

The Probability of Fixation in Populations of Changing Size

Sarah P. Otto and Michael C. Whitlock

Department of Zoology, University of British Columbia, Vancouver, BC, Canada V6T 1Z4

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ABSTRACT

The rate of adaptive evolution of a population ultimately depends on the rate of incorporation of beneficial mutations. Even beneficial mutations may, however, be lost from a population since mutant individuals may, by chance, fail to reproduce. In this paper, we calculate the probability of fixation of beneficial mutations that occur in populations of changing size. We examine a number of demographic models, including a population whose size changes once, a population experiencing exponential growth or decline, one that is experiencing logistic growth or decline, and a population that fluctuates in size. The results are based on a branching process model but are shown to be approximate solutions to the diffusion equation describing changes in the probability of fixation over time. Using the diffusion equation, the probability of fixation of deleterious alleles can also be determined for populations that are changing in size. The results developed in this paper can be used to estimate the fixation flux, defined as the rate at which beneficial alleles fix within a population. The fixation flux measures the rate of adaptive evolution of a population and, as we shall see, depends strongly on changes that occur in population size.

ADAPTATION ultimately depends upon the fixation of beneficial mutations. The probability that a beneficial allele will eventually fix within a population was first addressed by R. A. FISHER (1922, 1930a), J. B. S. HALDANE (1927) and S. WRIGHT (1931). Using a branching process approach developed by FISHER (1922), HALDANE (1927) demonstrated that the probability of fixation of a new beneficial allele in a large population is approximately $2s$, where s is the selective advantage of the allele. This surprisingly low value demonstrates that stochastic forces are important even in large populations, since any new mutation is represented by a small number of copies in the first few generations of its existence.

FISHER (1922, 1930a), HALDANE (1927) and WRIGHT (1931) based their analyses on several assumptions, including that families have a Poisson distribution of reproductive success, that population size is unchanging, and that the allele starts in a single copy. These models have been generalized in a number of ways, most notably by KIMURA (1957, 1962, 1964, 1970). KIMURA (1957, 1962) used a diffusion approximation to show that the probability of eventual fixation of an allele starting at frequency p with additive selective effect s is

$$\frac{1 - \exp[-4N_e s p]}{1 - \exp[-4N_e s]}, \quad (1)$$

where N_e is the variance effective size of a diploid population of census size N . If the population is large ($N_e s$

$\gg 1$), the probability of fixation of a new mutation ($p = 1/2N$) is approximately $2sN_e/N$ and depends on the ratio of the effective population size to census size. This formulation predicts the probability of fixation for arbitrary p and, by adjusting N_e , can describe populations with other distributions of reproductive success, as long as the population continues to have the same average size.

In nature, however, populations frequently change in size (ANDREWARTHA and BIRCH 1954; KREBS 1994), under the influence of a number of factors including varying physical conditions, resource availability, habitat availability, and predator density (BATZLI 1992). In addition, human disturbance is causing dramatic changes in the distribution and density of many, if not most, species (KERR and CURRIE 1995; SAMWAYS 1996).

Such changes in population size affect the persistence of beneficial mutations and hence the rate of adaptation of a population. FISHER (1930b) first suggested that the probability of fixation of beneficial alleles should increase in growing populations and decrease in shrinking populations. KOJIMA and KELLEHER (1962) confirmed this claim in a numerical analysis of populations changing in size. More generally, KIMURA and OHTA (1974) determined the probability of fixation in a population that follows a logistic model of population growth or decline; their results also confirm FISHER's claim. For populations that fluctuate in size, EWENS (1967) found that the fixation probability is approximately equal to $2s\bar{N}/N_e$, where \bar{N} is the harmonic mean of the population sizes in each generation, N_t . Subsequently, KIMURA (1970) conjectured that (1)

Corresponding author: Sarah P. Otto, Department of Zoology, 6270 University Blvd., University of British Columbia, Vancouver, BC, Canada V6T 1Z4. E-mail: otto@zoology.ubc.ca

may be used for populations that fluctuate over time, with N_e being replaced by \tilde{N} .

Building upon this work, the current paper examines changes in the probability of fixation under several scenarios for population size change. Approximations are presented for the probability of fixation of a beneficial allele in populations that are experiencing exponential growth or decline as well as logistic growth or decline. For populations that vary cyclically over time, the conditions are determined under which the harmonic mean approximation for N_e is accurate. These results are then used to determine the flux of beneficial mutations into a population. We then show that these formulae can also be used to determine the probability of fixation of deleterious mutations. Finally we discuss some implications of these results to evolutionary processes and conservation methods.

BACKGROUND

HALDANE (1927) used a branching process to determine the probability of fixation, a method that we will use in this paper to investigate the effects of changing population size. Here we briefly describe the method. HALDANE assumed that the number of offspring alleles per parent allele follows a Poisson distribution with a mean of one, such that the population remains approximately constant in size. Individuals carrying a new beneficial mutation have a higher reproductive success, with $1 + s$ times as many offspring on average. In a haploid population, s would measure the relative fitness advantage of a mutant. In a randomly mating diploid population, s would measure the relative fitness advantage of a heterozygote; the fitness of the mutant homozygote is irrelevant since the fate of the mutation is decided while homozygotes are still rare as long as selection is directional and inbreeding is rare.

We wish to estimate the probability that a mutant allele that appears in generation t will ultimately fix, P_t . Correspondingly, the probability of eventual loss of the allele is $1 - P_t$. More specifically, we define P_t as the probability that a single copy of an allele present at time t has descendants in the population after a very large amount of time has passed (which we will refer to as the fixation of the allele). The probability that an allele present in generation t eventually leaves no descendants, *i.e.*, that it is lost, is equal to the probability that each of its offspring fail to leave descendants in the long term, which is equal to the probability of having j offspring times the probability that all j alleles will ultimately leave no descendants, $(1 - P_{t+1})^j$, summed over all possible values of j . Since the number of offspring of an individual carrying a beneficial mutation is assumed to follow a Poisson distribution with mean $1 + s$,

$$1 - P_t = \sum_{j=0}^{\infty} e^{-(1+s)} \frac{(1+s)^j}{j!} (1 - P_{t+1})^j. \quad (2)$$

Evaluating the sum gives

$$1 - P_t = \exp[-(1+s)P_{t+1}] \quad (3)$$

(HALDANE 1927). Assuming that the population size and the selective advantage, s , remain constant over time, the fixation probability of a single copy of the beneficial allele is constant from one generation to the next ($P_t = P_{t+1}$). Throughout this paper, we will use P^* to denote the exact solution to (3) under these conditions. Taking the log of both sides of (3) and solving for s , we have

$$s = \frac{-\log [1 - P^*]}{P^*} - 1 \\ = \frac{P^*}{2} + \frac{P^{*2}}{3} + \frac{P^{*3}}{4} + O(P^{*4}) \quad (4)$$

(HALDANE 1927). This equation demonstrates that, if s is small, P^* will be small. Hence, ignoring terms of $O(s^2)$, $P^* \cong 2s$; the fixation probability of an allele is approximately twice its selective advantage.

PROBABILITY OF FIXATION WITH CHANGING POPULATION SIZE

In a discrete generation model, let the population size in generation t be N_t and let ΔN_t equal the change in size from generation t to $t + 1$ ($\Delta N_t = N_{t+1} - N_t$). In this case, the average number of offspring produced by an individual in the population is N_{t+1}/N_t . Making the same assumptions as in the case of constant population size above, the average number of adult offspring per mutant parent is $(1 + s)N_{t+1}/N_t$. Equation 3 then becomes

$$1 - P_t = \exp\left[-(1+s)\frac{N_{t+1}}{N_t}P_{t+1}\right] \\ = \exp\left[-(1+s)\left(1 + \frac{\Delta N_t}{N_t}\right)P_{t+1}\right] \quad (5)$$

(EWENS 1967). This equation demonstrates that if the population is growing ($\Delta N_t > 0$), the probability of fixation of the beneficial mutation is always higher than $2s$, as if the mutation had an even greater selective advantage. The increase in fixation probability occurs because in a growing population individuals carrying the mutant allele are more likely to have offspring. The allele is therefore less likely to be lost while it is rare and more likely to be established. Conversely, if the population is decreasing in size, individuals carrying the beneficial allele are more likely to fail to have offspring, increasing the chance that the allele will be lost from the population.

In what follows, we calculate the probability of fixation over time for different models of population

growth. These calculations will be based on (5) and its continuous time approximation,

$$\frac{dP_t}{dt} \cong -P_t \left(s + \frac{dN_t}{dt} \frac{1}{N_t} \right) + \frac{P_t^2}{2}, \quad (6)$$

which can be obtained from (5) under the assumption that s , P_t , and $(dN_t/dt)(1/N_t)$ are small and ignoring terms higher than second order. Equation 6 may also be derived from a diffusion model as shown in the APPENDIX. In the following sections, we solve (6) for specific cases of population size change.

A single change in population size: Consider the case where the population changes in size from N_0 in generation T to N_1 at generation $T + 1$, but remains constant at all other times. From generation $T + 1$ onward, the probability of fixation is P^* as before. In generation T , the probability of fixation can be found from (5) by setting $P_{T+1} = P^*$. With s and P^* assumed to be small, $P_T \cong P^*(N_1/N_0)$. To determine the value of P_t before generation T , we solve the differential Equation (6) with $dN_t/dt = 0$ to obtain

$$P_t \cong P^* \frac{N_1}{N_1 + (N_0 - N_1) e^{-s(T-t)}} \quad (7)$$

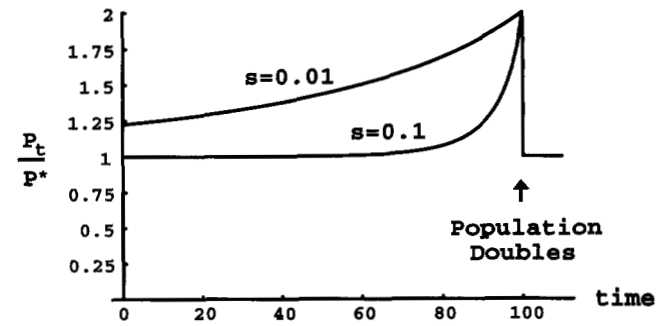
for $t \leq T$, where $P^* \cong 2s$. If a population grows by a factor r in a single generation, the fixation probability in the previous generation will also increase by r . This increase is propagated back in time to mutant alleles that appeared previously, but the effect decays at rate s (Figure 1). When s is small, this implies that population size changes can affect the fate of mutations that arose many generations earlier.

If the population size is N_1 in every generation except generation T when it is N_0 , we can use $P_T \cong P^*(N_1/N_0)$ in (5) to find that, to leading order, P_{T-1} equals P^* . Therefore, if a population changes in size for a single generation and then returns to its original size, the probability of fixation of a mutation is largely unaffected by the change in population size except for alleles that first appear in generation T .

Exponential growth (or decline): Consider next a population that changes exponentially in size at a constant rate, r , every generation, such that $\Delta N_t/N_t = r$. Equation 5 for P_t then takes on the same form as a population of constant size with $(1 + s)$ being replaced by $(1 + s)(1 + r)$, or approximately $1 + (s + r)$, assuming that r is also small. This indicates that the probability of fixation in a continuously growing or shrinking population is approximately $2(s + r)$. Examples are shown in Table 1. These comparisons demonstrate that the approximation is useful as long as s and r are both small and $s + r > 0$. When $s + r < 0$, the absolute number of mutant alleles is decreasing over time and the mutant allele will eventually go extinct.

Exponential growth directly augments the apparent selective advantage of beneficial mutations. This will

A



B

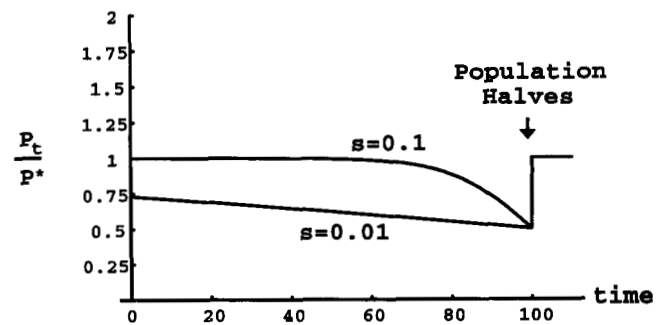


FIGURE 1.—Changes in the fixation probability of a beneficial mutation in populations that experience a single change in size in generation 100. (A) Population size doubles. (B) Population size halves. In each case, the probability of fixation is shown relative to what it would be in a population of constant size, P^* . Doubling or halving the population size has a corresponding effect on the fixation probability in the immediately preceding generation. Mutations that occur long before the population size change are affected only if the selection favoring them is weak.

have a major effect on the incorporation of weakly favorable mutations, which are fixed at a rate that is $1 + r/s$ times higher than populations of constant size. In contrast, in populations that are declining in size, beneficial mutations have a much higher chance of being lost, especially when they are weakly selected.

Logistic growth and decline: Exponential growth or decline in population size cannot continue indefinitely. The logistic equation incorporates density-dependent growth such that the reproductive rate of individuals decreases linearly with population size. We consider populations that follow the logistic equation in continuous time:

$$\frac{dN_t}{dt} = r \left(1 - \frac{N_t}{K} \right) N_t, \quad (8)$$

whose solution is

$$N_t = K \frac{N_0}{N_0 + e^{-rt}(K - N_0)}, \quad (9)$$

where r is the intrinsic rate of growth of the population and K is its carrying capacity. Since dN_t/dt changes over time whenever $N_t \neq K$, P_t necessarily changes over time.

TABLE 1
The probability of fixation with exponential change in population size

Growth rate	Selection coefficient			
	$s = 0.001$	$s = 0.005$	$s = 0.01$	$s = 0.05$
$r = 0.01$	0.0217 (0.022)	0.0295 (0.03)	0.0391 (0.04)	0.1118 (0.12)
$r = 0.001$	0.0040 (0.004)	0.0119 (0.012)	0.0217 (0.022)	0.0955 (0.102)
$r = -0.001$	NAN	0.0079 (0.008)	0.0178 (0.018)	0.0919 (0.098)
$r = -0.01$	NAN	NAN	NAN	0.0750 (0.08)

The numerical solution to (5) is shown, followed in parentheses by the approximation $2(r + s)$. NAN indicates that there is no positive solution to (5) for P_i and the allele is very unlikely to fix in large populations.

Using the chain rule, (6) can be rewritten as a function of current population size (dP_i/dN_t) rather than as a function of time. This gives

$$\frac{dP_i}{dN_t} \cong -P_i \frac{(Ks + (K - N_t)r)}{N_t r (K - N_t)} + P_i^2 \frac{K}{2N_t r (K - N_t)}. \quad (10)$$

Equation 10 can be solved directly to give the probability of fixation at any time as a function of the population size at that time:

$$P_i \cong \frac{2sK(s + r)}{sK + rN_t}. \quad (11)$$

As expected, this reduces to $2s$ when the population size is constant ($N_t = K$) and to $2(s + r)$ when the population is growing exponentially ($N_t \ll K$). The same estimate for the fixation probability may be obtained using the diffusion model studied by KIMURA and OHTA (1974) (see APPENDIX).

We examined (11) numerically and found it to provide an excellent approximation for P_i when s and r are small (<0.1). When s or r is large or the population size is small, the diffusion approximation, (A1), can be used with (A8) to provide a more accurate estimate of P_i . In Figure 2, (11) is compared with exact numerical solutions for P_i obtained from (5). Changes in population size have a large impact on the probability of fixation when the current population size, N_t , is far from the carrying capacity, K , and when selection is weak.

Population cycles: In many species, population size changes cyclically over time, such that population growth is soon followed by population decline (KREBS and MYERS 1974; MYERS 1988). For cyclically varying populations, we can use the fact that P_i should return to the same value every cycle to obtain a solution to (6):

$$P_i \cong \frac{2}{\exp[st] N_t \left(\int -\exp[-st] \frac{1}{N_t} dt \right)}. \quad (12)$$

The integral in (12) has two components: the first,

$\exp[-st]$, decays over time for $s > 0$ and the second varies as the reciprocal of population size, $1/N_t$. For cyclic populations, if the time taken for a population to return to the same size, τ , is much shorter than the time scale of selection ($s\tau \ll 1$), then little decay will occur within a cycle and N_t may be replaced by its harmonic mean, \bar{N} :

$$-\exp[-st] \frac{1}{N_t} \cong -\exp[-st] E \left[\frac{1}{N_t} \right] = -\exp[-st] \frac{1}{\bar{N}}. \quad (13)$$

In this case, (12) becomes

$$P_i \cong \frac{2s\bar{N}}{N_t}, \quad (14)$$

as obtained by EWENS (1967) using an iterative branching process method. Note that, since the effective population size of a fluctuating population is approximately \bar{N} , (14) reduces to $P = 2s\bar{N}/N_t$ (KIMURA 1970). However, this method provides insight into the conditions under which the harmonic mean approximation should break down. When selection is strong and/or populations cycle slowly ($s\tau \geq 1$), the exponential function within the integral of (12) will decay substantially within a cycle and it will then matter when in the cycle the mutation appears and how the population changes over the short term. In addition, populations with large fluctuations in size should be more poorly described by (14), since large amplitude fluctuations will magnify the decay within a cycle of the function integrated in (12). In either case, the harmonic mean approximation (14) should perform poorly.

We now examine some special cases of cyclically varying populations, starting with a population whose size varies sinusoidally:

$$N_t = \bar{N} + \alpha \sin [2\pi t/\tau], \quad (15)$$

where \bar{N} is the arithmetic average population size, α is the amplitude of fluctuations and τ is the period of the sine wave in generations. The integral in (12) cannot be solved directly using (15) for N_t , but the harmonic

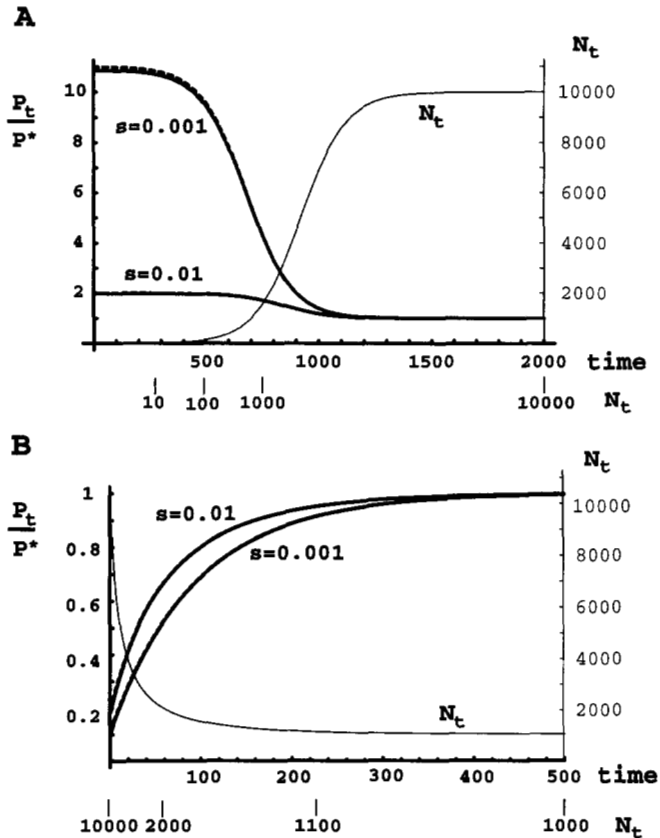


FIGURE 2.—Changes in the probability of fixation of a beneficial mutation under the logistic model. The heavy curves show the probability of fixation scaled to the expected fixation probability in a population of constant size, P^* . Dashed lines show the approximation from (11) and solid lines show the numerical solution to (5), although these curves are indistinguishable. The light curves show the size of a diploid population changing according to the logistic equation with $r = 0.01$. (A) An initial population size of one with a carrying capacity of 10,000. (B) An initial population size of 10,000 with a carrying capacity of 1000. The fixation probability is most strongly affected during the early generations when population growth is nearly exponential. This effect decreases as the population approaches carrying capacity.

mean of (15), $\tilde{N} = \sqrt{N^2 - \alpha^2}$, can be used in the approximation (14). This provides a remarkably accurate estimate of the change over time in the probability of fixation of new beneficial mutations when $s\tau \ll 1$ (Figure 3A). When $s\tau$ is small, the probability of fixation depends primarily on the current population size relative to the harmonic mean population size and is fairly insensitive to whether the population size will increase or decrease in the immediate future. The harmonic mean approximation breaks down, though, as $s\tau$ increases (Figure 3B), since the fate of a new mutation becomes more sensitive to whether the population is growing or shrinking when the mutation appears. If the population size is growing, the probability of fixation is higher than predicted by the harmonic mean approximation; if the population size is shrinking, the probability of fixation is lower than predicted. This

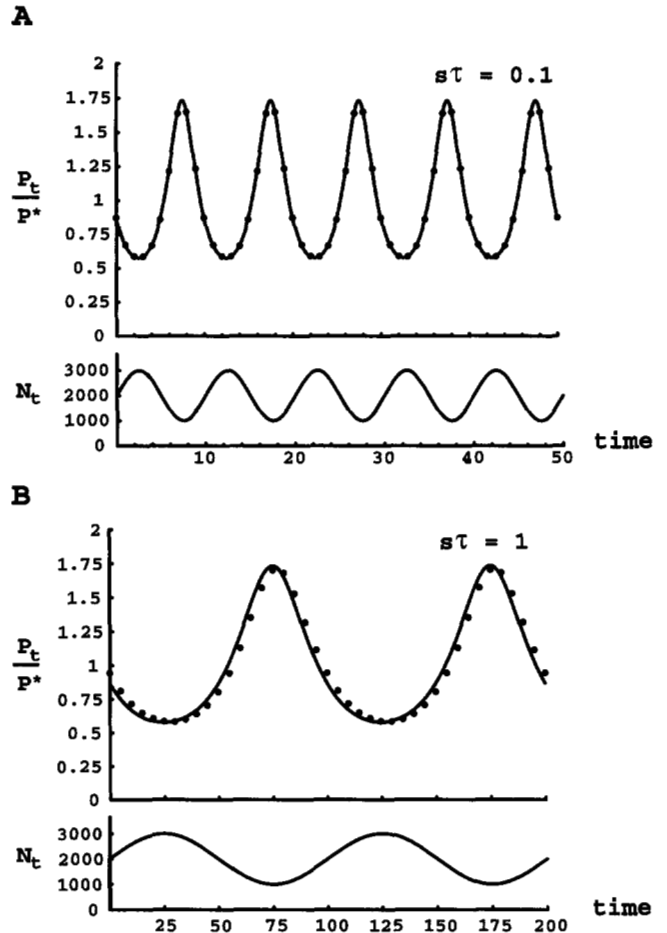


FIGURE 3.—Change in the probability of fixation of a beneficial mutation ($s = 0.01$) in a diploid population whose size varies sinusoidally. In each case, the population size varies with an amplitude of 1000 around an arithmetic mean size of 2000, as shown at the bottom of each graph. In the upper part of each graph, the probability of fixation is shown scaled to the expected fixation probability in a population of constant size, P^* . Dots show the numerical solution to (5) and curves show the harmonic mean approximation, $P_t \cong 2s\tilde{N}/N_t$, from (14). (A) Period, τ , of population size fluctuations equals 10 generations ($s\tau = 0.1$). (B) Period, τ , equals 100 generations ($s\tau = 1$). The harmonic mean approximation estimates the fixation probability extremely accurately when $s\tau$ is small, but less accurately when $s\tau$ is large.

causes the phase shift toward the right observed in Figure 3B.

Other cyclic functions show similar behavior, with the harmonic mean approximation, (14), working best when the cycle length is shorter than the time scale of selection. For example, we considered population size fluctuations described by a sine function on a natural log scale. This function is thought to often be a better descriptor of natural variation in population size (MYERS 1988). The harmonic mean of the log-sine function was determined numerically for parameters similar to those used in Figure 3. We again found that (14) provides an excellent estimate of P_t when $s\tau$ is small and that there is a phase shift to the right as $s\tau$ increases.

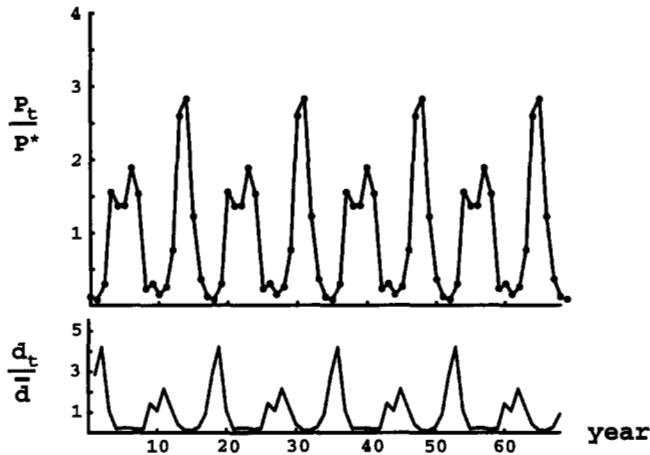


FIGURE 4.—Change in the probability of fixation of a beneficial mutation in snowshoe hare populations. Hare densities were measured within a 34 hectare trapping grid in Kluane, Yukon Territory, over a period of 20 years (data from KREBS *et al.* 1995 and C. KREBS, personal communication). Seventeen spring measurements of adult hare density (from 1980 to 1996) are used to define two cycles, which are typically 8–11 yr in length (KREBS 1996). The density over time divided by the mean density is shown at the bottom of the graph for four repetitions of the two basic cycles. The top part of the graph shows the probability of fixation of beneficial alleles over time, relative to the fixation probability in a population of constant size, P^* . Dots show the numerical solution to (5) and curves show the harmonic mean approximation, $P_t \cong 2s\bar{d}/d_t$. In this case, $s = 0.01$ and $s\tau = 0.085$, and the harmonic mean approximation accurately estimates the fixation probability.

Often, however, population size does not follow a simple function. In cases where populations have been measured over long periods of time, this data may be used directly in (5) to calculate the fixation probability over time. In many cases, total population size may not be known, but relative changes in population size or density may be available. Either of these types of data may be used in (5) to determine the probability of fixation at any point in a cycle. For instance, given density measurements, d_t , and assuming that the species range remains constant, we may replace N_{t+1}/N_t with d_{t+1}/d_t in (5), which may then be solved numerically. An example is shown in Figure 4 using fluctuations in density in snowshoe hares (KREBS *et al.* 1995; C. KREBS, personal communication). In this example, we have chosen $s\tau$ to be small ($s\tau = 0.085$) and the probability of fixation is very well approximated by (14) rewritten in terms of density, $P_t \cong 2s\bar{d}/d_t$. As selection becomes stronger, however, the probability of fixation becomes more sensitive to short-term changes in population size and the harmonic mean approximation again breaks down.

FIXATION RATES AND THE EFFECTIVE POPULATION SIZE

KIMURA (1970) conjectured that in populations of fluctuating size the probability of fixation of favorable

alleles depends on the ratio of effective to census population size and is approximately $2sN_e/N_t$. For models in which population size changes monotonically, KIMURA and OHTA (1974) found that the probability of fixation is approximately $2sZ_t/N_t$, where Z_t was interpreted as the “representative effective population size.” We, therefore, define the *fixation effective population size* as the solution to the equation: $P_t \cong 2sN_e/N_t$. For the models studied within this paper, this gives

$$N_e = \frac{N_0N_1}{N_1 + (N_0 - N_1)e^{-s(T-t)}} \quad (17)$$

for a population that changes from size N_0 (for $t \leq T$) to N_1 (for $t > T$) while $t \leq t$,

$$N_e = N_t(1 + r/s) \quad (18)$$

for a population with exponential growth or decline,

$$N_e = \frac{N_tK(s+r)}{sK + rN_t} \quad (19)$$

for a population with logistic growth or decline, and

$$N_e \cong \tilde{N} \quad (20)$$

for cyclically varying populations. In the first three cases, the fixation effective population size depends on both the current population size *and* on the selective effect of the allele. That is, there is no single effective population size that can be used to determine the probability of fixation for all new beneficial mutations in a population of changing size. The reason for this is that the sensitivity of the probability of fixation to future changes in population size depends on the time scale of the fixation event itself, which will vary with s . When s is large, only short-term population size changes will have an effect on the fate of a mutation, whereas when s is small, long-term changes in population size also become important.

As shown in the APPENDIX, the above estimates for N_e can be used in (1) to obtain an approximate solution for the fixation probability from the diffusion model. The advantage of the diffusion equation (1) is that it can be used to determine the probability of fixation under more general conditions, providing estimates for P_t when the population size is small and even when the allele is deleterious. In the next section, we evaluate the use of (1) under such conditions.

SMALL POPULATION SIZE AND DELETERIOUS MUTATIONS

In small populations, the diffusion equation (1) with (17)–(20) may be used to obtain the expected probability of fixation for beneficial alleles. Equation 1 may also be used to determine the expected probability of fixation for deleterious mutations with one caveat. Deleterious alleles have a much lower probability of fixation, but *conditional on fixation* the expected time until fixa-

TABLE 2
The probability of fixation for small N_e

Demographic model	Parameters	s	Predicted probability of fixation	Observed probability of fixation
Constant		0.01	0.0229	0.0227 (0.00015)
		-0.01	0.00316	0.00303 (0.000055)
Single change	$N_i = 200$ $\tau = 10$	0.01	0.0368	0.0365 (0.00019)
		-0.01	0.000990	0.000867 (0.000029)
	$N_i = 50$ $\tau = 10$	0.01	0.0161	0.0164 (0.00013)
		-0.01	0.00568	0.00571 (0.000075)
Exponential	$r = 0.001$	0.01	0.0245	0.0241 (0.00015)
		-0.01	0.00277	0.00277 (0.000053)
	$r = -0.001$	0.01	0.0214	0.0218 (0.00015)
		-0.01	0.00360	0.00355 (0.000059)
Logistic	$K = 200$ $r = 0.1$	0.01	0.0369	0.0364 (0.00019)
		-0.01	0.000980	0.000853 (0.000029)
	$K = 50$ $r = 0.1$	0.01	0.0161	0.0164 (0.00013)
		-0.01	0.00569	0.00552 (0.000074)
Sinusoidal	$\alpha = 90$ $\tau = 10$	0.01	0.0149	0.0153 (0.00012)
		-0.01	0.00629	0.00624 (0.000079)
	$\alpha = 90$ $\tau = 100$	0.01	0.0149	0.0186 (0.00014)
		-0.01	0.00629	0.00491 (0.000070)

Predicted values of the probability of fixation were obtained from the haploid version of (1) with N_e replaced by $N_e/2$. N_e is given by (17) for a single change in population size, by (18) for exponential growth, by (19) for logistic growth, and by (20) for sinusoidal fluctuations. Observed values of the probability of fixation were obtained from simulations in which a single allele with advantage or disadvantage s was introduced into a population of initial size, $N_0 = 100$. Values in parentheses are standard errors.

tion is the same for deleterious and beneficial alleles (MARUYAMA and KIMURA 1974; EWENS 1979, p. 151). Since N_e measures the effective population size over the time scale of the fixation event, it is therefore the same for deleterious and beneficial alleles that have selective effects of the same magnitude. Consequently, for any allele, the absolute value of s should be used in (17) – (20) to determine N_e . This value of N_e can then be used in (1) to determine the expected probability of fixation of deleterious alleles, with s in (1) retaining its negative sign.

To verify these predictions, Monte-Carlo simulations were performed using the Wright-Fisher model for a haploid population whose size changes over time. In the first generation, a single copy of a mutant allele was introduced into the population. Every generation, N_t individuals were sampled from the previous generation using a binomial distribution. The probability of sampling the mutant allele was set equal to its frequency in the previous generation times $(1 + s) / \bar{W}_{t-1}$, where \bar{W}_{t-1} was the mean fitness in the previous generation. The population was tracked until the mutant allele was either fixed or lost from the population. One million replicates were performed for each parameter set. The results are shown in Table 2, using $s = 0.01$ and $s = -0.01$, and assuming an initial population size of 100. Despite the fact that $N_e s$ was neither large nor always

positive in the simulations (as assumed in the APPENDIX), there is good agreement between the observed and predicted fixation probabilities (Table 2). In the case of a sinusoidally varying population size, the simulations were begun in the middle of the increase phase; we therefore expect (20) to underestimate the effective population size, especially when $s\tau$ is large, which is consistent with the observations.

Since deleterious alleles are more likely to fix with smaller values of N_e , shrinking populations are more likely to accumulate deleterious alleles than are growing populations. This result is exactly the opposite of that obtained for beneficial alleles, where the fixation probability increases with higher values of N_e . The fact that shrinking populations are more likely to incorporate deleterious alleles may partially account for the observation from simulations that, once populations accumulate several deleterious mutations and start declining in size, deleterious mutations accumulate more and more rapidly driving the population to extinction, a phenomenon known as mutational melt-down (LYNCH and GABRIEL 1990).

THE FLUX OF BENEFICIAL ALLELES

A more important measure of the rate of evolution of a population than the probability of fixation of an

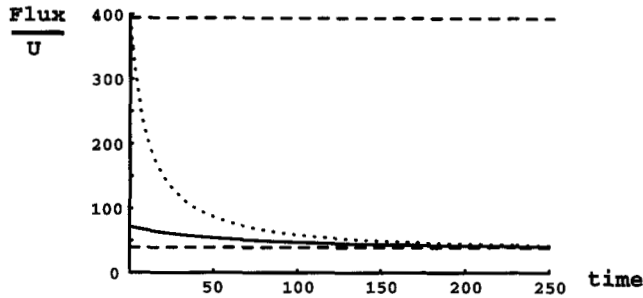


FIGURE 5.—Decrease in fixation flux in a diploid population declining in size according to the logistic equation. Parameters are the same as in Figure 2B with $s = 0.01$. Solid curve shows the fixation flux divided by the mutation rate ($2N_t P_t$), using (11) for P_t . Dotted curve shows the fixation flux divided by the mutation rate that would be observed if the probability of fixation remained constant at $P^*(2N_t P^*)$. The two dashed lines show the flux in populations of constant size: 10,000 (upper line) or 1000 (lower line). Notice that the fixation flux (—) is much lower than would be expected if the probability of fixation remained constant at P^* (· · · · ·).

allele is the total number of beneficial alleles that are incorporated (fixed) per generation, which we term the fixation flux. Letting U equal the genome-wide mutation rate to new beneficial alleles, the number of new beneficial mutations entering a diploid population per generation is $2N_t U$. If $2N_t U$ is small, then the fixation flux is approximately $2N_t U P_t$, *i.e.*, the number of new mutants times their expected probability of fixation. Written in terms of the fixation effective population size, this equals $4sUN_e$. If $2N_t U$ is large, however, beneficial alleles may appear simultaneously at different loci and interfere with the selective spread of one another, causing a reduction in P_t (BARTON 1995). Nevertheless, this reduction is modest when recombination rates are high, and the fixation flux is still approximately $4sUN_e$.

With exponential growth, the fixation flux is $4sUN_e(1 + r/s)$, which is $(1 + r/s)$ times higher than if the population remained constant at its current census size. The fixation flux is proportional to N_e and will necessarily be lower in small populations. For a given N_e , the fixation flux will be higher for populations that are expanding in size and lower for those that are shrinking. The reduction in fixation flux is especially severe for weakly favorable alleles, whose probability of fixation is effectively zero when $s < -r$. Selection in this case is rendered ineffective in shrinking populations, which will limit their ability to adapt to environmental change.

Similar results hold for logistic population growth, where now the fixation flux equals $4sUN_e K(s + r) / (sK + rN_e)$. Interestingly, since the fixation probability is sensitive to future changes in population size, the fixation flux approaches its asymptotic value, $4sUK$, faster than does the population size (Figure 5). When $s \ll r$, the fixation flux will be nearly equal to the flux of the population at carrying capacity and will be little affected by the current census size.

In cyclic populations, the fixation flux is approximately $4sUN_e$. This value does not vary over time and is always smaller than the fixation flux in a constant population with the same arithmetic mean size ($4sUN_e$), since $\bar{N} \leq \bar{N}$ is always true. For example, the fixation flux in snowshoe hare populations is approximately a quarter of what it would be in a constant population of the same average size. If the population size fluctuations are extreme, then the harmonic mean can be orders of magnitude smaller than the arithmetic mean, and the fixation flux will be substantially reduced. As noted earlier and illustrated in Figure 3, the harmonic mean approximation used in (14) is not accurate if selection is strong compared to the frequency of population size fluctuations or if population size fluctuations are extreme. This discrepancy becomes more apparent when looking at the fixation flux (Figure 6). When mutations occur while the population is expanding, a mutation has an increased probability of fixation due to the future short-term increase in population size, which is not well reflected in the long-term comparison of N_t to \bar{N} . The converse holds for mutations that occur while populations are decreasing in size. Consequently, the flux of mutations is increased during population expansions and decreased during population contractions (Figure 6). This has the interesting implication that populations will be slightly less able to adapt to whatever external conditions are associated with declines in population size (*e.g.*, higher predator density) than to conditions associated with increases in population size, especially if the period of the population cycle is long and selection is strong ($s\tau \gg 1$).

DISCUSSION

The probability of fixation of both beneficial and deleterious mutations is substantially affected by changes in population size. In growing populations, selection is more effective, increasing the probability that beneficial alleles are fixed and that deleterious alleles are lost. Conversely, in shrinking populations, selection is less effective: beneficial mutations are less likely to fix while deleterious alleles are more likely to fix. The reason that the probability of fixation of an allele depends on demographic patterns is straightforward. While a beneficial allele is rare, it may be lost in spite of its selective advantage if, by chance, all carriers fail to reproduce. If the population is growing, however, this is less likely to happen since the expected number of offspring per parent is increased. This will reduce the amount of sampling error or genetic drift that occurs. Similarly, in declining populations, all parents have fewer offspring on average and there is a higher chance that all parents carrying a beneficial allele will simply fail to leave offspring. This will increase the amount of genetic drift in the population. Beneficial alleles and deleterious alleles exhibit opposite behavior as a func-

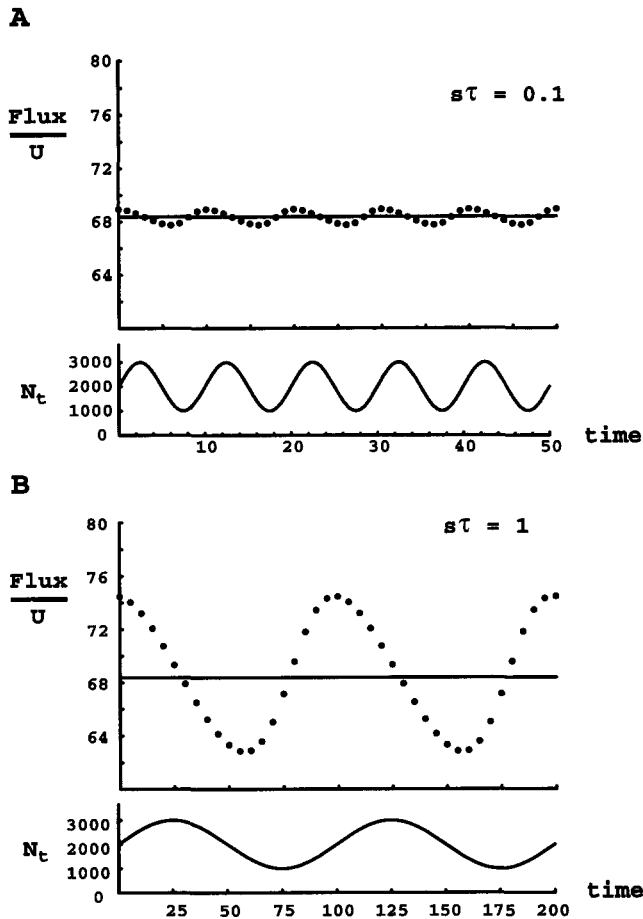


FIGURE 6.—Changes in the fixation flux of a beneficial mutation in a diploid population whose size varies sinusoidally. Population size fluctuations are shown at the bottom of each graph for comparison (parameters are the same as in Figure 3). The fixation flux divided by the mutation rate, $2N_t P_t$, is determined numerically using (5) (· · · · ·) and compared with the expectation from (14) that the fixation flux divided by the mutation rate should be constant over time, $2N_t P_t = 4s\bar{N}$. (A) Period, τ , of population size fluctuations equals 10 generations ($s\tau = 0.1$). (B) Period, τ , equals 100 generations ($s\tau = 1$). With increasing $s\tau$, the harmonic mean approximation for the fixation flux breaks down. The fixation flux then becomes sensitive to short-term changes in population size, being higher than expected when the population is growing and lower than expected when it is shrinking.

tion of changes in population size since increased genetic drift slows the selective spread of beneficial alleles but also slows the selective elimination of deleterious alleles.

The results presented in this paper use branching processes to find the probability of fixation, P_t , of a new allele. This technique is straightforward and easy to apply to models of population size change, but it is limited to the case where the allele is beneficial and the population size is large. We may, however, define a "fixation effective population size" by setting $P_t \equiv 2sN_e/N_t$ as in (17) – (20). The fixation effective population size can then be used in the more general formula, (1), based on a diffusion model (see APPENDIX).

It is critical to point out, however, that the fixation effective population size defined in this way is generally a function of the selection coefficient of the allele. It therefore does not meet the strict definition of an effective population size since it is not independent of the characteristics of the allele. We persist in using this term for two reasons. The first is that it makes sense that the fixation effective population size of an allele should depend on s in a population that is changing in size. s determines the time frame over which fixation occurs, and the probability of fixation should be sensitive to changes in population size only if they occur within this time frame. Second, as shown in the APPENDIX, N_e defined in this way can be used directly in the diffusion equation (1) for the probability of fixation, derived originally by KIMURA (1964) under the assumption of a constant population size. The diffusion equation can then be used to determine the probability of fixation for deleterious alleles (Table 2) and for alleles that are initially present in more than a single copy. For example, one can then calculate the fixation probability of beneficial alleles that were previously neutral or deleterious and that are already present in the population at some frequency. We now discuss the implications of these results to various processes of evolutionary and practical interest.

Models of speciation that include periods of small population size followed by population growth, such as CARSON's founder-flush model (CARSON 1975), suggest that the probability of fixation of favorable genes may be increased by a founder-flush process (SLATKIN 1996). While it is true that the probability of fixation of beneficial alleles present during the bottleneck is increased by the subsequent flush phase, many alleles will be lost during the bottleneck and few new mutations will occur while the population is of small size. Consequently, the number of beneficial mutations fixed per generation (the fixation flux) is nearly unchanged by a bottleneck. Consider the extreme case of a diploid population of size N_{Hi} that experiences a single generation bottleneck of size N_{Lo} . In the section on single changes in population size, we found that the probability of fixation of a beneficial allele is approximately $2s$ in every generation except the bottlenecked generation, in which case it is $2sN_{Hi}/N_{Lo}$. The fixation flux, however, is the probability of fixation times the current population size times the mutation rate, which remains roughly constant at $4sN_{Hi}U$, just as in a population without a bottleneck. In short, population bottlenecks do not change the fixation flux of beneficial alleles, at least for additively acting genes. Recessive alleles should behave quite differently (see ROBERTSON 1952; KIMURA 1962; SLATKIN 1996).

Thus far, we have assumed that relative fitnesses remain constant as populations change in size. Episodes of dramatic environmental change can, however, cause strong changes in the fitness of genotypes. For example,

think of the pattern of selection on pest insects associated with the application of a new pesticide. Under these circumstances, alleles for pesticide resistance that were previously neutral or deleterious will be strongly favored. Furthermore, while the remainder of the insect population will be reduced dramatically, the population size of those individuals carrying the resistance genes will increase if the population growth rates are at all density dependent. That is, while N_{t+1}/N_t will be <1 for the population as a whole, it will be >1 for those individuals that are resistant because the insecticides causing the population decline do not affect them and because there is less intraspecific competition as the nonresistant individuals die. Resistance alleles are therefore highly likely to fix despite the fact that the population as a whole is decreasing in size. This will not be true of alleles conferring partial resistance, however, since the population of partially resistant individuals is still likely to decline in size, resulting in a decreased fixation probability for these alleles. Hence, when extrinsic factors cause a reduction in population size, alleles of large effect are much more likely to fix both because they have a higher selective effect and because they are less affected by the extrinsic causes of population size decline. This pattern of large effects in response to strong selection has been observed repeatedly (ORR and COYNE 1992).

The conservation biology implications of the results presented in this paper are rather unfortunate. Conserving biological diversity will, in the long run, depend on the ability of populations to adapt to the dramatic environmental changes caused by mankind (SOULÉ 1983). Species that are highly commensal with humans and increasing in size will be all the more likely to incorporate new adaptive mutations. Declining populations, however, suffer a twofold blow. Not only is the number of new beneficial mutations dropping as a result of smaller and smaller population sizes, but the probability of fixation of each beneficial allele is declining as well. Consequently, the rate at which beneficial mutations are incorporated into the population will be much less than would be predicted as a result of the current population size (Figure 5). Adaptation to new environments in times of population decline will occur at a rate more closely proportional to the lowest population size, even if that low population size is still to come. Species that are not highly commensal with humans, whose population size and distribution are reduced as a consequence of human activity, will be less able to adapt to changing environmental circumstances and more likely to go extinct as a consequence.

In this article, we have developed simple formulae to describe the probability of fixation and fixation flux of beneficial and deleterious alleles under several models of population size change: a single change, exponential growth, logistic growth, and fluctuating size. These formulae can be used to determine the effect of demo-

graphic changes on the rate of adaptive evolution, defined as the rate of incorporation of beneficial alleles. In general, increases in population size make selection more effective and increase the rate of adaptation, while decreases in population size have the opposite effect. As we have seen, the effect of population size changes on the fixation probability of an allele can be quite dramatic, especially when the rate of growth or decline in the population is large relative to the selective effects of the alleles.

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APPENDIX

KIMURA and OHTA (1974) analyzed a time inhomogeneous diffusion model to determine the probability of fixation in populations changing in size over time. For alleles that start at low frequency, p , they found that an approximate solution to the diffusion equation is given by

$$P_t = \frac{1 - \exp[-4Z_t s p]}{1 - \exp[-4Z_t s]}, \quad (A1)$$

which has the same form as the solution, (1), found for the time homogeneous diffusion model in which the population size remains constant. Z_t was interpreted as the "representative effective population size that is applicable throughout the process of gene fixation." Z_t was shown to solve

$$\frac{dZ_t}{dN_t} = - \frac{(1 - \exp[-4Z_t s]) Z_t (N_t - Z_t)}{1 - (1 + 4Z_t s) \exp[-4Z_t s]} \frac{1}{N_t} \frac{dN_t}{dt}. \quad (A2)$$

To proceed further, KIMURA and OHTA (1974) assumed that $Z_t s$ is positive and large such that $\exp[-4Z_t s] \ll 1$ and $4Z_t s \exp[-4Z_t s] \ll 1$, in which case (A2) becomes

$$\frac{dZ_t}{dN_t} = - \frac{Z_t s (N_t - Z_t)}{N_t} \frac{dN_t}{dt}. \quad (A3)$$

Under the assumption that $Z_t s$ is large and positive, (A1) becomes

$$P_t \cong 4Z_t s p = 2s Z_t \frac{n}{N_t}, \quad (A4)$$

assuming that $2s Z_t n / N_t \ll 1$, where n is the initial number of copies of the allele in the population.

We now proceed to show that solving (A3) with (A4) for P_t is equivalent to solving the differential equation (6) obtained from the branching process. To begin, the derivative of (A4) with respect to t is

$$\frac{dP_t}{dt} = -2sn Z_t \frac{dN_t}{dt} \frac{1}{N_t^2} + 2sn \frac{dZ_t}{dt} \frac{1}{N_t}. \quad (A5)$$

Since

$$\frac{dZ_t}{dt} = \frac{dZ_t}{dN_t} \frac{dN_t}{dt},$$

we find that

$$\frac{dZ_t}{dt} = - \frac{Z_t s (N_t - Z_t)}{N_t}$$

from (A3). This may be used in (A5) along with the fact that $Z_t = P_t N_t / 2sn$ from (A4) to obtain

$$\frac{dP_t}{dt} = -s P_t - P_t \frac{dN_t}{dt} \frac{1}{N_t} + \frac{P_t^2}{2n}, \quad (A6)$$

which equals (6) when $n = 1$. Furthermore, in the branching process model, if we had assumed that there were n initial copies of the new allele, where n is not large, the probability that at least one allele would eventually fix would be $Q_t = 1 - (1 - P_t)^n \cong n P_t$. By the chain rule, since P_t solves (6), Q_t will solve a differential equation of the same form as (A6) for $n > 1$.

Therefore, estimates of the fixation probability obtained by the method of branching processes provide estimates for Z_t from (A4) that may be used in (A1) to give an approximate solution to the diffusion equation for the probability of fixation. Although this proof assumes that $Z_t s$ is large and positive, simulations indicate that Z_t estimated in this way can be used in (A1) to provide reasonable estimates of the fixation probability even when $Z_t s$ is small and when s is negative (Table 2).

For the particular model of logistic population growth, KIMURA and OHTA (1974) solved (A3) for the diffusion model, writing the solution as

$$Z_t = N_t \frac{\left(\frac{N_t}{K}\right)^{-1-s/r} \left(1 - \frac{N_t}{K}\right)^{s/r}}{\int_{N_t/K}^1 q^{-2-s/r} (1-q)^{s/r-1} dq}. \quad (A7)$$

The integral in this equation may, however, be evaluated to give

$$Z_t = \frac{KN_t(s+r)}{sK+rN_t}. \quad (A8)$$

Using this value of Z_t in (A4) and assuming that $n = 1$, we find that the probability of fixation is given by (11) as obtained by the method of branching processes.