Heredity **84** (2000) 452–457 *Received 5 November 1999, accepted 9 December 1999*

Local drift load and the heterosis of interconnected populations

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We use Wright's distribution of equilibrium allele frequency to demonstrate that hybrids between populations interconnected by low to moderate levels of migration can have large positive heterosis, especially if the populations are small in size. Beneficial alleles neither fix in all populations nor equilibrate at the same frequency. Instead, populations reach a mutation–selection–drift–migration balance with sufficient among-population variance that some partially recessive, deleterious mutations can be masked upon crossbreeding. This heterosis is greatest with intermediate mutation rates, intermediate selection coefficients, low migration rates and recessive alleles. Hybrid vigour should not be taken as evidence for the complete isolation of populations. Moreover, we show that heterosis in crosses between populations has a different genetic basis than inbreeding depression within populations and is much more likely to result from alleles of intermediate effect.

Keywords: deleterious mutations, heterosis, hybrid fitness, inbreeding depression, migration, population structure.

Introduction

Crow (1948) listed several reasons why crosses between individuals from different lines or populations might have increased fitness relative to more 'pure-bred' individuals, so-called 'hybrid vigour'. Crow commented on many possible mechanisms behind hybrid vigour, including a novel suggestion that genetic drift might cause the frequencies of deleterious recessive alleles to vary among populations, resulting in a net masking of their deleterious effects in hybrids. The extent of hybrid vigour expected in crosses among populations was not mathematically examined at that time; this note seeks to investigate the extent of hybrid vigour expected in interpopulational crosses carried out between populations at drift–mutation–selection–migration equilibria for deleterious recessive alleles.

The consequences of hybridization are not straightforward to predict — the fitness of hybrids between isolated populations or between closely related species varies widely (Charlesworth & Charlesworth, 1987; Arnold & Hodges, 1995). In nature some populations are inbred, and empirical studies indicate that fitness can be reduced (sometimes substantially) with inbreeding (Charlesworth & Charlesworth, 1987; Ralls *et al*., 1988; Lynch, 1989; Thornhill, 1993). Often crossbreeding to other populations alleviates the effects of inbreeding and genetic drift, producing offspring with higher fitness than the parents (see recent reviews on inbreeding in Thornhill, 1993). Decades of work in agricultural genetics confirms this pattern: when divergent lines are crossed their F_1 offspring often perform substantially better than the average of the parents (Falconer, 1981; Mather & Jinks, 1982).

The purpose of this paper is to explore whether geographically distinct populations can diverge in the frequency of alleles deleterious in all populations. In particular we are interested in whether substantial positive heterosis is possible when populations are connected by migration, and, if so, whether this 'hybrid vigour' is expected to be trivial or substantial. Populations connected by gene flow might seem to have no potential for heterosis, because any beneficial alleles brought into a population by migration should, on average, increase to approximately the same frequencies as in other populations. For this reason, it is often assumed that small amounts of gene flow prevent hybrid vigour. To assess this, we use Wright's distribution of equilibrium allele frequency in the infinite-island model. Surprisingly, we find that even with moderate levels of migration it is possible for hybrids to have substantially greater fitness than parental types, as a result of random differences in the frequency of deleterious alleles in different populations.

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Wright's distribution

We wish to describe the amount of heterosis expected in a cross between individuals from populations that are connected by some level of migration. To do so requires making certain assumptions about the genetic basis of heterosis. In this model we will deal with the heterosis that results from the masking of partially recessive deleterious alleles. It is possible to extend the methods described here to the other putative explanation for positive heterosis, overdominance.

We use Wright's distribution of equilibrium allele frequency (see Crow & Kimura, 1970). There are two types of allele per locus; one has normal fitness and the other has a lower fitness in homozygotes, $1–s$, relative to the normal allele. Expression of the deleterious allele is affected by a dominance coefficient, h, such that heterozygotes have fitness $1–hs$. The fitness of these genotypes is constant with respect to population. Fitness is multiplicative among loci. We assume that populations have symmetric migration among them at rate m. In all populations, mutation occurs from good to deleterious alleles at rate μ and at rate v in the other direction. The effective size of each population is N. The high-fitness allele occurs in population i with frequency p_i, and the overall average allele frequency is $\bar{p}$.

With these definitions, we can find the equilibrium probability density of allele frequencies, Ψ. By Wright's distribution, Ψ is:

$$\Psi(p) = Cp^{4Nv+4Nm\bar{p}\quad 1}(1\quad p)^{4N\mu+4Nm(1\quad \bar{p})\quad 1}\bar{W}^{2N}, \qquad (1)$$

where C is a normalization constant such that $\int_0^1 \Psi(p)\mathrm{d}p = 1$ and $\bar{W}(p) = 1\quad hs2p(1\quad p)\quad s(1\quad p)^2$ is the mean fitness of the population (Crow & Kimura, 1970). This model can be solved numerically by iteration until $\bar{p}$ equals the expected value of p (Barton & Rouhani, 1993).

The expected mean fitness at equilibrium within a population will be

$$\mathrm{E}[\bar{W}_{\mathrm{within}}] = 1\quad s\ 1 + 2\bar{p}(h\quad 1) + \mathrm{E}\left[p^2\right](1\quad 2h)\big), \qquad (2)$$

where E denotes expectation. Similarly, the expected fitness of hybrids between two populations will be

$$\bar{W}_{\mathrm{hybrid}} = 1\quad hs2\bar{p}(1\quad \bar{p})\quad s(1\quad \bar{p})^2. \qquad (3)$$

Of course, $\bar{p}$ and $\mathrm{E}[p^2]$ can be determined directly from Ψ.

The product of the mean fitness at each locus gives the fitness of an individual. If n is the number of loci in the genome that can mutate to a deleterious state and all loci have identical properties, these averages are given by

$$\begin{aligned}\bar{W}_{\mathrm{within}} &= (1\quad hs)^{2(\bar{p}\quad \mathrm{E}(p^2))n}(1\quad s)^{(1\quad 2\bar{p}+\mathrm{E}(p^2))n}\\ \bar{W}_{\mathrm{hybrid}} &= (1\quad hs)^{2\bar{p}(1\quad \bar{p})n}(1\quad s)^{(1\quad \bar{p})^2 n},\end{aligned} \qquad (4)$$

where the exponents represent the number of loci expected to be heterozygous or homozygous deleterious, respectively, in an individual. The heterosis is the increase in mean fitness of hybrids relative to the pure-bred individuals, i.e. $\frac{\bar{W}_{\mathrm{hybrid}}}{\bar{W}_{\mathrm{within}}}\quad 1$. Thus heterosis is a function of the strength and form of selection and of the difference in allele frequency between demes.

Results

Numerical integration of eqns (1) and (4) can be used to determine the expected fitness of pure-bred and hybrid individuals. Because the probability density function, Ψ, has singularities at $p = 0$ and $p = 1$ for low values of Nm and $N\mu$ (Fig. 1), care has to be taken when evaluating eqns (1) and (4). Therefore, numerical integration of eqns (1) and (4) was carried out using the techniques outlined in the appendix to Kimura *et al.* (1963). A MATHEMATICA notebook is available upon request from the authors for performing the calculations in this paper.

Many parameters determine the expected level of heterosis, including effective population size, selection coefficients, dominance coefficients, migration rates and mutation rates. However, most of these parameters are poorly known.

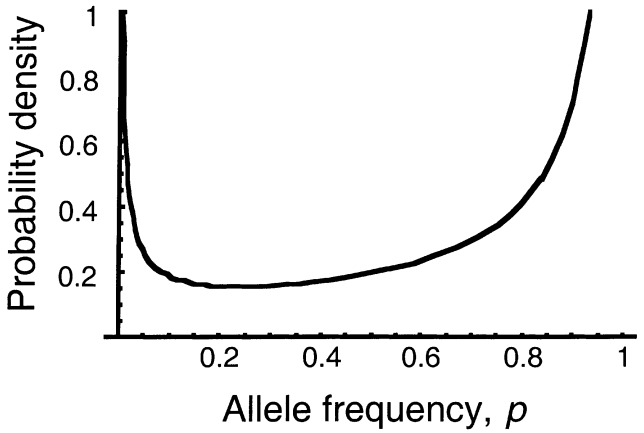

Fig. 1 The distribution of allele frequencies across populations. For the parameters that generate large heterosis, the distribution is a skewed U-shape, with many populations near fixation for either allele. In this example, $N = 1000$, $s = 0.0005$, $h = 0$, $m = 10^{-4}$, $\mu\ = 10^{-5}$ and $v = 10^{-7}$.

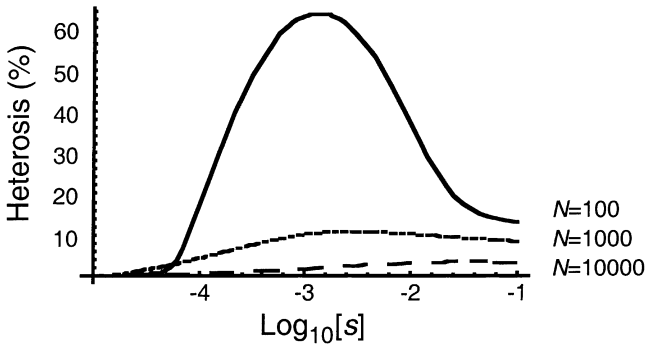

Fig. 2 The influence of effective population size on heterosis. The solid line corresponds to $N = 100$, the dotted line to $N = 1000$, and the dashed line to $N = 10\,000$. Parameters are $m = 0.001$, $h = 0.01$, $\mu = 10^{-5}$ and $v = 10^{-7}$. Heterosis is calculated multiplicatively across 10 000 loci in this and all of the figures.

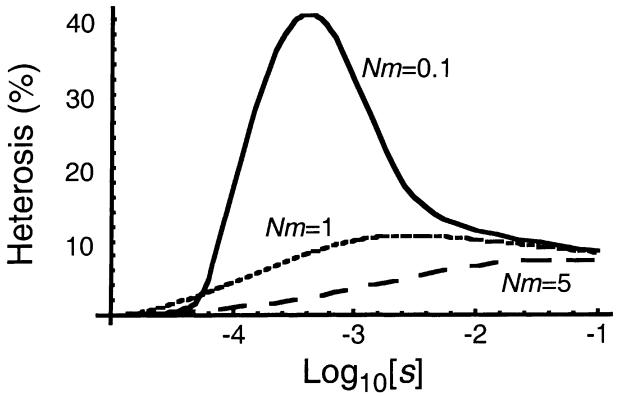

Fig. 3 The effect of migration rate on heterosis. In this graph, the solid line corresponds to $Nm = 0.1$, the dotted to $Nm = 1$, and dashed line to $Nm = 5$. Other parameter values are as in Fig. 2 with $N = 1000$.

The effective population size is clearly important (Fig. 2); smaller N leads to a higher level of genetic differentiation among populations and therefore a greater chance that one population will have alleles that rescue the inbreeding depression of other populations. Local N is not known for most species; when we do have information it is common for the effective size to be an order of magnitude smaller than the census population size, as a result of variance in reproductive success and fluctuations in population size over time (Frankham, 1995). For most values of the other parameters, the amount of the heterosis scales with Ns, $N\mu$ and Nm. Thus, the results presented in the next paragraphs, which all use $N = 1000$, are easily extrapolated to other values of N by scaling all the other parameters accordingly.

The number of loci that can negatively affect fitness is highly variable among species. In *Drosophila*, the number is of the order of 10^4. Estimates of the number of deleterious mutations per generation are also variable, but for most eukaryotes are on the order of 0.1–1 (Drake *et al.*, 1998). Taken together, this argues for an average per locus mutation rate to deleterious alleles on the order of 10^{-5}–10^{-4}; thus we have chosen to investigate this range most closely. For organisms with fewer cell generations per individual generation than *Drosophila*, the mutation rates may be much smaller (Drake *et al.*, 1998).

We know very little about the distribution of selective effects of deleterious mutations (Keightley, 1994), although it seems clear that there is a range of possible mutant effects. Estimates of the total decline in fitness per generation attributable to mutation alone are around 2% or more for *Drosophila* (Lynch & Walsh, 1998), which together with the mutation rate calculations above suggests an average homozygous effect of a new mutation around a few per cent. This average belies a great deal of variation and statistical uncertainty.

Generally, significant heterosis is observed whenever $Nm \leq 1$; with $Nm \ll 1$, heterosis can be extreme (Fig. 3). Alleles under weak selection have relatively little effect, because even cumulatively alleles of small effect cannot cause much depression of fitness. With moderately strong selection, on the other hand, allele frequencies can diverge but with enough fitness loss to result in noticeable heterosis (see Figs 3 and 4). As the strength of selection gets very strong, selection in large populations acts effectively to eliminate all new deleterious mutations and heterosis declines again. This pattern gets more pronounced for lower migration rates (Fig. 3).

Figure 4 shows the results for a range of dominance coefficient values. Completely or nearly completely recessive alleles show the greatest amount of heterosis whereas alleles that are only partially recessive ($h = 0.1$) contribute much less to the expected heterosis.

Not surprisingly, the observed levels of heterosis are very sensitive to the deleterious mutation rate (Fig. 5). Increasing the number of new mutations increases the expected heterosis. With very high mutation rates and weak selection, however, all populations have high frequencies of deleterious alleles and heterosis is negligible.

Discussion

One of the oldest observations of biology is that individuals produced by mating between relatives are more likely to have low fitness than random-bred individuals. Perhaps the most common form of nonrandom mating is the mating that occurs within

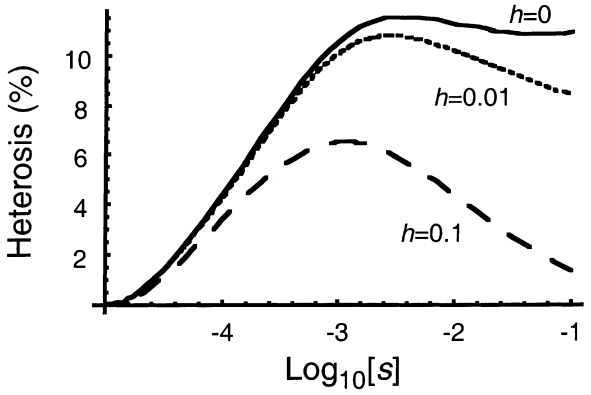

Fig. 4 The effect of varying the dominance coefficient on heterosis. The solid line corresponds to $h = 0$, the dotted line to $h = 0.01$, and the dashed line to $h = 0.1$. Other parameter values are as in Fig. 2 with $N = 1000$.

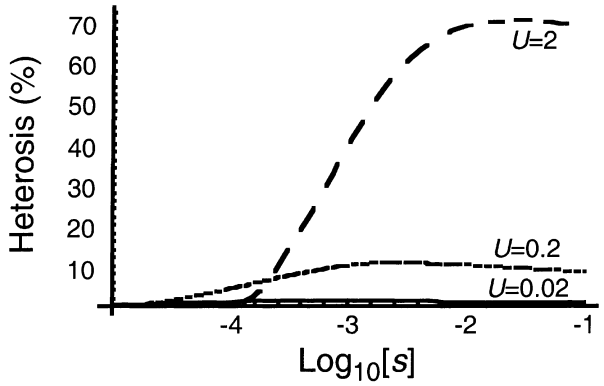

Fig. 5 The effect of the mutation raFte on heterosis. Higher deleterious mutation rates cause higher degrees of heterosis for $s \gg \mu$. (With $\mu \gg s$, nearly all populations are close to fixation for the deleterious allele, and the heterosis therefore is minimal.) The solid line corresponds to $\mu = 10^{-6}$ ($U = 2\mu n = 0.02$), the dotted to $\mu = 10^{-5}$ ($U = 0.2$), and the dashed line to $\mu = 10^{-4}$ ($U = 2$). Other parameter values are as in Fig. 2 with $N = 1000$.

local populations, where individuals are more related to one another than to randomly chosen members of the species. The degree to which locally bred pairs produce inbred offspring depends on the rate of migration between populations, and therefore the level of heterosis observed in crosses between populations is expected to decrease with increasing gene flow. It has often been assumed that even a small rate of gene flow would be sufficient to eliminate completely the differences in frequencies of selected alleles between populations; therefore, heterosis would not be observed with gene flow. Our analysis shows that even with appreciable rates of gene flow there can be substantial increase in the fitness of hybrids between populations. This heterosis is greatest with low gene flow, with recessive alleles of intermediate selective effect, and with high mutation rates.

Why is heterosis greatest with low N, low m, high μ, and intermediate s in subdivided populations? Genetic drift among populations, as well as the stochastic nature of mutation, causes allele frequencies to vary among local populations. As a result, offspring produced by parents from different demes are likely to have a slightly different set of deleterious alleles. If those alleles are partially recessive, their effects will be masked in hybrids and hybrid fitness will be higher than average. Thus, heterosis will be greatest when the frequencies of deleterious, recessive alleles are high, when the effects of those alleles on fitness are large, and when the frequency differences between populations are greatest. These factors are not likely to be maximized at the same time, however.

Genetic drift will be greatest when the effective size of local populations is smallest. Drift will be a more important force in determining allele frequencies when selection is weak and when the migration rate is low. Thus, genetic differentiation will be greatest with small N, low m, and small values of h and s.

When s is small, however, the amount of heterosis that is possible between populations is also small. Therefore, there are competing effects between the strength of selection and the degree of heterosis: small values of s allow genetic differentiation, but large values of s result in a greater potential for fitness change. As a result, the maximum heterosis occurs at intermediate values of s. Note that this is a different pattern than exhibited by the mutation load, which is insensitive to the strength of selection but is a function of the mutation rate alone. The difference comes from the fact that in the present case local genetic drift is important in determining the local frequencies of deleterious alleles, in addition to mutation and selection intensity. As a result, s does not cancel out in determining the genetic load. With population substructure, the total genetic load is also determined by what we might call 'local drift load', the reduction in mean fitness that results from local genetic drift. Heterosis in crosses among populations is a different phenomenon than the 'reverse' of inbreeding depression within populations. Heterosis will be caused by more alleles of smaller effect than inbreeding depression, which should be largely independent of the strength of selection (Charlesworth & Charlesworth, 1987).

We have suggested that intraspecific heterosis levels may be several per cent and sometimes tens of per cent. These values are not unreasonable relative to values often seen in natural populations. Studies that have estimated heterosis from between-population crosses

(primarily in plants) have found that it can be as large as 10–15% for individual fitness components and 50–75% for total fitness (Levin, 1984; Levin & Bulinska-Radomska, 1988; Dudash, 1990; Fenster, 1991; Van Treuren *et al.*, 1993). However, some of these studies involve species that have recently been fragmented into small, isolated populations by human disturbance. It is thus not clear whether these heterosis estimates are representative for species that have persisted under equilibrium conditions over longer periods of time.

Genes of one parental species often do not work well in combination with genes of another parental species (i.e. negative heterosis or outbreeding depression). Heterosis gained by masking deleterious recessives may be difficult to detect against this background. Hybrid disadvantage may take many forms, such as lower fertility or developmental and physiological incompetence (e.g. Coyne & Orr, 1989), or where developmental and physiological competence is high, hybrids may nevertheless be selected against because of poor performance in the wild (e.g. Grant & Grant, 1993; Hatfield & Schluter, 1999). Selection against hybrids also has the effect of lowering the effective migration rate. Conversely, positive heterosis can mask some of the outbreeding depression arising from diverged genomes or local adaptation. Whether hybrids are unfit or vigorous depends on the relative strength of these forces. The sorts of heterosis described in this paper are assumed to be independent of the environment, so of course the appropriate measures of comparison are made in a common garden experiment. Furthermore, there is great uncertainty about the values of the important parameters of these models. Therefore, it will not be straightforward to assess these results empirically. However, the observation of hybrid vigour should not be taken as evidence for the complete absence of gene flow between populations.

Finally, these results shed some light on the causes of the evolution of dispersal. In large populations, the strength of selection for avoiding mating locally is extremely small; in this case dispersal between populations could not evolve as a response to inbreeding depression. In contrast, for small populations the strength of selection against local mating can be quite high. However, a low level of migration between populations ($Nm \geq 5$, say) is sufficient to remove most of the selection pressure for increased migration rate.

Acknowledgements

T. H. was supported by grants from the Natural Science and Engineering Research Council (Canada) to D. Schluter, P.K.I. by a grant from the Swedish Foundation for International Cooperation in Research and Higher Education (STINT) and M.C.W. by a Natural Science and Engineering Research Council (Canada) grant. We would like to thank Dolph Schluter, Sally Otto, Cort Griswold, Jana Heilbuth, Steve Vamosi, Michael Doebeli, Jenny Boughman, Thomas Lenormand, Art Poon and Nick Barton for helpful discussions on this topic and/or comments on the manuscript.

References

ARNOLD, M. L. AND HODGES, S. A. 1995. Are natural hybrids fit or unfit relative to their parents? *Trends Ecol. Evol.*, **10**, 67–71.

BARTON, N. H. AND ROUHANI, S. 1993. Adaptation and the 'shifting balance'. *Genet. Res.*, **61**, 57–74.

CHARLESWORTH, D. AND CHARLESWORTH, B. 1987. Inbreeding depression and its evolutionary consequences. *Ann. Rev. Ecol. Syst.*, **18**, 237–268.

COYNE, J. A. AND ORR, H. A. 1989. Patterns of speciation in *Drosophila*. *Evolution*, **43**, 362–381.

CROW, J. F. 1948. Alternative hypotheses of hybrid vigor. *Genetics*, **33**, 477–487.

CROW, J. F. AND KIMURA, M. 1970. *An Introduction to Population Genetics Theory*. Harper & Row, New York.

DRAKE, J. W., CHARLESWORTH, B., CHARLESWORTH, D. AND CROW, J. F. 1998. Rates of spontaneous mutation. *Genetics*, **148**, 1667–1686.

DUDASH, M. R. 1990. Relative fitness of selfed and outcrossed progeny in a self-compatible protandrous species, *Sabatia angularis*: a comparison in three environments. *Evolution*, **44**, 1129–1139.

FALCONER, D. S. 1981. *Introduction to Quantitative Genetics*, 2nd edn. Longman, London.

FENSTER, C. B. 1991. Gene flow in *Chamaecrista fasciculata* (Leguminosae) II. Gene establishment. *Evolution*, **45**, 410–422.

FRANKHAM, R. 1995. Effective population size/adult population size ratios in wildlife: a review. *Genet. Res.*, **66**, 95–107.

GRANT, B. R. AND GRANT, P. R. 1993. Evolution of Darwin's finches caused by a rare climatic event. *Proc. R. Soc. B*, **251**, 111–117.

HATFIELD, T. AND SCHLUTER, D. 1999. Ecological speciation in sticklebacks: environment-dependent hybrid fitness. *Evolution*, **53**, 866–873.

KEIGHTLEY, P. 1994. The distribution of mutation effects on viability in *Drosophila melanogaster*. *Genetics*, **138**, 1315–1322.

KIMURA, M., MARUYAMA, T. AND CROW, J. F. 1963. The mutational load in small populations. *Genetics*, **48**, 1303–1312.

LEVIN, D. A. 1984. Inbreeding depression and proximity-dependent crossing success in *Phlox drummondii*. *Evolution*, **38**, 116–127.

LEVIN, D. A. AND BULINSKA-RADOMSKA, Z. 1988. Effects of hybridization and inbreeding on fitness in *Phlox*. *Am. J. Bot*., **75**, 1632–1639.

LYNCH, M. 1989. Design and analysis of experiments on random drift and inbreeding depression. *Genetics*, **120**, 791–807.

LYNCH, M. AND WALSH, B. 1998. *Genetics and Analysis of Quantitative Traits*. Sinauer Associates, Sunderland, MA.

MATHER, K. AND JINKS, J. L. 1982. *Biometrical Genetics: the Study of Continuous Variation*, 3rd edn. Chapman & Hall, New York.

RALLS, K., BALLOU, J. D. AND TEMPLETON, A. 1988. Estimates of lethal equivalents and cost of inbreeding in mammals. *Conserv. Biol*., **2**, 185–193.

THORNHILL, N. W. 1993. *The Natural History of Inbreeding and Outbreeding: Theoretical and Empirical Perspectives*. University of Chicago Press, Chicago.

VAN TREUREN, R., BIJLSMA, R., OUBURG, N. J. AND VAN DELDEN, W. 1993. The significance of genetic erosion in the process of extinction. IV. Inbreeding depression and heterosis effects caused by selfing and outcrossing in *Scabiosa columbaria*. *Evolution*, **47**, 1669–1680.