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Tipping the mutation–selection balance: Limited migration increases the frequency of deleterious mutants

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HIGHLIGHTS

- A birth-death model with migration is analyzed at mutation-selection balance.
- No assumptions are required about the strength of selection or mutation.
- Analytical approximations are tested against stochastic agent-based simulations.
- Limiting migration leads to more deleterious mutants at equilibrium.
- Limiting migration may lead to faster discovery of novel genotypes.

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ABSTRACT

Typical mutation–selection models assume well-mixed populations, but dispersal and migration within many natural populations is spatially limited. Such limitations can lead to enhanced variation among locations as different types become clustered in different places. Such clustering weakens competition between unlike types relative to competition between like types; thus, the rate by which a fitter type displaces an inferior competitor can be affected by the spatial scale of movement. In this paper, we use a birth-death model to show that limited migration can affect asexual populations by creating competitive refugia. We use a moment closure approach to show that as population structure is introduced by limiting migration, the equilibrial frequency of deleterious mutants increases. We support and extend the model through stochastic simulation, and we use a spatially explicit cellular automaton approach to corroborate the results. We discuss the implications of these results for standing variation in structured populations and adaptive valley crossing in Wright's "shifting balance" process.

1. Introduction

Most mutations affecting fitness appear to be deleterious (see review by Eyre-Walker and Keightley, 2007). A deleterious mutation is expected to persist in a population at a level influenced by the rate at which it is generated and the strength of selection against it. This mutation–selection balance was first developed mathematically by Haldane and Fisher in the 1920's in models that assumed well-mixed populations (Fisher, 1930; Haldane, 1927). However, many natural populations are not well mixed: individuals may not disperse, and even if they do, dispersal or migration is often restricted to nearby locations (Evans et al., 2009; Howells et al., 2013; Martin and Canham, 2010). Such limited movement may influence the proportion of deleterious mutants at equilibrium in several ways. In mating diploid populations, the Wahlund effect (in which population-level heterozygosity is depressed when subpopulations differ in allele frequency) combines with dominance relationships among genotypes to influence the frequency of deleterious mutant alleles (Roze and Rousset, 2004; Whitlock, 2002). In haploid asexual models, limiting migration increases between-deme variation and decreases within-deme variation, but the extent to which this shift in variation affects evolution is unclear.

Limitations to migration are not predicted to affect the equilibrium frequency of deleterious mutants in asexual populations when fitness is independent of local composition and density. For instance, Whitlock (2002) finds no effect of migration under a "hard selection" scheme (in which absolute fitness is determined solely by genotype, and thus demes of different compositions may

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differ in productivity). However, in "soft selection" regimes (in which relative fitness within a deme depends on genotype, but each deme's productivity is the same regardless of composition), demes enriched for mutants are as productive as demes enriched for wild types. Such mutant-rich demes may serve as competitive refugia. Thus, in soft selection schemes, limiting migration can increase the frequencies of deleterious mutants (Roze and Rousset, 2004; Whitlock, 2002).

As mutation, selection and migration occur in a subdivided population, both first-order moments (i.e., the mean) and higher-order moments (i.e., variance, skew, kurtosis, etc.) of allele frequencies across demes can change. Previous models have estimated higher-order moments (or related quantities like F_{ST}) in terms of first-order moments under an assumption of weak selection. In this paper, we take a different approach. We build an ecological model of a subdivided population, in which higher-order moments are dynamic variables. No assumptions about the strength of selection or mutation are required. Using this model, we find that limited migration increases the fraction of mutants at mutation–selection balance. However, our moment-closure approach (in which we express third-order moments in terms of lower-order moments) is exact only under total migration. Thus, our analytical results are accurate when there is minimal subdivision. Similar moment closure approaches have been used to model ecological neutrality, competition, and stability (Bolker and Pacala, 1997; Haegeman and Loreau, 2011; Neuhauser, 2002; Vanpeteghem and Haegeman, 2010). We use computer simulations to confirm that the fraction of mutants at equilibrium increases under limited migration (where the mathematical analysis is approximate). The simulations also show spatial segregation of types, suggesting that mutant-rich areas act as competitive refugia.

2. Mutation–selection balance in a subdivided population

In our model, a population inhabits a metapopulation of patches. Space is implicit in this model; all patches are equally "far" from any given patch. Migration between patches occurs at birth with a specified probability. When the probability is one, every offspring migrates to a random patch, and the population is essentially well mixed. When the probability is lowered slightly from one, there is a small chance an offspring will stay in its natal patch, and thus a modicum of spatial structure is introduced.

2.1. Terminology and life cycle

Consider two genotypes W and M, for wild type and mutant, respectively, inhabiting a metapopulation with an infinite number of patches. The population size of each patch is finite. In all that follows, genotype indices i and j will be used where $i,j\in\{W,M\}$ and $i\neq j$. The per capita birth rate of genotype i is given by $F_i(n_i,n_j)=f_i-\beta_i(n_i+\alpha_{ij}n_j)$, where n_i and n_j are the numbers of genotype i and j in the patch, f_i is the intrinsic growth rate of genotype i, β_i measures the effect of intra-genotypic competition, and α_{ij} is an inter-genotypic conversion factor (i.e., one individual of genotype j counts as α_{ij} individuals of genotype i). Genotype i dies with rate δ_i. Mutation from genotype i to j occurs during the birth process with probability $\mu_{i\to j}$. Migration also occurs at birth, when genotype i migrates to a random patch with probability m_i. The population evolves stochastically in continuous time.

2.2. Moment dynamics

Let $N_i(t)$ be the expected number of genotype i per patch at time t. For typographical convenience, we drop the explicit reference to time dependence in our notation for the terms and equations that follow (e.g., $N_i(t)$ is written N_i). In Appendix 1 we show that

$$\frac{dN_i}{dt}=(1-\mu_{i\to j})\,N_i\,F_i\left(N_{i|i},N_{j|i}\right)+\mu_{j\to i}\,N_j\,F_j\left(N_{j|j},N_{i|j}\right)-\delta_i\,N_i, \tag{1}$$

where $N_{i|j}$ is the expected number of individuals of genotype i in the patch of a randomly chosen individual of genotype j, with $i,j\in\{W,M\}$.

It can be shown that $N_{i|i}=N_i+\sigma_i^2/N_i$, where σ_i^2 is the variance in the number of genotype i. When individuals of the given genotype are uniformly distributed (i.e., variance is zero), this reduces to the mean N_i. Similarly, $N_{i|j}=N_i+C/N_j$, where C is the covariance between the numbers of genotypes i and j. When the two genotypes are independently distributed (i.e., covariance is zero) this term reduces to the mean N_i. Covariance may be positive, indicating association between types, or negative, indicating segregation of types.

Thus the dynamics of the first order moments N_i and N_j rely on second order moments σ_i^2, σ_j^2, and C. The equations governing the dynamics of these second order moments involve third order moments, the differential equations for the third order moments involve fourth order moments, and so on. Our task is similar to Hercules' battle with the Hydra (in spirit, not magnitude!). With each Hydra head Hercules sliced off, new heads popped up in its place. For each moment dynamical equation we describe, the description of new, higher-order moment equations becomes necessary. We must find a way to stem the endless flow of higher-order moments. Hercules seared the necks of the Hydra to prevent the regrowth of the heads; we close our system of differential equations by a second-order moment closure technique. We approximate third-order moments in terms of lower-order moments (see Appendix 1 for details), thus sealing the endless flow. Our moment closure approximation is exact when migration is absolute (i.e., $m_W=m_M=1$), and we are not limited by assumptions of near neutrality (Neuhauser, 2002). With this approximation, the dynamics for the second order moments are given by:

$$\begin{aligned}\frac{d\sigma_i^2}{dt}=\frac{dN_i}{dt}&+2\delta_i(N_i-\sigma_i^2)\\&+2(1-m_i)(1-\mu_{i\to j})\left\{f_i\sigma_i^2-\beta_i(N_i+2N_i\sigma_i^2)-\beta_i\alpha_{ij}(N_iC+N_j\sigma_i^2)\right\}\\&+2(1-m_j)\,\mu_{j\to i}\left\{f_jC-\beta_j2N_jC-\beta_j\alpha_{ji}(N_iC+N_j\sigma_i^2)\right\}\end{aligned} \tag{2}$$

$$\begin{aligned}\frac{dC}{dt}=&-(\delta_i+\delta_j)C+(1-m_i)(1-\mu_{i\to j})\left\{f_iC-\beta_i2N_iC-\beta_i\alpha_{ij}\left(N_jC+N_i\sigma_j^2\right)\right\}\\&+(1-m_j)\mu_{j\to i}\left\{f_j\sigma_j^2-\beta_j\left(N_j+2N_j\sigma_j^2\right)-\beta_j\alpha_{ji}\left(N_jC+N_i\sigma_j^2\right)\right\}\\&+(1-m_j)(1-\mu_{j\to i})\left\{f_jC-\beta_j2N_jC-\beta_j\alpha_{ji}(N_iC+N_j\sigma_i^2)\right\}\\&+(1-m_i)\mu_{i\to j}\left\{f_i\sigma_i^2-\beta_i(N_i+2N_i\sigma_i^2)-\beta_i\alpha_{ij}(N_iC+N_j\sigma_i^2)\right\}\end{aligned} \tag{3}$$

2.3. Mutation–selection balance

Our dynamical system contains many parameters. To simplify matters, we assume $m_W=m_M=m$, $f_W=f_M=f$, $\beta_W=\beta_M=\beta$, $\alpha_{WM}=\alpha_{MW}=1$, $\mu_{W\to M}=\mu$, and $\mu_{M\to W}=0$. Thus, we assume our genotypes are identical in all parameters except their death rates, which define a W to M mutation as deleterious (i.e. $\delta_M>\delta_W>0$), and their mutation rates. Consequently, we only consider viability selection in this analysis, though we simulate other possibilities below. We have also assumed that intra-genotypic competition is identical to inter-genotypic competition (the α parameters are set to unity), and that back mutation does not occur. This might be realistic if the mutation from wild type to the mutant involves a deletion, but even if this mutation is a base substitution, the