashed line to orange diamonds and purple crosses). Otherwise, for (on average) stationary interfaces, we see the enhanced roughness due to mutational meltdown (green triangles and red squares). The smaller plot shows the roughness at short times.

The interface width $\sigma_w(t)$ defined in equation (11). Without a bias, we expect that the interface coarsening should be described by voter-model-like dynamics [64] because the invader and bystander populations divide into each other without a surface tension. We generally expect a diffusive behavior $\sigma_w \propto t^{0.5}$ in this case, as opposed to $\sigma_w \propto t^{0.272}$ for a Fisher wave [57].

In figure 13 we see an enhanced roughening as $\mu \to \mu^\ast$ as we move along the phase transition boundary ($\nu = 0$): the limiting value $\nu$ of the exponent increases as we move along the phase transition line towards the mutational meltdown at $\mu = \mu^\ast$. Interestingly, near mutational meltdown, the width $\sigma_w$ seems to grow approximately diffusively with $\sigma_w \propto t^{0.5}$ (red squares in figure 13), whereas the non-mutating case $\mu = 0$ coarsens according to the power law $\sigma_w \propto t^{0.45}$ (blue circles in figure 13). We might have expected larger values for these exponents as the non-mutating case should be closest to the voter model dynamics where interfaces dissolve diffusively, similarly to the dynamics of $\sigma_w$ in the $d = 1 + 1$ case away from the meltdown transition [64]. However, generalizations of the voter model can yield different results for interface coarsening and determining the value of the exponent.
Figure 13. Interface roughening exponents $\nu(t)$ are calculated on the right plots for different combinations of $(b, \mu)$ indicated on the phase diagrams on the left, for varying values of $s = 0.3$ (top row), 0.1 (middle), and 0.05 (bottom). As we move along the critical line (blue circles, green triangles, and red squares), we show the enhancement of the boundary roughness from $\sigma_w \propto t^{0.45}$ to $\sigma_w \propto t^{0.5}$. We also indicated the voter model value $\nu_{voter} = 0.5$ with a dashed line. Away from the critical line (purple crosses and orange diamonds), we see the effects of Fisher wave dynamics. Here either the mutating population (orange diamonds) or the bystander (purple crosses) has a selective advantage, and the moving interface has a suppressed roughness at long times, approaching $\sigma_w(t) \propto t^{\nu_{Fisher}}$ with $\nu_{Fisher} \approx 0.272$ (bottom dashed lines in plots on the right), consistent with previous Fisher wave simulation results [57]. The phase diagrams have the same simulation parameters as in figure 5. The exponent curves on the right use interfaces that are initially 4000 cells long, and we average over 160 runs.

$\nu$ can be subtle [65]. Another possibility is that $\nu$ is suppressed due to our particular choice of lattice update rules with non-overlapping generations. It would be interesting to study the behavior with simulations with overlapping generations (independently dividing cells). Although the behavior for $d = 2 + 1$ is different from the $d = 1 + 1$ case where the domain wall roughening was clearly super-diffusive near mutational meltdown and diffusive away from it (see figure 7), we also find here that the mutational meltdown enhances the interface undulations by modifying the exponent $\nu$ associated with the interface width $\sigma_w \propto t^\nu$, increasing $\nu$ from a value of approximately 0.45 to 0.5. This roughness enhancement is more readily observed in the average magnitude $\sigma_w$ of the roughness, as we can see by comparing the blue circles ($\mu = 0$) and red squares ($\mu \approx \mu^*$) in figure 12. The $\mu \approx \mu^*$ case has a larger $\sigma_w$ throughout the time evolution of the competition. So, we conclude that approaching the mutational meltdown for an invader that remains relatively neutral to the bystander increases interface undulations.

When the invader and bystander are not relatively neutral, then the interface between them will move with some average speed $|v| > 0$. This has a more pronounced effect on the roughness than the approach to mutational meltdown. So, we shall now consider this case separately.

5.2.2. Fisher wave roughening, $|v| > 0$

The qualitative difference between $|v| > 0$ and $v \approx 0$ dynamics can be seen prominently if we consider an initially disc-like population of the invader strain. Then, any non-zero velocity will either shrink or grow the initial disc. An example of an $v < 0$ evolution is shown in figure 9(a) where the bystander strain invades the invader, which eventually dies out. Conversely, when $v \approx 0$, we can see in figure 9(b) that the boundary between the invader and bystander gradually dissolves. This illustrates the key feature that makes $|v| > 0$ different from the critical line: one of the populations (either the mutating population or the bystander) becomes unstable and will deterministically shrink in the presence of the other population.
Let us consider first the simplest case when $\mu = 0$ and we have an interface between a (non-mutating) fast-growing red strain and the yellow bystander. The orange diamond point data in figure 13 show what happens in this case. The interface behaves as a noisy Fisher–Kolmogorov–Petrovsky–Piskunov wave [50, 51] describing the invasion of the bystander. Without fluctuations (in the mean-field limit), these waves admit stationary shapes and we have no roughening over time. However, fluctuations prevent the formation of stationary wave fronts for the $d = 1 + 1$ and $d = 2 + 1$-dimensional cases. For $d = 2 + 1$, previous simulations [57] show that the interface width is expected to grow as $t^{\nu}$ with $\nu \approx 0.272$. This coarsening is consistent with our results for $\sigma_w$, as the orange diamond data points in the right panels of figure 13 approach the $\nu \approx 0.272$ limiting value at long times, indicated by the lower dashed line. The time until convergence, however, is quite long as the effective exponent $\nu(t)$ continues to decrease over the course of the entire simulation run time.

The case of a non-mutating $\mu = 0$ invader is interesting for $d = 2 + 1$ because we would naively expect our system to fall into the KPZ universality class. The average interface position $\langle x(t) \rangle$ could be interpreted as a kind of ‘height function’ and the interface width $\sigma_w$ should scale like $\sigma_w \propto t^{1/3}$ at early times, consistent with $d = 1 + 1$-dimensional KPZ dynamics. A broad class of systems fall into this universality class (see [43] for a review) as the KPZ equation includes the most relevant nonlinearity associated with lateral growth. However, we see here that the behavior is more subtle and we get behavior consistent with $\nu = 0.272$, as was found previously for noisy Fisher waves in a different model [57]. This complication in measuring the interface roughness was discussed and analyzed in previous work [55]. Our focus here, however, is not the particular exponent associated with the roughening but rather the effects of adding mutations. We will see that adding mutations does enhance the roughness, but only at short/intermediate times while the fast-growing, mutating strain maintains a significant fraction within the population.

Consider the portion of the phase diagram where the bystander can invade the mutating population due to fitness loss at a non-zero mutation rate $\mu$ (purple crosses in figure 13). Here, the evolution of our system begins at first as biased competition between two species (between fast-growing invaders and the bystander species) but as the fast-growing cells mutate and die off, the bystander population begins to invade the slow-growing species, and eventually we should find a Fisher wave of the bystander invading the less fit, mutating population. On the right side of figure 13 we see that the exponent $\nu(t)$ for the purple crosses at first is enhanced as we would expect near mutational meltdown ($\mu \approx \mu^*$). At later times, however, once a Fisher wave is established, the exponent eventually dips down and is consistent with a Fisher-wave-like coarsening [57]. One can track this especially easily in the $s = 0.15$ case (top row of figure 13) where we see that the purple cross data points follow the critical roughening points (red squares) and then transition to a slower roughening more consistent with a regular Fisher wave (orange diamonds). The evolution of $\sigma_w(t)$ for this case is also shown in figure 12. One sees here that at times $t < 1000$ (smaller plot), the purple cross data points have a larger width $\sigma_w(t)$ due to the mutational meltdown dynamics, but $\sigma_w(t)$ then crosses over to smaller values for longer times when the Fisher wave behavior dominates.

It is interesting that a similar phenomenon does not happen in $d = 1 + 1$ dimensions, where we always find super-diffusive behavior for any invader with $\mu \approx \mu^*$. As mentioned previously, for $d = 1 + 1$, the relative growth difference between the invader and bystander only appears to change the bias of the interface motion, without changing the wandering of the interface. Here, for $d = 2 + 1$, the relative growth rates change the roughening behavior. Thus, some of the effects of the approach to mutational meltdown are overwhelmed by the selective differences between bystander and invader: the interface roughness is strongly suppressed when either the invader or bystander has a selective advantage and the interface has an overall bias. Although we see some roughening on approach to mutational meltdown, the scaling of the roughening is dominated by either Fisher-wave scaling when $|v| > 0$ or voter model coarsening when $v = 0$. So, for $d = 2 + 1$, a rougher interface may be a good signature of the transition between successful and unsuccessful invasion as opposed to the internal mutational meltdown of the invader.

6. Conclusion

We have now analyzed a simple model of invasion of a stable, homogeneous population by a population acquiring deleterious mutations at a rate $\mu$. We examined this invasion in both one- and two-dimensions as a function of the mutation rate $\mu$, the selective advantage $s$ of the fast-growing strain within the mutating population, and the selective advantage $b$ of the bystander population. We have shown that the effectively small local population sizes (compared to a well-mixed population) suppress the probability that the invasion succeeds. This suppression can be understood by analyzing the motion of the boundary between the mutating population and the bystander population it is invading. We find a reasonable estimate of the phase transition position in the $(\mu, b, s)$ phase space, as shown in figures 4, 7, and 13. Our model assumed that cell motility within our population is suppressed, with the only cell rearrangements occurring due to cell division and local
competition for space. It would be interesting to consider the effects of a spatial motility as it has been demonstrated that some of the expected features of spatial dynamics, such as spatial heterogeneity and local fixation of strains is partially mitigated by increased cell motility [66].

Next, we considered the properties of the invasion front and showed that this front undulates more when the mutating population is near the meltdown transition at which it loses the fittest strain. For \( d = 1 + 1 \) dimensions, this transition is well-characterized by the directed percolation universality class, and we used properties of this class to understand the enhancement of the roughening. In the future, it would be interesting to compare our results to experiments. One possibility is to use microbial populations such as bacteria or yeast where one may design strains with varying \( (\mu, b, s) \). Another possibility would be to examine such invasions in cancers. For instance, it would be interesting to monitor the edges of a tumor over time as it either grows or shrinks. We predict that if the tumor begins losing fitness due to accumulated deleterious mutations (during treatment, for example), then we should be able to observe this transition to ‘mutational meltdown’ as a roughening of the tumor edges.

For \( d = 2 + 1 \) dimensions, we find a range of behaviors for the roughening interface. When the speed of the invasion front approaches zero, the interface roughens more significantly due voter-model-like coarsening. We also find an enhancement of the roughening as the mutating population approaches meltdown. On the other hand, when either the mutating invader or the bystander population has a selective advantage and the population interface develops an overall velocity, the roughening is suppressed, and we find roughening exponents consistent with those observed for noisy Fisher waves at long times. Therefore, the long-time behavior of the population interface roughness serves as an indicator of whether or not a selective sweep is occurring within the population: moving population fronts will be smoother than stationary ones in which the invader and bystander populations are relatively neutral. Here, unlike the \( d = 1 + 1 \) case, the approach to mutational meltdown has a smaller impact on the interface roughness (at long times) than the relative growth difference between the bystander and invader.

At intermediate times for \( d = 2 + 1 \), we see signatures of the meltdown as the interface roughens more rapidly when the mutating population is near the meltdown transition, even in the case when there is an overall bias to the interface motion (see smaller plot of figure 12). Also, we focused here on just one aspect of the roughening, namely the scaling of the interface width \( \sigma_w \propto t^\nu \). For very long times \( t \), the interface undulation size will eventually saturate due to the finite system size \( L \), and we might expect a general scaling form \( \sigma_w(t) \propto t^\nu f(t/L^{\beta}) \), with \( f(x) \) a scaling function and \( \beta \) a new critical exponent. The scaling properties of this saturation should also depend on the proximity to the mutational meltdown transition. It would also be interesting to consider a \( d = 3 + 1 \)-dimensional evolution such as the invasion of surrounding tissue by a compact cluster of cancerous cells. In this case, the invasion front would be an entire surface which could also pinch off and coarsen. Previous simulations of the noisy Fisher wave dynamics suggest that the situation in this case is similar to the \( d = 2 + 1 \) case considered here [57]. We would again expect to find some enhancement of the interface roughening when a mutating invader is near a mutational meltdown transition.

Interestingly, increased roughening is typically an indicator of more malignant cancerous growths, and the roughness of tumor edges has been a useful prognostic indicator in a wide variety of cancers [67]. Also, in general, increased heterogeneity results in a worse clinical prognosis [68]. While our results point to the possibility of an opposite correlation, our model does not take into account tumor vasculature or cancer cell motility. Conversely, most of the clinical studies focus on more mature tumors which have developed a vasculature. A vasculature would transport nutrients throughout the tumor and create a more complicated cell growth pattern than the one considered here. Hence, we expect our model to be relevant for early, small avascular tumors or regions of larger tumors lacking vasculature. These small tumors are not easily detected as they are typically just a few millimeters in size. Nevertheless, small spheroidal avascular tumors are good in vitro models for early cancer growth [69]. To test our predictions, it would thus be interesting to study the edges of small, spheroidal cultured tumors under a large mutational load. We may also verify some of our results in microbial range expansions (e.g., in yeast cell colonies grown on Petri dishes) where there is little cell motility. A promising experimental realization of a \( d = 2 + 1 \)-dimensional expansion may be a growing cylindrical ‘pillar’ of yeast cells, as realized in reference [70].

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References

[1] Petren K and Case T J 1996 An experimental demonstration of exploitation competition in an ongoing invasion Ecology 77 118–32

[2] Xavier J B and Foster K R 2007 Cooperation and conflict in microbial biofilms Proc. Natl Acad. Sci. USA 104 876–81

[3] Nadell C D, Drescher K and Foster K R 2016 Spatial structure, cooperation and competition in biofilms Nat. Rev. Microbiol. 14 589–600

[4] Bahl J, Vijaykrishna D, Holmes E C, Smith G J D and Guan Y 2009 Gene flow and competitive exclusion of avian influenza in natural reservoir hosts Virology 390 289–97

[5] Merino M M, Levayer R and Moreno E 2016 Survival of the fittest: essential roles of cell competition in development, aging, and cancer Trends Cell Biol. 26 776–88

[6] Willi Y, Fracassetti M, Zoller S and Buskirk J V 2018 Accumulation of mutational load at the edges of a species range Mol. Biol. Evol. 35 781–91

[7] Bossard L, Dupanloup I, Terannion O, Bruggmann R, Ackermann M, Peischl S and Excoffier L 2017 Accumulation of deleterious mutations during bacterial range expansions Genetics 207 669–84

[8] Foutel-Rodier F and Etheridge A 2020 The spatial Muller’s ratchet: surfing of deleterious mutations during range expansion Theor. Popul. Biol. 135 19–31

[9] Cahill D P, Kinzler K W, Vogelstein B and Lengauer C 1999 Genetic instability and Darwinian selection in tumours Trends Cell Biol. 9 M57–60

[10] Negrini S, Gorgoulis V G and Halazonetis T D 2010 Genomic instability—an evolving hallmark of cancer Nat. Rev. Mol. Cell Biol. 11 220–8

[11] Marusyk A and Polyak K 2010 Tumor heterogeneity: causes and consequences Biochim. Biophys. Acta Rev. Clin. 1805 105–17

[12] Martello L G, Ng C K Y, Piscuglia S, Weigel B and Reis-Filho J S 2014 Breast cancer intra-tumour heterogeneity Breast Cancer. Res. 16 R48

[13] Yoo J, Chong S, Lim C, Heo M and Hwang I G 2019 Assessment of spatial tumor heterogeneity using CT growth patterns estimated by tumor tracking on 3D CT volumetry of multiple pulmonary metastatic nodules PloS One 14 e0220550

[14] Sottoriva A et al 2013 A big bang model of human colorectal tumor growth Nat. Genet. 47 209–16

[15] McCormick C and Peischl S 2019 Range expansion theories could shed light on the spatial structure of intra-tumour heterogeneity Bull. Math. Biol. 81 4761–77

[16] Korolev K, Xavier J and Gore J 2014 Turning ecology and evolution against cancer Nat. Rev. Cancer 14 371

[17] McFarland C D, Korolev K S, Kryukov G V, Sunyaev S R and Mirny L A 2013 Impact of deleterious passenger mutations on cancer progression Proc. Natl Acad. Sci. USA 110 2919–24

[18] McFarland C D, Yaglom J A, Wojtkowiak J, Scott J, Morse D, Sherman M and Mirny L 2017 The damaging effect of passenger mutations on cancer progression Cancer Res. 77 4763–72

[19] McFarland C D, Mirny L A and Korolev K S 2014 Tug-of-war between driver and passenger mutations in cancer and other adaptive processes Proc. Natl Acad. Sci. USA 111 15138–43

[20] Muller H J 1964 The relation of recombination to mutational advance Mutat. Res. 1 2–9

[21] Gabriel W, Lynch M and Bürger R 1993 Muller’s ratchet and mutant meltdown Evolution 47 1744–57

[22] Muller F L et al 2012 Passenger deletions generate therapeutic vulnerabilities in cancer Nature 488 337–42

[23] Zhang Y et al 2019 Genetic load and potential mutational meltdown in cancer cell populations Mol. Biol. Evol. 36 541–52

[24] Gatenby R A, Grove O and Gillies R J 2013 Quantitative imaging in cancer evolution and ecology Radiology 269 8–15

[25] Chang R F, Wu W J, Moon W K and Chen D R 2005 Automatic ultrasound segmentation and morphology based diagnosis of solid breast tumors Breast Canc. Res. Treat. 89 179–87

[26] Martens E A, Kostadinov R, Maley C C and Hallatschek O 2011 Spatial structure increases the waiting time for cancer New J. Phys. 13 115014

[27] Hallatschek O, Hersen P, Ramanathan S and Nelson D R 2007 Genetic drift at expanding frontiers promotes gene segregation Proc. Natl Acad. Sci. USA 104 19926–30

[28] Hallatschek O and Nelson D R 2010 Life at the front of an expanding population Evolution 64 193–206

[29] Lavrentovich M O, Wahl M E, Nelson D R and Murray A W 2016 Spatially constrained growth enhances conversional meltdown Biophys. J. 110 2800–8

[30] Fusco D, Gralik M, Kayser J, Anderson A and Hallatschek O 2016 Excess of mutational jackpot events in expanding populations revealed by spatial Luria–Delbrück experiments Nat. Commun. 7 12760

[31] Chkheidze K, Heide T, Werner B, Williams M J, Huang W, Caravagna G, Graham T A and Sottoriva A 2019 Spatially constrained tumour growth affects the patterns of clonal selection and neutral drift in cancer genomic data PLoS Comput. Biol. 15 e1007243

[32] Gerlinger M et al 2012 Intratumor heterogeneity and branched evolution revealed by multiregion sequencing N. Engl. J. Med. 366 833–92

[33] Nguyen B, Upadhyaya A, van Oudenaarden A and Brenner M P 2004 Elastic instability in growing yeast colonies Biophys. J. 86 2740–7

[34] Kuhl J T, Leisner M and Frey E 2011 Range expansion with mutation and selection: dynamical phase transition in a two-species Eden model New J. Phys. 13 113013

[35] Shimaya T and Takeuchi K A 2019 Lane formation and critical coarsening in a model of bacterial competition Phys. Rev. E 99 042403

[36] Lavrentovich M O and Nelson D R 2014 Asymmetric mutationalism in two- and three-dimensional range expansions Phys. Rev. Lett. 112 138102

[37] Gilbert K J, Peischl S and Excoffier L 2018 Mutation load dynamics during environmentally-driven range shifts PLoS Genet. 14 e1007450

[38] Hinrichsen H 2000 Non-equilibrium critical phenomena and phase transitions into absorbing states Adv. Phys. 49 815–958

[39] Brú A, Albertos S, Subiza J L, García-Ayensa J I and Brú I 2003 The universal dynamics of tumor growth Biophys. J. 85 2948–61

[40] Drossel B and Kardar M 2000 Phase ordering and roughening on growing films Phys. Rev. Lett. 85 614–5

[41] Drossel B and Kardar M 1997 Model for growth of binary alloys with fast surface equilibration Phys. Rev. E 55 5026

[42] Horowitz J M and Kardar M 2019 Bacterial range expansions on a growing front: roughness, fixation, and directed percolation Phys. Rev. E 99 042134

[43] Halpin-Healy T and Zhang Y C 1995 Kinetic roughening phenomena, stochastic growth, directed polymers and all that. aspects of multidisciplinary statistical mechanics Phys. Rep. 254 215–414
Phys. Biol. 17 (2022) 066002 C E Castillo and M O Lavrentovich

[44] Lavrentovich M O, Korolev K S and Nelson D R 2013 Radial Domany–Kinzel models with mutation and selection Phys. Rev. E 87 012103

[45] Domany E and Kinzel W 1984 Equivalence of cellular automata to Ising models and directed percolation Phys. Rev. Lett. 53 311–4

[46] Giese A, Bjerkvig R, Berens M E and Westphal M 2003 Cost of migration: invasion of malignant gliomas and implications for treatment J. Clin. Oncol. 21 1624–36

[47] Lavrentovich M O 2015 Critical fitness collapse in three-dimensional spatial population genetics J. Stat. Mech. Theor. Exp. P05027

[48] Täuber U C, Howard M J and Hinrichsen H 1998 Multicritical behavior in coupled directed percolation processes Phys. Rev. Lett. 80 2165–8

[49] Otwinskiowski J and Krug J 2014 Clonal interference and Muller’s ratchet in spatial habitats Phys. Biol. 11 056003

[50] Fisher R A 1937 The wave of advance of advantageous genes Ann. Eugen. 7 355–69

[51] Kolmogorov A, Petrovsky N and Piscounov N 1937 Étude de l’équation de la diffusion avec croissance de la quantité de matière et son application a un problème biologique Moscow Univ. Math. Bull. 1 1–25

[52] Hallatschek O and Korolev K S 2009 Fisher waves in the strong noise limit Phys. Rev. Lett. 103 108103

[53] Doering C R, Burschka M A and Horsthemke W 1991 Fluctuations and correlations in a diffusion–reaction system: exact hydrodynamics J. Stat. Phys. 65 953–70

[54] Kardar M, Parisi G and Zhang Y C 1986 Dynamic scaling of growing interfaces Phys. Rev. Lett. 56 889–92

[55] Moro E 2001 Internal fluctuations effects on Fisher waves Phys. Rev. Lett. 87 238303

[56] Tripathy G and van Saarloos W 2000 Fluctuation and relaxation properties of pulled fronts: a scenario for nonstandard Kardar–Parisi–Zhang scaling Phys. Rev. Lett. 85 3536–9

[57] Riordan J, Doering C R and ben Avraham D 1995 Fluctuations and stability of Fisher waves Phys. Rev. Lett. 75 565–8

[58] Cox J T and Griffiths D 1986 Diffusive clustering in the two dimensional voter model Ann. Prob. 14 347–70

[59] Stokes A N 1976 On two types of moving front in quasilinear diffusion Math. Biosci. 31 307–15

[60] van Saarloos W 2003 Front propagation into unstable states Phys. Rep. 386 29–222

[61] Tejedor V, Bénichou O, Voituriez R, Jüngmann R, Simmel F, Selhuber-Unkel C, Oddershede L B and Metzler R 2010 Quantitative analysis of single particle trajectories: mean maximal excursion method Biophys. J. 98 1364–72

[62] Weinstein B T, Lavrentovich M O, Möbius W, Murray A W and Nelson D R 2017 Genetic drift and selection in many-allele range expansions PLoS Comput. Biol. 13 e1005866

[63] Korolev K S, Xavier J B, Nelson D R and Foster K R 2011 A quantitative test of population genetics using spatiogenetic patterns in bacterial colonies Am. Nat. 178 538–52

[64] Dornic I, Chaté H, Chave J and Hinrichsen H 2001 Critical coarsening without surface tension: the universality class of the voter model Phys. Rev. Lett. 87 045701

[65] Bordogna C M and Albano E V 2011 Study and characterization of interfaces in a two-dimensional generalized voter model Phys. Rev. E 83 046111

[66] Waclaw B, Bozic I, Pittman M E, Hruban R H, Vogelstein B and Nowak M A 2015 A spatial model predicts that dispersal and cell turnover limit intratumour heterogeneity Nature 525 261–4

[67] Davnall F et al 2012 Assessment of tumor heterogeneity: an emerging imaging tool for clinical practice? Insights Imag. 3 573–89

[68] Morris L G T, Riaz N, Desrichard A, Senbabaoglu Y, Hakimi A A, Makarov V, Reis-Filho J S and Chan T A 2016 Pan-cancer analysis of intratumor heterogeneity as a prognostic determinant of survival OncoTarget 7 10051–63

[69] Weiswald L B, Bellet D and Dangles-Marie V 2015 Spherical cancer models in tumor biology Neoplasia 17 1–15

[70] Vulin C, Meglio J M D, Lindner A B, Daetzer T, Murray A and Hersen P 2014 Growing yeast into cylindrical colonies Biophys. J. 106 2214–21