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Population structure and the rate of evolution

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HIGHLIGHTS

- We analysed a two patch model in which the spatial average of selection is zero.
- We examined effects of population size, migration and selection on the rate of evolution.
- For large population sizes, the size appears only in scaled parameters, not on its own.
- We assume that scaled migration and selection strengths are dependent due to ecology/evolution.
- Ecology/evolution affects how the rate of evolution varies with population size.

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ABSTRACT

The way population size, population structure (with migration), and spatially dependent selection (where there is no globally optimal allele), combine to affect the substitution rate is poorly understood. Here, we consider a two patch model where mutant alleles are beneficial in one patch and deleterious in the other patch. We assume that the spatial average of selection on mutant alleles is zero. We take each patch to maintain a finite number of N adults each generation, hence random genetic drift can independently occur in each patch. We show that the principal way the population size, N, when large, affects the substitution rate, R_∞, is through its dependence on two composite parameters. These are the scaled migration rate M ($\propto$ population size $\times$ migration rate), and the scaled selection intensity S ($\propto$ population size $\times$ beneficial effect of a mutant). Any relation between S and M that arises for ecological/evolutionary reasons can strongly influence the way the substitution rate, R_∞, depends on the population size, N. In the simplest situation, both M and S are proportional to N, and this is shown to lead to R_∞ increasing with N when S is not large. The behaviour, that R_∞ increases with N, is not inevitable; a more complex relation between S and M can lead to the opposite or other behaviours. In particular, let us assume that dM/dN is positive, as would occur if the migration rate were constant, S is not large, and S depends on M (i.e., $S=S(M)$). We then find that if $S(M)$ satisfies $S(M)>((1+M)/\sqrt{1+2M})S(0)$ then the substitution rate, R_∞, increases with N, but if $S(M)<((1+M)/\sqrt{1+2M})S(0)$ then R_∞ decreases with N.

1. Introduction

The relative importance of demography and selection, for a number of issues in modern evolutionary biology including the rate of evolution, has been a topic of active debate. The founders of population genetics held different views on this issue (Fisher, 1930; Haldane, 1932; Wright, 1968). In brief, Wright gave more importance to random genetic drift and population structure in shaping the pattern of genetic diversity than either Fisher or Haldane. Furthermore, following Kimura's development of the neutral theory of molecular evolution (Kimura, 1968), the debate intensified (Akashi et al., 2012).

For the rate of evolution, two aspects of demography have received much attention and continue to do so. These are

(i) the effects of population size (see, e.g., Ohta, 1972; Gillespie, 2001; Akashi et al., 2012; Balloux and Lehmann, 2012; Lanfear et al., 2014);
(ii) the effects of population structure (see, e.g., Gavrilets and Gibson, 2002; Frearn et al., 2013).

In an important paper, Ohta (1972) argued that the speed of evolution is likely to be higher in small populations than in large ones. Her main

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argument was based on the highly plausible idea that the environment experienced by a small population is likely to be more uniform than the corresponding environment of a large population. A random mutant is therefore more likely to be beneficial in a small population than in a large population – where it would have to be beneficial under a larger set of environmental conditions. In other words, decreasing the population size results in an increased proportion of beneficial new mutations, and further, "the mean selection coefficient of all beneficial mutants is also larger" (Ohta, 1972).

The measure of the speed of evolution which Ohta had in mind was the rate of substitution, which is defined as the mean number of mutations that fix/generation. Mutations stochastically arise in a population, and their subsequent fate is also stochastic: most new mutations are rapidly lost, but a small fraction achieve fixation. The rate of substitution characterizes the flux of new mutations which ultimately achieve fixation and hence lead to long lived changes in a population.

Assuming discrete generations, the rate of substitution can be decomposed into a product of two factors:

(i) the expected number of mutations that arise each generation in the population;
(ii) the probability of fixation of a new mutation.

The expected number of mutations that enter a given region of the genome of a population, each generation, is $2Nu$ where N is the number of adults in the population and u is the mutation rate of the genomic region. Thus if we focus on a single locus, then u is the allelic mutation rate, i.e., the probability that a gene in a gamete contains a genetic change, relative to the parental gene.

The probability of fixation of a new mutation has a mathematical form which depends on the selective effect of the mutation. Neutral mutations have a probability of fixation that equals their initial frequency, namely $1/(2N)$. For this case, the substitution rate is $2Nu \times 1/(2N)$,, i.e., it is simply equal to the mutation rate, u, and hence is independent of the population size (Kimura, 1983). This result seems surprisingly robust (Lanfear et al., 2014). There is a vast literature on the probability of fixation of a new mutation which is subject to selection (see, e.g., Fisher, 1930; Haldane, 1932; Kimura, 1962; and for recent work see, e.g., Waxman, 2011). These results can be used in the determination of the substitution rate, when mutations are selected.

Ohta's model involves a single population. A way to introduce environmental heterogeneity is to explicitly assume a subdivided population that consists of patches that are connected by migration. Since Wright's seminal work on this subject (Wright, 1931), subdivided populations and dispersal have played a major role in evolutionary biology. In particular, subdivided populations lie at the core of models of local adaptation (Savolainen et al., 2013). When these more complex (and more realistic) situations occur, the rate of substitution can show different dependencies on the population size. For example, the rate of substitution in a small population can (sometimes) be higher than that in a large population. This will occur if, for a small population, the probability of fixation of a mutation is sufficiently large that it more than compensates for the lower rate at which mutations enter the population. For example, in Ohta's model, the rate of substitution in a small population will be higher than that in a large population due to the latter's higher level of heterogeneity, and hence reduced effectiveness of selection (a higher proportion of mutations entering a large population are deleterious).

Let us consider the effects of selection and population subdivision on the substitution rate. In the simplest case of additive selection at a single locus in an unstructured randomly mating population, beneficial mutations result in a large population size producing a higher substitution rate than a small population size. By contrast, if the mutations are deleterious, then a large population size will produce a smaller substitution rate than a small population size (see, e.g., Lanfear et al., 2014).

In the case of a structured population with spatially dependent selection matters are more complex. When mutant alleles are *beneficial in one patch*, and the same alleles are *deleterious in another patch*, but the patches are connected by migration and the spatial average of selection on mutants is *zero*, it is unclear under which circumstances the substitution rate will be larger in a large population than in a small population. Another way of saying this is that it is unclear which has more influence on the substitution rate: the beneficial aspect of the alleles in one patch, or their deleterious aspect in the other patch.

In the present work, we investigate the dependence of the rate of substitution on population size, and in particular, the circumstances or conditions where it can be larger in a small subdivided population than a large subdivided population. While this is somewhat motivated by Ohta's hypothesis, we explicitly include

(i) finite population size,
(ii) population structure,
(iii) spatially dependent selection.

Frearn et al. (2013) have considered some specific spatial models, such as star-structured populations and two-dimensional lattices. Their main conclusion is that the time to fixation of new mutations, and thereby the rate of evolution, may be strongly affected by population structure. For instance, 'star graphs' increase the probability of fixation of positively selected mutations while simultaneously decreasing that of disadvantageous ones. However, the expected fixation time is significantly increased. It should be noted that the structure they are referring to is local population structure, and each node in the lattice or star graph is occupied by a single individual. These models are therefore quite different from the ones that are classically used in population genetics, where each node ($=$ deme or subpopulation) is occupied by many individuals that can be exchanged between populations. Gavrilets and Gibson (2002) considered population structure with selection having different directions in different demes. In their work, these authors determined approximations for the probability of fixation of a new mutant allele, within the framework of the diffusion approximation. They proceeded to discuss the implications of their results for the rate of substitution. Their main conclusion was that it is possible for small subdivided populations, with low migration rates, to have higher substitution rates than large subdivided populations, when the intensity of selection over space exceeds a threshold. Building on a few examples and limiting cases they conjectured that this would likely be true for a convex dependence of migration rate on population size.

We begin our analysis, of how the rate of substitution depends on the population size, by first specifying a simple model that we term the *Basic Model*. This model captures many of the essential features of the problem, and allows an exploration of the key issues.

In the Basic Model there are two patches in which each maintain N adults in each generation. When the population size of each patch, N, is finite, random genetic drift can occur. We shall work within the framework of a Wright–Fisher model for the two-patch system. Combining this model with ideas/results from diffusion analysis yields numerical results for a finite population that includes migration and selection. This allows us to analyse the dynamics of the system and to show that, to good accuracy, the rate of substitution, relative to the neutral rate of substitution, depends on only two composite parameters. These are the scaled rates of migration and selection, which we write as M and S, respectively, and are defined by

$$M = 4Nm, \quad S = 4Ns \tag{1}$$

where m is the probability of an individual migrating from one patch to another in one generation, and s (≥ 0) is the selection coefficient