Spatial Moran Models
II. Tumor growth and progression

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Abstract

We study the accumulation of mutations in a spatial Moran model on a torus in $\mathbb{Z}^d$ in which each cell gives birth at a rate equal to its fitness and replaces a neighbor at random with its offspring. Cells of type $k$ have relative fitness $(1 + s)^k$ and mutate to type $k + 1$ at rate $u_{k+1}$. When restricted to two cell types and no mutations, this model reduces to the biased voter model. We give a new result for the biased voter model that identifies the order of magnitude of the speed of propagation in the Bramson-Griffeath shape theorem, when $s$ is small. However, our main focus is on $\sigma_k$, the time of birth of the first type $k$ whose family line does not die out, and the growth of the number of type $k$ cells, $Z_k(t)$. This investigation is a first step in understanding the spatial structure of the genetic heterogeneity of solid tumors.

1 Introduction

Cancer initiation and progression are driven by the accumulation of mutations in cell populations. These mutations can confer changes to cellular reproduction rates and enable rapid growth and evolution of tumors. Understanding the dynamics of mutation accumulation in fixed or exponentially growing populations contributes to a better understanding of when and how cancers initiate, as well as the genetic diversity of tumors.

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There has been a substantial amount of previous modeling effort devoted to the study of temporal dynamics of mutation accumulation in cancer. These works have primarily been restricted to the setting of homogeneously mixed populations, and fallen into the following three categories: multi-type Moran models with a homogeneously mixing population of either (i) constant or (ii) exponentially growing size, and (iii) multi-type branching processes. We refer the reader to Part I of this work by Durrett and Moseley (2012) for a discussion of the literature in category (i). Systems of type (ii) have been studied by Beerenwinkel et al. (2007) and Durrett and Mayberry (2007), who have shown that there are traveling waves of selective sweeps. In category (iii) Durrett and Moseley (2009) and Bozic et al. (2010) studied systems in which individuals of type $k$ always have fitness $(1 + s)^k$. Durrett, Foo, Leder, Mayberry and Michor (2011a,2011b) generalized the results to the situation where fitness advances are random, and studied heterogeneity. In this work, we will be interested primarily in (iv) spatial Moran models of constant size.

Historically, the first spatial model of tumor growth is the one of Williams and Bjerknes (1972). In this model, there are two cell types: 0 (healthy) and 1 (tumor), with fitnesses 1 and $\lambda > 1$. The cell at $x$ gives birth at a rate equal to its fitness to an offspring that replaces the cell at one of the $2d$ nearest neighbors chosen at random. Bramson and Griffeath (1980,1981) proved the first rigorous results about the asymptotic behavior of this model, which is also called the biased voter model. In particular they proved a “shape theorem” for the asymptotic behavior of the process which is stated and used below.

The inspiration for the current paper comes from work of Martens and Hallatschek (2011) and Martens et al (2011) who consider a discrete time model in which at each step every individual is replaced by the offspring of a neighbor chosen with probability proportional to their fitness. Ignoring the fact that the entire population is replaced on every step and the detail that their lattice is shifted on each time step (e.g., in one dimension it is $\mathbb{Z}$ at even times and $\mathbb{Z} + 1/2$ at odd times), the dynamics are similar in spirit to the biased voter model. In both models, when the individual at $x$ is replaced, it will be by one of its neighbors chosen with probability proportional to fitness, but in the biased model the total replacement rate at $x$ is the average fitness of its neighbors. As we will see below, the continuous time formulation has the advantage that it simplifies many computations.

In Part I, Durrett and Moseley (2012) considered a spatial Moran model in which there are three types of cells (0, 1, and 2) all with fitness 1, and type $i$ cells mutate to type $i + 1$ cells at rate $u_i$. Under these assumptions, the waiting time to create a type 2 mutation was characterized. In the present paper we focus on the case in which new mutations have a selective advantage over the previous ones.

Throughout the paper we will use the following notation $f(t) \sim g(t)$ if $f(t)/g(t) \to 1$ as $t \to \infty$ and $f(t) = o(g(t))$ if $f(t)/g(t) \to 0$. $f(t) \gg (\ll) g(t)$ means that $f(t)/g(t) \to \infty$ (resp. 0) as $t \to \infty$ and $f(t) = O(g(t))$ means $|f(t)| \leq C g(t)$ for all $t > 0$. 

2
2 A spatial Moran model of tumor growth

Although we are mainly interested in studying processes on the torus $[-L, L]^d \cap \mathbb{Z}^d$, we first consider a spatial model of tumor growth on a lattice in $\mathbb{Z}^d$. Type $k$ cells have fitness $(1 + s)^k$. Each cell in the lattice replicates with rate equal to its fitness, and chooses a neighboring cell at random to replace with its offspring. In addition, type $i$ cells mutate to become type $i + 1$ cells with mutation rate $u_i$. Let $\phi_t(z)$ be the fitness of the cell at $z$ at time $t$. If we consider two neighboring sites $x \sim y$ then the value at $x$ will replace the one at $y$ at rate $\phi_t(x)/2d$ and $y$ will replace $x$ at rate $\phi_t(y)/2d$. In addition, we define $\sigma_i$ to be the time at which the first successful type $i$ cell arises (for $i = 1, 2$), and $\tau_i$ to be the time at which the first cell of type $i$ arises (whether successful or not).

This spatial Moran model described can be viewed as an extension of the biased voter model. In particular, the biased voter model is the spatial Moran model restricted to type 0 and type 1 cells, without any mutations. To study our model, it will be useful to describe some properties of the biased voter model.

2.1 Growth from a single type 1

Consider a biased voter model with two types 0 and 1 with fitnesses 1 and $\lambda > 1$. Then at each boundary edge connecting a 1 with a 0, the first event will be the 0 changing to 1 with probability $p = \lambda/(\lambda + 1)$ or the 1 changing the 0 with probability $1 - p = 1/(\lambda + 1)$. Thus if $\xi_t = \{x : \phi_t(x) = \lambda\}$ then while $\xi_t \neq \emptyset$, the size of the set, $|\xi_t|$, is a biased random walk which makes jumps at rate equal to the number of boundary edges: $|\partial \xi_t| = |\{x \sim y : x \in \xi_t, y \notin \xi_t\}|$. Elementary random walk results imply that if we start with one type 1 and let $T_k = \inf\{t : |\xi_t| = k\}$ then using a subscript of 1 to indicate starting from one individual with fitness $\lambda$

$$P_1(T_0 = \infty) = 1 - \frac{1 - p}{p} = 1 - \frac{1}{\lambda} = \frac{s}{1 + s}$$

if $\lambda = 1 + s$. Maruyama (1970, 1974) was the first to notice that the fixation probability is not changed by considering a spatial model, but this fact has been rediscovered by others, see Lieberman, Hauert, and Nowak (2005). Even in cancer we have selective advantages $s \ll 1$ so we will use the approximation

$$P_1(T_0 = \infty) \approx s. \quad (1)$$

Let $\xi_t^0$ be the set of sites occupied by individuals of type 1 at time $t$ when initially there is a single 1 at the origin at time 0. Bramson and Griffeath (1980, 1981) showed that, $\xi_t^0$ grows linearly and has an asymptotic shape $D$. That is, for any $\epsilon > 0$, there is a $t_\epsilon$ (which depends on the outcome $\omega$) so that on $\{T_0 = \infty\}$ we have

$$(1 - \epsilon)tD \cap \mathbb{Z}^d \subset \xi_t \subset (1 + \epsilon)tD \quad \text{for } t \geq t_\epsilon(\omega).$$
$D$ is convex and has the same symmetries as $\mathbb{Z}^d$. In $d = 2$ the limit shape looks like a ball, but is not exactly one.

Let $e_1$ be the first unit vector and define the growth rate $c_d(s)$ so that the intersection of $D$ with the $x$ axis is $[-c_d(s)e_1, c_d(s)e_1]$. It is easy to compute $c_1(s)$. If $\xi_t \neq \emptyset$ then $\xi_t = [l_t, r_t]$. The right edge $r_t$ increases by 1 at rate $\lambda$ and decreases by 1 at rate 1, so $r_t/t \rightarrow \lambda - 1 = s$, i.e., $c_1(s) = s$. The proof of Bramson and Griffeath implies that $c_d(s) \geq b_d s$ where $b_d$ is a positive constant. Martens et al. (2011) argue by analogy with results of Fisher (1937) that $c_d(s) = 2 \sqrt{m s}$ with $m = 1/4$, see their pages 1047 and 1053. As we have seen, this is false in $d = 1$. The next result shows that they are missing a logarithmic factor in $d = 2$. Our result only identifies the order of magnitude of the growth rate, but it seems unlikely that the constant for the speed of advance of traveling waves in Fisher’s PDE will be exactly equal to the one for the spatial model.

**Theorem 1.** As $s \rightarrow 0$ we have

$$c_d(s) = \begin{cases} O(s) & d = 1 \\ O(\sqrt{s}/\log(1/s)) & d = 2 \\ O(\sqrt{s}) & d \geq 3 \end{cases}$$

The proof of this result is found in Section 10 and is based upon the work of Durrett and Zähle (2007). They used a spatial Moran model to study hybrid zones. In their model each point in $\mathbb{Z}^d$ is occupied by a 1 or a 0. 1’s have fitness $1 + s$ in $(0, \infty) \times \mathbb{Z}^{d-1}$ and fitness 1 in $(-\infty, 0] \times \mathbb{Z}^{d-1}$, while 0’s have fitness 1 in $(0, \infty) \times \mathbb{Z}^{d-1}$ and fitness $1 + s$ in $(-\infty, 0] \times \mathbb{Z}^{d-1}$. There is a stationary distribution in which the density of 1’s $\rightarrow 1$ as $x_1 \rightarrow \infty$ and $\rightarrow 0$ as $x_1 \rightarrow -\infty$. The mathematical problem is to identify the width $w(s)$ of the hybrid zone (the distance needed for the frequency of 1’s to increase from $\epsilon$ to $1 - \epsilon$) as a function of the selective advantage $s$.

$$w(s) = \begin{cases} O(\sqrt{1/s}) & d \geq 3 \\ O(\sqrt{(1/s)\log(1/s)}) & d = 2 \\ O(1/s) & d = 1 \end{cases} \quad (2)$$

Note that $c_d(s) = O(1/w(s))$.

### 2.2 Time of the first successful type 1 mutant

Since we are considering processes on the torus $[-L, L]^d \cap \mathbb{Z}^d$, the first issue to consider is: what does it mean for a mutation to be successful on a finite set? When $\lambda = 1 + s$ formulas (24) and (25) imply that

$$P_1(T_k < T_0) = \frac{1 - (1 + s)^{-1}}{1 - (1 + s)^{-k}} \quad P_k(T_0 < \infty) = \lambda^{-k}$$
When \( s \to 0 \) and \( k \sim c/s \)

\[
P_1(T_k < T_0) \sim \frac{s}{1 - e^{-c}} \quad P_k(T_0 < \infty) \to e^{-c},
\]

so an appropriate finite size version of survival is reaching size \( \gg 1/s \).

Results in Section 6 will show that this takes time of order

\[
\ell(s) = \begin{cases} 
  s^{-2} & d = 1 \\
  s^{-1} \log(1/s) & d = 2 \\
  s^{-1} & d = 3
\end{cases}
\]  

(3)

so in order to have enough room for our little drama of survival to play out, we must assume \( L \gg \ell(s)^{1/2} \), i.e., if \( N \equiv L^d \) then \( N \gg \ell(s)^{d/2} \). Our methods force us to assume a little more

\[(A0) \quad (1/u_1) \gg \ell(s)^{(d+2)/2} \]  

(4)

assumptions that will be in force throughout the paper. For a typical value of \( s = 0.01 \) this condition is satisfied when \( u_1 < 10^{-6} \). Unfortunately in our concrete example in Section 4.2, we have that \( u_1 \approx 10^{-5} \).

Since mutations occur at rate \( Nu_1 \) and are successful with probability \( s \), it is almost obvious that:

**Theorem 2.** If \( s, u_1 \to 0 \) then \( P(\sigma_1 > t/Nu_1 s) \to e^{-t} \).

To prove this, we consider the space-time set \( G_r \) of \( (x, q) \in \mathbb{Z}^d \times [0, r] \) with \( ||x||_\infty \leq L \) so that the biased voter model (constructed on the graphical representation described in Section 5) survives in the sense defined above. We then show that if \( R = t/Nu_1 s \) then \( |G_R|/NsR \to 1 \) in probability and the desired result follows.

Condition (A0) comes up in estimating the covariance of the events \( A_{x,q} = \{(x, q) \in G_r\} \). To do this we take the conservative approach that \( A_{x,q} \) and \( A_{x',q'} \) are independent if the processes starting at \( x \) at time \( q \) and at \( x' \) at time \( q' \) do not collide before they have run for \( O(1/\ell(s)) \) units of time. It is intuitive that simply sharing a few offspring in common does not cause a significant correlation of the survival events, but it seems difficult to get a good numerical estimate.

### 2.3 A simplified model with deterministic growth

The Bramson-Griffeath shape theorem suggests a simplification to our model. When the successful mutations occur, they initiate expanding clones that grow like a ball (in the usual \( \ell_2 \) norm) whose radius at time \( t \) is \( c_d(s)t \). This model is a simplification of the biased voter dynamics, but it is also a generalization. Borrowing a term from physics, this is a mesoscopic model. It does not depend on the microscopic details of interactions between cells, as long as they produce a shape theorem when they have grown to include a large number of cells. While this approach ignores a number
of biological details that are incorporated into complex “agent-based models,” see Cristini and Lowengrub (2010) or Deisboeck and Stamatakis (2011), it allows for explicit computations rather than being restricted to simulation of systems with only a few thousands of cells.

To summarize, in our simplified model we have two possibilities for each newly created type 1 mutation. It can either be a successful type 1 (which occurs with probability $s$), or it can be an unsuccessful type 1 with probability $1-s$. The successful type 1 mutations are modeled as expanding balls, and the unsuccessful type 1 mutations are modeled using the standard biased voter model dynamics but now conditioned on eventual extinction.

If we are in a situation where successful mutations to type $k+1$ only come from descendants of successful type $k$ mutations, our simplified model is the polynuclear growth (PNG) model of Prähöfer and Spohn (2000). In that system, mutations occur at rate 1, and when they land on a point with height $k$ produce a linearly growing disk at height $k+1$. The one-dimensional PNG model can be studied in great detail thanks to connections to increasing sequences in random permutations and random matrices, see Ferrari and Prähöfer (2006). However, very little is known in dimensions $d \geq 2$. While convergence of the scaled one dimensional profile of the PNG model to solutions of Kardar-Parisi-Zhang (1986) equation is an interesting mathematical result, the state of the spatial Moran model after hundreds or thousands of mutations is not relevant to studying cancer.

#### 2.4 Takeover by 1’s

Consider now the special case of our simplified model with deterministic growth in which the mutation rates $u_i \equiv u$ and we start with no individuals of type 1, i.e., $\xi_0 = \emptyset$. The time until the first successful type 1 mutation will be

$$t_{\text{mut}} = O(1/L^d u s)$$

The time to takeover the system $t_{\text{fix}} = O(L/c_d)$. Setting $t_{\text{mut}} = t_{\text{fix}}$ and solving we see that if

$$L \ll L_c = \left( \frac{c_d}{su} \right)^{1/(d+1)}$$

then we will have sequential fixation: mutations will fix faster than they arise, and the times between successive mutations that do not die out will be exponential with mean $1/t_{\text{mut}}$.

These calculations are from Martens et al. (2011). We now add an idea that Chatterjee and Durrett (2011) used to study Aldous’ “gossip process.” A site $x$ will be type 1 at time $t$ if there is a mutation in the space-time cone \{$(y, r) : |y-x| < c_d(t-r)$\}, so

$$P(x \in \xi_t) \approx 1 - \exp \left( -us \int_0^t (c_d r)^d \, dr \right) \approx 1 - \exp \left( -us \frac{c_d d^{d+1}}{d+1} \right)$$ (6)
This quantity will go from $\epsilon$ to $1 - \epsilon$ at times of order \((1/suc)^{1/(d+1)} = L_c/c_d\).

To prepare for later developments, we note that the number of successful type 1 mutations by this time will be

$$K_{pos} = \frac{L_c}{c_d} \cdot L^d su = L^d \left(\frac{su}{c_d}\right)^{d/(d+1)} = (L/L_c)^d.$$  \quad (7)

### 3 Waiting time for $\sigma_2$

In some applications, breast cancer for example, early mutations compromise the DNA replication machinery resulting in a drastically increased mutation rate. Thus it is important to drop the assumption \(u_1 = u_2\). There are three cases depending on the value of

$$\Gamma = (Nu_1s)^{d+1}(c_d^d u_2 s)^{-1},$$

which as we will see shortly is related to the number of successful type 1 mutations necessary to create a successful type 2 mutation. Throughout this section, we are taking the limit as \(s, u_1, u_2 \to 0\).

#### 3.1 $\Gamma \to 0$

In his Cornell Ph.D. thesis, Stephen Moseley studied the asymptotic behavior of the waiting time \(\tau_2\) for the first mutation to type 2 when this occurs in the first successful type 1 family and before it reaches fixation. Replacing \(u_2\) in his result by \(u_2 s\) we get a result for \(\sigma_2\), the time of the first successful type 2 mutation.

**Theorem 3.** If we assume,

\begin{align*}
(A1) & \quad \left(\frac{c_d}{u_2 s}\right)^{d/(d+1)} \ll N \ll \left(\frac{c_d^d u_2 s}{u_1 s}\right)^{1/d+1} \quad (A2) \\
\end{align*}

and \((A3)\) \(u_2 \ll 1/\ell(s)\) then \(P(\sigma_2 > t/Nu_1 s) \to \exp(-t)\).

Here \(\ell(s)\) is the quantity defined in (3). To connect with the title of the subsection note that \((A2)\) is the condition \(\Gamma \to 0\).

To explain the conditions of Theorem 3, note that under our simplified model, if the type 2 mutation occurs before type 1’s reach fixation, it will occur \(O(t_2)\) units of time after the type 1 mutation where

$$\int_0^{t_2} (c_d r)^d dr = O(1/u_2 s).$$

That is, \(t_2 = O((c_d^d u_2 s)^{-1/(d+1)})\). At that time the radius of set of 1’s

$$c_d t_2 = O((c_d^d / u_2 s)^{1/(d+1)}).$$
so we need to have
\[(c_d/u_2s)^{d/(d+1)} \ll L^d = N\] (8)
for the computation of the integral to be valid. When \(u = u_1 = u_2\), (A1) says \(L \gg L_c\), which is the opposite of the sequential fixation condition (5).

If we let \(\sigma_1\) be the time of the first successful 1 mutation then by Theorem 2
\[P(\sigma_1 > t) \approx \exp(-tNu_1s),\] (9)
so for the result in Theorem 3 to hold we must have \(\sigma_2 - \sigma_1 \ll \sigma_1\), which requires
\[t_2 = (c_d^{d}u_2s)^{1/(d+1)} \ll 1/Nu_1s\]
or rewriting things in terms of \(N\)
\[N \ll \frac{(c_d^{d}u_2s)^{1/(d+1)}}{u_1s}\] (10)
In the special case \(u_1 = u_2 = u\) this is the opposite of (8) so the theorem is vacuous. However if \(u_2 \gg u_1\), then there are parameter values to which this result can be applied.

Finally, we have to consider the possibility that the successful mutation to type 2 occurs among the descendants of a type 1 mutation that does not reach fixation. Lemma 6.2 will show that if \(\xi^0_t\) is the set of 1’s in a supercritical biased voter model with \(\lambda = 1 + s\) and \(T_0\) is the time at which the process dies out then
\[E\left(\int_0^{T_0} |\xi^0_t| dt \bigg| T_0 < \infty\right) \leq C\ell(s)\]
where \(\ell(s)\) was defined in (3).

Mutations to type 2 that land on an unsuccessful type 1 family will succeed with a probability between \(s\) and \(2s\), since when they grow outside the unsuccessful type 1 family they will be competing with type 0’s. Since the expected number of type 1 mutations before the first successful one is \(1/s\), the expected number of successful mutations to type 2 that occur in these families is \(\leq u_2\ell(s) \cdot 2 \to 0\) by (A3).

**Remark.** In Theorems 3 and 4, the fact that the probability of success is \(\leq 2s\) will be sufficient, however in Theorem 5 we will need exact asymptotics. To avoid the difficult probability of calculating the probability of success of a type 2 mutation landing at a random location on the space-time set occupied by unsuccessful type 1 families, we will introduce a “fudge factor” \(1 \leq \rho_2 \leq 2\) and assume that this probability is asymptotically \(\rho_2s\). Although the factor \(\rho_2\) is annoying from a mathematical point of view, in practical applications our uncertainty about the mutation rates \(u_i\) is larger than our knowledge of the value of \(\rho_2\).
3.2 $\Gamma \rightarrow I^{d+2}$

The choice of notation for the limit will make more sense when the reader has seen the definitions of $K$ and $J$. Let $\gamma_d$ be the volume of ball of radius 1 in $d$ dimensions,

$$
\gamma_1 = 2, \quad \gamma_2 = \pi, \quad \gamma_3 = 4\pi/3
$$

then we have

**Theorem 4.** If we assume $(A1)$, $(A3)$, and $\Gamma \rightarrow I^{d+2}$ then

$$
P(\sigma_2 > t/Nu_1s) \rightarrow \exp\left(-\frac{\gamma_d(t/I)^{d+2}}{(d+1)(d+2)}\right).
$$

As in the case $\Gamma \rightarrow 0$, when $u_1 = u_2$, $(A1)$ implies $L \gg L_c$. Since $\Gamma \sim 0$ we do not have $\sigma_2 - \sigma_1 \ll \sigma_1$ and there is time for other successful type 1 mutations to happen. However, under the assumption $\Gamma \rightarrow I^{(d+2)}$ the expected number before time $\sigma_2$ is finite, so as in the Theorem 3, $(A3)$ implies that we can ignore the possibility that the successful type 2 comes from a type 1 family that dies out.

To explain the limit, let $t' = t/(Nu_1s)$ to simplify notation. A well-known formula for Poisson processes, which can be found in Parzen (1999) or on page 421 of Komarova (2007), implies

$$
P(\sigma_2 > t') = \exp\left(-u_2s \int_0^{t'} Nu_1s \cdot \gamma_d c_d^{d} \frac{(t' - r)^{d+1}}{d+1} dr\right)
$$

To see this note that a successful type 1 mutation born at time $r$ will cover a space-time volume of

$$
v(r) = \gamma_d c_d^{d}(t' - r)^{d+1}/(d+1)
$$

by time $t'$. Such mutations happen at rate $Nu_1s$ and when they do produce a Poisson number of successful type 2 mutations with mean $u_2sv(r)$. The desired formula now follow from well-known properties of the Poisson process.

Substituting $t' = t/Nu_1s$ and using $(Nu_1s)^{d+1}(c_d^{d}u_2s)^{-1} \rightarrow I^{d+2}$ the expression above converges to

$$
\exp\left(-\frac{\gamma_d(t/I)^{d+2}}{(d+1)(d+2)}\right)
$$

which is the desired result.

3.3 $\Gamma \rightarrow \infty$

In this case there will be a large number, $K$, of successful type 1 mutations before the first successful type 2 mutant occurs. Since the number of successful mutations is
large if we let $Z_1^*(t)$ be the 1’s at time $t$ that are descended from successful 1 mutations then

$$Z_1^*(t) \approx EZ_1^*(t) = \int_0^t Nu_1 s \cdot \gamma c_d^d(t - r)^d dr = Nu_1 s \cdot \gamma c_d^d \frac{t^{d+1}}{d+1}$$  \hspace{1cm} (12)$$

A new feature in this case is that the first successful 2 may come from a type 1 family that dies out. If we let $Z_0^1(t)$ be the 1’s at time $t$ that are descended from unsuccessful 1 mutations then using $\bar{E}_1$ for expected value for a biased voter model starting with a single 1 and conditioned to die out. Then for large $t$ we have

$$Z_0^1(t) \approx EZ_0^1(t) = \int_0^t Nu_1 |\xi_{t-r}| dr \sim Nu_1 \int_0^\infty |\xi_r| dr \sim Nu_1 \alpha d \ell(s)$$  \hspace{1cm} (13)$$

where the last result follows from the discussion in the proof of Lemma 9.2 regarding type 1 families that reach size $1/s$, and Lemma 2 from Part I which tells us that the remaining small families can be neglected.

The constant $\alpha_d$ in (13) is related to the boundary size of the biased voter model in $d$ dimensions, which is discussed in part I. In particular, let $\beta_2 = \pi$ and for $d \geq 3$ let $\beta_d$ be the probability that two simple random walks started at 0 and $e_1 = (1,0,...,0)$ never hit. The constant $\alpha_d$ is defined to be 1 if $d = 1$ and $1/\beta_d$ if $d \geq 2$. The relationship between $\beta_d$ and the boundary size can be inferred from the duality between the voter process and the coalescing random walk; the specific relation is given in (27).

We can now write

$$P(\sigma_2 > t) \approx \exp(-u_2 s \int_0^t EZ_1^*(r) dr - u_2 \rho_2 s \int_0^t EZ_0^1(r) dr)$$

$$= \exp(-u_2 s \left[ Nu_1 s \gamma c_d^d \frac{t^{d+1}}{(d+1)(d+2)} + Nu_1 \alpha_d \ell(s) u_2 \rho_2 s \right])$$  \hspace{1cm} (14)$$

Define $J = 1/u_2 \ell(s)$ and

$$K = \Gamma^{1/(d+2)} = (Nu_1 s)^{(d+1)/(d+2)} \cdot (c_d^d u_2 s)^{-1/(d+2)}.$$  \hspace{1cm} (15)$$

$K$ is (the order of magnitude of) the number of successful type 1 mutations needed to get a successful type 2 mutation from a successful type 1 family. In order to derive the formula for $K$ evaluate the amount of space time volume created by $K$ disjoint and successful type 1 mutations created at time 0 and solve for $K$ such that this volume $= 1/u_2 s$. For more detail see Section 9.1. $J$ is (the order of magnitude of) the number of successful type 1 mutations needed to get a successful type 2 mutation from an unsuccessful type 1 family. Note that in the second statement we are measuring time in terms of the number of successful type 1 mutations, which occur roughly every $1/Nu_1 s$ units of time.
**Theorem 5.** If \( u_1 \leq u_2, \Gamma \to \infty, (A3) \) then

\[
P(\sigma_2 > t/Nu_1 s) \sim \exp \left(-\frac{\gamma_d(t/K)^{d+2}}{(d+1)(d+2)} - \rho_2 \alpha_d(t/J)\right)
\]

This is actually three results. If \( J/K \to \infty \) then

\[
P(\sigma_2 > Kt/Nu_1 s) \to \exp \left(-\frac{\gamma_d t^{d+2}}{(d+1)(d+2)}\right)
\]

If \( J/K \to 0 \) then

\[
P(\sigma_2 > Jt/Nu_1 s) \to \exp (-\rho_2 \alpha_d t)
\]

If \( K/(J+K) \to \theta \in (0,1) \) then

\[
P(\sigma_2 > (K+J)t/Nu_1 s) \to \exp \left(-\frac{\gamma_d(t/\theta)^{d+2}}{(d+1)(d+2)} - \rho_2 \alpha_d(t/(1-\theta))\right)
\]

To prepare for their proofs note that if \( u_1 = u_2 \) then

\[
K = N^{(d+1)/(d+2)} \left(\frac{u s}{c_d}\right)^{d/(d+2)} = K_{pos}^{(d+1)/(d+2)}
\]

by (7). Thus if \( u_1 \leq u_2 \) and \( K \) is large (as it is when \( \Gamma \to \infty \)) then \( K \ll K_{pos} \) so \( \sigma_2 \) occurs before the 1’s reach positive density.

### 3.4 Growth of the type 2’s

The approach used in the previous subsection can be extended to study \( \sigma_3 \), the time of the first successful type 3. To do this we first need to study the growth of \( Z_2(t) \). Using (12) and (13) we have

\[
EZ_*^s(t) = \int_0^t dr \int_0^t u_2 s \cdot Nu_1 s \gamma_d c_d (t-r)^d dr + \int_0^t u_2 \rho_2 s \cdot Nu_1 \ell(s) \alpha_d \gamma_d (2s^2) (t-r)^d dr
\]

Here the speed \( c_d(2s + s^2) \) comes from the fact that after the type 1 family which gave rise to the 2 dies out the 2’s with fitness \((1 + s)^2\) are competing against 0’s with fitness 1. Now that if we expand out \((t-r)^d\) then each term will produce a multiple of \( t^{d+2} \), so

\[
\int_0^t (t-r)^d \, dr = \kappa_{2,d} t^{d+2}
\]

Evaluating the integrals we have

\[
EZ_*^s(t) = u_2 s \cdot Nu_1 s \cdot \frac{\gamma_d^2 c_d(s)^2}{d+1} \cdot \kappa_{2,d} t^{d+2} + u_2 \rho_2 s \cdot Nu_1 \ell(s) \alpha_d \gamma_d c_d(2s + s^2) \frac{t^{d+1}}{d+1}
\]
In addition to (17) we also need the members of unsuccessful families

\[ EZ_2^0(t) = \int_0^t dr u_2 EZ_1(t-r) E_1|\xi(r)| \]

\[ = EZ_1(t)u_2\ell(s)\alpha_d \]  \hspace{1cm} (18)

The approximation comes from assuming \( EZ_1(t-r) \approx Z_1(t) \) for the \( r \)'s that contribute to the sum. It is always an upper bound.

If we are in the regime where there are many successful type 2 mutations before the first successful type 3 then \( Z_2(t) \approx EZ_2(t) \) and hence

\[ P(\sigma_3 > t) \approx \exp \left( -\int_0^t EZ_2(r)u_3s dr \right) \] \hspace{1cm} (19)

This assumes that by time \( \sigma_3 \) the 1’s have not reached fixation, which seems to be a reasonable assumption for cancer.
4 Numerical Examples

To help understand the conditions that specify the various regimes of behavior in our theorems, we will consider some concrete examples. For simplicity we will restrict our attention to \( d = 2 \), which is relevant to cancers of the skin, colon, and female reproductive system.

4.1 Phase diagram for \( s = 0.01 \) in \( d = 2 \)

In a study of glioblastoma and colorectal cancer, Bozic et al (2010) concluded that the average selective advantage of somatic mutations was surprisingly small, 0.004. Here we adopt a slightly larger value, 0.01. In this subsection we will set \( N = 10^c \), \( u_1 = 10^{-a} \), and \( u_2 = 10^{-b} \), where \( a, b, \) and \( c \) are all positive constants, and determine the regions in which our theorems can be applied. To identify the order of magnitude of these constants we note that cells have a diameter of roughly \( 10^{-5} \) m so there are \( 10^6 \) in \( 1 \) cm\(^2 \), and \( 10^8 \) in \((10 \text{ cm})^2\). The point mutation rate has been estimated, see Jones et al. (2008), to be \( 5 \times 10^{-10} \) per nucleotide per cell division.

To compute the \( u_i \) this number needs to be multiplied by the number of targets. In some cases there are a small number of nonsynonymous mutations that achieve the desired effect, while in other cases there may be hundreds of possible mutations that knock out the gene and there may be a number of genes which can be hit. Bozic et al (2008) state that in their applications there are 34,000 possible mutations. Thus mutation rates can range from \( 10^{-9} \) to \( 10^{-5} \), or can be larger after the mechanisms that govern DNA replication are damaged.

To begin the study of our special case \( s = 0.01 \) and \( d = 2 \), we note that

\[
c_2 = \left(\frac{s}{\ln(1/s)}\right)^{1/2} = 0.0466 \quad \log(c_2) = -1.322
\]

\[
l(s) = \ln(1/s)/s = 460.5 \quad \log(l(s)) = 2.663
\]

Here \( \log \) is the base 10 logarithm.

In order to get started we need to check the technical conditions (A0) \((1/u_1) \gg l(s)^{(d+2)/2}\). To identify the boundaries between the various regimes we will replace \( \ll \) by \(<\). If we do this we need

\[
a > 5.362
\]

Condition (A1) says \((c_d/u_2s)^{d/(d+1)} \ll N\). If we again replace \( \ll \) by \(<\), then the condition is

\[
(0.0466 \cdot 10^{b+2})^{2/3} < 10^c,
\]

which after taking logarithms and simplifying can be written as

\[
b - 3c/2 < -0.67. \quad (20)
\]

We skip over (A2), which is \( \Gamma \to 0 \), because we will consider \( \Gamma \) later. Condition (A3), which is \( u_2 \ll 1/l(s) \) is now simply

\[
b > 2.66. \quad (21)
\]
Figure 1 shows the parameter regime in which (A1) and (A3) apply (upper right region between the two dashed lines), when $s = 0.01$ and $d = 2$. To reduce to two dimensions we have assumed $b = a - 2$.

![Figure 1: Parameter region delineated by assumptions (A1) and (A3), for $s = 0.01$, $d = 2$, and $b = a - 2$ (upper right region between the dashed lines). The vertical line is (A3). The color at each point represents the value of log $\Gamma$. The dot represents the parameters used the example for colorectal cancer.](image)

To determine the specific regimes in which Theorems 3, 4, and 5 hold, we must consider whether the parameter $\Gamma$ tends to zero, infinity, or a positive real number. When $d = 2$ and $s = 0.01$

$$\Gamma = (Nu_1s)^{d+1}(c_d u_2 s)^{-1}$$

$$\log(\Gamma) = 3(c - a - 2) - (-2.644 - b - 2) = 3(c - a) + b - 1.356$$

(22)

Figure 1 shows the value of log $\Gamma$ at each point in the plane when $b = a - 2$. In contemplating the size of $\Gamma$ it is important to remember that we are interested in $K = \Gamma^{1/(d+2)}$ which is the number of successful mutations before $\sigma_2$ and its relationship to $J = 1/u_2 \ell(s)$ which in our example has log $J = b - 2.65$.

### 4.2 Application to colorectal cancer initiation

For a concrete example, we consider the process of cancer initiation in the sigmoid colon. The cells of the colon are subdivided into partially-isolated subpopulations
of proliferative units, called **colonic crypts.** Each crypt is thought to contain approximately 4-20 stem cells which give rise to approximately 2000 differentiated cells (Nicolas et al, 2007; Bach et al, 2000). These stem cells divide and may accumulate genetic mutations which spread until most stem cells within the crypt carry that mutation. Clonal expansion among crypts is possible via crypt bifurcation: a process during which a single crypt subdivides into two separate crypts via partitioning and regrowth of the stem and differentiated cell populations. If the stem cells within a crypt carry a mutation which is advantageous to cellular fitness, the rate of crypt bifurcation may be elevated, leading to clonal expansion of the number of crypts carrying the mutation.

Here, following the example of Martens et al (2011), we take each colonic crypt to be a single ‘agent’ in the model and consider a ‘lattice’ of crypts in the tissue of the sigmoid colon. The process of crypt bifurcation can then be thought of as analogous to the dynamics of the biased voter model. Specifically, when a crypt bifurcates we assume that it replaces a neighboring crypt. We consider the domain of the process to be the inner surface of the colon, which is a cylindrical structure; thus $d = 2$. Using the estimate of approximately 16 crypts per square mm (Cheng et al, 1984), we obtain an estimate of $N = 945000$ crypts in the entire sigmoid colon.

It has been observed that the incidence of colon cancer is higher in people who suffer from diseases of the colon such as ulcerative colitis and Crohn’s disease. In such patients, the mutation rate $u_1$ per crypt cycle per crypt division time (in patients with predisposing conditions) is approximated to be $10^{-5}$ (thus $a = 5$), using baseline estimates of $10^{-10}$ for the mutation probability in a single nucleotide per cell division, $\sim 10$ target genes important in colorectal cancer initiation, and approximately 3 days between stem cell divisions in a crypt ((Totarfumo et al, 1987; see Martens et al, 2011 for a detailed description of this calculation). Here, the condition (A0) is not quite satisfied; however since we believe this condition can be improved, we will still proceed to see what these theorems can tell us.

It is widely accepted that a sequence of multiple mutations is necessary for the initiation of colon cancer. For example, a single defective allele of the gene **Adenomatous polyposis coli** (APC) can result in a condition in which the intestinal epithelium is studded with benign polyps. However, additional mutations (e.g. in genes p53 or kRAS) are required to initiate cancer. Furthermore, it has been suggested that inactivation of one APC allele may induce chromosomal aberrations (Ceol et al, 2007); therefore we consider the case where $b = a - 2 = 3$.

In the following we are interested in understanding the dynamics of mutation accumulation in the sigmoid colon for patients with conditions such as ulcerative colitis and Crohn’s disease. These conditions may often affect only a small portion of the colon; thus we consider $N = 10^c$ for $c = 4, 5, 6$. Using Figure 1 we observe that for $a = 5, b = 3$, as the size of the affected part of the colon increases, the system dynamics change from the regime of Theorem 3 ($c = 4$) to the regime of Theorem 4 ($c = 5$) and Theorem 5 ($c = 6$). This provides us with some insight into how the
spatial process of initiation may very between individuals with differing severity of predisposing conditions.

We next consider the expected time for a crypt to acquire two hits once ulcerative colitis or Crohn’s disease has already begun to affect crypt dynamics, for a more realistic estimates of $c = 6$. For these parameters Theorem 5 holds. Here $J = 2.17$ and $K = 14.6$; Thus we can simplify the approximation in Theorem 5 by ignoring the term within the exponential involving $K^{-4}$, and thus we obtain that $E[\tau_2] \approx 68.1$ crypt cycles. If we assume that a crypt cycle takes 50 days, this corresponds to estimates of approximately 9.3 years.
5 Construction and duality

To make the paper self-contained and to recall some facts that may not be widely known, we will now construct the two type biased voter model and explain its duality with coalescing branching random walk. Section 3 is devoted to proofs of useful facts about the biased voter model. Theorems 2, 3, and 4, are proved in Section 4, 5, and 6. The proof of Theorem 7 is hidden away in Section 7 because it relies on different techniques, and follows easily from results of Durrett and Zähle (1997).

To construct the biased voter model, we follow the approach in Griffeath (1978). Associated with each order pair \((x, y)\) of nearest neighbors, we have two Poisson processes, \(T_{n}^{x,y,v}, n \geq 1\) and \(T_{n}^{x,y,b}, n \geq 1\) with rates \(1/2d\) and \((\lambda - 1)/2d\). Here, all of the Poisson processes are independent, and together constitute the graphical representation. At each time \(t = T_{n}^{x,y,v}\) we draw an arrow \((y, t) \rightarrow (x, t)\) and put a \(\delta\) at \((x, t)\), while at each time \(t = T_{n}^{x,y,b}\) we draw an arrow \((y, t) \rightarrow (x, t)\). We think of arrows at little tubes that allow fluid to flow in the direction indicated, while the \(\delta\)'s are dams that stop the passage of the fluid. The \(\delta\)'s occur just before the arrows so they don't block the fluid that flows through them.

Given an initial set \(A\) of sites that are occupied by 1's, the set of sites that are occupied by 1's at time \(t\) is the set \(\xi_{t}^{A}\) of points that are wet if fluid is injected at points of \(A\) at time 0. By checking cases, one can see that the effect of an arrow-\(\delta\) from \(y\) to \(x\) is as follows:

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<tbody>
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The first case should be clear. In the second the arrow spreads the fluid from \(y\) to \(x\). In the third the \(\delta\) at \(x\) stops the fluid, but there is nothing from \(y\) to replace it, while in the fourth case there is. Thus the arrow-\(\delta\) produces a voter model step: \(x\) imitates \(y\).

If we remove the \(\delta\), then the only third line changes and the overall result is a birth from \(y\) to \(x\), with the two particles coalescing to one if \(x\) is already occupied:

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<tr>
<td>(x)</td>
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</table>
The graphical representation has the useful property that it constructs the biased voter model for all initial conditions on the same probability space. As Harris (1976) noted this implies that the constructed processes are additive:

$$\xi_t^{A \cup B} = \xi_t^A \cup \xi_t^B.$$  \hfill (23)

since a space-time point can be reached from $A \cup B$ at time 0 if and only if it can be reached from $A$ or from $B$. A consequence of additivity is that $A \to \xi_t^A$ is increasing, a property that is called “attractive.”

An important reason for constructing a process from a graphical representation is that it allows us to construct a dual process. Let $\zeta^{x,t}$ be the set of points at time $t - r$ that can be reached by a path that does down the graphical representation and crosses the arrows in the direction OPPOSITE their orientation. If we recall that the $\delta$’s occur just before the arrows on the way up then we see that the effect of an arrow-$\delta$ from $y$ to $x$ on the dual process is

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In words this is a coalescing random walk. If there is a particle at $x$ it jumps to $y$. If there is also a particle at $y$ the two coalesce to 1. It is easy to see that an arrow without a $\delta$ has the same effect in the dual as it did in the forward process except that now the birth is from $x$ to $y$.

Given a set of sites $B$, let $\zeta^{B,t}_s = \bigcup_{x \in B} \zeta^{x,s}_s$. It is immediate from the definitions that

$$\{\xi^A_t \cap B \neq \emptyset\} = \{\zeta^{B,t}_s \cap A \neq \emptyset\}$$

i.e., the two events are equal. To get rid of the subscript $t$ from the dual process, we note that if $t < t'$ then the distribution of $\zeta^{B,t'}_r$ for $r \leq t$ is the same as $\zeta^{B,t}_r$ for $r \leq t$. Invoking Kolmogorov’s extension theorem there is process $\zeta^B_r$ defined for all time $r \geq 0$ that has the same distribution as $\zeta^{B,t}_r$ for $r \leq t$. This process satisfies

$$P(\xi^A_t \cap B \neq \emptyset) = P(\zeta^B_r \cap A \neq \emptyset)$$

In what follows, we will be interested in the biased voter model with mutation $0 \to 1$ at rate $u_i$. Mutation can be incorporated into the graphical representation by adding independent Poisson processes $\mathcal{T}^{x,\delta}_n$, $n \geq 1$ with rate $u_i$. If we let $\hat{\xi}_i^A$ be the biased voter model with mutation starting with $A$ occupied at time $t$, and suppose that there are mutations at $x_i$ at times $t_1 < t_2 < \ldots t_k < t$ then

$$\hat{\xi}_t = \hat{\xi}_t^A \cup \xi^{x_1,t_1}_t \cup \cdots \cup \xi^{x_k,t_k}_t$$
where $\xi^{x_i,t_1}_t$ is the biased voter model without mutation starting with $x_i$ occupied at time $t$.

In our proofs, it will be useful to be able to quantify the notion that two processes, $\xi_t^A$ and $\xi_t^B$ or $\xi_t^{x_1,t_1}$ and $\xi_t^{x_2,t_2}$ are independent when they don’t hit each other. To do this we use a coupling due to David Griffeath (1978). We define the first process on a graphical representation, and the second on an independent graphical representation with the caveat that events in the second process that involve an edge $(x, y)$ where $x$ or $y$ is occupied in the first process must use the first graphical representation, so that the pair of processes has the correct joint distribution.
6 Results for the biased voter model

6.1 Upper bounds

Our goal is to bound the size of type 1 families that later die out. The first step is to determine the effect on the process of conditioning it to die out. In the proofs in this section we will sometimes use $1 \leq \lambda \leq 2$ to get rid of $\lambda$'s from the formulas.

**Lemma 6.1.** Let $\xi^0_t$ is the set of 1's in a supercritical biased voter model with $\lambda = 1+s$ and $T_0$ is the time at which the process dies out. Let $\bar{\xi}_t$ be the biased voter model with the roles of 1 and 0 interchanged, i.e., 1's give birth at rate 1, and 0's give birth at rate $\lambda$.

$$(\{\xi^0_t, t \leq T_0\} | T_0 < \infty) =_d \{\bar{\xi}_t, t \leq T_0\}$$

**Proof.** If $\xi^0_t = A$ with $|A| = k$ and $|\partial A| = \ell$ then $|\xi^0_t|$ grows to size $k+1$ at rate $\lambda \ell$, and shrinks to size $k-1$ at rate $\ell$, so the transition probability of the embedded discrete time chain is

$$p(k, k+1) = \frac{\lambda}{1+\lambda}, \quad p(k, k-1) = \frac{1}{1+\lambda}$$

If we let $\varphi(x) = \lambda^{-x}$ then it is easy to check that

$$\varphi(k) = p(k, k+1)\varphi(k+1) + p(k, k-1)\varphi(k-1)$$

hence if $a < x < b$ then

$$P_x(T_a < T_b) = \frac{\varphi(b) - \varphi(x)}{\varphi(b) - \varphi(a)} \quad P_x(T_b < T_a) = \frac{\varphi(x) - \varphi(a)}{\varphi(b) - \varphi(a)}$$

Let $a = 0$, $x = 1$, and $b \to \infty$ in the first formula

$$P_k(T_0 < \infty) = \lambda^{-k}.$$  \hspace{1cm} (25)

If we condition a random walk with positive drift to hit 0 then the conditioned process has

$$\bar{p}(k, k+1) = \frac{p(k, k+1)\varphi(k+1)}{\varphi(k)} = \frac{1}{1+\lambda}, \quad \bar{p}(k, k-1) = \frac{\lambda}{1+\lambda}$$

In words, the result is a random walk with the probabilities of up and down interchanged. Conditioning $\xi_t$ to hit 0 does not change the exponential holding times, and desired result follows. \hfill $\square$

The next three results are numerical upper bounds. As in part I these are based on the fact that when $k$ is large, the size of the boundary in the biased voter model

$$\partial(k) \sim \begin{cases} 
2d\beta_k & d \geq 3 \\
4\beta k / \log k & d = 2.
\end{cases}$$

(27)
When $s = 0$ this follows from (I1) on page 202 of Cox, Durrett, and Perkins (2002). To extend this to the subcritical biased voter model we will use Girsanov’s formula:

Let $P_0$ be the voter model in which a 1 next to a 0 forces it to flip at rate $(1 + s/2)/2d$ and vice versa a 0 next to a 1 forces it to flip at rate $(1 + s/2)/2d$.

Let $P_s$ be the subcritical voter model in which a 1 next to a 0 forces it to flip at rate $1/2d$ and vice versa a 0 next to a 1 forces it to flip at rate $(1 + s)/2d$.

The speed up in $P_0$ is a harmless linear transformation of the time scale, but it makes the rates at which things happen $= (2 + s)/2d$ on each discordant edge. Thus when we look at the Radon-Nikodym derivative it will only depend on the embedded chain.

$$\frac{dP_s}{dP_0} = (\frac{2}{2 + s})^{n_+} (\frac{2 + 2s}{2 + s})^{n_-}$$  \hspace{1cm} (28)

where $n_+$ is the number of up jumps and $n_-$ is the number of down jumps. Rewriting the RN derivative we have

$$\frac{dP_s}{dP_0} = (\frac{2}{2 + s})^{n_+-n_-} (\frac{4 + 4s}{4 + 4s + s^2})^{n_-} \leq 1$$  \hspace{1cm} (29)

so events that have small probability under $P_0$ (e.g., the boundary size deviating from the stated formula) also have small probability under $P_s$.

**Lemma 6.2.** Let $\xi_t$ be the subcritical biased voter model defined in Lemma 6.1.

$$g(k) \equiv E_k \left( \int_0^{T_0} |\bar{\xi}_t| \, dt \right) \leq Ck\ell(s)$$

where $\ell(s)$ was defined in (3)

**Proof.** Due to the additivity property of the biased voter model (23) it suffices to prove the result when $k = 1$. Let $\bar{S}_n$ be the simple random walk that jumps according to $\bar{p}$ defined in (26) and note that $|\bar{\xi}_t|$ is a continuous time version of $\bar{S}_n$ that jumps approximately at rate $q(k)$ when in state $k$ and makes jumps according to $\bar{p}$. Let $T_k^+ = \min\{n \geq 1 : S_n = k\}$. By considering the expected number of visits to $k$ and the amount of time spent there on each one we have

$$E_1 \left( \int_0^{T_0} |\bar{\xi}_t| \, dt \right) = \sum_{k=1}^{\infty} \frac{\bar{P}_1(T_k < T_0)}{\bar{P}_k(T_k^+ = \infty)} \cdot \frac{k}{q(k)}$$  \hspace{1cm} (30)

By symmetry and (24)

$$\bar{P}_1(T_k < T_0) = P_{k-1}(T_0 < T_k) = \frac{\lambda^{-k} - \lambda^{-(k-1)}}{\lambda^{-k} - 1} = \frac{\lambda - 1}{\lambda^k - 1}$$  \hspace{1cm} (31)
Using symmetry and (24) again,

\[
\bar{P}_k(T_k + T_{k-1} = \infty) = \frac{\lambda}{1+\lambda} \bar{P}_{k-1}(T_0 < T_k) = \frac{\lambda}{1+\lambda} P_1(T_k < T_0)
\]

\[
= \frac{\lambda}{1+\lambda} \frac{\lambda^{-1} - 1}{\lambda^{-k} - 1} = \frac{\lambda - 1}{(1+\lambda)(1 - \lambda^{-k})}, \tag{32}
\]

so we have

\[
\bar{P}_1(T_k < T_0) \bar{P}_k(T_k + T_{k-1} = \infty) = \left( \frac{\lambda - 1}{\lambda^{-k} - 1} \right) \left( \frac{1 + \lambda}{\lambda - 1} \right) \lambda^{-k}(\lambda^k - 1) = \lambda^{-k}(1 + \lambda)
\]

and (30) becomes

\[
E \left( \int_0^{T_0} |\xi_t| \, dt \right) = (1 + \lambda) \sum_{k=1}^{\infty} \lambda^{-k} \cdot \frac{k}{q(k)} \tag{33}
\]

In one dimension \( q(k) = (1 + \lambda), \) so doing some algebra and using the formula for the mean of the geometric distribution, the quantity in (33) is

\[
\sum_{k=1}^{\infty} k\lambda^{-k} = \frac{1/\lambda}{(1 - 1/\lambda)} \sum_{k=1}^{\infty} k\lambda^{-(k-1)}(1 - 1/\lambda)
\]

\[
= \frac{1/\lambda}{(1 - 1/\lambda)^2} \leq Cs^{-2} \tag{34}
\]

From this we see that \( q(k) \sim (1 + \lambda)\beta_d k, \) in \( d \geq 3, \) so the quantity in (33) is

\[
\frac{1}{\beta_d} \sum_{k=1}^{\infty} \lambda^{-k} = \frac{1}{\beta_d} \cdot \frac{1/\lambda}{1 - 1/\lambda} \leq Cs^{-1} \tag{35}
\]

In \( d = 2 \) we have \( q(k) \sim (1 + \lambda)\beta_2 k / \log k \) so the quantity in (33) is

\[
\frac{1}{\beta_2} \sum_{k=1}^{\infty} \lambda^{-k} \log k \leq Cs^{-1} \log(1/s) \tag{36}
\]

To see the last inequality note that for \( k \leq 1/s^2, \) \( \log k \leq 2 \log(1/s) \) and as \( s \to 0 \) we can ignore the contribution from \( k > 1/s^2. \)

In order to conclude that the limit of the expected values is the expected value of the limit we need a bound for the second moment. We begin with the case \( k = 1. \)

**Lemma 6.3.** Let \( \bar{\xi}_t \) be the subcritical biased voter model defined in Lemma 6.1.

\[
E_1 \left( \int_0^{T_0} |\bar{\xi}_t| \, dt \right)^2 \leq C \ell(s)^2 / s. \]
Proof. Using the Markov property

\[
E_k \left( \int_0^{T_0} |\xi_t^0| \, dt \right)^2 = 2E_k \int_0^{T_0} \, dr \, |\xi_r^0| \int_r^{T_0} |\xi_t^0| \, dt
\]

\[
= 2E_k \int_0^{T_0} \, dr \, |\xi_r^0| g(|\xi_r^0|) \leq 2C \ell(s) E_k \int_0^{T_0} \, dr \, |\xi_r^0|^2
\]

by Lemma 6.2. Thus by the reasoning that lead to (33)

\[
E_1 \left( \int_0^{T_0} \xi_t \, dt \right)^2 \leq 2C \ell(s) \cdot (1 + \lambda) \sum_{k=1}^\infty \lambda^{-k} \cdot \frac{k^2}{q(k)}
\]

(37)

The remainder of the proof is similar to the previous argument

\[d = 1 \quad q(k) = (1 + \lambda) \sum_{k=1}^\infty k^2 \lambda^{-k} \leq Cs^{-3}\]

\[d \geq 3 \quad q(k) \sim (1 + \lambda) \beta_3 k \quad \frac{1}{\beta_3} \sum_{k=1}^\infty k \lambda^{-k} \leq Cs^{-2}\]

\[d = 2 \quad q(k) \sim (1 + \lambda) \beta_2 k \log k \quad \frac{1}{\beta_2} \sum_{k=1}^\infty \lambda^{-k} k \log k \leq Cs^{-2} \log(1/s)\]

Recalling the definition of \(\ell(s)\), we see that the right-hand side is always \(C \ell(s)/s\) and we have proved the desired result. \(\square\)

Lemma 6.4. Let \(\bar{\xi}_t\) be the subcritical biased voter model defined in Lemma 6.1.

\[
E_j \left( \int_0^{T_0} |\bar{\xi}_t| \, dt \right)^2 \leq \frac{C}{s} \cdot \frac{j^3}{q(j)} + \frac{C}{s} \lambda^j \ell(s) s^2
\]

Note that when \(j = a/s\) both terms on the right are \(C_a \ell(s)/s^2\).

Proof. When \(j \geq k\), \(P_j(T_k < T_0) = 1\) while for \(j \leq k\), (31) becomes

\[
P_j(T_k < T_0) = P_{k-j}(T_0 < T_k) = \frac{\lambda^{-k} - \lambda^{-(k-j)}}{\lambda^{-k} - 1} = \frac{\lambda^{j-1}}{\lambda^k - 1}
\]

(38)

The formula in (32) has not changed

\[
P_k(T_k^+ = \infty) = \frac{\lambda - 1}{(1 + \lambda)(1 - \lambda^{-k})}
\]

so we have

\[
h(k) \equiv \frac{P_j(T_k < T_0)}{P_k(T_k^+ = \infty)} = \begin{cases} 
(1 + \lambda) \frac{1 - \lambda^{-k}}{\lambda - 1} & k \leq j \\
(1 + \lambda)(\lambda^j - 1) \frac{\lambda^{-k}}{\lambda - 1} & k \geq j
\end{cases}
\]

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To bound the first part of the sum we consider the cases $q(j) = O(1)$, $q(j) = O(j/\log(j))$, and $q(j) = O(j)$ for $d = 1, 2$ and $d \geq 3$ to get

$$\sum_{k=1}^{j} h(k) \frac{k^2}{q(k)} \leq \frac{C}{s} \cdot \frac{j^3}{q(j)}$$

which is the first term on the right-hand side of the lemma. For the second part of the sum, we use

$$\sum_{k=j}^{\infty} h(k) \frac{k^2}{q(k)} \leq C \lambda^j \sum_{k=j}^{\infty} \lambda^{-k} \frac{k^2}{q(k)}$$

so using the computation for (37) in the previous lemma gives the second term. 

6.2 Limit theorems

Our first step is to generalize Lemma 1 from part I. Let $T_k$ be the first time $|\xi_0 t| = k$ and let

$$a(n) = \begin{cases} n^2 & d = 1 \\ n \log n & d = 2 \\ n & d \geq 3 \end{cases}$$

(This time there is no 2 in the definition for $d = 2$.)

Lemma 6.5. Let $\xi^n_t$ be the biased voter model with $\lambda = 1 - 1/n$.

$$\left( \frac{|\xi^n_{t_n+\epsilon a(n)t}|}{n} \right| T_{n\epsilon} < \infty \right) \Rightarrow (Y_t|Y_0 = \epsilon) \quad (39)$$

where $\Rightarrow$ indicates convergence in distribution of the stochastic processes.

$$dY_t = \begin{cases} -dt + \sqrt{2} dB_t & d = 1 \\ -\beta dY_t dt + \sqrt{2\beta d} dW_t & d \geq 2 \end{cases}$$

In $d = 1$ the process is stopped when it hits 0. In $d \geq 2$, 0 is an exit boundary so we don’t have to stop the process.

Proof. In $d = 1$ the result is trivial. The size of the set increases by 1 at rate $(1 - 1/n)$ and decreases by 1 at rate 1, so if $\xi^n(n^2t) = k$

infinitesimal mean $= n^2 \cdot \frac{1}{n} \cdot \frac{-1}{n} = -1$

infinitesimal variance $= n^2 \cdot \frac{1}{n^2} \cdot \left( 2 - \frac{1}{n} \right) \to 2$

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In this and the next two calculations the first factor is the time scaling, the second comes from the fact that jumps change the scaled process by $1/n$. The third term is the difference of the rates in the first case and the sum in the second.

The one-dimensional case is easy because the size of the boundary, i.e., number of $0-1$ edges is always $2$ until the process dies out. Using the formulas for the boundary size in (27), we see that in $d \geq 3$ if $\xi^n(nt) = k$ with $k/n = x$ then

$$\text{infinitesimal mean} = n \cdot \frac{1}{n} \cdot -\beta_d k \cdot \frac{1}{n} \to -\beta_d x$$

$$\text{infinitesimal variance} = n \cdot \frac{1}{n} \cdot 2\beta_d k \cdot \frac{1}{n} \to 2\beta_d x$$

while in $d = 2$ if $\xi^n(tn \log n) = k$ with $k/n = x$ then

$$\text{infinitesimal mean} = n \log n \cdot \frac{1}{n} \cdot -\beta_d k \cdot \frac{1}{n \log k} \to -\beta_d x$$

$$\text{infinitesimal variance} = n \log n \cdot \frac{1}{n^2} \cdot 2\beta_d k \cdot \log k \to 2\beta_d x$$

Having shown the convergence of infinitesimal mean and variance to that of a stochastic differential equation with a well-posed martingale problem, the result follows. See e.g., Theorem 4.1 on page 354 in Ethier and Kurtz (1986).

In $d \geq 2$, Lemma 6.5 can be extended to a measure valued limit. We begin by describing the limit. A measure valued process $X_t$ is a super-Brownian motion with branching rate $\gamma$, diffusion coefficient $\sigma^2$ and drift $\theta$ if it is a solution of the following martingale problem. Let $\Delta$ denote the Laplacian, and use $\mu(f)$ to denote the integral of the function $f$ with respect to the measure $\mu$. For all $\phi \in C^\infty_K(\mathbb{R}^d)$ (smooth functions with compact support)

$$Z_t(\phi) = X_t(\phi) - X_0(\phi) - \int_0^t X_s(\sigma^2 \Delta \phi/2 + \theta \phi) \, ds$$

is a martingale with variance process

$$\langle Z(\phi) \rangle_t = \int_0^t X_s(\gamma \phi^2) \, ds$$

**Lemma 6.6.** Suppose $d \geq 2$ and let $X^n_t$ be the measure that assigns mass $1/n$ to each point $a(n)^{-1/2} \xi_{T_{nt} + a(n)t}^n$. If $X^n(0)$ converges weakly to a limit, then $(X^n(0)|T_{nt} < \infty)$ converges weakly to a super-Brownian motion with branching rate $2\beta_d$, diffusion coefficient $1$, and drift $-\beta_d$.

**Proof.** For $d \geq 3$ this is a special case of Theorem 1.3 in Cox and Perkins (2005) since the biased voter model is a special case of the voter model perturbation they consider. The situation is not as clean in the more difficult case of $d = 2$. To quote Ed Perkins, it is an easier argument than the Lotka-Volterra models considered in Theorem 1.2 of Cox and Perkins (2008).
We mention this result because we think it is interesting. Unfortunately it does not give us what we need to prove the following:

**Lemma 6.7.** Let $\delta > 0$. If $M$ is large then the probability an unsuccessful type 1 family will last for time $\geq M\ell(s)$ or will escape from a cube of radius $M\ell(s)^{1/2}$ is $\leq \delta s$.

In $d = 1$ the biased voter model is an interval when it is not empty so Lemma 6.5 shows that the conclusion is valid in this case as well. To prove this in $d \geq 2$ we will combine the first half of Theorem 4 from Bramson, Cox, and LeGall (2001) with the trivial fact that the voter model dominates the biased voter model. Their result concerns the ordinary voter model with kernel $p(x,y)$. That is, voter at $x$ changes opinions at rate 1, and imitates the one at $y$ with probability $p(x,y)$ where $p(x,y) = p(0,y-x)$ is irreducible and symmetric with $p(0,0) = 0$ and $\sum_x p(0,x)x_j = \sigma^2 \delta(i,j)$. Here $\delta(i,j) = 1$ if $i = j$ and 0 otherwise. To get a limit, we scale space so that the voters live on $\mathbb{Z}^d / \sqrt{n}$, run time at rate $n$ and denote the resulting voter model by $\xi^n_t$. Let $m_n = n / \log n$ in $d = 2$ and $n$ in $d \geq 3$, and define a measure valued process by

$$X^n_t = \frac{1}{m_n} \sum_{y \in \xi^n_t} \delta_y$$

We write $X_{t}^{N,0}$ when the initial state is $\xi^n_0 = \{0\}$. Let $D$ be the space of functions from $[0, \infty)$ into the space of finite measures on $\mathbb{R}^d$ that are continuous in the weak topology.

**Theorem 6.** Assume $d \geq 2$ and let $N_0$ be the excursion measure of super-Brownian motion on $\mathbb{R}^d$ with branching rate $2\beta_d$ and diffusion coefficient $\sigma^2$.

Let $\alpha > 0$ and let $F$ be a bounded continuous function on $D$ with $F(\omega) = 0$ if $\omega_t = 0$ for $t \geq \alpha$. Then

$$\lim_{N \to \infty} m_N E F(X^N_{t}) = N_0(F)$$

The excursion measure is defined by starting the super process from $\epsilon \delta_0$, multiplying the probability measure by $1/\epsilon$ and letting $\epsilon \to 0$. See Section 3 of Bramson, Cox, and LeGall (2001) and references therein for more details. This is the super-process analogue of starting Brownian motion at $\epsilon$, killing it when it hits 0, considering the limit of $(1/\epsilon)$ times the probability measure, which defines Ito’s excursion measure. See Chapter XII of Revuz and Yor (1991) for a thorough treatment. In most cases the killed Brownian motion $\bar{B}_t$ dies out quickly but when $\epsilon < 1$

$$(1/\epsilon) P_\epsilon(\max_t \bar{B}_t > 1) = 1$$

**Proof of Lemma 6.7.** First consider the unbiased voter model. In the set-up for Theorem 6 take $n = 1/s$ in $d \geq 3$, and $n = (1/s) \log(1/s)$ in $d = 2$, i.e., $n = \ell(s)$, so $m_n \sim 1/s$. The weak convergence result and the fact that the excursion measure has compact support gives the result for the ordinary voter model. The result for the subcritical biased voter model follows by comparison. \hfill \Box
7 Proof of Theorem 2

As mentioned in the introduction we will consider the space-time set $G_r$ of $(x, q)$ so that the biased voter model constructed on the graphical representation in Section 5 survives, i.e., it reaches size $\gg 1/s$. To approximate this, we will consider $G_r^M$ the set of points so that the biased voter model escapes from

$$(x, q) + [\pm M\ell(s)^{1/2}, M\ell(s)^{1/2}]^d \times [0, M\ell(s)]$$

where $\ell(s)$ was defined in (3). Let $\delta > 0$. It follows from Lemma 6.7 that if $M$ is large enough then

$$P((x, q) \in G_r^M - G_r) \leq \delta s$$  \hspace{1cm} (40)

To get bounds on the size of $|G_r^M| = \int_0^r dq \{x : (x, q) \in G_r^M\}$ we note that if $\|x - x'\| \leq 2M\ell(s)^{1/2}$ or $\|q - q'\| > M\ell(s)$ then the events $(x, q) \in G_r^M$ and $(x', q') \in G_r^M$ are independent. From this it follows that

$$\text{var}(|G_r^M|) = \sum_{x : \|x\| \leq L} \sum_{x' : \|x'\| \leq L} \int_0^r dq \int_0^r dq' \text{cov}(1_{(x, q) \in G_r^M}, 1_{(x', q') \in G_r^M})$$

$$\leq Nr \cdot (4M\ell(s)^{1/2})^d \cdot 2M\ell(s) \cdot p_M,$$

where $p_M = P((x, q) \in G_r^M)$. We need to show that $\text{var}(|G_r^M|) \ll (E|G_r^M|)^2$ where

$$(E|G_r^M|)^2 = (Nrp_M)^2$$

By (A0) $(1/u_1) \gg \ell(s)^{(d+2)/2}$, which implies that when $R = t/nu_1s$, $Rp_M \gg 1$. It follows from Chebyshev’s inequality that

$$|G_r^M|/NRp_M \to 1 \text{ in probability.}$$

Using (40) now we see that if $k$ is large

$$P(|G_r^M - G_r| > k\delta sNR) \leq 1/k$$

Since $\delta$ is arbitrary, it follows that

$$|G_r|/NRs \to 1$$

and the proof of Theorem 2 is complete.
8 Proofs of Theorems 3 and 4

Proof of Theorem 3. By the discussion in Section 3, it suffices to show that $\sigma_2$ is close to $\sigma_1$ the time of the first successful type 1 mutation. In particular we can show that

$$Nu_1s(\sigma_2 - \sigma_1) \rightarrow 0,$$

as $N \rightarrow \infty$ and $u_1s \rightarrow 0$. Since $P(\sigma_1 > t) = e^{-Nu_1st}(1 + o(1))$, establishing (41) will establish that $P(\sigma_2 > t) = e^{-Nu_1st}(1 + o(1))$.

We will establish (41) through the following three steps. First, we will show that the first successful type 2 mutant does not arise before the first successful type 1 mutant (i.e. $\sigma_2 \geq \sigma_1$) using (A3). Then, we will establish that the first successful type 2 mutant in fact arises from the family of the first successful type 1 mutant. Using this fact in conjunction with (A1) and (A2), it will then be shown that (41) holds.

The first step is to show that the first successful type 2 mutant does not come from any unsuccessful type 1 families that arise before $\sigma_1$. Let us define $U$ to be the number of unsuccessful type 1 mutants that arise before $\sigma_1$. $U$ then has a geometric distribution with mean $s$, according to our simplified model. Then

$$P(\sigma_2 < \sigma_1) \leq 1 - E \exp \left( -u_2s \sum_{i=1}^{U} \int_{0}^{T_0} Z_1^i(s)ds \bigg| T_0^i < \infty \right)$$

$$\leq u_2sE[U]E \left( \int_{0}^{T_0} Z_1^i(s)ds \bigg| T_0^i < \infty \right) \leq u_2\ell(s) \ll 1,$$

where the first inequality is not an equality due to possible overlap of the unsuccessful type 1 families or interference with unsuccessful type 2 families, and the final asymptotic inequality is (A3).

Next, we will argue briefly that the first successful type 2 mutant actually comes from the first successful type 1 mutant (as opposed to any subsequent type 1 families). Let us introduce some notation: $\sigma_{1,i}$ is the time of creation of the $i$-th successful type 1 mutant, and similarly, $\hat{\sigma}_{1,i}$ is the time of creation of the first successful type 2 mutant from the type 1 family started at time $\sigma_{1,i}$. Then by the previous definition $\sigma_1 = \sigma_{1,1}$. We now claim that with high probability $\sigma_2 = \hat{\sigma}_{1,1}$. There are only two possible alternatives: it arose from an unsuccessful type 1 family that arises after $\sigma_1$, or $\sigma_2 = \hat{\sigma}_{1,i}$ for some $i \geq 2$. By the argument in the previous display we know that the first alternative does not occur with high probability. Next by definition for $i \geq 2$, $\sigma_{1,i}$ is on average $i/Nu_1s$ time units greater than $\sigma_{1,1}$. As we will see shortly, $\hat{\sigma}_{1,i} - \sigma_{1,i}$ is negligible compared to $1/Nu_1s$ and therefore we conclude that with high probability $\sigma_2 = \hat{\sigma}_{1,1}$.

Next we will show that $(\hat{\sigma}_{1,i} - \sigma_{1,i})Nu_1s \rightarrow 0$. Consider the amount of space-time volume occupied by the type 1 clone up until $t$ time units after $\sigma_1$, where $t < \hat{\sigma}_{1,1}$.
Now, if no unsuccessful type 2 mutations arise to interfere with the growth of this clone, the total space-time volume occupied until time $t$ is

$$g(t) = \frac{c dt^{d+1}}{d+1},$$

where we have made use of (A1) to say that this form of $g(t)$ is valid for the range of $t$ considered. Then, we have that

$$P(\hat{\sigma}_{1,i} - \sigma_{1,i} > t) = \exp (-u_2 s g(t))$$

so

$$P(Nu_1 s(\hat{\sigma}_{1,i} - \sigma_{1,i}) > t) = \exp \left( \frac{-u_2 sc dt^{d+1}}{(d+1)(Nu_1 s)^{d+1}} \right) \to 0$$

where the last limit comes from (A2). Finally, we need to take care of the effects of unsuccessful type 2 mutations that arise from this clone during this time – they will decrease the space-time volume of the cone. Denote the modified space-time volume as $\tilde{g}(t)$, and denote $V(t)$ to be the number of unsuccessful type 2 mutations that arise before time $t$. Then $V(t)$ is distributed like Poisson$(g(t)u_2)$, so

$$\tilde{g}(t) = g(t) - V(t)\ell(s)$$

$$= g(t)(1 - \ell(s)u_2) + \ell(s)(u_2g(t) - V(t)),$$

and therefore

$$\frac{\tilde{g}(t)}{g(t)} = (1 - \ell(s)u_2) + \ell(s)\frac{u_2}{g(t)}(u_2g(t) - V(t)).$$

By (A3) the first term on the RHS of the previous display goes to 1, and using Chebyshev we see that if $g(t) = k/u_2$ for some $k > 0$ then the second term goes to 0.

Proof of Theorem 4. As mentioned in the discussion when this result was stated, arguments in the previous proof show that we can ignore the possibility of the successful type 2 comes from a type 1 family that dies out. In addition there is the issue of overlap of successful type 1 clones overlapping, however by using the techniques in the proof of Lemma 9.1 in the next section it is easily shown that these overlaps are insignificant. The remainder of the proof is given right after the statement of the theorem.
9 Proof of Theorem 5

There are three cases corresponding to the three limit theorems stated after the result. Define $Z^*_1(r)$ to be the number of descendants of successful type $i$ mutations at time $r$ and define $Z^0_1(r)$ to be the number of descendants of unsuccessful type 1 mutations at time $r$.

9.1 $J \gg K$

In this case the successful type 2 will come from a successful type 1 family. To simplify notation define

$$H_1(t) = \frac{\gamma d}{u_2 s} \frac{t^{d+2}}{(d+1)(d+2)}, \quad \text{and} \quad T_1(t) = \frac{Kt}{Nu_1 s}$$

Since successful type 2 mutations occur at rate $u_2 s$ the desired result follows immediately from

**Lemma 9.1.** Under the assumptions of Theorem 5 if $J/K \to \infty$ then

$$\frac{1}{H_1(t)} \int_0^{T_1(t)} Z^0_1(r) \, dr \to 0 \quad \text{and} \quad \frac{1}{H_1(t)} \int_0^{T_1(t)} Z^*_1(r) \, dr \to 1$$

in probability as $u_1, u_2$ and $s$ go to 0.

**Proof.** The first thing is show that the contribution from unsuccessful type 1 mutations is negligible. The expected total number of unsuccessful type 1 mutations by time $T_1(t)$ is approximately $tK/s$. Therefore by Lemma 6.2 their expected total space-time contribution is $\sim tK\ell(s)/s$. Recalling that $J = 1/u_2\ell(s)$,

$$K \ll \frac{1}{u_2\ell(s)} \quad \text{implies} \quad \frac{K\ell(s)}{s} \ll \frac{1}{u_2 s}$$

The next step is to show that we can assume that the volumes covered by distinct successful type 1 families are disjoint. By the light-cone argument used to derive (6), the volume $A_T$ covered by type 1 families up to time $T$ has

$$E(A_T) = N \int_0^T 1 - \exp(-\lambda_t) \, dt \quad \text{with} \quad \lambda_t = u_1 s \cdot \frac{\gamma d \ell^{d+1}}{(d+1)}$$

while if $B_T$ is the volume covered by at least two successful type 1 families

$$E(B_T) = N \int_0^T 1 - \exp(-\lambda_t)(1 + \lambda_t) \, dt$$
The discussion before (16) implies that $\lambda_{T_1} \to 0$. Since $e^{-x} \geq 1 - x$, we always have $1 - e^{-x}(1 + x) \leq x^2$. In the other direction, if $\delta$ is small and $0 < x < \delta$, $1 - e^{-x} \geq x/2$. Combining our results we see that

$$E(B_{T_1}) \leq 2\lambda_{T_1}E(A_{T_1})$$

so Markov’s inequality implies that overlaps can be ignored.

Recall that Theorem 2 tells us that successful type 1 mutations happen at times $0 < t_1 < t_2 < \ldots$ of a Poisson process with rate $Nu_1s$. Note that if we condition on the number $M$ of mutations that have occurred by time $Kt/Nu_1s$ then $\{t_1, t_2, \ldots t_M\}$ has the same distribution as $\{v_1, v_2, \ldots v_M\}$ where the $v_i$ are independent random variables uniform on $[0, Kt/Nu_1s]$. Let $X_i$ be the space-time volume covered by the type 1 family starting at $v_i$. Since $v_i$ is uniform,

$$EX_i = \frac{\gamma_d c_d^d}{(d + 1)(d + 2)} \cdot \left(\frac{Kt}{Nu_1s}\right)^{d+1}$$

(42)

where $\gamma_d$ is the geometric constant defined in (11). The random sum $S_M = X_1 + \cdots + X_M$ has

$$ES_M = EX_iEM$$

var $(S_M) = EM\text{var} \, X_i + \text{var} \, (M)(EX_i)^2 = EME^2X_i$$

(43)

(44)

since $M$ is Poisson and hence has $EM = \text{var} \, M$. To get an upper bound on $EX_i^2$, suppose the mutation occurs at time 0, and replace the cone by a cylinder to get

$$X_i \leq \gamma_d \left(c_d \frac{Kt}{Nu_1s}\right)^d \frac{Kt}{Nu_1s}$$

Since $EM = Kt$, using (42) it follows that

$$\text{var} \, (S_M) \leq CKt \left(\frac{Kt}{Nu_1s}\right)^{2d+2} = C\left(\frac{ES_M}{Kt}\right)^2$$

Since $K \to \infty$, Chebyshev’s inequality implies $S_M/ES_M \to 1$. Using (42) and (43)

$$ES_M = \frac{\gamma_d c_d^d}{(d + 1)(d + 2)} \cdot \left(\frac{Kt}{Nu_1s}\right)^{d+2} \to \gamma_d \left(c_d \frac{Kt}{Nu_1s}\right)^d \to H_1(t)$$

(45)

The last result gives asymptotics for the volume covered by successful type 1 families, when we have ignored the possibility of further type 2 mutations. Now unsuccessful type 2 mutations occur at rate $u_2$ and have expected space time volume $\ell(s)$. Assumption (A3) implies $u_2\ell(s) \to 0$ so the loss of volume can be ignored. □
9.2  $J \ll K$

In this case the successful type 2 will come from an unsuccessful type 1 family. Let

$$H_2(t) = \frac{\alpha_d t}{u_2 s}, \quad \text{and} \quad T_2(t) = \frac{tJ}{Nu_1 s}.$$ 

As in the previous result it suffices to show

**Lemma 9.2.** Under the assumptions of Theorem 5 if $J/K \to 0$ then

$$\frac{1}{H_2(t)} \int_0^{T_2(t)} Z^0_1(r) \, dr \to 1 \quad \text{and} \quad \frac{1}{H_2(t)} \int_0^{T_2(t)} Z^*_1(r) \, dr \to 0,$$

in probability as $u_1, u_2$ and $s \to 0$.

The second part of the result follows easily from Lemma 9.1. To see this note that $H_i(t) = c_i(d, t)/u_2 s$, while the earlier calculation, see (45), implies

$$E \int_0^{T_2(t)} Z^*_1(r) \, dr \sim (J/K)^{d+2} H_1(t) = o(H_2(t)).$$

To prove the first part of this result we need some information about unsuccessful type 1 families. The probability that a subcritical voter model $\xi^0_t$ with $\lambda = 1 - s$ hits $\epsilon/s$ is

$$\frac{(1 + s) - 1}{(1 + s)^{\epsilon/s} - 1} \approx \frac{s}{e^\epsilon - 1} \approx \frac{s}{\epsilon}$$

(46) Taking $\epsilon = 1$ in the last result, $n = 1/s$ in (39), and noting $a(1/s) = \ell(s)$ we see that type 1 families reach $1/s$ with probability $s$, and their total man-hours before extinction is approximated by

$$\left. \frac{\ell(s)}{s} \left( \int_0^{T_0} Y_s \, ds \right) \right|_{Y_0 = 1}.$$ 

Thus contributions to the mean that come from type 1 families that reach size $1/s$ are $O(\ell(s))$.

To turn the result for the order of magnitude into a limit theorem we need to compute the mean of the contribution of a large family. Let $Y_t$ be the limit process defined in Lemma 6.5.

**Lemma 9.3.**

$$g(x) \equiv E_x \left( \int_0^{T_0} Y_r \, dr \right) = \begin{cases} x^2/2 + x & d = 1 \\ x/\beta_d & d \geq 2 \end{cases}$$
Proof. The infinitesimal generator of $Y$ is

$$Lf = \begin{cases} f''(x) - f'(x) & d = 1 \\ \beta_d x f''(x) - \beta_d x f'(x) & d \geq 2 \end{cases}$$

Intuitively, $g$ is the solution of $Lg = -x$ on $(0, \infty)$ with $g(0) = 0$, but care is needed because $(0, \infty)$ is unbounded and we have only one boundary condition. To be precise, $g = \lim_{m \to \infty} g_m$ where $Lg_m = -x$ in $(0, m)$ and $g_m(0) = g_m(m) = 0$. The limit exists since for fixed $x$, $m \to g_m(x)$ is increasing. From the limit result we see that $g$ can be characterized as the minimal nonnegative solution of $Lg = -x$ on $(0, \infty)$ with $g(0) = 0$, since any other nonnegative solution has $h \geq g_m$ for all $m$.

In $d \geq 2$ the differential equation is

$$g''(x) - g'(x) = 1$$

The solution we want is $g(x) = x/\beta_d$. To check that this is the minimal solution note that if $h$ is another solution then $\delta = g - h$ satisfies $\delta'' - \delta' = 0$ so $\delta = c$ or $\delta(x) = e^x$.

For a direct derivation of $g(x) = x/\beta_d$, note that since 0 is absorbing

$$E_x \left( \int_0^{T_0} Y_r \, dr \right) = \int_0^\infty E_x Y_r \, dr = \int_0^\infty x e^{-\beta_d r} \, dr = x/\beta_d$$

where the second equality follows from $(d/dr) E_x Y_r = -\beta_d E_x Y_r$.

In $d = 1$ we want to solve

$$g''(x) - g'(x) = -x$$

If we guess $g(x) = x^2/2 + x$ then $g'(x) = x + 1$ and $g''(x) = 1$ so we have a solution. Minimality holds for the same reason as before. To see that $g(x) \sim x^2/2$ as $x \to \infty$, note that starting from $x$, $Y_t \approx x - t$ when $t = cx$ and the area under the triangle will be $x^2/2$.

For a direct derivation use Itô’s formula to conclude that

$$Y_t^2/2 - Y_0^2/2 = \int_0^t Y_r \, dY_r + \frac{1}{2} \int_0^t \langle Y \rangle_r$$

$$= \text{martingale} - \int_0^t Y_r \, dr + t$$

since $dY_r = \sqrt{2} dB_r - dr$ and $\langle Y \rangle_r = 2r$. Taking $t = T_0$, the expected value $E_x$, and leaving the reader to check this is legitimate, we have

$$-x^2/2 = -E_x \int_0^{T_0} Y_r \, dr + E_x T_0$$

Since $E_x T_0 = x$ this agrees with the previous computation. \qed
Proof of Lemma 9.2. The number of unsuccessful type 1 mutations by time $tJ/Nu_1s$ is $\sim tJ(1-s)/s$. Dropping the $1-s$ and using (46), the number of “large” families, i.e., those that reach $\epsilon/s$ before they die out will be $\sim tJ/\epsilon$. Using (39) we see that the expected number of man hours in a type I family after it reaches $\epsilon/s$ is

$$\frac{\ell(s)}{s} E_\epsilon \left( \int_0^{T_0} Y_r \, dr \right)$$

In Lemma 9.3 we showed the expected value $\sim \alpha_d \epsilon$ as $\epsilon \to 0$, where $\alpha_1 = 1$ and $\alpha_d = 1/\beta_d$ for $d \geq 2$. Combining our calculations and recalling that $J = 1/\ell(s)u_2$ we see that the expected number of man hours up to time $tJ/Nu_1s$ in the families of unsuccessful type 1 mutations after they reach size $\epsilon/s$ is

$$\sim \frac{t}{\epsilon} \cdot \frac{1}{\ell(s)u_2} \cdot \frac{\ell(s)}{s} \cdot \alpha_d \epsilon = \alpha_d t / u_2 s$$

By repeating the of proof Lemma 2 in I, we see that the contribution from type 1 families before they reach $\epsilon/s$ (including the ones that never do, is of the same order of magnitude as (47) but with a constant that tends to 0 as $\epsilon \to 0$, so they can be ignored. The next step is to argue that if the large families evolved on independent graphical representations the result would follow from the law of large numbers. To do this we note that by (44) the variance of the sum of the Poisson mean $tJ/\epsilon$ families that reach size $\epsilon/s$ by time $tJ/Nu_1s$ is bounded by a quantity that is for $\epsilon \leq 1$

$$\sim \frac{t}{\epsilon} \cdot \frac{1}{\ell(s)u_2} \left( \frac{\ell(s)}{s} \right)^2 C_d^2 \epsilon,$$

using the result of Lemma 6.3. This quantity is $\ll$ the square of the mean since $\ell(s) \ll 1/u_2$. Thus the fact that the total space-time volume is asymptotically $1+o(1)$ times the mean follows from Chebyshev’s inequality.

The last detail is to show that overlaps can be ignored. As discussed at the beginning of this subsection, most of the space-time volume of type 2 families that die out comes from families that reach size $\epsilon/s$ and there will be $\sim J/\epsilon$ of them. Lemma 6.7 implies that these families occupy a region in space time that is of size $O(\ell(s)^{d/2} \cdot \ell(s))$. If we throw $J/\epsilon$ such rectangles into a region of size $N \times J/Nu_1s$ then the probability that one of them will hit the first rectangle is of order

$$\frac{J}{\epsilon} \cdot \frac{\ell(s)^{(d+2)/2}}{J/u_1s} = \frac{u_1s\ell(s)^{(d+2)/2}}{\epsilon} = \rho$$

which goes to 0 by (A0).

Let $U(t)$ be the total man hours of large unsuccessful families until time $T_2(t)$ and $\tilde{U}(t)$ be the total man hours, ignoring any loss from overlaps, of large unsuccessful families until time $T_2(t)$. 

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From the previous calculation, $E[U(t)] \geq (1 - \rho)E[\tilde{U}(t)] = (1 - \rho)\alpha_d t/(u_2 s)$ where $\rho \to 0$ as $s \to 0$. Therefore $E[U(t)] \sim E[\tilde{U}(t)]$ as $s \to 0$. Since $U(t) \leq \tilde{U}(t)$ due to additivity, it follows that $U(t)/\tilde{U}(t) \to 1$, and hence $U(t) \sim \alpha_d t/(u_2 s)$.

\[ \square \]

9.3 $K/(J + K) \to \theta \in (0, 1)$

In this case the successful type 2 may come from a successful or an unsuccessful type 1 family.

$$T_3(t) = \frac{t(J + K)}{N_{u_1 s}}.$$  

As in the two previous cases the desired result follows immediately from

**Lemma 9.4.** Under the assumptions of Theorem 5 if $K/(J + K) \to \theta \in (0, 1)$ then

$$u_2 s \int_0^{T_3(t)} Z^0_1(r) \, dr \to \frac{\gamma_d (t/\theta)^{d+2}}{(d + 1)(d + 2)} \quad \text{and} \quad u_2 s \int_0^{T_2(t)} Z^*_1(r) \, dr \to \frac{\rho_2 \alpha_d}{1 - \theta},$$

in probability as $u_1, u_2$ and $s \to 0$.

This result can be easily proved by combining the last two proofs.
10 Proof of Theorem 1

Lower bound. The proof is similar to that of (2) from Durrett and Zähle (1997), but is simpler because the system is spatially homogeneous. The first step is to recall the duality between the biased voter model and coalescing random walk. For more details see Bramson and Griffeath (1981). Let $\eta_t$ be the coalescing random walk in which:

(i) particles jump at rate 1 to a randomly chosen neighboring site.
(ii) particles give birth at rate $s$ to a particle sent to a randomly chosen neighboring site.
(iii) if a particle lands on an occupied site (due to jump or a birth) then the two coalesce to 1

If we let $\eta_t^B$ be the system starting with $\eta_0^B = B$ and let $\xi_t^A$ be the biased voter model starting from $\xi_0^A = A$ then the two systems satisfy the duality equation:

$$P(\xi_t^A \cap B \neq \emptyset) = P(\eta_t^B \cap A \neq \emptyset)$$

In $d \geq 3$ random walks are transient, so there is positive probability $\gamma_d$ that an offspring will never coalesce with its parent. The idea behind the proof of (2) is to run time at rate $1/s$, scale space by $1/\sqrt{s}$ and show that the rescaled coalescing random walk converges to a branching Brownian motion $\zeta_t$ in which

(i) particles perform independent standard Brownian motions
(ii) give birth to new particles at rate $\beta_d$.

In order to achieve weak convergence we have to remove the particles that coalesce with their parents, because these result in temporary increases of the population that last (on the sped up time scale) for times of order $s$. To do this we ignore the new born particles for time $\tau(s) = \sqrt{s}$ before we assign them mass 1.

In $d = 2$ random walks are recurrent but the probability an offspring does not coalesce with its parent for time $> t$ is

$$\sim 2\pi\sigma^2/(\log t) \quad (48)$$

where $\sigma^2 = 1/d$ is the variance of one coordinate of the random walk. To compensate for the fact that most particles coalesce with their parents we run time at rate $h(s) = (1/s)\log(1/s)$, so that there are $O(1)$ offspring that don’t coalesce with their parents and scale space by $\sqrt{h(s)}$. We ignore the new born particles for time $\tau(s) = 1/\sqrt{\log(1/s)}$ (on the sped up time scale) before we assign them mass 1. The rescaled coalescing random walk converges to a branching Brownian motion $\zeta_t$ in which

(i) particles perform independent standard Brownian motions
(ii) give birth to new particles at rate $2\pi\sigma^2$. 

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Once the convergence to coalescing random walk is established, the lower bound on the speed following from a block construction. Let $I = [-L, L]^d$, let $e_1$ be the first unit vector, and for each $m$ let $I_m = 2Lme_1 + I$. Let $\zeta_t$ be a modification of the branching Brownian motion in which particles are killed when they land outside $[-4L, 4L]^d$. Calculations on page 1760 of Durrett and Zähle (2007) show that for any $\epsilon > 0$, we can pick $K$ large enough so that if there are at least $K$ particles in $I_0$ in $\zeta_0$ then with probability $\geq 1 - \epsilon$ we have $|\zeta(L^2) \cap I_{-1}| \geq K$ and $|\zeta(nL^2) \cap I_m| \geq K$.

For integers $m \geq 0$ and $n$ with $m + n$ even let $\theta(m, n) = 1$ if $|\zeta(nL^2) \cap I_m| \geq K$. The result in the previous paragraph implies that $\eta$ dominates 1-dependent oriented percolation with density $1 - \epsilon$. Let $r_n = \sup \{m : \theta(m, n) = 1\}$. A result in Durrett (1984), see (2) on page 1030, implies that if $\epsilon < 3^{-72}$ then on the set where the oriented percolation does not die out, $\lim \inf_{n \to \infty} r_n/n \geq 1/2$. Recalling the scaling involved in the limit gives the lower bound.

The Upper bound is proved by comparing the dual process with the branching process obtained by ignoring coalescence. The asymptotic shape of a branching random walk was studied in $d$-dimensions by Biggins (1978) after earlier work by him, Kingman, and Hammersley. See the paper cited for references. Here, we consider the speed of spread in the first coordinate so we can project onto the $x$-axis to reduce to a one dimensional process. In this context the results are easy and almost four decades old, but the details are simple and we are concerned with the asymptotic behavior of the constant as $s \to 0$ so we give the details here.

Let $Z_t$ be the branching process at time $t$. The number of particles to the right of $at$ is

$$EZ_t(at, \infty) = e^{st}P(S_t \geq at)$$

where $S_t$ is a random walks that takes steps that are $\pm 1$ with equal probability at rate $(1 + s)/d$ The steps have moment generating function

$$\phi(\theta) = \frac{e^\theta + e^{-\theta}}{2}$$

so the continuous time walk has

$$\psi_t(\theta) = E \exp(\theta S_t) = \exp \left( \frac{(1+s)t}{d} \phi(\theta) - 1 \right)$$

To bound $EZ_t(at, \infty)$ we begin by noting that

$$P(S_t \geq at) \leq e^{-\theta at} \psi_t(\theta)$$

$$= \exp \left( -t \left[ \theta a - \frac{1+s}{d} \phi(\theta) - 1 \right] \right)$$

To optimize over $\theta$ we take the derivative of the term in square brackets to conclude that we should pick $\phi'(\theta_a) = ad/(1 + s)$. Since

$$\phi'(x) = \frac{e^x - e^{-x}}{2} \sim x$$

as $x \to 0$.
we have $\theta_a \sim a d/(1+s)$ as $a \to 0$. Since $\phi(\theta_a) - 1 \sim \theta_a^2/2$, with this choice of $\theta_a$ the term in square brackets is asymptotically

$$\frac{a^2 d}{1 + s} - \frac{1 + s}{d} \frac{a^2 d^2}{2(1 + s)^2} = \frac{a^2 d}{2(1 + s)}$$

In view of (49) we can conclude that $a$ is an upper bound on the asymptotic speed if

$$\frac{a^2 d}{2(1 + s)} > s \quad \text{or} \quad a > \sqrt{\frac{2s}{d}}$$

The last calculation provides the correct upper bound for $d \geq 3$. To prove the result in $d = 2$ we will compare the dual process with a branching random walk, where if multiple offspring land on one site they are all retained. Modifying the construction of Durrett and Zähle (2007) we ignore new born particles for time $1/s$, and add them to the dual only if they have not collided with their parents. To define the branching random walk, we will look at the locations of descendants of the particle at 0 at time $s^{-(1+\epsilon)}$. To make successive pieces independent, particles born at times in $[s^{-(1+\epsilon)} - 1/s, s^{-(1+\epsilon)}]$ are only required to avoid colliding with their parents until time $s^{-(1+\epsilon)}$. With this convention the mean at time $s^{-(1+\epsilon)}$ is

$$\leq \exp \left( s^{-(1+\epsilon)} \cdot \frac{Cs}{\log(1/s)} + \frac{1}{s} \cdot s \right)$$

(50)

At times $m/s^{1+\epsilon}$, each existing particle gives birth to an independent copy of this set translated by their location. Formula (50) implies that the exponential growth rate of the branching random walk has been reduced to $\leq 2C's \log(1/s)$. Repeating the calculation for the case $d = 3$ now gives the desired bound on the speed.
References


