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Heterosis increases the effective migration rate

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Individuals coming from the same subpopulation are more likely to share deleterious mutations at any given locus than hybrids formed between parents from different populations. Offspring of migrants therefore may experience heterosis and have higher fitness than resident individuals. This will, in turn, result in the immigrant alleles being present in higher frequencies than predicted from neutral expectations and thus a higher effective migration rate. In this paper we derive a formula to calculate the effective migration rate in the presence of heterosis. It is shown that the effect of heterosis on the migration rate can be substantial when fitness reduction within local populations is severe. The effect will be more pronounced in species with relatively short map lengths. Furthermore the heterosis effect will be highly variable throughout the genome, with the largest effect seen near selected genes and in regions of high gene density.

Keywords: drift load; gene flow; heterosis; migration; population structure; recombination

1. INTRODUCTION

Perhaps the most important genetic consequence of small population size is the increased propensity for genetic drift to act. In small populations slightly deleterious alleles are rendered effectively neutral and can therefore drift to appreciable frequencies or even become fixed (Wright 1937; Kimura *et al.* 1963). A deleterious allele therefore imposes a higher load in small populations, and the combined drift-induced load over many loci can sometimes be quite severe (Kimura *et al.* 1963; Crow 1993). Reduced fitness of individuals in small populations is a common phenomenon that has been documented for a large variety of species, including both plants and animals (see Charlesworth & Charlesworth (1987) for a review) and the fixation of deleterious alleles can ultimately be a serious threat to population persistence (Lande 1994; Lynch *et al.* 1995*a*,*b*).

Gene flow reduces drift load because it enables unrelated individuals to breed and reintroduces genetic variation into a population. The effects of gene flow have been the subject of a large body of both theoretical and empirical work (Slatkin 1985). Many of the models of gene flow have implicitly assumed that there is no difference in fitness between migrant and resident individuals (Slatkin 1985). This assumption is not always true; for example, ecological selection against hybrid offspring can substantially reduce gene flow between populations (Petry 1983; Bengtsson 1985; Barton & Bengtsson 1986). Similarly, heterosis observed between populations can influence the effective rate of gene flow. Individuals from the same population are more likely to share deleterious recessive mutations at any given locus than hybrids formed between parents from different populations (Charlesworth *et al.* 1997). In the absence of severe outbreeding depression, offspring of migrants will display heterosis and have an increased fitness over resident individuals. As beneficial alleles introduced by the immigrant sweep through the population, other alleles, linked to the loci under selection, will 'hitchhike' (*sensu* Maynard Smith & Haigh 1974) to higher frequencies than predicted from neutral expectations and will thus yield a higher effective migration rate.

Here we develop a model that explicitly takes the effect of heterosis into account to calculate the effective migration rate. We show that the effect of heterosis can be substantial, but that it also will be highly variable throughout the genome with the most pronounced effects seen in regions of high gene density and for regions close to loci contributing to heterosis. Parts of the genome may therefore experience elevated rates of gene flow, up to an order of magnitude higher than the neutral expectation. Finally, while we focus on heterosis as the mechanism generating a selective advantage to migrant offspring, it is worth pointing out that any situation where an advantageous allele is introduced into a population will result in a higher effective migration rate of linked alleles, due to hitchhiking (see Schierup *et al.* (2000) for an example with balancing selection).

2. A MODEL FOR THE EFFECTIVE MIGRATION RATE

The allele frequency under mutation–selection–drift balance is a complex function of the effective population size, forward and backward mutation rates, and strength of selection. At equilibrium, the distribution of allele frequencies can be found from Wright's distribution (Wright 1937). For low migration rates ($Nm < 1$) and weakly deleterious alleles ($Ns < 1$) this distribution is U-shaped, with populations being close to fixation for either the wild-type or the deleterious allele. Local populations accumulate deleterious mutations somewhat independently, and individuals from different populations will be carrying slightly different sets of deleterious alleles. A consequence of this is that offspring of an immigrant will display heterosis due to the masking of the mildly deleterious alleles that occur in high frequencies in the recipient population. Strongly deleterious alleles have virtually no chance of occurring in high frequencies or becoming fixed unless populations are very small and will therefore contribute almost nothing to heterosis (Whitlock *et al.* 2000).

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Heterosis will generate a direct selective advantage to the offspring of a migrant such that they will have a higher than average number of offspring. Here we will develop a model that allows us to approximate the effective migration rate due to heterosis. The amount of fitness gain expected in crosses between individuals from different subpopulations is a function of both the details of the genetic load (i.e. the number of loci involved, the distribution of effects, etc.) and the history of inbreeding in the population (Whitlock *et al.* 2000). Here we use the amount of heterosis present at the point in time when an immigrant arrives to predict the genetic effects of migration, and we do not discuss the complex feedback between these processes (see also Whitlock *et al.* 2000).

Let δ_i be the difference in relative fitness, due to a single locus, between an individual with a native genotype and an individual with a hybrid genotype at that locus. For the simple model where the fitness of wild-type homozygotes, heterozygotes and homozygotes for a deleterious allele are equal to unity, $1 - h_i s_i$ and $1 - s_i$, respectively, δ_i is given by

$$\delta_i = \frac{s_i(q_{r,i} - q_{m,i})(q_{r,i} + h_i(1 - 2q_{r,i}))}{1 - q_{r,i}s_i(q_{r,i} + 2h_i(1 - q_{r,i}))}, \quad (1)$$

where $q_{r,i}$ and $q_{m,i}$ are the frequencies of the deleterious allele in the recipient and donor population, respectively. If the deleterious allele is close to fixation in the resident population ($q_{r,i} \approx 1$) and absent from the migrants, $\delta_i \approx s_i(1 - h_i)/(1 - s_i)$.

For most loci, δ_i is zero, because the immigrants are bringing in the same alleles that are already present in the recipient population. For other loci, however, δ_i is positive, because the migrant allele partially masks the deleterious effects of a native allele. Also note that if the immigrant carries deleterious alleles at some loci, δ_i can be negative and the heterozygote might be less fit than the native homozygote. On average, however, the expected value of δ_i is positive if net heterosis is positive.

A large number of loci are assumed to contribute to heterosis; therefore we assume that the selection coefficient per locus (s_i) is weak. The deterministic increase in frequency of the wild-type allele ($1 - q_i$) is thus rather slow, and δ_i does not change much over the time before recombination breaks down the association between the selected alleles and the marker allele. In the derivations that follow we assume δ_i to be constant to reduce the analytical complexity of the problem. This assumption is relaxed in the simulations below.

If the recombination rate between a neutral locus j and a selected locus i is r_{ij}, then the probability that the neutral locus stays associated with a favourable allele for at least t generations before recombination breaks up the association is $(1 - r_{ij})^t$. If we assume that the population is large enough and that selection on individual loci is weak ($\delta_i < r_{ij}$) so recombination occurs before immigrant alleles reach high frequencies, the expected number of copies of the neutral locus at time τ is $1 + \Sigma_{t=0}^{\tau}\delta_i(1 - r_{ij})^t$ times as great as initially or approximately $1 + \delta_i/r_{ij}$ if τ is large. This approach is analogous to earlier studies focusing on the reduction in gene flow across a hybrid zone (Bengtsson 1985; Barton & Bengtsson 1986).

If fitness effects of different loci interact multiplicatively (i.e. there is no epistasis) the total heterosis effect on a neutral locus j, Λ_j can then be approximated by

$$\Lambda_j \approx \prod_{\text{all selected genes } i} \left(1 + \frac{\delta_i}{r_{ij}}\right), \quad (2)$$

where the product is taken over all loci contributing to heterosis in the offspring.

In deriving equation (2) we have made some simplifying assumptions. As stated above, we have assumed δ_i to be constant over the time when the heterosis effect takes place. We have also assumed that higher-order linkage disequilibrium among selected loci can be neglected. When a migrant enters a population, linkage disequilibrium is at its maximum and it is possible that this will create a synergistic effect among the selected loci. The predictions based on equation (2) are thus conservative and may underestimate the effect of heterosis on the effective migration rate. These assumptions are relaxed in the simulations below.

If a particular marker locus is near a locus under strong selection (such that $\delta_i > r_{ij}$), then the local dynamics will dominate the genome-wide effects. In this case, the approximations given in this paper will overestimate the effects of selection at linked loci on effective migration.

Given equation (2), it is possible to define the effective migration rate at locus j, $m_{e(j)}$, as

$$m_{e(j)} = m\Lambda_j. \quad (3)$$

Note that our definition of Λ is analogous to Bengtsson's 'gene-flow factor' which measures the reduction in gene flow across a hybrid zone (Bengtsson 1985).

The degree of genetic differentiation among populations at the neutral locus is then given by substituting equation (3) into the standard equations for the equilibrium between drift and migration (Wright 1951)

$$F_{ST(j)} \cong \frac{1}{4\mathcal{N}m_{e(j)} + 1}.$$

To gain further insight we need to derive approximations to equation (2). Let there be n selected loci which contribute to the heterosis effect, such that the total heterosis is $H = \Pi_j(1 + \delta_j) - 1 \cong \Sigma_j\delta_j$. If δ_i/r_{ij} is small, $(1 + \delta_i/r_{ij})$ can be approximated by $\exp(\delta_i/r_{ij})$, and the total heterosis effect can therefore be approximated by

$$\Lambda_j \approx \exp\left(\sum_{i=1}^{n} \frac{\delta_i}{r_{ij}}\right). \quad (4)$$

Further, if δ_i is independent of $1/r_{ij}$, then, on average, this will be equal to

$$\Lambda_j \approx \exp\left(\frac{H}{\tilde{r}}\right), \quad (5)$$

where $\tilde{r} = n/(\Sigma_i 1/r_{ij})$ is the harmonic mean recombination rate between the marker locus and all selected loci. This is the complement to a result gained by Barton & Bengtsson (1986) for selection against hybrids. The average recombination rate is very sensitive to small values; the overall heterosis effect on a locus will thus

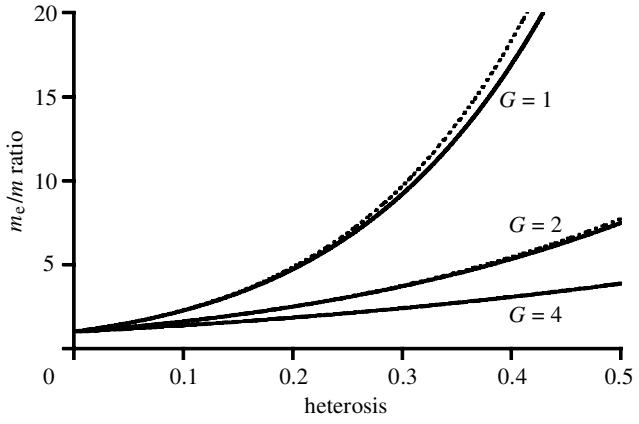

Figure 1. Ratio of effective migration rate (m_e) to the neutral migration rate (m). The calculations assume $n = 1000$ identical loci, evenly distributed across the genome. Heterosis, the increase in fitness of migrant offspring over resident individuals is defined as $(1+\delta)^n - 1$ where δ is given by equation (1). Results are shown for three different map lengths $G = 1$, $G = 2$ and $G = 4$ Morgans, corresponding to harmonic mean recombination rates equal to $\tilde{r} = 0.122$, $\tilde{r} = 0.198$ and $\tilde{r} = 0.298$, respectively. Solid lines correspond to equation (2) and dashed lines correspond to the approximation given in equation (5).

depend strongly on the selected loci most closely linked to it. For a given number of selected loci, the heterosis effect will increase as the total map length gets small or as the number of genes in a linkage group gets large. Figure 1 plots the solutions to equation (2) and the approximation given by equation (5) for varying values of the harmonic mean recombination rate.

3. SIMULATIONS

We performed Monte Carlo simulations to check the accuracy of the analytic theory. In all simulations, the recipient population was initiated in a mutation–selection–drift balance, calculated from Wright's distribution of allele frquencies (Wright 1937). In each replicate simulation one migrant was introduced.

In one set of simulations, migrants were assumed to carry a set of loci segregating for a deleterious allele in the recipient population but fixed for a wild-type allele in the immigrant. The immigrant individual was thus free of deleterious alleles.

We also performed simulations where immigrants carried an additional set of loci fixed for a wild-type allele in the recipient population but segregating for a deleterious allele in the hypothetical donor population. In these simulations the immigrants thus carried, on average, the same number of deleterious alleles as an average member of the recipient population. These simulations were therefore performed to specifically test whether deleterious alleles introduced by the immigrant have any effect on the relationship between heterosis and the effective migration rate.

For all simulations we modelled a linear chromosome of map length G Morgans, with a neutral locus in the middle of the chromosome. The neutral locus was flanked by the two different sets of $n = 32$ selected loci, evenly distributed over the length of the chromosome. Recombination frequency between loci was specified at the start of each simulation using Haldane's mapping function $R(x) = (1 - \exp[-2x])/2$, where x is the distance between two loci in Morgans (Haldane 1919). Because the selected loci are uniformly distributed, the distance between two adjacent loci is the same for all loci on the chromosome.

The neutral locus was initially fixed for one allele, and the immigrant individuals introduced into the population were carrying two copies of another (neutral) allele. The simulations were continued until the population reached quasi-equilibrium or the introduced neutral allele was either lost or fixed. Because quasi-equilibrium was usually reached within 50–100 generations, mutation was, for simplicity, ignored in the simulations. We then recorded the frequency of the neutral allele and calculated the effective migration rate as the ratio of the observed frequency to the expected frequency under neutral assumptions.

All simulations were performed using a recipient population of size $N = 100$ diploid individuals. A per locus

Table 1. *Effective migration rate from simulations and predicted values based on analytical theory*

(Simulations assume that immigrants are free of deleterious alleles. All simulations used a population size of $N = 100$. 'no del' indicates simulations where immigrants are assumed to be free of deleterious mutations while 'del' indicates simulations where immigrants also carry deleterious mutations. A dash indicates simulations not performed. All simulations use $n = 32$ selected loci, all recessive ($h = 0$) and a map length of $G = 2$ Morgans, unless otherwise stated.)

	heterosis	no del		del
		predicted	mean (s.e.)	mean (s.e.)
$G = 1$	0.0	1.0	1.18 (0.32)	—
	0.05	1.38	1.36 (0.39)	1.22 (0.31)
	0.10	1.89	2.09 (0.48)	1.77 (0.39)
	0.25	4.64	5.54 (1.12)	4.22 (0.72)
	0.40	10.61	11.58 (1.67)	8.11 (0.78)
	0.50	17.30	20.16 (1.99)	11.23 (0.90)
$G = 2$	0.0	1.0	—	—
	0.05	1.22	1.20 (0.30)	1.36 (0.30)
	0.10	1.48	1.63 (0.38)	1.56 (0.35)
	0.25	2.62	2.81 (0.48)	2.30 (0.39)
	0.40	4.51	4.56 (0.60)	3.98 (0.54)
	0.50	6.42	7.15 (0.75)	5.28 (0.63)
$G = 4$	0.0	1.0	1.0 (0.25)	—
	0.05	1.15	1.15 (0.35)	1.09 (0.28)
	0.10	1.32	1.38 (0.40)	1.32 (0.31)
	0.25	2.0	2.08 (0.44)	2.06 (0.40)
	0.40	3.01	3.28 (0.47)	2.67 (0.46)
	0.50	3.92	4.59 (0.55)	3.15 (0.47)
$h = 0.2$	0.0	1.0	—	—
	0.05	1.22	1.29 (0.32)	1.22 (0.29)
	0.10	1.48	1.52 (0.34)	1.48 (0.32)
	0.25	2.62	2.74 (0.47)	2.61 (0.46)
	0.40	4.51	4.37 (0.57)	4.15 (0.57)
	0.50	6.42	6.75 (0.71)	5.04 (0.61)

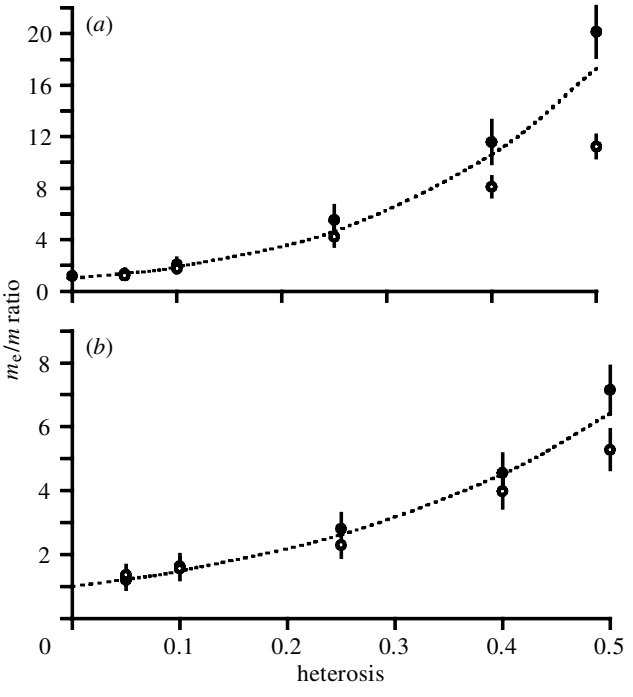

Figure 2. Simulations and predicted values for the effective migration rate with a map length of (*a*) $G = 1$ Morgan and (*b*) $G = 2$ Morgans. Theoretical predictions are shown as dashed lines and were calculated from equation (5). Results from two sets of simulations are shown: immigrant is free of deleterious alleles (filled circles) and immigrant also carry deleterious alleles (open circles). All simulations used a population size of $N = 100$ with $n = 32$ loci contributing to heterosis. For simulations where immigrants carry deleterious alleles an additional set of 32 loci is included; see § 3 for further details. Error bars denote approximate standard errors.

mutation rate of $\mu = 0.00156$ (genomic mutation rate $U = 0.1$) was used to calculate the equilibrium frequencies of the deleterious alleles in both the donor and recipient populations from the Fisher–Wright model (Wright 1937). Each set of parameter combinations were replicated 2000 times. The results from the simulations are summarized in table 1. Figure 2 shows results from a representative set of simulations with theoretical predictions based on equation (5) shown as dashed lines.

Simulations agreed quite well with predicted values from the analytical theory when the immigrant was assumed to be free of deleterious mutations. For large heterosis values, however, simulations yielded slightly higher m_e/m ratios than expected based on the analytical theory. This presumably arises from linkage disequilibrium between the selected loci. Linkage disequilibrium for the selected loci is maximal when the immigrant enters the population, and this could create a synergistic effect among the selected loci. As noted, linkage disequilibrium was ignored in the derivations above, and the predictions based on equation (5) are thus conservative, slightly underestimating the effect of heterosis on the effective migration rate.

Introducing deleterious alleles with the immigrants acts to slightly reduce the effective migration rate below the expectations based on the analytical theory (figure 2). However, this effect is only noticeable for strong heterosis (25% or greater). The effect of migrant deleterious recessive alleles is very small because they are not often expressed in their deleterious state, while still linked to the marker allele.

4. DISCUSSION

Heterosis is expected to be most pronounced for values of $Ns \approx 1$. While more weakly deleterious alleles can more easily drift to high frequencies, even the combined effects of many such loci are not enough to substantially reduce fitness (Whitlock *et al.* 2000). Similarly, alleles under strong selection can not diverge in frequency between populations and will thus not contribute much to heterosis (Whitlock *et al.* 2000). Recessive alleles can generally drift to higher frequencies because they are not expressing their deleterious effects until combined in homozygous form. Heterosis is therefore expected to be most pronounced for populations with low N_e and for alleles with small h, small to intermediate s-values and for populations connected by weak gene flow ($Nm < 1$) (Whitlock *et al.* 2000). However, rare dispersal events are thought to have a disproportionately large influence on differentiation among populations (Slatkin 1985; Nichols & Hewitt 1994). Heterosis is therefore expected to be greatest for situations where gene flow can be expected to have the greatest impact in shaping the genetic structure.

A few of our results are worth emphasizing here. First, the effect studied in this paper requires a substantial reduction in fitness within local populations to have a notable impact on the effective migration rate (fitness reduction of around 25% or more, see below). Second, the effective migration rate is predicted to be highly variable throughout the genome, with the largest effect on neutral variation in regions of high gene density. Similar results have been observed for the converse situation where migrant offspring have reduced fitness, for instance with gene flow through a cline (Petry 1983; Bengtsson 1985; Barton & Bengtsson 1986). Thus, when variable levels of molecular diversity are observed across the genome this might not be caused by the direct effects of selection or drift *per se*, but rather by the interaction of selection and drift with gene flow to generate regions with different effective migration rates.

There are also similarities between the heterosis effect we have studied and models of background selection, the reduction in neutral genetic variation arising from selection against weakly deleterious alleles (Charlesworth *et al.* 1993). Background selection is known to be most effective in regions of the genome with low recombination rate, and reduces the effective population size experienced by linked loci (Charlesworth *et al.* 1997). Background selection will thus increase the effects of drift compared to the case without background selection. The heterosis effect discussed in this paper will, to a certain extent, work in the opposite direction, because migration will reintroduce variation to a population. It is interesting to note that two studies have found reduced diversity (differentiation) between populations, compared to theoretical expectations, when studying the effects of background selection in subdivided populations (Charlesworth *et al.* 1997; Pamilo *et al.* 1999). Both Charlesworth *et al.* (1997) and Pamilo *et al.* (1999) suggested that between-population

heterosis could account for the discrepancy between theoretical and empirical results, but did not study this in further detail.

Levels of inbreeding depression have been documented for a wide variety of organisms, mainly in plants (reviewed in Charlesworth & Charlesworth 1987; Husband & Schemske 1996). A few studies have also estimated heterosis from between population crosses and have found it to average 10–15% for individual fitness components and 70–80% for total fitness (Levin 1984; Levin & Bulinska-Radomska 1988; Dudash 1990; Fenster 1991; Van Treuren *et al.* 1993). Dudash (1990) also showed that estimates of heterosis from greenhouse and common garden experiments in *Sabatia angularis* were magnified when the same experiments were repeated in the field. Estimates of heterosis from greenhouse and common garden experiments are therefore, if anything, underestimating the true magnitude of heterosis in natural populations. While these studies are certainly not a random sample, they suggest that between-population heterosis could be an important factor in increasing the effective gene flow, at least in plants. Given a heterosis of around 50%, there can easily be a five- to tenfold difference between the observed and expected migration rate.

There are currently few data available in the literature that can be used directly to discern how important heterosis might be in increasing the effective migration rate among populations. Laboratory studies have indicated that a single immigrant into a small, partially inbred population can have large impact on mean fitness in subsequent generations. Carson (1961) and Spielman & Frankham (1992) showed that immigration of a single haploid genome resulted in a two- or threefold increase in mean fitness and population size in laboratory populations of *Drosophila melanogaster*. However, both of these studies suffer from some drawbacks. Spielman & Frankham (1992) employed populations with high inbreeding coefficients ($F = 0.5$), and this may not accurately reflect levels of inbreeding in most natural populations. Similarly, Carson's study involved populations with multiple visible mutations used as genetic markers (Carson 1961). Some of these mutants are likely under selection and superiority of wild-type flies over flies carrying multiple markers might partially explain the large response observed.

Field data from natural populations are even more scarce, a major exception being an experimental introduction of house mice on the Isle of May, Scotland. The Isle of May mice were highly inbred, as evidenced by a lack of variation at allozyme loci (Berry *et al.* 1991). Berry and co-workers (Berry *et al.* 1991; Jones *et al.* 1995) found that marker alleles present only in introduced mice increased rapidly in frequencies over the first few of years after introduction. A later study showed that this increase could, to a large extent, be explained by a higher male mating success among immigrant males (Jones *et al.* 1995). The reason for the higher mating success of immigrant males is not entirely clear, but female choice to reduce the effects of inbreeding is perhaps the most plausible explanation (Jones *et al.* 1995).

Finally, if the heterosis effect we have discussed in this paper is common, it has consequences for using genetic methods to estimate gene flow in natural populations. As noted above, the effect will be highly variable throughout the genome, and a neutral locus tightly linked to a selected locus will be dragged along as the immigrant alleles sweep through the population. Such hitchhiking effects will lead to substantially higher effective migration in regions of the genome with low recombination. Because neutral loci can be expected to show varying degrees of genetic differentiation depending on how close to a selected locus they occur, it will be hard to produce reliable estimates of gene flow using genetic methods (Slatkin 1985; Whitlock & McCauley 1999).

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