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Allele fixation in a dynamic metapopulation: Founder effects vs refuge effects

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ABSTRACT

The fixation of mutant alleles has been studied with models assuming various spatial population structures. In these models, the structure of the metapopulation that we call the "landscape" (number, size and connectivity of subpopulations) is often static. However, natural populations are subject to repetitive population size variations, fragmentation and secondary contacts at different spatiotemporal scales due to geological, climatic and ecological processes. In this paper, we examine how such dynamic landscapes can alter mutant fixation probability and time to fixation. We consider three stochastic landscape dynamics: (i) the population is subject to repetitive bottlenecks, (ii) to the repeated alternation of fragmentation and fusion of demes with a constant population carrying capacity, (iii) idem with a variable carrying capacity. We show by deriving a variance, a coalescent and a harmonic mean population effective size, and with simulations that these landscape dynamics generate repetitive founder effects which counteract selection, thereby decreasing the fixation probability of an advantageous mutant but accelerate fixation when it occurs. For models (ii) and (iii), we also highlight an antagonistic "refuge effect" which can strongly delay mutant fixation. The predominance of either founder effects or refuge effects determines the time to fixation and mainly depends on the characteristic time scales of the landscape dynamics.

1. Introduction

The study of the fixation of novel alleles has known many developments since the beginning of population genetics (Fisher, 1922; Haldane, 1927; Wright, 1931). Fixation probabilities and times to fixation are indeed important factors influencing, among others, the rate of evolution, the genetic load (Whitlock, 2002; Theodorou and Couvet, 2006), and the level of genetic diversity (Vuilleumier et al., 2008). The importance of understanding and characterizing allele fixation is linked to its practical implications: for example, conservation generally tries to restore genetic diversity in small and/or fragmented populations which risk extinction (Gao and Zhang, 2005; Bohme et al., 2007); in public health, maintenance of resistance alleles to drugs is a major problem (Heinemann, 1999; McLean, 1995).

Most natural populations are subdivided into partially isolated demes (Hanski and Gaggiotti, 2004). Following Keymer et al. (2000) we call the spatial structure of a subdivided population the "landscape"; we define it as the number, the size, and the connectivity of subpopulations. The landscape strongly affects how drift and selection act (Barton and Whitlock, 1997; Colas et al., 2002; Roze and Rousset, 2003; Whitlock, 2004). It thus influences allele fixation probability and time. Understanding these influence is of great importance especially today because of intense landscape fragmentation due to human activities; many populations consist now of small demes poorly connected, leading to high local extinction risk (Wilcox and Murphy, 1985; Hanski and Gaggiotti, 2004).

There is an abundant literature about mutant fixation in subdivided populations (see *e.g.* the review of Charlesworth et al., 2003; Patwa and Wahl, 2008). Many spatial structures have been analyzed, in particular island, stepping-stone, spatially continuous, source–sink, and extinction–recolonization models. For populations of constant size such that migration does not change allele frequencies in the whole population, spatial structure does not affect allele fixation probability. Other spatial structures generally decrease the fixation probability of advantageous mutants.

The landscape described by most of these models is static, or at most only one component of the landscape is varying. First, the number of patches is constant over time. Second, the size of demes is often considered as constant. Many authors analyzed population size variations (one size change, exponential/logistic growth or decline, size fluctuation), but only for one isolated population (see for example Ewens, 1967; Kimura and Ohta, 1974; Otto and Whitlock, 1997; Barton and Whitlock, 1997; Wahl and Gerrish,

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2001; Iizuka, 2001; Iizuka et al., 2002; Heffernan and Wahl, 2002; Lambert, 2006). Note that extinction–recolonization models could be considered as models with population size variations since each deme can become extinct. Third, the connectivity of subpopulations via migration is assumed constant over time, except in Whitlock and Barton (1997) and Whitlock (2003).

However, all components of the landscape are dynamic simultaneously in natural populations. For example, external factors can cause variations of connections between demes, to the point where connectivity either falls to its minimum (unconnected demes, *e.g.* vicariance) or rises to its maximum (fusion of demes, *e.g.* postglacial secondary contacts) (Young et al., 2002). Climatic variations as well as volcanic events can cause sea level changes resulting in separations and fusions of islands (Cook, 2008). Repeated changes of the water level causing fragmentation and fusion of lakes are known in the Great African Lakes (Owen et al., 1990; Delvaux, 1999; Galis and Metz, 1998; Stiassny and Meyer, 1999). At a different spatiotemporal scale, the number and size of populations can vary because of dispersal and recolonization events (establishment of new colonies and their later fusion) (DeHeer and Kamble, 2008; Vasquez and Silverman, 2008). All aspects of the spatial structure of a population can change because of new ecological interactions, *e.g.* the emergence or extinction of a predator or parasite (Batzli, 1992). Contemporary fragmentation of habitat due to human action is also always changing the landscape (Davies et al., 2006).

These spatial processes cause, repeatedly, bottlenecks and fragmentation of subpopulations. These two phenomena are well known, but have been studied separately and, most of the time, when occurring only once. Their association and their repetition have no simple outcome regarding allele fixation: bottlenecks and fragmentation are expected to decrease the fixation probability of a beneficial allele (Otto and Whitlock, 1997; Wahl and Gerrish, 2001; Whitlock, 2003), but they can increase or decrease the time to fixation, in particular depending on the effective size of the population (Whitlock, 2003). Moreover, to keep the number of demes of a fragmenting population constant, models generally assume repetitive extinctions. However, the spatial processes listed above do not necessarily lead to repetitive local extinctions. They can also lead, repeatedly, to the fusion of entire subpopulations. To our knowledge, such periodic fusions (repetitive secondary contacts) have not yet been studied regarding allele fixation, except in Jesus et al. (2006).

In this paper, we examine how such dynamic landscapes can alter fixation probability and time to fixation of a mutant allele, with or without selection. We consider three landscape dynamics: a population subject to repetitive bottlenecks (Model 1) and a population subject to the repeated alternation of fragmentation and fusion of demes (Model 2), that is, alternatively divided into two demes or undivided, with population size variations but a constant carrying capacity (Model 2a) and with a variable carrying capacity (Model 2b). Note that Wahl and Gerrish (2001) examined the effects of cyclic bottlenecks in experimental conditions, *i.e.* regular and severe bottlenecks. In contrast, we take into account the stochasticity of the occurrence of bottlenecks and any intensity of bottlenecks. We derive diffusion approximations based on the assumption of a large population. Depending on the characteristic time scales of the landscape dynamics, our models can mimic each of the spatial processes listed above. Our results constitute a first step in analyzing the rate of evolution, and then speciation, in dynamic landscapes.

2. The models

2.1. Within-deme population dynamics

We use a population genetics haploid model with two types, mutants and residents, representing individuals carrying two different alleles, respectively. This model, referred to as the Moran model or Moran process (Moran, 1962), is embedded into a model of landscape dynamics, specified below. The Moran process is similar to the Wright–Fisher model (Wright, 1931), but in continuous time (overlapping generations). It is a stochastic process which describes a finite population of constant size and based on the following mechanism: during an infinitesimal time dt, a birth or death event can occur or not; if it does, the population at time $t + dt$ is updated from that of time t by randomly selecting an individual to reproduce and then, independently, randomly selecting an individual to be removed. Each individual with birth rate b has a probability $b\,dt$ to reproduce during dt.

Each resident reproduces at rate $b = 1$ and each mutant at rate $b = 1 + s$ where s is its selective advantage (see Table 1 for a summary of the notation). For an undivided isolated population whose allele frequency fluctuates via a Moran process, classical results and approximations are known for the fixation probability and time to fixation and will be used as reference results of unstructured populations in a static landscape (Wright, 1931; Kimura, 1962; Kimura and Ohta, 1969; Ewens, 2004).

Table 1
Notation and range of numerical values.

Variables:		
X_t	Overall number of mutants at time t	
x_t	Overall frequency of mutants at time t	
Parameters:		Numerical values used:
s	Selective advantage of mutants	From −0.25 to 0.25
x_0	Initial frequency of mutants	From 0.001 to 0.1
g	Bottleneck rate	From 0.0001 to 10
d	Intensity of bottlenecks	From 0 to 0.99
f	Fragmentation rate	From 0.0001 to 10
c	Fusion rate	From 0.0001 to 10
p	"Asymmetry parameter"	From 0.5 to 0.99 (symmetrical to $p \in]0; 0.5]$)
N	Carrying capacity at state 1 (undivided)	From 50 to 1000
Outputs:		
U	Fixation probability of a mutant allele	
T	Time to fixation of a mutant allele, conditional on its fixation	

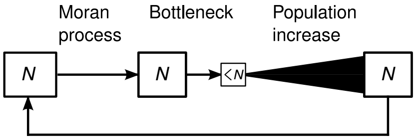

Fig. 1. Model 1, repeated bottlenecks. Model 1 describes landscape dynamics which consist of repeated bottlenecks. Bottlenecks occur at rate g. Each individual dies with probability d during a bottleneck. The size of the population is indicated at each step. After each bottleneck, the population reaches its carrying capacity N via a pure birth process. Between bottlenecks, mutant allele frequencies fluctuate via a Moran process.

2.2. Model 1: Repeated bottlenecks

Model 1 consists of a population which undergoes repeated decreases in population size (Fig. 1). We are mostly interested in bottlenecks, that is, severe reductions in population size. Bottlenecks occur stochastically at exponential rate g. The higher g is, the more often a bottleneck is likely to occur. The intensity of bottlenecks is characterized by d: during a bottleneck, each individual has a probability d to die; the number of surviving individuals is thus drawn from a binomial distribution. Note that we assume that the selective advantage of mutants does not convey resistance to bottlenecks: d is identical for residents and mutants.

Just after a bottleneck, we assume that the population reaches its carrying capacity (size N) instantaneously. Indeed, an initial