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The probability of establishment of an advantageous mutant in a subdivided population

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Summary

A method is developed for calculating the probability of establishment of an allele which is favoured in some places, but not others, in a large subdivided population. This method is quite general, and could be used to calculate the chance that any system which is linear near an absorbing boundary will move away from that boundary. The results are applied to a population distributed along one dimension. Only mutants which arise within a distance $\sim \sigma/\sqrt{2s}$ of the region in which they are favoured stand an appreciable chance of establishment. The net chance of establishment of mutations distributed randomly across the habitat will be decreased by gene flow if selection against them is sufficiently strong. However, if the mutations are only weakly deleterious outside some limited region, gene flow may increase the net chance of establishment.

Introduction

Most new mutations are lost within a few generations, even if they are at a selective advantage, and even if the population is infinitely large. Fisher (1930) showed that the probability of establishment of a new allele is approximately twice its selective advantage in the heterozygote. Maruyama (1970) has shown that this result also holds for a subdivided population, provided that migration is symmetric, and selection does not vary from place to place (see also Slatkin, 1981). This effect of sampling drift reduces the rate of evolutionary advance, and (other things being equal) favours the accumulation of alleles of large effect.

However, species rarely encounter uniform conditions: alleles may be advantageous only within limited regions. Nagylaki (1975) and Walsh (1983) have shown that if the region in which the allele is favoured is sufficiently large then the allele can be established at high frequency in this region. If the region is small, then the selective advantage of the allele within the region must be much larger than any deleterious effects outside, if it is to be established.

This paper extends these deterministic results on the ability of populations to adapt to local conditions, to include stochastic effects. The aim is to find the probability that a mutant which arises somewhere within a very large population will be established at appreciable frequency. We first derive a general expression for the probability of establishment, which applies to any system which is linear near an absorbing boundary. This is then applied to the particular case of a one-dimensional population.

General results

Consider a system which can be described by a set of positive variables, x_i. These might, for example, be a set of gamete frequencies, or a set of allele frequencies in different subpopulations. We assume that deterministic forces are weak enough, and population size large enough, that evolution under stochastic forces can be approximated by a diffusion equation. Let the probability of establishment, given an initial state p_i, be $F(p_i)$. 'Establishment' can be said to have occurred when the system moves beyond some arbitrary boundary ($x_i > x^* > 0$, say). The expected change (δx_i) in each generation is m_i, and the variance of changes is v_{ij}. Then, F is given by the Kolmogorov forward equation (Ewens, 1979, p. 134):

$$0 = \sum_i m_i \frac{\partial F}{\partial p_i} + \sum_i \sum_j \frac{v_{ij}}{2} \frac{\partial^2 F}{\partial p_i \partial p_j}. \quad (1)$$

The boundary conditions are that $F = 0$ when $p_i = 0$ for all i, and $F = 1$ when $p_i > x^*$ for all i. Now,

expand m_i and v_{ij} in a Taylor series about $p_i = 0$. We assume that the first derivatives are not zero:

$$m_i = s\sum_j L_{ij} p_j + O(p^2), \tag{2a}$$

$$v_{ij} = \frac{p_i}{2N}\delta_{ij} + O(p^2). \tag{2b}$$

Here, s is a measure of selection strength, and $1/N$ is a measure of the rate of random drift. $L_{ij} = (\partial m_i/\partial p_j)/s$ is a matrix which gives the effects of selection, gene flow, etc. The diagonal form of the variance (2*b*) is obtained immediately if the p_i are allele frequencies in demes of effective size N. However, the form is not restrictive, since it can be obtained by a suitable change of variables for any v_{ij}. We now suppose that x^*, the boundary at which establishment is taken to occur, is extremely small: this assumption is reasonable, provided that the population is sufficiently large ($4Ns \gg 1$): establishment will then be almost certain even at low x^*, since there will be a very large ($\geqslant 2Nx^*$) *number* of alleles in each deme. Then, since we are only concerned with the region, $0 < p_i < x^*$, terms of order p^2 become negligible.

Pollak (1966) develops essentially the same model, in terms of a branching process. He shows how the probability of establishment can be derived from the probability generating function associated with this branching process. The method developed here differs in that it is based on the diffusion equation (1). This is only an approximation to the branching process studied by Pollak, but on the other hand, it describes a wider variety of population structures.

When the new allele is rare ($p \leqslant x^* \ll 1$ everywhere), the chance that the offspring of two mutants will interact with each other is negligible ($\sim x^{*2}$). Therefore, even if many alleles are introduced simultaneously, they will be lost independently of each other: mathematically,

$$(1-F(\underline{p}_1+\underline{p}_2)) = (1-F(\underline{p}_1))(1-F(\underline{p}_2)).$$

(This argument is developed rigorously by Pollak (1966, (2.6)).) The probability of establishment must therefore take the form:

$$F(p) = 1-\exp(-2N\sum_i \psi_i p_i). \tag{3}$$

Substituting (2) and (3) into (1) gives:

$$0 = \sum_i (2s\sum_j L_{ij} p_j \psi_i - p_i \psi_i^2). \tag{4a}$$

This is satisfied if

$$\psi_i^2 = 2s\sum_j \psi_j L_{ji} \quad \text{for all } i. \tag{4b}$$

We see that $\psi_i = 0$ is always a solution, and that if $\Sigma_j L_{ji} = 1$ for all i, $\psi_i = 2s$ is also a solution; the latter corresponds to Maruyama's (1970) result for uniform selection and symmetric migration.

It is conceivable that (4*b*) may have more than one solution. If establishment is impossible in an infinite population (i.e. if all eigenvalues of L_{ij} are negative), then it can be shown that only the solution $\psi_i = 0$ exists (see Appendix). If at least one eigenvalue is positive, establishment is possible, and so we require $\psi_i > 0$ for at least some i. Close to the threshold for establishment, when the leading eigenvalue is small, (4*b*) has a unique solution, proportional to the product of the leading eigenvalue and eigenvector (see Appendix). In the special cases described below, there is also a unique positive solution; however, this has not been proved to be true in general.

One-dimensional models

Suppose that a series of demes are arranged in an infinite line, and exchange a proportion $m/2$ of their individuals with each neighbour in every generation. An allele has selective advantage sf_i in deme i. In the limit of weak selection ($s \ll m < 0{\cdot}5$), the deterministic evolution of such a population can be approximated by a continuous diffusion equation (Nagylaki, 1975):

$$\frac{\partial p}{\partial t} = Lp, \quad \text{where } L = \frac{\partial^2}{\partial x^2} + f(x);$$

$$\frac{\partial p}{\partial x} = 0 \quad \text{as} \quad |x| \to \infty, \tag{5}$$

($x = i\varepsilon/l$, ε = deme spacing, $l = \sqrt{(\sigma^2/2s)}$, $\sigma = m\varepsilon^2$, $t = s$ times no. of generations).

Since migration is assumed to be symmetric, $L_{ij} = L_{ji}$, and so (4*b*) becomes, in the continuous approximation:

$$\phi^2(x) = L\phi; \quad \frac{\partial\phi}{\partial x} = 0 \quad \text{as} \quad |x| \to \infty, \tag{6}$$

(here and below, $\phi = \psi/2s$).

This continuous limit can readily be derived from (4*b*), in the same way as (5) above (see Nagylaki, 1975).

(a) *Step selection*

Suppose that $f(x) = -\beta s\,(p(x < 0)$, and $+1$ $(x \geqslant 0)$. The allele is favoured on the right, but selected against to the left. Equation (6) then has solution (Fig. 1).

$$\left.\begin{aligned}\phi(x) &= \frac{3\beta}{(\cosh((x-\alpha_-)\sqrt{B})-1)} \quad (x<0),\\ &= \frac{1}{3(1+\beta)} \quad (x=0),\\ &= 1-\left(\frac{3}{\cosh(x+\alpha_+)+1}\right) \quad (x>0),\end{aligned}\right\} \tag{7}$$

(where α_+, α_- are chosen so that the solutions match at $x = 0$). When the allele is extremely disadvantageous on the left ($\beta = \infty$), mutants introduced there are immediately eliminated ($\psi = 0$ for $x < 0$). However, alleles introduced on the right can be established there,

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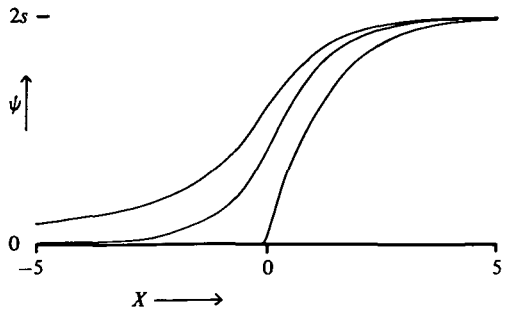

Fig. 1. The probabilities of establishment, for stepped selection. The selection coefficient is $+s$ for $x > 0$, and $-\beta s$ for $x < 0$. Values are plotted for $\beta = 0, 1, \infty$, in decreasing order of probability. The x axis is labelled in units of the characteristic scale, $l = \sqrt{(\sigma^2/2s)}$.

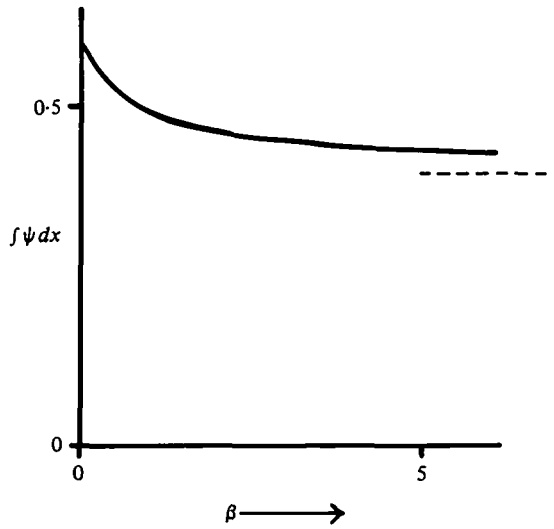

Fig. 2. The net probability of fixation ($\int \psi\, dx$) for stepped selection. The x axis is in units $\sqrt{(\sigma^2/2s)}$. Values are plotted for $s = 0{\cdot}05$; changes in s would cause proportionate changes in ψ. The integral was arbitrarily truncated at $x = +5$; since the probability of fixation converges to 0·1 for large x, an increase in this truncation point by one unit would raise the graph by 0·1.

and their probability of establishment rises to approximately the panmictic limit ($2s$) when $x \gtrsim 2$ (Fig. 1). As the selective disadvantage, βs, decreases, the probability of establishment rises. When the allele is neutral on the left ($\beta = 0$), new mutants have an appreciable chance of establishment even if they arise well away from the region where they are favoured. In the limit $\beta \to 0$, (7) tends to $\phi = 6/(x-\alpha_-)^2$ for $x < 0$; thus, the chance of fixation decreases algebraically, rather than exponentially, with distance.

In most cases, the rate of mutation will be the same everywhere. Then the net probability of establishing a mutation per generation is $2\rho\mu \int \psi\, dx$, where ρ is the density of diploid individuals. The integral of ψ can be calculated numerically, and is plotted against β in Fig. 2. Values there are for $s = 0{\cdot}05$; changes in s will change ψ in proportion. (The integral was truncated arbitrarily at $x = +5$.) The net probability of establishment can be compared with that in the absence of gene flow: $2s \times 5 = 0{\cdot}5$. When β is small ($< 0{\cdot}87$) gene flow *increases* the net probability: mutants arising on the left, where they are not favoured, may move to the right, and be established there. However, when β is large, the net probability is *decreased* by gene flow: mutants arising on the right, where they are favoured, may move to the left and be lost.

(b) *A local pocket*

Suppose that $f(x) = -\beta$ outside a region of width W centred on $x = 0$; $f(x) = 1$ within this region. Equation 4*b* has solution:

$$\phi(x) = \frac{3\beta}{\cosh((x-\alpha)\sqrt{\beta}) - 1} \quad (|x| < W/2), \tag{8a}$$

$$= \frac{3\beta}{\cosh((x+\alpha)\sqrt{\beta}) - 1} \quad (|x| > W/2), \tag{8b}$$

I can find no explicit solutions for the central region ($|x| < W/2$). However, (6) can be integrated to give:

$$x = \sqrt{\frac{6}{b}} F\left(\sin^{-1}\sqrt{1 - \left[\frac{(\phi(0) - \phi(x))}{a}\right]},\ (a/b)\right), \tag{8c}$$

where

$$F(\phi, k) = \int_0^{\phi} \frac{d\alpha}{\sqrt{[1 + k^2 \sin^2 \alpha]}}$$

is the elliptic integral;

$$a = \tfrac{3}{4}[(2\phi(0) - 1) + \sqrt{(1 + \tfrac{4}{3}\phi(0) - \tfrac{4}{3}\phi^2(0))}],$$

$$b = \tfrac{3}{4}[-(2\phi(0) - 1) + \sqrt{(1 + \tfrac{4}{3}\phi(0) - \tfrac{4}{3}\phi^2(0))}].$$

By matching the derivatives of ψ at $|x| = W/2$ one can also obtain:

$$\phi(W/2) = \phi(0)\sqrt{\left(\frac{1 - 2\phi(0)/3}{1 + \beta}\right)}. \tag{8d}$$

By combining (8*c*) and (8*d*), one obtains a relation between the width of the local region, W, and the maximum probability of establishment ($\psi(0) = 2s\phi(0)$). In the limit where the region is so narrow that the allele has almost no chance of establishment ($\psi(0) \to 0$), this relation reduces to:

$$\beta_{\max} = \tan^2(W/2). \tag{9}$$

This agrees with the threshold obtained by Nagylaki's (1975) deterministic analysis: if β exceeds this value, there is no positive solution for $\psi(x)$.

Figure 3 shows the probability of fixation as a function of position, for an allele favoured only in a region $W = 2l$ wide. This was calculated numerically using a stepping-stone model with 21 demes ($m = 0{\cdot}4$, $s = 0{\cdot}05$). Values with larger numbers of demes or weaker selection did not differ appreciably. The graph shows the cases $\beta = 0, 1$; when $\beta > \tan^2(2/2) = 2{\cdot}43$, establishment becomes impossible.

The net probability of establishment ($\int \psi\, dx$) is plotted in Fig. 4, for the case $s = 0{\cdot}05$. Values were integrated over a range of x large enough to be

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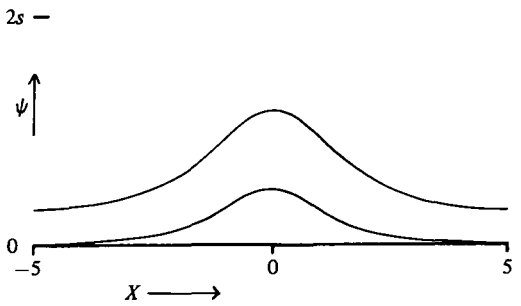

Fig. 3. As for Fig. 1, but for an allele favoured only in a local pocket of width $W = 2$. The disadvantage about this pocket is proportional to $\beta = 0$ (upper curve), $\beta = 1$ (lower curve).

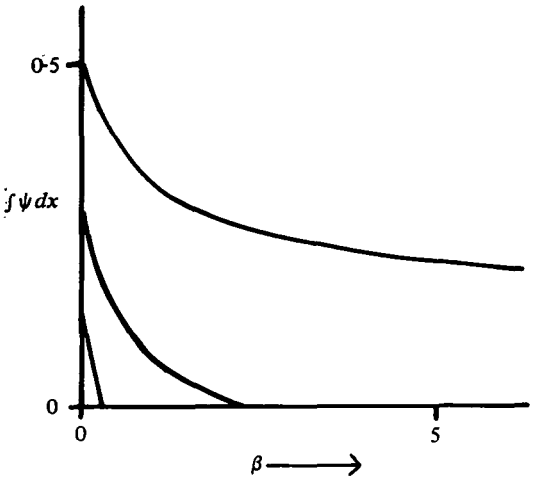

Fig. 4. As for Fig. 2, but for an allele favoured only in a local pocket of width $W = 4$ (upper curve), $W = 2$ (middle curve), $W = 1$ (lower curve). Beyond a threshold $\beta = \tan^2(W/2)$, establishment is impossible. $s = 0{\cdot}05$, as above.

effectively infinite. The curves correspond to the cases $W = 1, 2, 4$, in increasing order of probability. They may be compared with the net probability in the absence of gene flow, which is $2sl \times 1, 2, 4 = 0{\cdot}1l, 0{\cdot}2l, 0{\cdot}4l$. As for stepped selection, gene flow increases the net probability when β is small, but decreases it when β is large. When $W < \pi l$, establishment is impossible when β exceeds the critical value $\tan^2(W/2)$. However, when $W > \pi l$, establishment is possible regardless of the strength of selection against the allele outside the pocket. The net probability therefore converges to a definite value as β becomes large.

Simulations

The application of (4*b*) to a linear stepping-stone model was checked by simulating the increase of a single new mutant. The population was assumed to be infinite: the simulations therefore followed the number of copies of the new allele, rather than its frequency. (Total population size is irrelevant to an allele at vanishingly low frequency.) In other respects, the method was identical to that of Slatkin (1981). In each generation, and each deme, a number (n_i) of genes produce a much larger number of offspring. Selection, followed by migration, then act deterministically. Finally, a small number of genes is sampled to found the next generation; this number is chosen from a Poisson distribution with expectation

$$(1-m)\,w_i\,n_i + (m/2)\,(w_{i+1}\,n_{i+1} + w_{i-1}\,n_{i-1}),$$

where $w_i = 1 + sf_i$ is the fitness of the new allele relative to the old. (Since the common allele does not appear explicitly in the simulation, this model, and the above theory, also apply to the chances of establishment of a whole population in a linear habitat following a founder event; s is then a measure of the intrinsic rate of increase.) To the extent that the spatial and stochastic diffusion approximations hold, the results should not depend on details of the population structure.

Table 1 gives results for 21 demes, with $m = 0{\cdot}4$, $s = 0{\cdot}05$ (these values were chosen to give results reasonably quickly, and yet close to the continuous approximation). A sharp transition from $f(x) = 1$ to $f(x) = -\beta$ at x_0 was approximated by setting $f = 0$ at the deme corresponding to x_0. With these parameters, the demes are quite widely spaced, relative to the characteristic scale set by migration and selection ($\varepsilon = 0{\cdot}5l$). Nevertheless, the theoretical predictions given by the approximation of spatial continuity ((7) and (8)) are very close to those derived by exact numerical solution of (4*b*).

The simulations give probabilities reasonably close to those expected: only 3 out of 36 likelihood-ratio (G) tests are statistically significant, at the 5% level. However, the overall $\chi^2_{36} = 62{\cdot}84$ is significant at the 0·5% level. The simulated probabilities tend to be lower than the theoretical expectation; this discrepancy may be because $s = 0{\cdot}05$ is appreciable, or because the diffusion approximation breaks down when only a few mutant alleles are present. However, the discrepancy is not large: of the 27 runs where the expected probability was greater than 1%, the largest % relative error $(100 \times (O-E)/E)$ was −22·7% (not significant), and the average was −6·4%.

The average times to establishment and loss, together with their standard deviations, are given in Table 1. Times to loss are essentially independent of initial position, and of the pattern of selection: they lie between 5·0 and 10·2 generations. This is consistent with Kimura and Ohta's (1969) results for advantageous alleles. Times to establishment are somewhat arbitrary, since establishment is taken as certain when more than 200 copies of the allele are present. The time expected if increase were deterministic is $\ln(200)/0{\cdot}05 = 106$ generations: this is approximately the same as the mean from the simulations. However, alleles which arise far from the region in which they are favoured take somewhat longer to become established, since they must move into that region before increasing.

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Table 1. *The results of simulations (see text for details)*

Initial position: deme...		2	4	6	8	10	12	14	16	18
	x = ...	−4	−3	−2	−1	0	1	2	3	4
(*a*) Step selection										
$\beta = 0$	Observed ψ	0·011 75	0·019 00	0·022 00	0·030 25	0·050 50	0·080 00	0·094 75	0·090 00	0·090 50
	Exact ψ	0·013 59	0·016 66	0·022 58	0·033 82	0·057 32	0·082 60	0·093 29	0·097 45	0·098 98
	Diffusion ψ	0·011 50	0·015 49	0·021 99	0·033 63	0·057 74	0·082 84	0·093 34	0·097 55	0·099 10
	χ^2_1	1·06	1·28	0·06	1·62	3·58	0·36	0·10	2·58	3·31
	t (estab.)	153·5	147·8	117·8	101·1	92·9	82·5	75·7	73·6	74·4
	$Sd(t)$ (estab.)	59·8	63·0	53·5	42·3	47·8	30·8	30·1	25·4	27·0
	t (loss)	8·0	7·1	6·7	5·9	6·4	5·9	5·6	5·5	5·2
	$Sd(t)$ (loss)	18·6	17·5	14·7	11·5	13·0	11·4	10·6	10·3	9·6
	No. of iterations	4000	4000	4000	4000	4000	4000	4000	4000	4000
$\beta = 1$	Observed ψ	0·000 00	0·002 50	0·003 75	0·011 75	0·039 25	0·066 00	0·082 25	0·090 75	0·092 25
	Exact ψ	0·000 73	0·001 84	0·004 96	0·013 68	0·039 49	0·074 17	0·089 86	0·096 11	0·098 44
	Diffusion ψ	0·000 66	0·001 81	0·004 96	0·013 87	0·040 82	0·074 82	0·090 20	0·096 32	0·098 64
	χ^2_1	*5·85*	0·85	1·30	1·16	0·02	*8·12*	2·91	1·35	1·76
	t (estab.)	—	108·2	120·8	91·3	88·7	81·7	77·5	76·2	71·9
	$Sd(t)$ (estab.)	—	20·8	48·6	25·0	29·4	27·6	27·4	28·7	28·3
	t (loss)	5·00	5·3	5·2	5·2	5·4	6·2	5·8	5·6	5·4
	$Sd(t)$ (loss)	8·55	9·0	8·9	9·4	10·2	12·0	11·1	11·4	9·0
	No. of iterations	4000	4000	4000	4000	8000	8000	4000	4000	4000
(*b*) Local pocket										
$W = 4$ demes	Observed ψ	0·015 25	0·018 25	0·028 75	0·042 25	0·060 75	0·040 50	0·030 75	0·020 00	0·014 75
$\beta = 0$	Exact ψ	0·015 82	0·019 94	0·028 18	0·044 82	0·057 15	0·044 82	0·028 18	0·019 94	0·015 82
	χ^2_1	0·08	0·60	0·05	0·63	0·94	1·80	0·93	0·00	0·30
	t (estab.)	157·2	143·8	125·6	114·2	112·2	115·2	135·0	144·3	154·0
	$Sd(t)$ (estab.)	66·1	60·6	53·9	55·2	55·3	54·6	62·3	73·0	62·5
	t (loss)	6·7	6·4	6·6	7·1	7·9	7·1	6·6	7·3	6·7
	$Sd(t)$ (loss)	15·2	14·9	15·6	14·9	19·7	16·8	15·4	18·4	14·7
	No of iterations	4000	4000	4000	4000	4000	4000	4000	4000	4000
$W = 4$ demes	Observed ψ	0·000 25	0·001 75	0·006 00	0·011 50	0·022 75	0·011 25	0·005 75	0·000 25	0·000 25
$\beta = 1$	Exact ψ	0·000 78	0·001 96	0·005 27	0·014 55	0·023 13	0·014 55	0·005 27	0·001 96	0·000 78
	χ^2_1	1·95	0·09	0·39	2·80	0·03	3·30	0·17	*9·56*	1·95
	t (estab.)	—	171·1	171·0	156·91	151·6	155·1	167·6	—	—
	$Sd(t)$ (estab.)	—	47·9	94·6	69·92	76·4	98·3	78·5	—	—
	t (loss)	5·1	5·4	6·1	7·7	10·2	7·3	6·2	5·2	4·8
	$Sd(t)$ (loss)	9·4	11·4	15·3	21·5	27·7	22·1	15·5	10·0	8·4
	No. of iterations	4000	4000	4000	4000	4000	4000	4000	4000	4000

A single allele was released at some initial position in a chain of 21 demes (numbered 0–20). This position is given in terms of deme number, and distance $x = i\varepsilon/\sqrt{(\sigma^2/2s)}$. The first row for each set of parameters gives the proportion of runs in which a threshold of 200 copies was reached. This can be compared with the *exact* prediction for the stepping-stone model (4*b*), and the *diffusion* approximation ((7) and (8)). The χ^2_1 value is twice the log-likelihood ratio for the comparison between observed and exact ψ. Deviations significant at the 5% level in italics. The remaining rows give the mean and standard deviations of the times to establishment and loss, and finally, the number of replicates for each case.

Discussion

The dependence of the probability of establishment on the initial position of the mutant is straightforward. When an allele is at an advantage s only within some limited region, the probability increases from zero outside this region towards a maximum of $2s$ within it (Fig. 1). The transition occurs over a characteristic distance $l = \sqrt{(\sigma^2/2s)}$; if the region in which the allele is favoured is small relative to this distance, then establishment may be unlikely or impossible. Even if the disadvantage is relatively small outside ($\beta \ll 1$), mutants far from the region in which they are favoured ($\gg \sigma/\sqrt{[2\beta s]}$) have little chance of establishment. If the allele is precisely neutral outside, the situation is somewhat different. The probability of establishment then declines only algebraically ($\sim x^{-2}$) with distance from the favourable region. Thus, although distant mutants still have little chance of increasing, the net contribution of mutations from outside may become large. Indeed, in two dimensions, the contribution of mutations far from the region in which they are favoured is expected to be much greater than that from within the region ($\int r^{-2} r\,dr \to \infty$).

These results confirm the intuition that even when an allele can become established at high frequency in a limited area, thus aiding adaptation to conditions in that area, the rate of adaptation may be limited by lack of suitable variation: only mutants from the vicinity of this area can contribute. This conclusion depends, of course, on the assumption that adaptation occurs through the accumulation of new alleles. If it relies instead on polygenic variation maintained by recurrent mutation, or on adjustment of balanced polymorphisms, then local adaptation may occur more readily.

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Appendix

Relation of fixation probabilities to eigenvalues

Since the main application is to one-dimensional models, derivations are given for these. However, the same method gives analogous results for the discrete case (4*b*).

Let $\phi(x) = \psi(x)/2s$ be represented by a sum of eigenfunctions, $e_i(x)$, of the operator L.

$$\phi(x) = \sum_i \alpha_i e_i(x). \tag{A 1}$$

For simplicity, the range of x is assumed to be finite, so that the eigenvalues, λ_i, are discrete. The eigenfunctions are normalized so that $\int e_i(x) e_j(x)\,dx = \delta_{ij}$, where $\delta_{ij} = 1$ if $i = j$, and 0 otherwise.

Consider the integral of the product of $\phi(x)$ and (6)

$$\int \phi^3\,dx = \int \phi L\phi\,dx = \sum_i \lambda_i \alpha_i^2. \tag{A 2}$$

Since $\phi(x)$ is proportional to the probability of establishment it must be positive or zero everywhere; therefore the left-hand side cannot be negative. But, if all eigenvalues are negative, the right-hand side cannot be positive. Therefore, establishment is only possible if at least one eigenvalue positive. (This proof was suggested by S. Rouhani.)

Now, consider the situation just beyond this threshold: λ_1 is small and positive, whereas all other eigenvalues are negative, and of order 1. The index i now denotes all $i > 1$. From the fact that $\lambda_1 \alpha_1^2 + \Sigma_i \lambda_i \alpha_i^2 > 0$, we have $\lambda_1 \alpha_1^2 > \Sigma_i |\lambda_i| \alpha_i^2$, and hence $\alpha_1 \gg \alpha_i$. So, to a first approximation, $\phi(x)$ is proportional to $\alpha_1 e_1(x)$. To find the coefficient of proportionality, substitute (A 1) into (6)

$$\alpha_1^2 e_1^2 + O(\alpha_1 \alpha_i) + O(\alpha_1^2) = \alpha_1 \lambda_1 e_1 + \sum_i \alpha_i \lambda_i e_i. \tag{A 3}$$

Multiplying by e_1 or e_i, and integrating, gives:

$$\alpha_1^2 \int e_1^3\,dx + O(\alpha_1 \alpha_i) + O(\alpha_1^2) = \alpha_1 \lambda_1 \tag{A 4a}$$

$$\alpha_1^2 \int e_1^2 e_i\,dx + O(\alpha_1 \alpha_i) + O(\alpha_i^2) = \alpha_i \cdot \lambda_i \tag{A 4b}$$

Hence (excluding the trivial case $\alpha_i = 0$, $\alpha_1 = 0$)

$$\alpha_1 = \frac{\lambda_1}{\int e_1^3\,dx} + O(\lambda_1^2), \tag{A 5a}$$

$$\alpha_i = \frac{\lambda_1^2 \int e_1^2 e_j\,dx}{\lambda_i \int e_1^3\,dx} + O(\lambda_1^3), \tag{A 5b}$$

therefore

$$\psi(x) = \frac{2s\lambda_1 e_1(x)}{\int e_1^3\,dx} + 0(\lambda_1^2). \tag{A 5c}$$

Near the threshold, the probability of fixation is proportional to the leading eigenvalue (λ_1) and the leading eigenfunction ($e_1(x)$). However, when λ_1 is large, the probability of fixation will be a complicated mixture of eigenfunctions.