On the structure of genealogical trees in the presence of selection

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Abstract

We investigate through numerical simulations the effect of selection on two summary statistics for nucleotide variation in a sample of two genes from a population of \( N \) asexually reproducing haploid individuals. One is the mean time since two individuals had their most recent common ancestor \( (T_s) \), and the other is the mean number of nucleotide differences between two genes in the sample \( (d_s) \). In the case of diminishing epistasis, in which the deleterious effect of a new mutation is attenuated, we find that the scale of \( d_s \) with the population size depends on the mutation rate, leading then to the onset of a sharp threshold phenomenon as \( N \) becomes large.

Key words: genealogical trees, coalescent, infinite-sites model
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1 Introduction

The rapid accumulation of DNA sequence data in the last two decades resulted in a shift of emphasis in population genetics from a prospective approach, which focuses on the changes in the population composition with time, to a retrospective approach, which explores the patterns of similarities between the different sequences to obtain information about the evolutionary history of those sequences. Although neutral genealogical processes have been the subject of much attention in those decades, culminating with Kingman’s Coalescent Theory [1] (see [2,3] for reviews), very little is known about genealogical processes with selection (see [4–6] for a few exceptions). The purpose of this paper is to study numerically the effect of selection on two widely

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used summary statistics for nucleotide variation in a random sample of two
genes, namely, the mean time since their most recent common ancestor, $T_s$, 
and the average distance (measured by the number of different nucleotides
in homologous sites) between them, $d_s$. This last quantity is easily measured
from DNA sequence data and, within the neutral evolution assumption, can be
used to estimate the product between the effective population size $N_e$ and the
mutation rate per gene per generation $U$ [2]. In this paper we show that this
estimation procedure holds also in the case of diminishing epistasis, provided
that $U$ is not too small.

2 Model

We consider a haploid population of $N$ individuals or genes that evolves ac-
cording to the discrete-time Wright-Fisher model with selection and mutation
[7]. Here, haploid means that each individual has only one copy of each chromo-
some as, for instance, the mitochondrial genes which are inherited maternally.
In this sense, we will use interchangeably the term gene and individual to refer
to the unit of selection. An individual is represented by an infinite sequence
of sites, each labeled 0 or 1: the bit 0 denotes the original (ancestral) type,
and the bit 1 a mutant type. The fitness of an individual with $k$ mutations
is $w_k = (1 - s)^k$ where $s \in (0, 1)$ is the selective advantage per site of the
original nucleotide type, and $\alpha \geq 0$ is the epistasis parameter. The case $\alpha = 1$
corresponds to absence of epistasis, i.e., each new mutation reduces the fitness
of the individual by the same amount, irrespective of the number of previous
mutations. The case $\alpha > 1$ (synergistic epistasis) models the situation where
the disadvantageous effect of a new mutation increases with the number of
mutations already present, while the case $\alpha < 1$ (diminishing epistasis) cor-
responds to the situation where the deleterious effect of a new mutation is
attenuated. The mutation mechanism is such that a mutant offspring gets a
mutation at a single new site that has never before seen a mutation. In par-
ticular, we assume that the probability that $k$ new mutations occur in one
individual is given by the Poisson distribution

$$M_k = e^{-U} \frac{U^k}{k!},$$

where $U$ is the mean number of new mutations per individual per generation.
The relevant quantities that characterize the population are measured after
the procedures of selection and mutation, in that order. The model presented
above is the celebrated infinite-sites model [8,9] which has been widely used
by population geneticists to describe the DNA variability observed in samples
of genes in the case of neutral mutations ($s = 0$).
3 Analytical results

In the neutral limit \((s = 0)\) as well as in the strong-selection limit \((s = 1)\) we can easily calculate \(T_s\) and \(d_s\) analytically [5,10]. Clearly, the value of the epistasis parameter is irrelevant in those limits.

We consider first the neutral limit. Let \(T_{\alpha\beta}\) be the time in generations since the latest common ancestor of individuals \(\alpha\) and \(\beta\). In the following we will calculate the probability \(P_0(T)\) that two randomly chosen individuals have \(T_{\alpha\beta} = T\). The notation \(\langle\ldots\rangle\) stands for an average over independent populations. The probability that two individuals have no common ancestor in the preceding generation is simply \((1 - 1/N)\). So for \(N\) large the probability that their ancestors, \(t\) generations ago, are all different is \(e^{-t/N}\). Hence the probability that the latest common ancestor of the two individuals lived exactly at \(T\) generations ago is given by

\[
P_0(T) = \left[1 - e^{-(T+1)/N}\right] - \left[1 - e^{-T/N}\right] \approx \frac{e^{-T/N}}{N},
\]

from where we obtain \(T_0 = N\). The relevant time scale in the neutral case is thus proportional to \(N\). The probability distribution \(P_s(T)\), which determines the statistical properties of the genealogies, depends on such factors as the population size, geographic structure and the distribution of fitness among the individuals. It should be stressed that neutral mutations (i.e., mutations that do not affect the fitness of the individuals) have no effect on the genealogies of random samples [2] and so Eqn. (2) holds true irrespective of the value of the mutation rate \(U\). Of course, the distance (the number of different nucleotides) between two sampled sequences depends strongly on the mutation process. For instance, for \(U = 0\) all sequences in the sample are identical. In the sequel we will calculate analytically the distribution of distances between two sampled sequences.

We assume that during each time interval \(dt\) each sequence has a probability \(Udt\) of mutating to a new one that has never before been present in the population. Thus, in the neutral case the probability \(\phi^0_n(t)\) that a sequence differs from its ancestral on \(n\) sites after the divergence time \(t\) obeys the equation

\[
\frac{d\phi^0_n(t)}{dt} = U \left[\phi^0_{n-1}(t) - \phi^0_n(t)\right]
\]

This continuous-time formulation yields the same results as the discrete-time model presented before in the limit of large \(N\), since in that case the relevant time scale is of order of \(N\) generations, and so it is much larger than the time unit, i.e., one generation.
whose solution is the Poisson distribution

$$\phi^0_n(t) = e^{-Ut} \frac{(Ut)^n}{n!}. \quad (4)$$

Hence the average distance between an individual and its ancestor increases linearly with time $\bar{t}_0 = Ut$. In a more general context the steady accumulation of unfavorable mutations in an asexual population is referred to as the Muller’s ratchet [5].

Let $\overline{W}_n^0$ be the probability that the distance between two sampled individuals is equal $n$. Since in an asexual population the individuals are all descended from a common ancestor at some point in the past we can write

$$\overline{W}_n^0 = \int_0^\infty dT \overline{P}_0(T) \phi^0_n(2T). \quad (5)$$

Using Eqns. (2) and (4), the integral can easily be evaluated yielding

$$\overline{W}_n^0 = \frac{\lambda}{(\lambda + 1)^{n+1}} \quad (6)$$

where $\lambda = 1/2UN$. Hence, $\overline{d}_0 = 1/\lambda = 2UN$.

We turn now to the analysis of the strong-selection limit ($s = 1$). Since only individuals with $k = 0$ mutations can generate offspring there is no difference in the fitness of the breeding individuals. This limit is similar to the neutral limit in the sense that the probability of two individuals having the same parent is $1/N_0$ where $N_0$ is the number of individuals with $k = 0$ mutations. Clearly, at any generation $N_0$ is random variable distributed according to the binomial distribution

$$B(N_0) = \binom{N}{N_0} e^{-UN_0} \left(1 - e^{-U}\right)^{N-N_0}. \quad (7)$$

If $U$ is of order 1 and $N$ is large we have $N_0 \approx \overline{N}_0 = Ne^{-U}$ so that $\overline{d}_1 = 2U$. The probability distribution of the distance $d_1$ between two sampled individuals is equally easy to obtain: it is simply given by $M_{2d_1}$ so that $\overline{d}_1 = 2U$. We must note that since the probability of extinction in one generation is $B(0)$, the population will ultimately become extinct in a time of order of $1/B(0)$. However, if $U$ is not of order of $N$ the extinction times become so large that these events cannot be observed in the simulations described in the sequel.
Fig. 1. (a) Mean time since the most recent common ancestor of two randomly chosen individuals as a function of the mutation rate $U$ for $\alpha = s = 0.5$. (b) Average distance between two sampled individuals as a function of $U$. The convention is $N = 30$ (○), 50 (∆), 100 (∗), and 300 (∇). The dashed curve is $\exp(-U/s)$ while the solid lines are guides to the eyes.

4 Simulations

At any given time we keep track of the number of mutations $k_i$ on each individual $i = 1, \ldots, N$, as well as of the identity of their parents. This information allows us to obtain the most recent common ancestor of any two individuals and also the distance between them. To create a new generation from a given one we assume, as usual, that the number of offspring that each individual contributes to the new generation is proportional to its relative fitness, $w_i/\overline{w}$ where $\overline{w} = \sum_i w_i$ is the total fitness of the population. The offspring has all the mutations of its parent plus a random number $k$ of new mutations distributed according to the Poisson distribution $M_k$ given by Eqn. (1). The initial population is composed of $N$ individuals without mutations whose evolution we follow through typically 1000 generations. We then go backward in time to determine the common ancestors of each pair of individuals. We typically average our results over 300 independent runs.

Here we present only the results for diminishing epistasis ($\alpha = 0.5$). A more complete and detailed discussion will be presented elsewhere. In Fig. 1 we show the dependence of $\overline{T}_s$ and $\overline{d}_s$ on the mutation rate $U$ for $s = 0.5$ and several values of the population size $N$. One the one side, for small $U$ we find
that both $T_s/N$ and $d_s$ are practically independent of $N$. In fact, similarly to the strong-selection limit, in this regime we find $T_s/N \approx \exp(-U/s)$ and $d_s \approx 2Us$. On the other side, for $U$ large we find a regime reminiscent of the neutral limit, in which $T_s/N$ becomes independent of the mutation rate. In this case we can define an effective population size $N_e$, which depends on $s$ and $N$ but not on $U$, such that $T_s = N_e$ and $d_s \approx 2UN_e$. As expected, we find that $N_e$ decreases with increasing $s$ since the number of breeding individuals decreases with $s$. More specifically, $N_e$ seems to decrease like $N^{1-s}$ for $s$ not too close 1. Interestingly, as illustrated in Fig. 1b the different scaling of $d_s$ with $N$ in these two regimes leads to an abrupt increase of this quantity at a finite value of $U$, which may signal the existence of a phase transition in the thermodynamic limit $N \to \infty$. We note that these features are not observed for $\alpha \geq 1$.

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