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IS THE POPULATION SIZE OF A SPECIES RELEVANT TO ITS EVOLUTION?

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Abstract.—This paper examines aspects of genetic draft, the stochastic force induced by substitutions at one locus on the dynamics of a closely linked locus. Of particular interest is the role of population size on genetic draft. Remarkably, the rate of substitution of weakly selected advantageous mutations decreases with increasing population size, whereas that for deleterious mutations increases with population size. This dependency on population size is the opposite of that for genetic drift. Moreover, these rates are only weakly dependent on population size, again contrary to the strong dependency of drift-based dynamics. Four models of the strongly selected loci responsible for genetic draft are examined. Three of these exhibit a very weak dependency on population size, which implies that their induced effects will also be weakly dependent on population size. Together, these results suggest that population size and binomial sampling may not be relevant to a species' evolution. If this is the case, then a number of evolutionary conundrums are resolved.

Key words.—Binomial sampling, genetic draft, genetic drift, hitchhiking, molecular evolution, natural selection, population size.

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Evolutionary forces are often divided into two sorts: stochastic and deterministic (Wright 1955). Genetic drift is considered to be the most important of the stochastic forces in the evolution of natural populations. Its effects may be summarized by the first two moments of the change in the frequency of a neutral allele,

$$E\{\Delta x\} = 0 \quad \text{and} \tag{1}$$

$$\text{Var}\{\Delta x\} = \frac{x(1-x)}{2N}, \tag{2}$$

where x is the frequency of the allele and N is the population size. The variance in the change points out the important role played by population size in evolution. When genetic drift interacts with the deterministic forces of selection and/or mutation, we obtain some fundamental quantities that have shaped much of our intuition about evolution: $4Nu$ is the nucleotide heterozygosity at neutral loci, where u is the rate of mutation to new alleles; $2Nus$ is the substitution rate of advantageous mutations, where $s > 0$ is the selective advantage of new alleles; and $2Nus/(e^{2Ns} - 1)$ is the substitution rate of deleterious mutations ($s < 0$). Each of these three expressions exhibits a strong dependency on population size, which quite naturally leads to the prediction that we should see the footprint of population size in any appropriate observation we choose to make on natural populations. In fact, the footprint should be huge, because the population sizes of contemporary species commonly differ by several orders of magnitude.

The history of molecular evolution studies has been that there are no conspicuous footprints of population size (Lewontin 1974; Kimura 1983; Gillespie 1991). For example, estimates of silent (Nachman 1997) or amino acid (Nevo et al. 1984) variation among species are distressingly similar, suggesting at face value that the effective sizes of most species—from bacteria to humans—are within one order magnitude of each other (Lewontin 1974), a conclusion that belies our understanding of the relative abundances of species.

Several hypotheses have been proposed to account for the insensitivity of molecular evolution to population size. Ohta (1973, 1976, 1992) has shown that if amino acid mutations are slightly deleterious, then protein variation should be insensitive to population size. However, her theory does not easily account for the insensitivity of the rate of protein evolution to N. Cherry (1998), building on the work of Hartl et al. (1985), described an epistatic model that evolves toward $Ns \approx 1$, which causes rates of substitution across species to converge. Neither of these theories applies to neutral variation, and thus they may not be able to account for the insensitivity of silent variation to population size. Nei and Graur (1984) argued that a combination of population bottlenecks and historical effects may blunt the effects of N on evolution. Finally, Maynard Smith and Haigh (1974) suggested that hitchhiking is analogous to bottlenecks in its ability to reduce genetic variation and render it less sensitive to population size.

Maynard Smith and Haigh's hypothesis languished until a series of studies demonstrated that genetic variation is reduced in regions of low recombination (Aguadé et al. 1989; Miyashita 1990; Berry et al. 1991; Begun and Aquadro 1992; Aguadé and Langley 1994). Hitchhiking provides an obvious explanation for this phenomenon, although other mechanisms, such as background selection (Charlesworth et al. 1993; Charlesworth 1994), can account for the reduction as well. If hitchhiking is important in regions of low recombination, then it is worthwhile entertaining the possibility that it is important in regions of normal recombination as well. If so, then we must seriously consider Maynard Smith and Haigh's (1974) claim that hitchhiking may remove the dependency of molecular evolution on population size.

In two recent papers (Gillespie 2000a,b), I have viewed hitchhiking as a stochastic force analogous to genetic drift. I called this force ''genetic draft'' to emphasize its similarity to genetic drift and to carry on the hitchhiking metaphor. These studies are based on computer simulations of a neutral locus that is tightly linked to a locus under strong directional selection. Figure 1 is a typical result of such a simulation. It demonstrates two important aspects of genetic draft: (1)

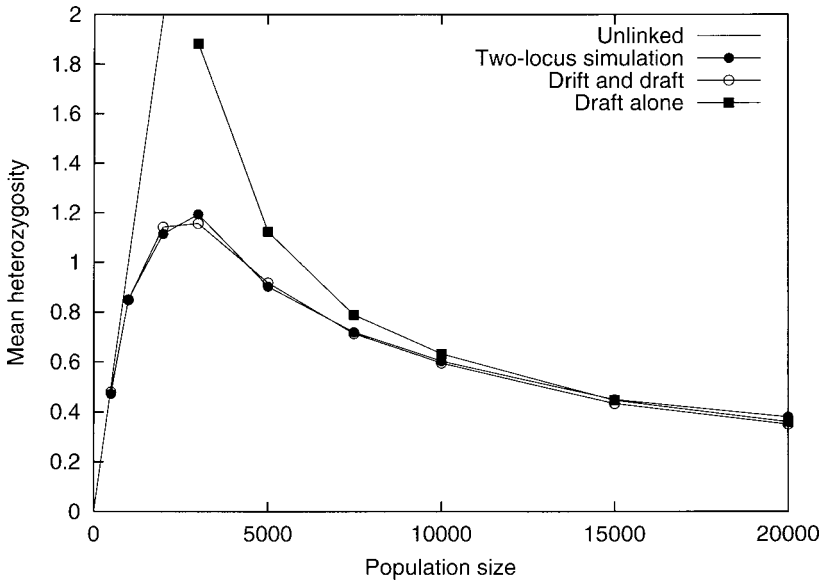

FIG. 1. The mean heterozygosity at a neutral locus that is tightly linked to a strongly selected locus. The mutation rate at the neutral locus is $u = 2.5 \times 10^{-4}$. For the strongly selected locus, the selection coefficient $\sigma = 0.1$ and the mutation rate $v = 5 \times 10^{-7}$. The curve marked ''Drift and draft'' comes from equation (8) and that marked ''Draft alone'' comes from equation (5). In both cases $y = 1$ and ρ_N is obtained from the two-locus simulation. The ''Unlinked'' curve is for an isolated neutral locus.

the mean heterozygosity at the neutral locus ultimately decreases as a function of population size; and (2) once N is sufficiently large, the heterozygosity becomes relatively insensitive to N. A third important aspect of genetic draft is that its stochastic dynamics share many properties with those of genetic drift.

If we assume that hitchhiking events form a Poisson process and occur very quickly relative to the time between them, then the first two moments of the change in the frequency of a hitchhiking neutral allele in an infinite population may be approximated by

$$E\{\Delta x\} = 0 \quad \text{and} \tag{3}$$

$$\text{Var}\{\Delta x_i\} = x(1 - x)\rho_N E\{y^2\}, \tag{4}$$

where y, a random variable, is the ultimate frequency of the single copy of the neutral allele that happens to be linked to the strongly selected mutation and ρ_N is the rate of substitution at the strongly selected locus (Gillespie 2000a). The distribution of y is determined, in part, by the amount of recombination and the strength of selection at the strongly selected locus. Thus, even though hitchhiking alleles move in jumps rather than diffusing like drifting alleles, the first two moments of their change are the same if we simply exchange $1/2N$ in drift-based evolution for $\rho_N E\{y^2\}$ for draft-based evolution. Because much of our understanding of the consequences of genetic drift depend only on these two moments, this understanding carries over unaltered for drafting alleles. For example, the mean heterozygosity for an infinite-sites, no-recombination model of a gene in an infinite population is

$$\frac{2u}{\rho_N E\{y^2\}}, \tag{5}$$

rather than $4Nu$ as for a drift-based model. This function is plotted in Figure 1 (the curve labeled ''Draft alone'') and does, in fact, converge to the simulated values as $N \to \infty$.

In a finite population where both drift and draft are at work, the variance in the change in x is

$$\text{Var}\{\Delta x\} \approx x(1 - x)\left(\frac{1}{2N} + \rho_N E\{y^2\}\right), \tag{6}$$

which shows immediately that the variance effective size is

$$N_e = \frac{N}{1 + 2N\rho_N E\{y^2\}}. \tag{7}$$

The heterozygosity predicted by this effective size is

$$\frac{4Nu}{1 + 2N\rho_N E\{y^2\}}, \tag{8}$$

which is also graphed in Figure 1 (the curve labeled ''Drift and draft''). The agreement with the simulations is excellent, which gives some confidence that the use of N_e is appropriate in this context.

This brief summary of work on genetic draft shows that surprisingly little in population genetics would change if draft were the main stochastic force acting in natural populations. The one big change involves the role played by population size. For neutral drafting alleles, the dependency of the heterozygosity on N is the opposite of that of drifting alleles. In the next section we will see that the same is true for weakly selected drafting alleles. That is, we will see that the rate of substitution of advantageous mutations decreases with increasing population size, whereas the rate of substitution of deleterious mutations increases with population size. In all three of these cases, population size has its greatest effect via ρ_N, which is an increasing function of population size. (For example, see the curve labeled ''Shift model'' in Figure 6.) I will show in a later section that ρ_N is itself insensitive

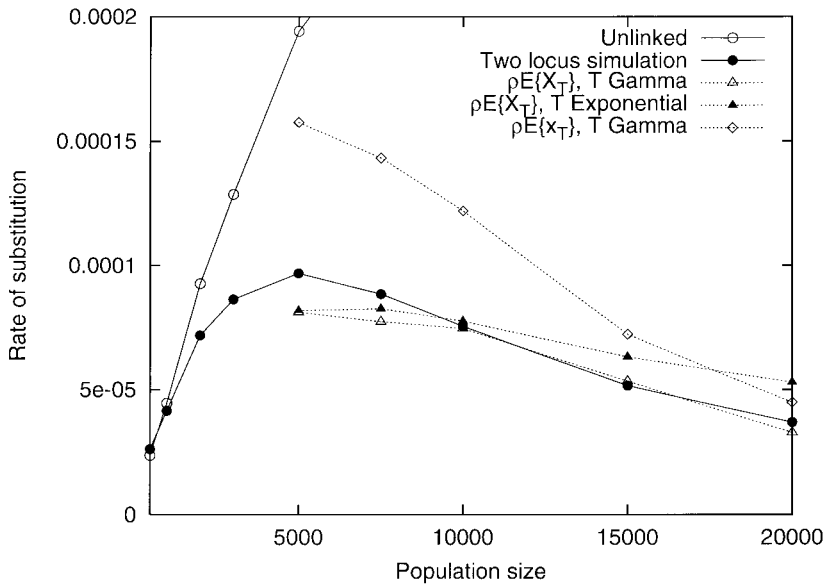

FIG. 2. The rate of fixation of advantageous mutations at a weakly selected locus linked to a strongly selected locus. For the weakly selected locus $u = 5 \times 10^{-6}$ and $s = 0.005$. For the strongly selected locus, $\sigma = 0.1$ and $v = 5 \times 10^{-7}$. The two curves labeled $\rho E\{X_T\}$ use equation (9) and the curve labeled $\rho E\{x_T\}$ uses equation (13).

to N for some very plausible models of evolution. This raises the uncomfortable possibility that population size may play only a minor role in evolution. This conjecture, which is the major conclusion of this paper, removes the lack of dependency of molecular evolution on population size from the list of evolutionary conundrums.

WEAKLY SELECTED LOCI

In this section I will examine the rate of substitution of weakly selected advatangeous and deleterious alleles that are subject to the combined effects of genetic drift and draft. For simplicity, I will only consider that case of complete linkage between the weakly and strongly selected loci.

The curve labeled ''Two-locus simulation'' in Figure 2 is the rate of substitution of weakly selected advantageous mutations at a locus that is linked to a strongly selected locus. The figure shows the surprising result that the rate of substitution of advantageous mutations ultimately decreases with increasing population size. By contrast, the curve labelled ''Unlinked'' shows that the rate of substitution at a weakly selected locus with the same parameters but without a linked strongly selected locus increases with population size. Once again, we have both a qualitative and a quantitative difference between drift- and draft-based dynamics. An effective size interpretation of these differences, like the one that proved so valuable for variation at a linked neutral locus, does not work as well for weakly selected loci. Rather, it appears that the best way to understand this pattern is to consider the fate of weakly selected alleles as they increase following a selective sweep.

When a hitchhiking event occurs (i.e., a substitution occurs at the strongly selected locus), the probability that a copy of a particular weakly selected allele hitchhikes is the frequency of that allele at the time of the hitchhiking event. Let X_t be the frequency of a weakly selected allele, where time is set to begin (i.e., $t = 0$) at the previous hitchhiking event. The stochastic process $(X_t)_0^\infty$ reflects the combined effects of drift, mutation, and selection. If the time between hitchhiking events is represented by the random variable T, then the probability that the weakly selected allele hitchhikes to fixation is $E_X\{X_T \mid T\}$. The rate of substitution is the rate of substitution of strongly selected alleles, ρ_N, times the probability that a weakly selected allele hitchhikes,

$$k = \rho_N E_T\{E_X\{X_T \mid T\}\} = \rho_N E\{X_T\}. \quad (9)$$

Because this result depends on the transient dynamics of X_t, an exact analytic expression is difficult to obtain. However, Monte Carlo evaluation is possible by using a direct simulation of X_t and an approximate distribution for T.

The distribution of the time between hitchhiking events turns out to be important as seen in the disparate results for the gamma and exponential distributions for T illustrated in Figure 2. For each point on these curves, the moments for the distribution of T are obtained from the simulated properties of the strongly selected locus. For example, when $N = 15{,}000$, the mean time between substitutions at the strongly selected locus is 888 generations and the standard deviation is 709 generations. Thus, the substitutions occur more regularly than for a Poisson process. The departure from the Poisson process is often measured by the index of dispersion,

$$R = \frac{\mathrm{Var}\{T\}}{E\{T\}^2}. \quad (10)$$

When $N = 15{,}000$, $R = 0.63$, which indicates a remarkable level of regularity. If we assume (incorrectly) that the hitchhiking events form a Poisson process, then T will be exponentially distributed and $R = 1$. The fact that the curve for gamma distributed times is below that for exponential distributed times (for sufficiently large N) shows that the more

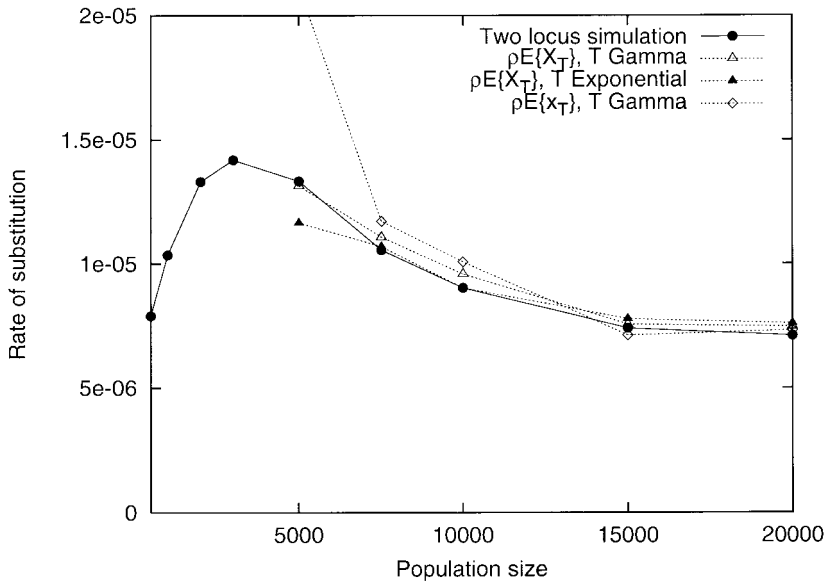

FIG. 3. The rate of fixation of advantageous mutations at a weakly selected locus linked to a strongly selected locus. For the weakly selected locus $u = 5 \times 10^{-6}$ and $s = 0.001$. For the strongly selected locus, $\sigma = 0.1$ and $v = 5 \times 10^{-7}$.

uniform spacing of strongly selected substitutions lowers the average rate of weakly selected substitution.

The Monte Carlo calculation of $\rho_N E\{X_t\}$ for gamma distributed times is very accurate. This might seem remarkable because the calculation implicitly assumes that the substitution process at the strongly selected locus is a renewal process. Were this not the case, then the distribution of T would depend on the previous history of the strongly selected substitution process. Fortunately, simulation studies suggest that the substitution process at the strongly selected locus for standard population genetics models is indistinguishable from a renewal process (Gillespie 1993, 1994a,b; Cutler 2000).

The dependency of the rate of substitution of weakly selected alleles on the distribution of the times between hitchhiking events depends, among other factors, on the strength of selection at the weakly selected locus. In Figure 3, for example, the strength of selection at the weakly selected locus is one-fifth that in Figure 2. With this reduction, the dependency of $E\{X_T\}$ on R has become very weak as evidenced by the closeness of the curves for the exponential and gamma distributed times.

The agreement between the rate of substitution in the simulation and the Monte Carlo calculation of $\rho_N E\{X_t\}$ gives us confidence that this approach captures most of the relevant dynamics at the weakly selected locus, at least as they pertain to the rate of substitution. However, it is not very instructive for understanding why the substitution rate decreases with population size or why the index of dispersion plays a role. The most expedient approach to this understanding is to approximate the dynamics at the weakly selected locus with the differential equation

$$\frac{dx}{dt} = sx(1 - x) + u(1 - x), \tag{11}$$

whose solution is

$$x_t = \frac{u}{s}\frac{e^{(s+u)t} - 1}{1 + (u/s)e^{(s+u)t}}. \tag{12}$$

Although this approach ignores the role played by genetic drift, Norman (1975) has shown that $X_t \to x_t$ as $N \to \infty$. Thus, we can expect our approximation to become more accurate with increasing population size. Evidence for this is given in Figures 2 and 3, which plot

$$\rho_N E\{x_T\}. \tag{13}$$

The agreement is better than might be expected because, by assumption, genetic drift plays no role in the dynamics of rare alleles. Apparently, recurrent mutation is sufficiently strong in these simulations that it and selection dominate the effects of drift.

Equation (13) may be further approximated under the assumption that selection is so weak that the allele frequency will not be very large when the first hitchhiking event occurs and that $|s| \gg u$. Under these assumptions, equation (12) may be approximated by

$$x_t \approx \frac{u}{s}(e^{st} - 1). \tag{14}$$

The probability that an allele hitchhikes is its frequency averaged over the time T until the next hitchhiking event. Let this time be gamma distributed according to

$$\frac{b^{-c}}{\Gamma(c)} t^{c-1} e^{-t/b}. \tag{15}$$

The mean of this distribution is $\mu = bc$; the ratio of the variance to the square of the mean is $R = 1/c$, which is the asymptotic index of dispersion of the point process. The probability that the weakly selected allele hitchhikes is the expectation of equation (14) with respect to equation (15), or

$$E\{x_T\} = \frac{u}{s}[(1 - s\mu R)^{-1/R} - 1]. \tag{16}$$

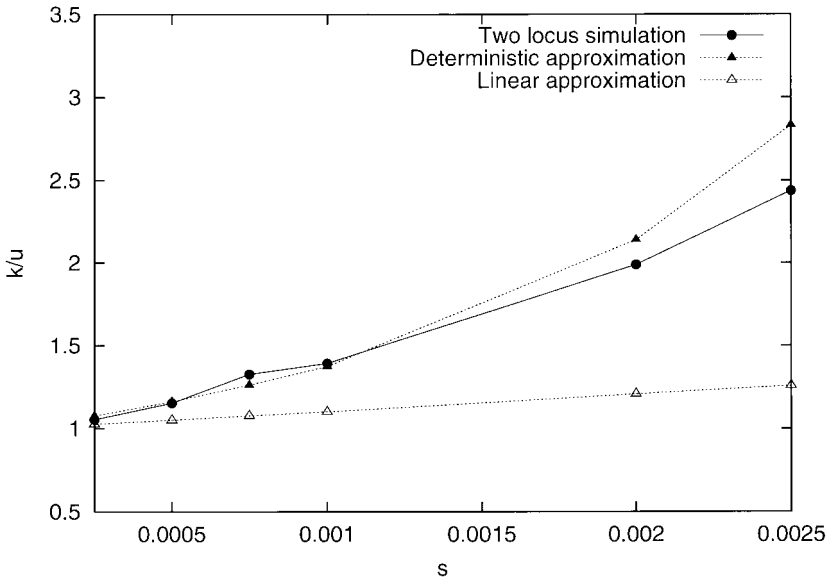

FIG. 4. The rate of fixation of advantageous mutations at a weakly selected locus linked to a strongly selected locus. For the weakly selected locus $u = 5 \times 10^{-6}$. For the strongly selected locus, $\sigma = 0.1$ and $\nu = 5 \times 10^{-7}$. The population size is $N = 20000$. The curve labeled ''Deterministic approximation'' uses equation (17); that labeled ''Linear approximation'' uses equation (19).

Note that this formula is only valid when $s\mu R < 1$. The rate of fixation, k, is ρ_N times this:

$$k = \rho_N E\{x_T\} = \rho_N \frac{u}{s}[(1 - s\mu R)^{-1/R} - 1]. \quad (17)$$

This rate, which is graphed on Figure 4 (the curve labeled ''deterministic approximation''), is remarkably accurate for small s.

Equation (17) yields to the following approximations

$$k \approx \frac{u}{s}(e^{s\mu + s^2\mu^2 R/2} - 1) \quad \text{and} \quad (18a)$$

$$k \approx u\mu(1 + s\mu R/2). \quad (18b)$$

Because $\rho_N = 1/\mu$, we have, finally,

$$k \approx u\left(1 + \frac{sR}{2\rho_N}\right). \quad (19)$$

This result captures most of the phenomenology seen in the simulations. First, the rate of substitution is inversely related to ρ_N. If ρ_N increases with population size, then the rate of substitution of advantageous mutations will decrease with population size, as we saw in the simulations. Second, the rate of substitution is an increasing function of R. Thus, as hitchhiking events become more regular (R decreases), the rate of substitution will decrease as well. Conversely, the rate of substitution at the weakly selected locus will be higher if the substitutions at the strongly selected locus are more clumped than random. Finally, the dependency of the rate of substitution on R becomes weaker as s decreases.

The approximation captured in equation (19) is rather poor as seen by the curve labeled ''linear approximation'' in Figure 4. It improves as $s \to 0$, but the rate of convergence is very slow. It is given here mainly to make the points found in the previous paragraph. These same points may be gleaned from equation (17) by examination of the derivatives of k with respect to R and ρ_N, as may be verified by the reader.

The dependency of k on R is intriguing and deserves more discussion. Hitchhiking events will, on average, inhibit the fixation of weakly selected advantageous mutations. With each event, the population is made nearly homozygous. Just after an event, new weakly selected advantageous mutations will be very rare. During this period, subsequent hitchhiking events will be unlikely to pull one of these new mutations to fixation. In fact, a burst of hitchhiking events will have about the same effect as would a single event. Thus, if the hitchhiking events are clustered ($R > 1$) , they will have less of an inhibitory effect on substitutions than if they are random ($R = 1$).

The situation of weakly selected deleterious mutations shows a similar contrariness as illustrated in Figure 5. In this case the rate of substitution increases with population size, exactly the opposite of its behavior under drift alone. In addition, the rate does not show the extreme sensitivity to N exhibited by an isolated locus. The figure also gives the Monte Carlo calculations for the two distributions of T and using X_t and x_t.

Equations (17) and (19) may be adapted for deleterious substitutions by simply changing the sign of s. From this we see that the rate of substitution increases with N (because ρ_N increases with N) and that the rate of substitution increases as the index of dispersion decreases. Because hitchhiking is the only way that these mutations can fix in a very large population, it makes sense that if the hitchhiking events are more evenly spaced ($R < 1$) they will be more effective at fixing these mutations that if they form a Poisson process ($R = 1$).

The simulations and equation (17) show that rates of substitution depend on population size through population size's effect on ρ_N. As long as ρ_N increases with N, we have the

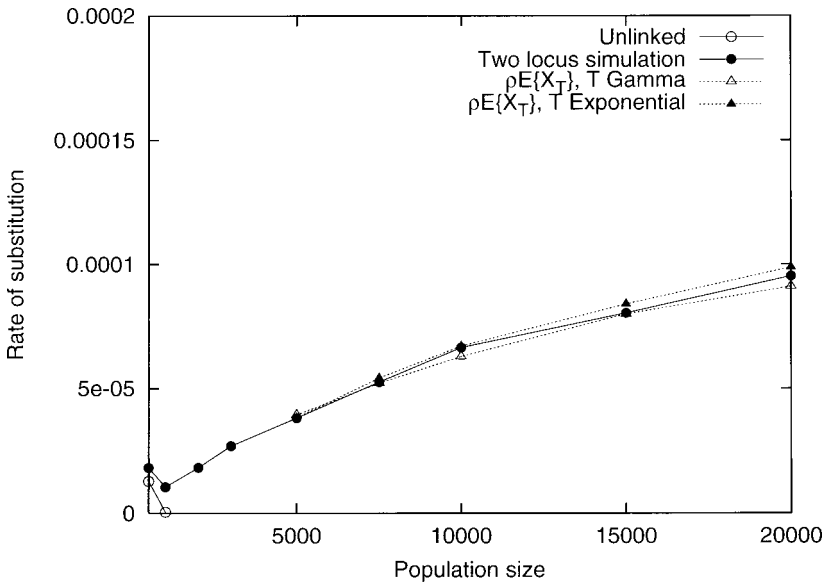

FIG. 5. The rate of fixation of deleterious mutations at a weakly selected locus linked to a strongly selected locus. For the weakly selected locus $u = 2.5 \times 10^{-4}$ and $s = -0.005$. For the strongly selected locus, $\sigma = 0.1$ and $v = 5 \times 10^{-7}$.

contrary behavior described above. If ρ_N did not change with N, then the rate of substitution of weakly selected mutations would be independent of N. This possibility is explored in the next section.

STRONGLY SELECTED LOCI

Figure 6 illustrates the rate of substitution, ρ_N, in four population genetics models with relatively strong selection as a function of population size. These models were chosen because they all reduce the heterozygosity at a linked neutral locus (Gillespie 1997). In three of these models, ρ_N quickly asymptotes, becoming essentially independent of N when N is sufficiently large. Could it be that evolution at strongly selected loci in natural populations is insensitive to population size? The answer to this question depends on our understanding—or our intuition—about adaptive evolution.

In all four of the models illustrated in Figure 6, ρ_N is strongly concave, but the reasons depend on the details of the models. The shift model (Ohta and Tachida 1990) is closest to our usual sense of positive selection: Each successive substitution has the same selective advantage over its predecessor. The rate of substitution for this model is often approximated by $\rho_N = 2Nvs$ (Kimura 1983), but this approximation is only accurate when alleles do not interfere with one another, as seen by comparing the curve labeled ''2Nsv'' to that labeled ''Shift model.'' Otherwise, clonal selection induces the concavity (Haigh 1978; Gerrish and Lenski 1998; Orr 2000). (The shift model illustrated in Fig. 6 has the same parameters as used for the two-locus simulations reported in the previous section.)

The shift model, while mathematically convenient, may not be a particularly faithful representation of adaptive evolution. The problem is centered on the assumption of a continuous supply of advantageous mutations with roughly the same selection coefficient. This property effectively removes history from the evolutionary process. That is, one might well imagine that a sequence of substitutions would improve the adaptation of a species to its environment and that subsequent advantageous mutations would have a much smaller effect on fitness. The shift model does not have this behavior and, as a result, should probably not be used as a model of adaptive evolution.

Under more realistic models, an evolutionary challenge might be met by a few large adaptive changes followed by a series of much smaller refinements, much as described in the models of Gillespie (1983, 1984) and Orr (1998, 2000). However, in models of this sort, evolution would stagnate; thus, some form of explicit environmental change is required for continuous evolution.

Environmental change is incorporated in the other three models in Figure 6. The two TIM models are models of selection in a random environment with no balancing component (Takahata et al. 1975; the model gets its name from the first initials of the authors of the original paper). Alleles are assigned selection coefficients that change randomly over time. Thus, at any epoch, there is a most-fit allele, a next-most-fit allele, and so forth. The ordering of alleles changes though time, which causes the continuous evolution. The two models illustrated in the figure differ in the time-scale of environmental change. In the short time-scale TIM model, the selection coefficients change each generation, allowing the model to be approximated by a diffusion process whose drift coefficient for the ith allele is

$$E\{\delta x_i\} = \sigma^2 x_i(F - x_i), \tag{20}$$

where F is the homozygosity of the population (Takahata et al. 1975). As N increases, F decreases (due to the greater mutational input), which in turn makes it more difficult for new alleles to enter the population (because $E\{\delta x_i\}$ is smaller)—hence, the concavity in ρ_N. Other models with drift coefficients of the same functional form, such as SAS-CFF and overdominance models, will exhibit the same insensitiv-

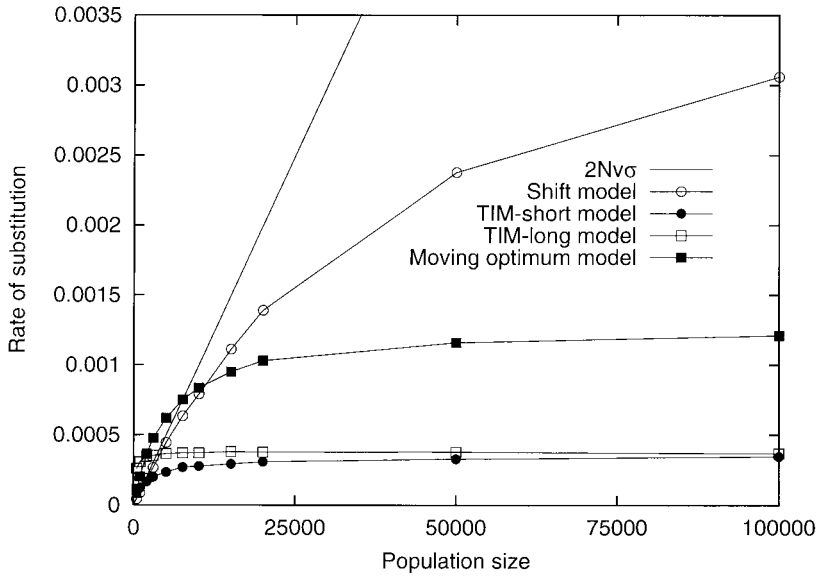

FIG. 6. Simulation results on the rate of substitution, ρ_N, for four models with strong selection. For the shift model, $\sigma = 0.1$ and $v = 5 \times 10^{-7}$. The line marked ''$2Nv\sigma$'' corresponds to this shift model. For the two TIM models, $\sigma = 0.1$ and $v = 2.5 \times 10^{-5}$. For the TIM-long model the mean time between changes in fitness is 5000 generations. For the moving optimum model, $v = 10^{-6}$ and the fitness function is $e^{-\alpha x^2}$, where $\alpha = 0.1$ and x is the deviation of a genotype from the optimum. The optimum is an autoregressive process with $\sigma = 2$ and changes on a time scale of 1000 generations. The phenotypic contribution of a new mutation is that of its parent allele plus a standard Gaussian random variable.

ity to population size (Gillespie 1999). It is not clear at this time why ρ_N appears to reach an asymptote rather than, say, increase very slowly with N. This is a fertile area for future work.

In the long time-scale TIM model, the environment changes very slowly relative to the time required to complete a substitution. In this model, the most-fit allele will retain its exalted position for many generations before the environment changes enough that some other allele displaces it, often accompanied by a burst of substitutions (for a description of these dynamics, see Gillespie 1993) Once a particularly fit allele becomes common, it is very difficult to displace it. The reason follows from the theory of records (see Glick 1978) as adapted to this context by Gillespie (1994a). Thus, even though the mutational input increases linearly with N, the rate of record breaking, which is equivalent to the rate of appearance of advantageous mutations, increases with ln (N). Once N becomes sufficiently large, further increases have essentially no effect on the rate of substitution; the entire process becomes driven by environmental changes.

The moving-optimum model is based on the (nonmoving) optimum model described in Gillespie (1994b). The model posits an optimal phenotype and alleles that contribute additively to that phenotype. For this study, the optimum is made to change slowly through time. Just as with the TIM model, there will be at any epoch a most-fit allele (in a marginal sense, as this is a diploid model), a next-most-fit allele, and so forth. When the environment changes sufficiently, the most-fit allele is displaced in a flurry of substitutions just as in the TIM model. The insensitivity to N arises for the same reasons as for the TIM model.

The fact that diverse models share the insensitivity to N is the most important message from Figure 6, because we do not know at this time which model best represents the dynamics of strongly selected loci. The shift model shows the strongest dependency on population size but is the most suspect biologically. The change in ρ_N for the other three models quickly approaches zero with increasing N and, at the same time, are biologically much more compelling. Thus, we must entertain the possibility that the evolution of strongly selected loci is insensitive to population size and, as a consequence via genetic draft, the evolution of weakly selected loci is insensitive to population size as well.

DISCUSSION

The results of the preceding two sections show that there is a region of parameter space where population size is only a minor player in the evolution of species. This raises the very real possibility that we have placed undo importance on N as a parameter. Fortunately, if we simply replace N by $1/2\rho_N E\{y^2\}$, much of our understanding of the consequences of stochastic forces acting on populations remains intact. The big gain is that the missing footprints of N no longer seem curious.

This does not mean that genetic drift is not an important evolutionary force. Very rare alleles, such as new mutations, will be bounced around by genetic drift. However, the dynamics of rare drifting alleles is essentially independent of population size, as originally discovered by Fisher (1958) when he used branching process theory to describe the fixation probability of new mutations. When rare alleles become common, genetic draft may take over as the dominant stochastic force. Thus, my message is not that drift is unimportant, but that population size is unimportant. This is an important distinction. As a corollary, when drift is affecting

rare alleles, it does not involve binomial sampling. Rather, the dynamics of rare alleles are determined by their distributions of offspring number. Thus, binomial sampling is a casualty of the evolutionary theory espoused in this paper.

I now come to the critical question: Is there any reason to believe that natural populations are in a region of parameter space where genetic draft is likely to occur? The answer must be yes for genomes or regions of genomes with little or no recombination. This would include mitochondria, many prokaryotes, and regions of chromosomes with reduced recombination. The fact that genetic variation is lower in regions of reduced recombination provides strong evidence that draft is operating there.

Some very rough calculations show that draft may also be important in regions of the *Drosophila* genome with normal recombination. A typical block of 10,000 bases contains one gene and $r \approx 0.0001$ between the first and last bases. A selected substitution anywhere in this block with a 0.1% advantage ($r/s \approx 0.1$) will cause most of the block to become nearly homozygous. A typical rate of amino acid substitution for a gene is $\rho = 10^{-7}$. Equation (8) with N very large shows that we would expect the per nucleotide heterozygosity to be around $2u/\rho = 0.02$ for a typical neutral mutation rate (as inferred from the substitution rate) of $u = 10^{-9}$. This figure agrees very well with $\pi = 0.03$ seen in *D. simulans*. (Note that this result can be stated another way: If one substitution out of every 100 is strongly selected, then draft can easily account for the observed variation. This ratio is striking close to the one in 400 ratio obtained by Kaplan et al. [1989].) This is certainly a much better fit than we get using a drift-based model with realistic (i.e., greater than 10^6) population sizes. There are many factors that could increase the effectiveness of draft such as a tendency for genes or chiasmata to cluster rather than be uniformly distributed across the genome.

It is worth dwelling on the notion that draft might be operating in regions of low recombination and drift in regions of normal recombination. If ρ_N is increasing with N for strongly selected loci in both regions, then two things are very different in the dynamics of weakly selected loci in the two regions vis-à-vis their dependency on N: (1) the slopes of the rates of substitution of weakly selected loci as a function of N have different signs in the two regions; and (2) the sensitivity to N are vastly different in the two regions. Because N is viewed as central to our understanding of the molecular evolution, we should expect the evolutionary history of mitochondria or bacteria to be fundamentally different than that of nuclear genes in regions of normal recombination. That no fundamental differences have been observed suggests that both may be marching to the same drummer, which is most likely genetic draft.

Genetic draft provides new support for Ohta's theory that most amino acid substitutions are mildly deleterious (Ohta 1973, 1976, 1992). One of the important aspects of this theory is that it can account for the absence of a generation-time effect in proteins by the plausible assumption that population size is inversely proportional to generation time. The equivalent assumption for genetic draft is that ρ_N (per generation) is proportional to generation time. This is reasonable if one posits that most evolution is in response to a changing environment and that the amount of environmental change seen each generation will be less for species with short generation times. (It is also a restatement of the genetic clock.) We must assume that strongly selected advantageous substitutions are clocklike and are responsible for the clocklike behavior of linked, weakly selected mildly deleterious alleles. The crude approximation for the rate of substitution of mildly deleterious alleles given by equation (19) suggests immediately that the high index of dispersion of proteins may be due to fluctuations in ρ_N. If Ohta's theory is based on draft rather than drift, its major flaw is removed: The rate of substitution no longer depends on population size.

Taken together, the observations presented above suggest a radical new view of the stochastic forces at work in natural populations. The major stochastic force acting on common alleles is due to linked selection; this force is called genetic draft. Rare alleles, alleles whose frequency are close to $1/N$, are subject to the combined stochastic forces of genetic drift and genetic draft. Note, however, that the action of drift on such alleles is effectively independent of population size (Fisher 1958) and does not involve binomial sampling. The trajectories of common alleles between hitchhiking events are essentially deterministic. In very small populations, drift will be an important force. As N increases, draft begins to predominate and place an upper bound on the levels of variation. This view greatly diminishes population size's role in population genetics. With it goes the strong dependency of genetic variation on N, which removes the greatest enigma of molecular population genetics. Paradoxically, not much else changes as the second-order properties of draft are so similar to those of drift.

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Literature Cited

Aguadé, M. and C. H. Langley. 1994. Polymorphism and divergence in regions of low recombination. Pp. 67–76 *in* B. Golding, ed. Non-neutral evolution: theories and molecular data. Chapman and Hall, New York.

Aguadé, M., N. Miyahista, and C. H. Langley. 1989. Reduced variation in the *yellow-achaete-scute* region in natural populations of *Drosophila melanogaster*. Genetics 122:607–615.

Begun, D. J., and C. F. Aquadro. 1992. Levels of naturally occurring DNA polymorphism correlate with recombination rates in *Drosophila melanogaster*. Nature 356:519–520.

Berry, A. J., J. W. Ajioka, and M. Kreitman. 1991. Lack of polymorphism on the *Drosophila* fourth chromosome resulting from selection. Genetics 129:1111–1117.

Charlesworth, B. 1994. The effect of background selection against deleterious mutations on weakly selected, linked variants. Genet. Res. 63:213–227.

Charlesworth, B., M. T. Morgan, and D. Charlesworth. 1993. The effect of deleterious mutations on neutral molecular variation. Genetics 134:1289–1303.

Cherry, J. L. 1998. Should we expect substitution rate to depend on population size? Genetics 150:911–919.

Cutler, D. J. 2000. Understanding the overdispersed molecular clock. Genetics 154:1403–1417.
Fisher, R. A. 1958. The genetical theory of natural selection. Dover, New York.
Gerrish, P. J., and R. E. Lenski. 1998. The fate of competing beneficial mutations in an asexual population. Genetica 102/103: 127–144.
Gillespie, J. H. 1983. A simple stochastic gene substitution process. Theor. Popul. Biol. 23:202–215.
———. 1984. Molecular evolution over the mutational landscape. Evolution 38:1116–1129.
———. 1991. The causes of molecular evolution. Oxford Univ. Press, New York.
———. 1993. Substitution processes in molecular evolution. I. Uniform and clustered substitutions in a haploid model. Genetics 134:971–981.
———. 1994a. Substitution processes in molecular evolution. II. Exchangeable models from population genetics. Evolution 48: 1101–1113.
———. 1994b. Substitution processes in molecular evolution. III. Deleterious alleles. Genetics 138:943–952.
———. 1997. Junk ain't what junk does: neutral alleles in a selected context. Gene 205:291–299.
———. 1999. The role of population size in molecular evolution. Theor. Popul. Biol. 55:145–156.
———. 2000a. Genetic drift in an infinite population: the pseudohitchhiking model. Genetics 155:909–919.
———. 2000b. The neural theory in an infinite population. Gene 261:11–18.
Glick, N. 1978. Breaking records and breaking boards. Amer. Math. Monthly 85:2–26.
Haigh, J. 1978. The accumulation of deleterious genes in a population: Muller's ratchet. Theor. Pop. Biol. 14:251–267.
Hartl, D. L., D. D. Dykhuizen, and A. M. Dean. 1985. Limits of adaptation: the evolution of selective neutrality. Genetics 111: 655–674.
Kaplan, N. L., R. R. Hudson, and C. H. Langley. 1989. The hitchhiking effect revisited. Genetics 123:887–899.
Kimura, M. 1983. The neutral theory of molecular evolution. Cambridge Univ. Press, Cambridge, U.K.
Lewontin, R. C. 1974. The genetic basis of evolutionary change. Columbia Univ. Press, New York.
Maynard Smith, J., and J. Haigh. 1974. The hitch-hiking effect of a favorable gene. Genet. Res. Camb. 23:23–35.
Miyashita, N. 1990. Molecular and phenotypic variation of the *Zw* locus region in *Drosophila melanogaster*. Genetics 125:407–419.
Nachman, M. W. 1997. Patterns of DNA variability at X-linked loci in *Mus domesticus*. Genetics 147:1303–1316.
Nei, M., and D. Graur. 1984. Extent of protein polymorphism and the neutral mutation theory. Evol. Biol. 17:73–118.
Nevo, E., A. Beiles, and R. Ben-Shlomo. 1984. The evolutionary significance of genetic diversity: ecological, demographic and life history correlates. Pp. 13–213 *in* G. S. Mani, ed. Evolutionary dynamics of genetic diversity. Springer-Verlag, Berlin.
Norman, M. F. 1975. Approximation of stochastic processes by Gaussian diffusions, and applications to Wright-Fisher genetic models. SIAM J. Appl. Math. 29:225–242.
Ohta, T. 1973. Slightly deleterious mutant substitutions in evolution. Nature 246:96–98.
———. 1976. Role of very slightly deleterious mutations in molecular evolution and polymorphism. Theor. Pop. Biol. 10: 254–275.
———. 1992. The nearly neutral theory of molecular evolution. Annu. Rev. Ecol. Syst. 23:263–286.
Ohta, T., and H. Tachida. 1990. Theoretical study of near neutrality. I. Heterozygosity and rate of mutant substitution. Genetics 126: 219–229.
Orr, H. A. 1998. The population genetics of adaptation: the distribution of factors fixed during adaptive evolution. Evolution 52: 935–949.
———. 2000. The rate of adaptation in asexuals. Genetics 155: 961–968.
Takahata, N., K. Ishii, and H. Matsuda. 1975. Effect of temporal fluctuation of selection coefficient on gene frequency in a population. Proc. Natl. Acad. Sci. USA 72:4541–4545.
Wright, S. 1955. Classification of the factors of evolution. Cold Spring Harbor Symp. Quant. Biol. 20:16–24D.

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