

Maximum geographic range of a mutant allele considered as a subtype of a Brownian branching random field

(population genetics/selective neutrality/migration/mutation)

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ABSTRACT A rare allelic type is modeled as a field of individuals diffusing independently in d -dimensional space ($d = 1, 2, \dots$), in which individuals are replaced by random numbers of offspring at a constant rate. In an infinite-allele model with selectively identical alleles, the offspring distribution would have mean $1 - u$, in which u is the mutation rate; otherwise mean $(1 - u)w$, in which w is the relative fitness of the allele. Let $p(x)$ be the probability that some descendent of an individual initially at zero diffuses unilaterally as far as x ($d = 1$), or else the probability that some descendent of an individual at x diffuses within $a > 0$ of the origin ($d \geq 2$). A nonlinear differential equation is found for $p(x)$ that is solvable for $d = 1$ and related to Emden's equation for $d \geq 2$. For $p(x) \geq 10^{-4}$ and $u \leq 10^{-5}$, genetic drift is more important than mutation in the behavior of $p(x)$ ($d = 1$). If $u = 0$ and $w = 1$, $p(x) \sim C/x^2$ as $x \rightarrow \infty$ for $d \leq 3$. As a mathematical application, it is shown that if the initial distribution is uniform Poisson, a bounded open set K is visited by individuals in the field at arbitrarily large times if $d \geq 2$ but not if $d = 1$.

1. Introduction

Assume we have a population that is subject to mutation at a particular genetic locus. Each new mutant is considered to be of a distinguishable type wholly new to the population. If the total population is roughly stable and the mutants are selectively equivalent, each new allelic type will eventually die out. This will happen not only because of genetic drift, but also because the mutation rate (with no return mutation) makes any subtype effectively disadvantageous. A natural question is how far geographically will members of a new allelic type spread before the entire family becomes extinct, and what are the relative effects of genetic drift and mutation on the distribution of maximum range.

We model this situation by assuming that individuals diffuse independently of one another in d -dimensional space R^d ($d = 1, 2, \dots$) according to Brownian motion with rate σ , in which σ is independent of type. In any time interval of length dt , each individual, with probability dt , dies and is replaced by a random number of offspring (with zero offspring if the individual dies childless). The offspring diffuse away from the location of the parent and begin dying and reproducing themselves, and so forth. Selective neutrality is expressed by the offspring distribution having mean $1 - u$, in which u is the mutation rate. If the mutant allele has relative fitness w instead of being selectively neutral ($w = 1$), the offspring distribution has mean $(1 - u)w$.

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We are interested in the probability

$$p(x) = \text{probability that an allelic type initiated by a mutation at zero has some descendent that diffuses as far as } x \text{ (unilaterally)} \quad [1.1]$$

in one dimension ($d = 1$), and in higher dimensions

$$p(x) = \text{probability that an allelic type initiated at } x \text{ has some descendent that diffuses within distance } a > 0 \text{ of the origin.} \quad [1.2]$$

The condition $a > 0$ in [1.2] is necessary because higher-dimensional Brownian motion, with probability 1, never hits a preassigned point.

The assumptions of the model will be satisfied if there is no density-dependent population regulation acting on the subtype, and if the subtype is sufficiently rare so that essentially all mutant genes are carried in heterozygote form. See refs. 1-3 for discussions of branching process models in genetics in general, and ref. 4 for branching process models with migration structure.

In what follows, distances are scaled so that $\sigma = 1$; i.e., x^2 is in terms of the variance of migration per unit time (in higher dimensions, each component has unit variance per unit time). We also assume the model is not a pure death process; i.e., more than one offspring at a death is possible, and the offspring distribution has at least a finite third moment.

In one dimension, we show

$$p(x) \sim \frac{12u}{\nu^2} \frac{\exp(-x\sqrt{2u})}{[C(u,x)\sqrt{u} + 1 - \exp(-x\sqrt{2u})]^2} \quad [1.3]$$

uniformly in x ($x \geq 0$) for small u under some mild assumptions about the dependence of the offspring distribution on u . Here ν^2 is the variance of the offspring distribution, and $C(u,x)$ is a bounded function of u and x . In [1.3], \sim means that the limit of the ratio is 1, here as $u \rightarrow 0$ uniformly in x . In particular

$$p(x) \sim C_1 u e^{-x\sqrt{2u}} \quad [1.4]$$

for small u if $x\sqrt{2u} \geq \epsilon > 0$, in which $C_1 = C_1(u,x)$ is bounded, and

$$p(x) \sim \frac{6}{\nu^2 x^2} \quad [1.5]$$

as $x \rightarrow \infty$ for $u = 0$ or $x\sqrt{u} \rightarrow 0$. If the mutant allele is deleterious rather than neutral, [1.3]-[1.5] hold with u replaced by

$$\bar{u} = 1 - (1 - u)w = u + s - us, \quad w = 1 - s. \quad [1.6]$$

The estimate 1.5 is more relevant for neutral alleles, because

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if x is large and u is small, the assumptions of the model will tend to break down.

For Moranian offspring distributions—i.e., no offspring with some probability and two offspring with the complementary probability—we have the exact solution ($x \geq 0, u = 0$)

$$p(x) = \frac{6}{(x + \sqrt{6})^2} \quad [1.7]$$

in one dimension, and an exact solution similar to [1.3] for $u > 0$ (see §3 below). The values in Table 1 were calculated from these exact solutions. As the table indicates, the descendants of an individual at x (including itself) have about a 4% chance of diffusing 10σ in a particular direction from x before the entire family becomes extinct, due to genetic drift alone. Indeed, the mutation rate $u = 10^{-5}$ changes $p(x)$ by less than 1% for $x \leq 75$ and less than 10% for $x \leq 250$ ($p \approx 10^{-4}$). The last column in the table refers to deleterious alleles (see [1.6]).

A higher-dimensional model in which only one coordinate is considered reduces to the one-dimensional case. Thus the distribution of the maximum increase or decrease in latitude or longitude by the descendants of an individual is also given by [1.3]–[1.7]. In general in higher dimensions, let $x = \|x\|$ be the distance from the origin scaled as before, and fix $u = 0$. Then as $x \rightarrow \infty$

$$p(x) \sim \frac{2(4-d)}{\nu^2 x^2} \text{ (dimensions } d \leq 3), \quad [1.8]$$

and $p(x) \sim 1/[(\nu x)^2 \log(\nu x)]$ if $d = 4$ (see §4 below). Note the lack of dependence on $a > 0$ (see [1.2]) and the weak dependence on dimension for $d \leq 3$. For Moranian offspring distributions, $p(x) \sim C_o(d)/(\nu x)^{d-2}$ for $d > 4$.

Our methods do not work for the other possible generalization of [1.1] to higher dimensions; i.e., with “as far as x ” in [1.1] replaced by “as far as distance x from the origin” in [1.2]. In that case [1.8] is most likely correct in all dimensions, with perhaps d replaced by 1 or $2 - d$.

Crump and Gillespie (5) (see also ref. 6) consider branching random walks and discuss, among other things, $p(x)$ for nearest-neighbor migrations in an infinite one-dimensional lattice. They estimate (essentially)

$$p(x) \leq \pi(0, x) \approx e^{-x\sqrt{2u}} \quad [1.9]$$

for an expression $\pi(0, x)$ and quote *Drosophila* recapture data of Dobzhansky and Wright (7) to estimate $\sigma \leq 0.447 \text{ km} \approx 0.278 \text{ miles}$ (1 mile = 1.6 km). Due to an apparent numerical error, they estimate $x = 200 \text{ miles} \approx 720\sigma$ for $p(x) = 0.01$ ($u = 10^{-6}$) rather than $x = 905 \text{ miles} \approx 3246\sigma$, which is the value that follows from their argument. From Table 1, $p(3246) \approx 1.2 \times 10^{-7}$. Indeed [1.3] indicates that $p(x)$ should be smaller than

Table 1. $p(x)$ for Moranian offspring distributions ($d = 1$)

x	u			
	0	10 ⁻⁶	10 ⁻⁵	10 ⁻²
5	0.10812	0.10812	0.10811	0.09964
10	0.03871	0.03871	0.03870	0.03039
20	0.01191	0.01190	0.01190	0.00552
30	0.00570	0.00570	0.00569	0.00126
40	0.00333	0.00333	0.00332	0.00030
50	0.00218	0.00218	0.00217	0.00007
75	0.00100	0.00100	0.00099	≈10 ⁻⁶
100	0.00057	0.00057	0.00056	≈10 ⁻⁷
200	0.00015	0.00015	0.00014	≈10 ⁻¹⁴
500	0.00002	0.00002	0.00002	≈10 ⁻³²
1000	0.00001	0.00001	≈10 ⁻⁶	≈10 ⁻⁶³
3246	6 × 10 ⁻⁷	1.2 × 10 ⁻⁷	≈10 ⁻¹⁰	≈10 ⁻²⁰¹

[1.9] by a factor of $12u$ in this range of x , assuming $\nu = 1$. The probability that a new selectively neutral *Drosophila* allele will diffuse from coast to coast of the United States (2500 miles $\approx 9000\sigma$) is $p(9000) \approx 4 \times 10^{-11}$ according to the exact solution of Table 1; their estimate was 2.8×10^{-6} . Crow and Morton (8) give evidence for $\nu^2 \approx 1.2$ –3.0 for offspring of females, and ≈ 3.0 –6.0 for males in a variety of populations, so ν should perhaps be slightly larger than 1. These models do not include the possibility that a small number of individuals may travel long distances by special events, as Crump and Gillespie point out. See Richardson (9) for a review article on animal migration behavior.

A closely allied question is the probability that two genes chosen at random a distance x apart are of the same allelic type. This is in fact of order [1.9], although there are difficulties defining an equilibrium model in this case (§3.3 and §4 of ref. 4).

The same questions can be asked for discrete “stepping stone” models (10, 11) and their continuous analogs (12). The asymptotic behavior of $p(x)$ is not known for these models, although the upper bound 1.9 does hold (13). It can be shown, however, that $\int p(x)dx = \infty$ if $u = 0$ for these models (see ref. 13, or argue as in §5), so $p(x) \sim C/x^2$ could not hold for $d = 1$.

See §5 for an application of [1.8] to the behavior of critical Brownian branching random fields.

2. An equation for $p(x)$

The complementary probability $q(x) = 1 - p(x)$ for $p(x)$ is

$$q(x) = \text{probability that no descendent of an individual initially at } x \text{ ever diffuses within distance } a > 0 \text{ of the origin.} \quad [2.1]$$

By independence, the probability that no descendent of a group of n individuals located initially at x_1, x_2, \dots, x_n diffuses within distance a of the origin is $q(x_1)q(x_2) \dots q(x_n)$. Thus [2.1] for an individual who is known to die at time zero at x is

$$\sum_{n=0}^{\infty} p_n q(x)^n = f[q(x)], \quad [2.2]$$

in which p_n is the probability that the individual is replaced by n offspring and $f(z) = \sum p_n z^n$. This, we claim, leads to the equation

$$(\frac{1}{2}) \nabla^2 q(x) = -\{f[q(x)] - q(x)\} \quad [2.3]$$

for $q(x)$. First, set

$$T_t q(x) = (2\pi t)^{-d/2} \int q(x) \exp[-(x - y)^2/2t] dy.$$

This is the expected value of $q(x_t)$, in which x_t is the position of the individual at time t given that it has not yet died. If $q(y)$ is three times continuously differentiable for $\|y\| > a$, then by Taylor's formula

$$T_t q(x) = q(x) + (\frac{1}{2}) \nabla^2 q(x)t + 0(t^{3/2}) \quad [2.4]$$

locally uniformly in x , in which $0(t^{3/2})$ represents a locally bounded function of x and t multiplied by $t^{3/2}$. The probability that the individual diffuses within distance a of the origin by a small time t is $0(\exp[-c^2/2t])$, in which $c = \|x\| - a$, with the same convention for 0. If $\|x\| \geq a + \epsilon$ for $\epsilon > 0$, this probability can be ignored within $0(t^2)$. By summing over the events that the individual either does not or does die by time t and using [2.4], we conclude

$$q(x) = (1 - t)T_t q(x) + t \sum p_n q(x)^n + 0(t^2)$$

from [2.2]. Hence $[T_t q(x) - q(x)]/t = T_t q(x) - f[q(x)] + 0(t)$, and [2.3] follows from another application of [2.4].

If $q(x)$ is not necessarily three-times continuously differentiable for $\|x\| > a$, the above argument implies that $q(x)$ is a *weak solution* of [2.3] in the sense of Weyl's Lemma [see, e.g., McKean (ref. 14, chapter 4)]. However, any weak solution of [2.3] is necessarily infinitely continuously differentiable and satisfies [2.3] in the usual sense (14).

See the paper by Sawyer (15) and the references therein for a general discussion of nonlinear equations of the form [2.3] associated with branching random fields.

Finally, because $q(x) = 1 - p(x)$ depends only on $x = \|x\|$ in d dimensions, [2.3] reduces to

$$p''(x) + \frac{d-1}{x} p'(x) - h[p(x)] = 0 \quad [2.5]$$

in which

$$p(a) = 1, h(z) = 2[f(1-z) - (1-z)]. \quad [2.6]$$

3. One dimension

Fix $d = 1$. Then by [2.5]

$$p'(x)^2 - \int_{p(x)}^{p(x)} 2h(z)dz = \text{constant}. \quad [3.1]$$

By definition, $p(x) \downarrow p(\infty) = c \geq 0$ as $x \rightarrow \infty$. Because $\lim_{x \rightarrow \infty} p'(x)$ exists by [3.1] it is zero, and

$$\int_{p(x)}^1 \frac{dy}{\left[\int_c^y 2h(z)dz \right]^{1/2}} = x \quad [3.2]$$

identically in x (using $p(0) = 1$). Note that the integral must diverge as $x \rightarrow \infty$. Also $\sum np_n = f'(1) = 1 - u \leq 1$ and $f(z) \equiv z$ under our assumptions, so $h(z) > 0$ for $0 < z \leq 1$ and $c = 0$. We consider four cases.

Case 1: If $\{p_n\}$ is Moranian with $u = 0$, then $p_0 = p_2 = 1/2$ and $h(z) = 2[f(1-z) - (1-z)] = 1 + (1-z)^2 - 2(1-z) = z^2$. Solving [3.2] for $p(x)$ yields [1.7].

Case 2: If $\{p_n\}$ is Moranian with $u > 0$, then $p_0 = (1+u)/2$ and $p_2 = (1-u)/2$. Thus $h(z) = (1+u) + (1-u)(1-z)^2 - 2(1-z) = z(2u + (1-u)z)$ and

$$x = \int_{p(x)}^1 \frac{dy}{y\sqrt{2u + by}}, \quad b = (2/3)(1-u).$$

After some manipulation

$$p(x) = \frac{8uE}{(1-bE)^2}, \quad E = \frac{\exp(-x\sqrt{2u})}{(\sqrt{2u} + \sqrt{2u + b})^2} \quad [3.3]$$

$$= \frac{12u[1 + 0(\sqrt{u})]\exp(-x\sqrt{2u})}{\{\sqrt{12u + 1 - \exp(-x\sqrt{2u})} + 0(u)\}^2},$$

in which 0 is used in the same sense as in §2.

For an arbitrary offspring distribution, $f(1-z) = 1 - c_1z + (1/2)c_2z^2 + 0(z^3)$ if $\sum n^3 p_n < \infty$, and

$$h(z) = 2[f(1-z) - (1-z)] = 2(1-c_1)z + c_2z^2 + 0(z^3). \quad [3.4]$$

Case 3: An arbitrary offspring distribution with $u = 0$, $\sum n^3 p_n < \infty$. Then $c_1 = f'(1) = \sum np_n = 1$ and $c_2 = f''(1) = \sum n(n-1)p_n = \nu^2$, and $h(z) = (\nu z)^2 + 0(z^3)$ by [3.4]. The identity $A^{-1/2} - B^{-1/2} = (B-A)/[\sqrt{AB}(\sqrt{A} + \sqrt{B})]$ applied in [3.2] then yields $p(x) = 6/[\nu x + 0(1)]^2 = 6/(\nu x)^2 + 0(1/x^3)$, in which $0(1)$ represents a bounded function of x .

Case 4: Here we consider a family of offspring distributions $\{p_n(u)\}$ depending on a parameter $u > 0$ such that $f(z, u) = \sum p_n(u)z^n$ satisfies

$$f'(1, u) = \sum np_n(u) = 1 - u, f''(1, u) = \nu^2 + 0(u), \quad [3.5]$$

$$f^{(3)}(1, u) \leq \text{constant} < \infty.$$

Moranian offspring distributions with mean $1 - u$ and Poisson offspring distributions with mean $1 - u$ both satisfy [3.5] with $\nu^2 = 1$. By [3.4], $h(z) = 2uz + \nu^2 z^2 + 0(uz^2) + 0(z^3)$, and as in Cases 2-3

$$x = \int_{p(x)}^1 \frac{dy}{y\sqrt{2u + ey}} + \int_{p(x)}^1 0 \left(\frac{y^3(u+y)}{[y^2(u+y)]^{3/2}} \right) dy$$

$$= \frac{2}{\sqrt{2u}} \{\log \dots\} + D(x, u)$$

as in [3.3], in which $e = (2/3)\nu^2$ and $D(x, u)$ is bounded uniformly in x and u . The asymptotic formula 1.3 follows.

Supercritical offspring distributions (i.e., with $\sum np_n > 1$) can be handled in the same way. Then $c = 1 - q$ for $q = \min\{z: f(z) = z\}$ in [3.2], and

$$p(x) = c + 0(e^{-bx}), \quad b = |h'(c)|^{1/2}, \quad x \geq 0$$

for large x . Here c is the probability of nonextinction for the corresponding branching process without geographical structure.

4. Higher dimensions

Suppose $u = 0$ and $d > 1$. Then by [3.4]

$$p''(x) + \frac{d-1}{x} p'(x) - \nu^2 p(x)^2 g[p(x)] = 0, \quad p(a) = 1 \quad [4.1]$$

in which $g(z) = 1 + 0(z)$ for small z . If $g(z) = 1$ (i.e., if the offspring distribution is Moranian), [4.1] is an equation of Emden-Fowler type. Hence

$$p(x) \sim 2(4-d)/(\nu x)^2, \quad 2 < d < 4, \quad [4.2]$$

$$\sim 2/[(\nu x)^2 \log(\nu x)], \quad d = 4,$$

$$\sim C(d)/(\nu x)^{d-2}, \quad d > 4$$

for large x (16). It remains to extend [4.2] to $d = 2$, and in general to prove [4.2] for $2 \leq d \leq 4$ and $p(x)$ satisfying the more general equation 4.1. Fowler's arguments are not sufficient for this.

First, assume $d = 2$. Variation of multipliers applied to [4.1], together with the boundary condition $p(x) \leq 1$ for large x , yields

$$p(x) = 1 - \int_a^x \log(y/a) h[p(y)] y dy$$

$$- \log(x/a) \int_x^\infty h[p(y)] y dy. \quad [4.3]$$

Thus, $\int_a^\infty h[p(y)] y dy < \infty$, which implies $p(x) \rightarrow 0$, and by [4.3]

$$p(x) = \int_x^\infty [\log(y/a) - \log(x/a)] h[p(y)] y dy$$

$$= \int_x^\infty z^{-1} \int_z^\infty \nu^2 p(y)^2 g[p(y)] y dy dz.$$

Set $v(x) = 4/(\nu x)^2$ and $w(x) = p(x)/v(x)$. Then

$$w(x) = 4x^2 \int_x^\infty z^{-1} \int_z^\infty w(y)^2 g[p(y)] y^{-3} dy dz. \quad [4.4]$$

Note

$$4x^2 \int_x^\infty z^{-1} \int_z^\infty y^{-3} dy dz = 1. \quad [4.5]$$

We claim there exists a sequence $x_n \rightarrow \infty$ such that $w(x_n) \rightarrow$

1. If not, either $w(x) \geq c > 1$ for all $x \geq x_0$ and some x_0 , or else $w(x) \leq c < 1$ for this range. Both, however, lead to contradictions of [4.4]–[4.5], because $\lim_{y \rightarrow \infty} g[p(y)] = 1$ and $w(y)$ enters the right-hand side of [4.4] quadratically. It remains to extend $w(x_n) \rightarrow 1$ to $\lim_{x \rightarrow \infty} w(x) = 1$.

Fix $c > 1$, and let $u(x) = p(x) - cv(x)$. Assume $g[p(x)] \geq 1/c$ for $x \geq x_0$. Because $v(x)$ satisfies [4.1] with $g(z) = 1$, by subtraction

$$u''(x) + \frac{d-1}{x} u'(x) - (v^2/c)u(x)[p(x) + cv(x)] \geq 0 \quad [4.6]$$

for $x \geq x_0$. Because $w(x_n) \rightarrow 1$, $u(x_n) < 0$ for sufficiently large n . However, standard arguments applied to [4.6] imply that $u(x)$ cannot have any positive local maxima for $x > x_0$. Hence $u(x) \leq 0$ for large x , or $p(x)/v(x) \leq c$. Because $c > 1$ was arbitrary, and the same argument also works for $u(x) = v(x) - cp(x)$, we conclude $\lim_{x \rightarrow \infty} p(x)/v(x) = 1$.

If $d \neq 2$, [4.3] is replaced by

$$p(x) = (a/x)^{d/2} \left\{ 1 - \int_a^x [a^{2-d} - y^{2-d}] h[p(y)] y^{d-1} dy / (d-2) \right\} - \{1 - (a/x)^{d-2}\} \int_x^\infty h[p(y)] y dy / (d-2). \quad [4.7]$$

If $d \leq 4$ and $p(x) \approx c/x^{d-2}$ for $c > 0$, then $\int_a^\infty p(y)^2 y^{d-1} dy = \infty$, which, by [4.7] and [3.4], implies $p(x) < 0$ for large x . Hence $x^{d-2}p(x) \rightarrow 0$ and

$$p(x) = \int_x^\infty [x^{2-d} - y^{2-d}] h[p(y)] y^{d-1} / (d-2) = \int_x^\infty z^{1-d} \int_z^\infty h[p(y)] y^{d-1} dy dz$$

and the same arguments go through, with minor modifications if $d = 4$.

5. An application to critical Brownian branching random fields

Assume that individuals are initially distributed as a Poisson random field in d -dimensional space R^d with mean density cdx , and thereafter diffuse and “branch” as in §1, in which the offspring distribution is assumed to have mean 1. Let $N_t(A)$ be the number of individuals in the set A at time t . In dimensions $d \leq 2$, “clumps” form and take over large areas at high densities; in particular $E[N_t(A)] = cm(A)$ but $\text{Var}[N_t(A)] \rightarrow \infty$ if $m(A) > 0$ (4, 17). Regions between clumps tend to become empty; e.g., $P[N_t(K) > 0] \rightarrow 0$ as $t \rightarrow \infty$ for bounded sets K and $d \leq 2$ (argue as in §8 of ref. 18). A natural question is, does K actually become and remain empty, or does it continue to have

visitors indefinitely, but perhaps more and more infrequently? If the latter happens with probability 1, K is called *persistent*; if the former with probability 1, *impersistent* (13). It turns out that bounded open sets are persistent for $d = 2$ (in spite of $P[N_t(K) > 0] \rightarrow 0$) but are impersistent if $d = 1$.

To see this, delete all initial individuals whose descendants never reach $K = \{x: \|x\| < a\}$. By independence, the resultant random field $\{M(A)\}$ is also Poisson, with mean

$$E[M(A)] = c \int_A p(x) dx \quad [5.1]$$

for $p(x)$ in [1.2]. Thus K will be persistent if $E[M(R^d)] = \infty$ [which implies $M(R^d) = \infty$ with probability 1] and impersistent if $E[M(R^d)] < \infty$, because the descendants of a finite number of individuals eventually become extinct due to genetic drift. However, $E[M(R^2)] = \infty$ but $E[M(R^1)] < \infty$, by [5.1] and [1.8].

See refs. 17–20 for other results about branching random fields. We are indebted to R. T. Durrett for the observation that our argument for impersistence yields persistence as well.

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