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A STOCHASTIC SPATIAL PROCESS TO MODEL THE PERSISTENCE OF SICKLE-CELL DISEASE

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We consider a gene with two alleles. Allele A is normal, allele S is abnormal. Individuals with genotype SS have a severe disease called sickle-cell disease. Individuals with genotype AS are not sick, and it is thought that they are more resistant to malarial infection than individuals with genotype AA. This could explain why the allele S has persisted in regions where malaria is endemic. We use a stochastic spatial process to test this hypothesis. For our model, we show that if the genotype AS has an advantage over the genotype AA, then the allele S will persist in the population even if the genotype SS is not viable.

1. Introduction. Consider a population in which each individual has one of the three genotypes AA, AS and SS, where A denotes the normal allele and S denotes the abnormal allele. Individuals with genotype AS are not sick. Individuals with genotype SS have a severe form of anemia called sickle-cell disease, and have a relatively low fitness. Even so, the allele S has persisted and reaches frequencies as high as 16 percent in West and Central Africa. It was observed that the geographical areas where sickle-cell disease is highest coincide with the areas where malaria has a high incidence. This led Haldane (1949) to suggest that the heterozygote AS might have an increased resistance to malarial infection. For more on sickle-cell disease, see Cavalli-Sforza and Bodmer (1971). We propose to test Haldane's hypothesis using a stochastic spatial process that models the evolution of the population. For the model we consider, we will show that persistence of the allele S is possible even if the genotype SS is not viable. This is the case for a related disease called thalassemia for which individuals with genotype SS usually do not reach reproductive age.

We assume that individuals can have only genotypes AA and AS (SS is not viable). We think of each site of $\mathbf{Z}^d$, the d-dimensional integer lattice, as being occupied by an individual of type 0 (genotype AA) or type 1 (genotype AS). In order to describe the evolution of our "interacting particle system," we introduce the following notation. The state of the system at time t is denoted

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by η_t, an element of $\{0,1\}^{\mathbf{Z}^d}$. Denote by $\|\cdot\|$ the Euclidean norm on $\mathbf{Z}^d$, and for $x \in \mathbf{Z}^d$ and $\eta \in \{0,1\}^{\mathbf{Z}^d}$, define

$$n_0(x,\eta) = \left|\{y \in \mathbf{Z}^d\colon \|y-x\| = 1 \text{ and } \eta(y) = 0\}\right|,$$
$$n_1(x,\eta) = \left|\{y \in \mathbf{Z}^d\colon \|y-x\| = 1 \text{ and } \eta(y) = 1\}\right|,$$

where $|\cdot|$ denotes cardinality. That is, $n_i(x,\eta)$ is the number of type-i individuals in the configuration η in the neighborhood of x. The evolution of the process depends on two parameters $\lambda > 0$ and $p \in [0,1]$. Each site x, independently of all other sites, changes its type in the configuration η according to the following transition rates:

$$\begin{aligned} &0 \to 1 \quad \text{at rate } \lambda n_1(x,\eta), \\ &1 \to 0 \quad \text{at rate } n_0(x,\eta) + \lambda p n_1(x,\eta). \end{aligned} \tag{1}$$

Thus, parents with genotype 1 have birth rate $2d\lambda$, and parents with genotype 0 have birth rate $2d$. When giving birth, the individual at site x chooses a site y at random from its $2d$ nearest neighbors, and mates with the individual at that site, replacing that individual with its offspring. If both parents are of type 0, the offspring is of type 0 (i.e., the type at y is unchanged). If the parent at site x is type 0 and the parent at site y is type 1, the offspring is type 0. If the parent at site x is type 1, and the parent at site y is type 0, the offspring is type 1. Finally, if both parents are type 1, then the offspring is type 0 with probability p and type 1 with probability $1-p$. Of course, this is a very simple model. In particular, we do not distinguish between sexes.

The fact that two 1's may give birth to a 0 reflects the disadvantage in viability that allele S has. But for $\lambda > 1$, S has an advantage over the allele A in terms of birth rate. Our main concern is to determine whether or not it is possible for the allele S to survive indefinitely in the population. The following result shows that survival is possible for $\lambda > 1$ but not possible for $\lambda \le 1$.

THEOREM 1. (a) *Assume that* $\lambda > 1$. *Then there is* $p_c > 0$ *such that, if* $p < p_c$, *then the* 1*'s survive. That is, in any dimension* $d \ge 1$, *there is a stationary distribution for* η_t *that puts positive mass on configurations with infinitely many* 1*'s.*

(b) *Assume that* $\lambda \le 1$ *and* $p > 0$. *Then the* 1*'s die out. That is, in any dimension* $d \ge 1$, *for every initial configuration* η_0 *and site* x, *there is a random time* T_x *such that* $\eta_t(x) = 0$ *for all* $t \ge T_x$. *For* $\lambda = 1$, $P(\eta_t(x) = 1) \to 0$ *exponentially fast.*

In terms of our original motivation, (a) shows that the allele S can survive for $p < p_c$ if the genotype AS has even a small advantage over AA. Unfortunately, our method of proof does not give useful bounds on p_c. Not surprisingly, (b) shows that if AS has no advantage over AA, then the allele S disappears.

Observe that if we set $p = 0$, then the rates given by (1) specify the interacting particle system known as the *biased voter model*. [See Durrett (1988), Chap. 3 for a survey of this model.] Interestingly, our theorem shows that this new model has the same critical value as the biased voter model: the 1's may survive for $\lambda > 1$ and die out for $\lambda < 1$. Unlike the biased voter model, our sickle-cell model is not monotone in any apparent way. For instance, the density of 1's at time t is not a monotone function of the initial density of 1's. The standard coupling does not show any monotonicity in p. However, as we will show later, the biased voter model ($p = 0$) can be coupled to η_t with any $p > 0$ in such a way that the biased voter model has more 1's at any time.

For $\lambda > 1$, Theorem 1(a) shows that the 1's can survive if p is small enough. It is natural to ask whether or not increasing p sufficiently will result in extinction of the 1's. In the next result we show, under some restrictions, that this is the case.

THEOREM 2. *Assume that* $d = 1$ *and* $\lambda \in (1, 2)$. *Then, if* $p > (\lambda - 1)/\lambda$, *the* 1*'s die out. That is, for any initial configuration and every site* x *in* Z, *there is a random time* T_x *such that* $\eta_t(x) = 0$ *for all* $t \geq T_x$ *with probability* 1.

We suspect that the conclusion of Theorem 2 holds for any $d \geq 1$ and all $\lambda > 1$, but we are only able to prove a weaker version of this; see Theorem 3 below. Furthermore, Theorem 1(a) and Theorem 2 suggest that, at least for $d = 1$ and $\lambda \in (1, 2)$, there is a "phase transition" in the parameter p, with survival of 1's for small p and extinction of 1's for large p. Unfortunately, lack of monotonicity prevents us from proving that there is a $p^* \in (0, 1)$ with survival of the 1's for all $p < p^*$ and extinction of 1's for all $p > p^*$.

We now compare our results to predictions of a "mean field" [as in Levin and Durrett (1996)] version of our model. Let us start at time 0 with a translation-invariant distribution, with a positive density of both 0's and 1's. Then at all times t, the distribution of $\eta_t(x)$ is translation invariant, and $u(t) = P(\eta_t(x) = 1)$ does not depend on x. From the dynamics (1), it is straightforward to derive the differential equation

$$\begin{aligned} u'(t) = \lambda \sum_{y:\, y \sim x} P(\eta_t(x) = 0,\, \eta_t(y) = 1) - \sum_{y:\, y \sim x} P(\eta_t(x) = 1,\, \eta_t(y) = 0) \\ - \lambda p \sum_{y:\, y \sim x} P(\eta_t(x) = \eta_t(y) = 1), \end{aligned}$$

where $y \sim x$ means that y is one of the $2d$ nearest neighbors of x. If we assume that the above probabilities factor, and make use of translation invariance, we obtain the equation

$$u' = 2d\lambda u(1 - u) - 2du(1 - u) - 2d\lambda p u^2,$$

or

$$\frac{u'}{u^2} = 2d\frac{\lambda - 1}{u} - 2d(\lambda - 1 + \lambda p). \tag{2}$$

For $\lambda \neq 1$, setting $v = 1/u$ transforms (2) into

$$v' = -2d(\lambda - 1)v + 2d(\lambda - 1 + \lambda p),$$

which gives

$$v(t) = 1 + \frac{\lambda p}{\lambda - 1} + e^{-2d(\lambda - 1)t}\left[v(0) - 1 - \frac{\lambda p}{\lambda - 1}\right]. \tag{3}$$

Suppose first that $\lambda < 1$. Then, since $v(0) = 1/u(0) > 1$, it follows from (3) that $u(t) = 1/v(t) \to 0$ as $t \to \infty$. If $\lambda > 1$, then (3) implies that

$$\lim_{t \to \infty} u(t) = \frac{\lambda - 1}{\lambda - 1 + \lambda p}. \tag{4}$$

In the critical case $\lambda = 1$, the solution of (2) is

$$u(t) = \frac{u(0)}{1 + 2d\lambda p t u(0)},$$

and we see that $u(t)$ tends to 0 at rate $1/t$. This contrasts with the conclusion of Theorem 1b, in which there is exponential convergence to 0.

We note that the limit in (4) is strictly positive for all $\lambda > 1$ and all $p > 0$. Thus, we do not see the "phase transition" in p that holds for the spatial model in dimension 1 [Theorems 1(a) and 2]. This is a rather unusual phenomenon and one might suspect that this happens only for the model in $d = 1$. As the following theorem shows, this is not so.

THEOREM 3. *In any* $d \geq 1$ *and for any* $\lambda > 0$, *there is* p_c' (*possibly larger than* 1) *such that, if* $p > p_c'$, *then the* 1'*s die out.*

Of course, the interpretation of the model changes if we allow $p > 1$ (note that the rates (1) still make sense in this case). One may think of the model with $p > 1$ as a demographic model (1 represents an individual, 0 represents a vacant site), where crowding is taken into effect.

2. Proof of Theorem 1. Following Harris (1972), we give a "graphical" construction of η_t and some auxiliary processes. Let $\{S^{x,y}, T^{x,y}: x, y \in \mathbf{Z}^d, \|x - y\| = 1\}$ be independent Poisson processes, where the intensities of $S^{x,y}$ and $T^{x,y}$ are 1 and λ, respectively. In addition, let $\{U_n(x, y), x, y \in \mathbf{Z}^d, \|x - y\| = 1, n \geq 1\}$ be independent Bernoulli random variables with parameter p. At each arrival time of $S^{x,y}$, if there is a 0 at x and a 1 at y, then the 1 at y is replaced by a 0. At the nth arrival time of $T^{x,y}$, if there is a 1 at x and a 0 at y, then the 0 at y is replaced by a 1. If there is a 1 at x and a 1 at y, and $U_n(x, y) = 1$, then the 1 at y is replaced by a 0. Given an initial configuration η_0, this gives a construction of our sickle-cell process η_t. For

$A \subset \mathbf{Z}^d$, η_t^A will denote the process with initial state $\eta_0^A = 1_A$. It will be convenient to regard η_t as a set-valued process by identifying η_t with $\{x\colon \eta_t(x) = 1\}$.

Using the same Poisson processes, we construct another process which we denote ξ_t. The transition rules for ξ_t are the same as those for η_t, except that the rule involving the $U_n(x, y)$ is not used (so a 1 cannot kill a 1 in ξ_t). Thus, ξ_t is the biased voter model, and is the same process as η_t when $p = 0$. For $\lambda > 1$, $P(|\xi^{\{0\}}| > 0, \forall t) > 0$. It is clear from the construction that for any p, if $\eta_0 \subset \xi_0$, then, with probability 1, $\eta_t \subset \xi_t$ for all times t.

Proof of Theorem 1(a). The basic idea is to show that the sickle-cell process η_t for $p = 0$ dominates, in a precise sense, a supercritical oriented percolation process. This will imply, by continuity, that there is a $p_c > 0$ such that this domination also holds for all $p < p_c$. Furthermore, whenever this domination holds, η_t has a stationary distribution which puts positive mass on configurations with infinitely many 1's. We follow the treatment of this "renormalization" method, which was introduced in Bramson and Durrett (1988), given in Chapter 4 of Durrett (1995).

Fix $\lambda > 1$. For finite, positive L and ρ, let $\xi_t^{L,\rho}$ denote the biased voter model, modified so that no transitions from a 0 to a 1 are allowed at any site outside of $B(\rho L)$, and which has initial state $1_{B(L)}$. Here $B(K) = [-K, K]^d \cap \mathbf{Z}^d$. We will prove the following: there exists a finite constant $\rho \geq 3$ such that, for $\delta > 0$, there exist finite positive constants L and T such that

$$P\big(\xi_T^{L,\rho}(x) = 1 \text{ for all } x \in B(3L)\big) > 1 - \delta. \tag{5}$$

Since $B(\rho L) \times [0, T]$ is a bounded region of space-time, we may choose $p_c > 0$ such that, for all $p < p_c$, (5) holds with $\eta_T^{L,\rho}$ replacing $\xi_T^{L,\rho}$. By Theorem 4.4 of Durrett (1995), it follows that, for $p < p_c$, η_t must have a stationary distribution which puts positive mass on configurations with infinitely many 1's.

To prove (5), we need some results from Bramson and Griffeath (1980, 1981). In these papers, an asymptotic shape theorem for the biased voter model is proved. That is, Theorem 1 of Bramson and Griffeath (1980) states that, for $\lambda > 1$, there is a norm on $\mathbf{R}^d$, with unit ball B, such that, for all $\varepsilon > 0$,

$$\begin{aligned} P\big((1-\varepsilon)tB \cap \mathbf{Z}^d \subset \xi_t^{\{0\}} \subset (1+\varepsilon)tB \cap \mathbf{Z}^d \\ \text{for all large } t \,\big|\, |\xi^{\{0\}}| > 0, \forall t\big) = 1. \end{aligned} \tag{6}$$

In order to prove (5), we need two results used in the proof of the shape theorem (6).

The first result we need is (19b) in Bramson and Griffeath (1980), which shows that $\xi_t^{B(L)}$ must grow at a certain minimal rate. The result says that there are finite positive constants r, C_1, α_1 and L_0 such that, for all $L \geq L_0$,

$$P\big(B(rt) \subset \xi_t^{B(L)}, \forall t \geq 0\big) \geq 1 - C_1 \exp(-\alpha_1 L). \tag{7}$$

Since $B(rt) \supset B(3L)$ for $t \geq 3L/r$, it follows from (7) that, for $T = 3L/r$,

$$P\big(B(3L) \subset \xi_T^{B(L)}\big) \to 1 \quad \text{as } L \to \infty. \tag{8}$$

The second result we need is a special case of Lemma 1 of Bramson and Griffeath (1980), which shows that $\xi_t^{B(L)}$ cannot grow too fast. The result says that there are finite positive constants R, c_2, C_2, α_2 and L_0 such that, for all $L \geq L_0$ and all $t \geq 0$,

$$P\big(\xi_s^{B(L)} \not\subset B(Rt + c_2 L),\ \forall s \leq t\big) \leq C_2 \exp(-\alpha_2 t). \tag{9}$$

If we set $\rho = (c_2 + (3R/r)) \vee 3$, then (9) implies that, for $T = 3L/r$, as $L \to \infty$,

$$P\big(\xi_s^{B(L)} \not\subset B(\rho L),\ \forall s \leq T\big) \to 0 \quad \text{as } L \to \infty. \tag{10}$$

Clearly, (8) and (10) imply (5). □

Proof of Theorem 1(b). Consider first the case $\lambda < 1$ and $p > 0$. Then, regardless of the initial condition, η_t must have infinitely many 0's at time $t = 1$ with probability 1. (Each 0 at time zero has positive probability of remaining a 0 for one time unit. Hence, if there are infinitely many 0's at time 0, there will be infinitely many at time 1. On the other hand, each nearest-neighbor pair of 1's has positive probability of creating, before time 1, a 0 that will survive until time 1. If there are infinitely many such pairs at time 0, there will be infinitely many 0's at time 1.) Now we construct a new process $\bar{\xi}_t$, $t \geq 1$. We set $\bar{\xi}_1 = \eta_1$, and then, for $t > 1$, we let $\bar{\xi}_t$ follow the same transition rules as ξ_t. Thus, $\bar{\xi}_t$, $t \geq 1$, is a biased voter model, but now, since $\lambda < 1$, 0's are the favored type. Furthermore, $\eta_t \subset \bar{\xi}_t$ for $t \geq 1$.

The Bramson–Griffeath shape theorem (6) still applies, but with the role of 1's and 0's reversed. That is, there is an $r > 0$ such that each 0 in $\bar{\xi}_1$ has positive probability of creating a process of 0's that contains, for all t sufficiently large, a box of side $2r(t-1)$. Since there are infinitely many 0's in $\bar{\xi}_1$, there is probability 1 that some 0 will create such a process. That means that, for each site x, $\bar{\xi}_t(x)$ will be 0 with probability 1 for all large t. Since $\eta_t \subset \bar{\xi}_t$, the same conclusion holds for η_t.

Now we consider the critical case $\lambda = 1$ and $p > 0$. To facilitate our proof, we give a different construction of η_t and ξ_t. Let $\{V^{x,y}, W^{x,y}\colon x, y \in \mathbf{Z}^d, \|x - y\| = 1\}$ be independent Poisson processes, where the intensities of $V^{x,y}$ and $W^{x,y}$ are 1 and p, respectively. We define ξ_t as follows. At each arrival time of $V^{x,y}$, the value at site y is replaced by the value at site x. We use the same transition rules in defining η_t, but also, at the arrival times of $W^{x,y}$, if there is a 1 at both x and y, the 1 at site y is changed to a 0. It is easy to see that ξ_t is the basic voter model [see Durrett (1988), Chapter 3 or Liggett (1985), Chapter V], η_t is our sickle-cell process, and if $\eta_0 \subset \xi_0$, then, with probability 1, for all times t, $\eta_t \subset \xi_t$.

For a given site z and time t, the value of $\xi_t(z)$ is easily determined by reading the Poisson processes $V^{x,y}$ backwards in time from time t [Durrett (1988)]. We may define a random walk Z_s, $s \leq t$, such that $Z_0 = z$, Z_s is independent of the arrivals in the $V^{x,y}$ in $[0, t-s]$, completely independent of the $W^{x,y}$, and $\xi_t(z) = \xi_0(Z_t)$. We will show that the path of Z_s is "exposed" to many events determined by the $W^{x,y}$ Poisson processes that will, with high probability, prevent the occurrence of $\eta_t(z) = 1$. Here are the details.

Let $V_n^{x,y}$ denote the nth arrival time of $V^{x,y}$, and let $W_n^{x,y}$ denote the nth arrival time of $W^{x,y}$. For times $t \geq 1$ and sites z, define

$$\tau(z,t) = \sup\{V_n^{y,z}\colon \|y-z\| = 1,\ V_n^{y,z} \leq t\}.$$

We put $\tau = \infty$ if the event is empty. On the event $\{\tau < t,\ \tau = V_n^{y,z}\}$, put $\bar{y} = y$, so that $\bar{y}$ is the random site that last influences z before time t using only the $V^{x,y}$ Poisson processes. Now define

$$\sigma(z,t) = \inf\{W_k^{\bar{y},z}\colon W_k^{\bar{y},z} > \tau\}.$$

That is, σ is the first time after τ that an arrival in $W^{\bar{y},x}$ can cause the 1 at x to be replaced by a 0. For $t \geq 1$ and site z, we define the event

$$\Gamma(z,t) = \begin{cases} t-1 < \tau(z,t) < t, \\ \sigma(z,t) < t, \\ \{V_l^{x,\bar{y}},\ l \geq 1\} \cap (\tau(z,t), \sigma(z,t)] = \varnothing,\ \forall x, \\ \{W_l^{x,\bar{y}},\ l \geq 1\} \cap (\tau(z,t), \sigma(z,t)] = \varnothing,\ \forall x. \end{cases}$$

The event $\Gamma(z,t)$ is independent of the arrivals during $[0, t-1]$ in the $V^{x,y}$ and $W^{x,y}$ Poisson processes. Furthermore, $\eta_t(z) = 0$ on $\Gamma(z,t)$, since the 1 at $\bar{y}$ kills the 1 at site z just before time t, and $\varepsilon = P(\Gamma) > 0$.

Let $[t]$ denote the greatest integer less than or equal to t. For $i = 0, 1, \dots, [t]-1$, define

$$\Gamma_i = \Gamma(Z_i, T-i).$$

Then, by construction, the events Γ_i are independent, $P(\Gamma_i) = \varepsilon$ for each i and $\eta_t(z) = 0$ if any of the Γ_i occur. Thus, no matter what the initial state η_0 is,

$$P(\eta_t(z) = 1) \leq (1-\varepsilon)^{[t]-1}.$$

This shows that $P(\eta_t(z) = 1)$ tends to zero exponentially fast, and it is a standard argument to show that there must be a last (random) time that $\eta_t(z)$ can be 1. □

3. Proof of Theorem 2. In this proof we follow Andjel and Schinazi (1996). Recall that $d = 1$. For a given initial configuration η_0, we will construct a family of sickle-cell processes η_t^j, $j \in \mathbf{Z}$, such that at all times t, $\eta_t \subset \bigcup_j \eta_t^j$. Then, we will obtain exponential estimates on the growth of the η_t^j which will imply that, for any site x, $\eta_t(x)$ must be 0 for all large times t.

Fix an arbitrary initial configuration η_0. Let

$$f(0) = \inf\{x \geq 0\colon \eta_0(x) = 1\}$$

and

$$f(j) = \inf\{x > f(j-1)\colon \eta_0(x) = 1\} \quad \text{for } j \geq 1.$$

Similarly, let

$$f(-1) = \sup\{x < 0\colon \eta_0(x) = 1\}$$

and

$$f(j) = \sup\{x < f(j+1)\colon \eta_0(x) = 1\} \quad \text{for } j \le -2.$$

With the same Poisson processes and random variables used in our original construction of η_t, let η_t^j denote the sickle-cell process with $\eta_0^j = \{f(j)\}$. Let

$$r_t^j = \sup\{x\colon \eta_t^j(x) = 1\}, \qquad l_t^j = \inf\{x\colon \eta_t^j(x) = 1\},$$

and $B_t^j = [l_t^j, r_t^j] \cap \mathbf{Z}^d$. We note that, by construction,

$$\eta_t \subset \bigcup_j \eta_t^j$$

(strict inclusion may hold because a 1 may kill a 1), and

$$\eta_t \subset \bigcup_j B_t^j. \tag{11}$$

We turn now to an analysis of the B_t^j. The process r_t^j jumps to the right one unit with rate λ since there is a 0 to the right of r_t^j (i.e., $\eta_t(r_t^j + 1) = 0$). On the other hand, r_t^j jumps to the left at least one unit with rate 2, if both r_t^j's nearest neighbors are 0's, or rate $1 + \lambda p$, if r_t^j's nearest neighbors are a 0 and a 1. Thus, if

$$\lambda < \min(2, 1 + \lambda p),$$

then r_t^j can be coupled to a random walk with a drift to the left. Consequently, for

$$\lambda \in (1,2) \quad \text{and} \quad p > \frac{\lambda - 1}{\lambda}, \tag{12}$$

standard random walk estimates imply that there exist finite, positive constants C and γ such that

$$P\big(\exists t \ge 0\colon r_t^j = f(j) + k\big) \le Ce^{-\gamma k}. \tag{13}$$

By symmetry, (12) also implies

$$P\big(\exists t \ge 0\colon l_t^j = f(j) - k\big) \le Ce^{-\gamma k}. \tag{14}$$

Furthermore, since r_t^j has a drift to the left, and l_t^j has a drift to the right, each B_t^j will be empty with probability 1 for all large t.

Now fix $x \in Z$. If j is such that $x > f(j)$, then by (13),

$$P\big(\exists t \ge 0\colon x \in B_t^j\big) = P\big(\exists t \ge 0\colon r_t^j = x\big) \le Ce^{-\gamma(x - f(j))}.$$

Similarly, if j is such that $x < f(j)$, then (14) implies

$$P\big(\exists t \ge 0\colon x \in B_t^j\big) = P\big(\exists t \ge 0\colon l_t^j = x\big) \le Ce^{-\gamma(f(j) - x)}.$$

These inequalities imply that

$$\sum_j P\big(\exists t \ge 0\colon x \in B_t^j\big) < \infty.$$

By the Borel–Cantelli lemma, with probability 1, there exists a positive integer J such that, for all $|j| > J$ and all times $t \geq 0$, $x \notin B_t^j$. But this fact and (11) imply that if $\eta_s(x) = 1$, then $x \in B_s^j$ for some $|j| \leq J$. But each of the B_s^j, $|j| \leq J$, will eventually be empty. Let T_x be the first time at which all B_s^j, $|j| \leq J$, are empty. Thus, $\eta_s(x) = 0$ for all $s \geq T_x$. □

4. Proof of Theorem 3. For this result, p can be any positive number. Because of that, the construction given in Section 2 above does not apply, so we give another graphical construction. Let $\{S^{x,y}, T^{x,y}, V^{x,y}\colon x, y \in \mathbf{Z}^d, \|x - y\| = 1\}$ be independent Poisson processes, where the intensities of $S^{x,y}$, $T^{x,y}$ and $V^{x,y}$ are 1, λ and λp, respectively. At each arrival time of $S^{x,y}$, if there is a 0 at x and a 1 at y, then the 1 at y is replaced by a 0. At each arrival time of $T^{x,y}$, if there is a 1 at x and a 0 at y, then the 0 at y is replaced by a 1. At each arrival time of $V^{x,y}$, if there is a 1 at x and a 1 at y, then the 1 at y is replaced by a 0. Given an initial configuration η_0, this gives a construction of the process η_t for any $p > 0$.

Let A be a finite subset of $\mathbf{Z}^d$. We will show that the following holds for large p. There exists an a.s. finite (random) time T_A such that the space-time region $A \times [T_A, \infty)$ ($\subseteq \mathbf{Z}^d \times [0,\infty)$) contains no 1's. We prove this in the case $d = 2$; no new difficulties emerge when $d \geq 3$ or $d = 1$.

The following type of argument was introduced by Durrett and Schinazi (1993). We define two space–time regions:

$$\mathscr{A} = [-2L, 2L]^2 \times [0, 2T], \qquad \mathscr{B} = [-L, L]^2 \times [T, 2T],$$

where L and T are integers to be chosen later. Define $\mathscr{C}$ to be the part of the "boundary" of the box $\mathscr{A}$:

$$\mathscr{C} = \{(m, n, t) \in \mathscr{A}\colon |m| = 2L \text{ or } |n| = 2L \text{ or } t = 0\}.$$

We will compare the process η_t to a certain dependent percolation process on the set $\mathscr{S} = \mathbf{Z}^2 \times \mathbf{Z}_+$, where $\mathbf{Z}_+ = \{0, 1, 2, \dots\}$. We say that the site (k, m, n) in $\mathscr{S}$ is *wet* if there are no 1's in the box $(kL, mL, nT) + \mathscr{B}$, *regardless of the states of sites in the boundary* $(kL, mL, nT) + \mathscr{C}$. Note that the event $\{(k, m, n)$ is wet$\}$ depends only on the existence (or not) of paths of 1's within $\mathscr{A}$. We require this uniformity on the states of the boundary in order to ensure that the percolation process in $\mathscr{S}$, although dependent, has an interaction with only finite range. Sites which are not wet are called *dry*.

Let $\varepsilon > 0$. We will show that there exist L, T and $p_c' > 0$ such that

$$P((k, m, n) \text{ is dry}) < \varepsilon \quad \text{if } p > p_c'. \tag{15}$$

We start by showing that the probability estimate above holds for the case $p = \infty$. Then, using a continuity argument, we will deduce that it must hold for sufficiently large p. By translation-invariance, it suffices to consider the site $(0, 0, 0) \in \mathscr{S}$.

Assume that $p = \infty$. For this process, as soon as two 1's become nearest neighbors, one of them is selected at random (each with probability 1/2), and instantly replaced by a 0. In particular, each time a 1 gives birth to a new 1, the parent or the child is immediately replaced by a 0. Let η_t^y be the process starting from a single 1 at site y at time 0, and note that

$$\eta_t \subset \bigcup_{y \in \eta_0} \eta_t^y.$$

We let

$$\tau^y = \inf\{t > 0\colon \eta_t^y(x) = 0 \text{ for all } x\},$$

and claim that

$$P(\tau^y > t) = e^{-4t}. \tag{16}$$

This is so because at all times t, η_t^y has at most one 1, and the transition rate for that 1 to become a 0 is always 4 ($2d$ in $d = 2$).

Next, we claim that there are finite positive constants C and γ such that

$$P(\eta_t^y(x) = 1 \text{ for some } t \ge 0) \le Ce^{-\gamma\|y-x\|}. \tag{17}$$

To see this, we start with the inequality

$$\begin{aligned} &P(\eta_t^y(x) = 1 \text{ for some } t \ge 0) \\ &\quad \le P(\tau^y > c\|y-x\|) \\ &\qquad + P(\tau^y \le c\|y-x\|,\ \eta_t^y(x) = 1 \text{ for some } t \ge 0), \end{aligned} \tag{18}$$

where c is a constant to be chosen later. Up to time τ^y, the process η_t^y has exactly one 1. For this 1 to be at x, we need at least $\|y-x\|$ successive births, and these "births" occur at rate 4λ. Let X denote a Poisson random variable with mean $4\lambda c\|y-x\|$. Then

$$P(\tau^y \le c\|y-x\|,\ \eta_t^y(x) = 1 \text{ for some } t \ge 0) \le P(X \ge \|y-x\|).$$

We choose c so that $4\lambda c < 1/2$. By a standard exponential estimate, there are finite positive constants C' and γ' such that

$$P(X \ge \|y-x\|) \le C'e^{-\gamma'\|y-x\|}.$$

It follows from this inequality, (16) and (18) that (17) must hold for suitable C and γ.

Suppose now that $(x,t) \in \mathscr{B}$ is such that $\eta_t(x) = 1$. Then, there must exist some point $(x',t') \in \mathscr{C}$ such that (a) $\eta_{t'}(x') = 1$ and (b) there exists a "chain" of 1's from (x',t') to (x,t) lying entirely within $\mathscr{A}$. Such (x',t') must lie either on the "bottom" of $\mathscr{C}$ (i.e., have $t' = 0$), or on one of its "sides" (i.e., have $t' \ne 0$). In the former case, the process $\eta_t^{x'}$ originating at (x',t') must have survived at least time T (i.e., $\tau^{x'} > T$) before it reaches $\mathscr{B}$. In the latter case, it must create a 1, at some time, a distance at least L away from its starting point. It follows from (16) and (17) that

$$P((0,0,0) \text{ is dry}) \le 8CT(4L+1)e^{-\gamma L} + (4L+1)^2e^{-4T}.$$

We may set $T = L$, and take L sufficiently large so that

$$P((0,0,0) \text{ is dry}) \leq \varepsilon/2 \quad \text{for } p = \infty.$$

For fixed λ, since $\mathscr{A}$ is a bounded space–time region, it is easy to see that, for finite p, the above probability converges as $p \to \infty$ to the probability for $p = \infty$. Thus, there is a finite p'_c such that (15) holds.

We now position oriented edges between sites in $\mathscr{L}$ in order to obtain a percolation model. Let $\mathscr{A}(k, m, n) = (kL, mL, nT) + \mathscr{A}$. For each pair $(k, m, n), (x, y, z) \in \mathscr{L}$, we draw an oriented edge from (k, m, n) to (x, y, z) if and only if $n \leq z$ and $\mathscr{A}(k, m, n) \cap \mathscr{A}(x, y, z) \neq \emptyset$. The wet sites on the ensuing directed graph constitute a (dependent) percolation model. There exists an absolute constant K, depending only on the number d of dimensions (here, $d = 2$), such that any set of sites of $\mathscr{L}$ have independent states whenever the graph-theoretic distance between any pair of such sites exceeds K. Furthermore, there exist positive finite constants δ, ν such that the following two statements hold. First, the number of self-avoiding oriented paths on $\mathscr{L}$, having length r and any given endpoint, is no larger than δ^r. Second, any self-avoiding path of length r contains at least νr sites, the distance between any pair of which exceeds K.

Let $x \in \mathbf{Z}^2$ and let T_x be the supremum of all times t such that $\eta_t(x) = 1$. We claim that T_x is a.s. finite if p is sufficiently large. Suppose that $T_0 > TM$. Then there exists m $(\geq M - 1)$ with the property that $(0, 0, m)$ is the endpoint of an oriented dry path of $\mathscr{L}$ whose other endpoint has the form $(x, y, 0)$ for some $x, y \in \mathbf{Z}^2$. By the above remarks,

$$P(T_0 > TM) \leq \sum_{m \geq M-1} \sum_{r \geq m} \delta^r \kappa^{\nu r}, \tag{19}$$

where $\kappa = P((0,0,0) \text{ is dry})$. By (15), we may choose p'_c such that the right-hand side of (19) is finite whenever $p > p'_c$ and $M \geq 2$. When this holds, the right-hand side approaches 0 as $M \to \infty$, implying that T_0 is a.s. finite as required. □

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