HETEROZYGOTE DEFICIENCIES UNDER LEVENE'S POPULATION SUBDIVISION STRUCTURE

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This note is intended to serve two purposes. First I wish to show that maintenance of genetic variability by means of spatial environmental heterogeneity could give rise to a deficiency of heterozygous genotypes compared with the numbers predicted by Hardy-Weinberg in random mating populations. This is placed in the context of Levene's (1953) spatial model. Second, I discuss the often-observed heterozygote deficiencies at some enzyme loci in cactophilic Drosophila (Barker and Mulley 1976; Barker 1981; Barker et al. 1986a; Thomas and Barker 1990; but see Quezada-Diaz et al. 1992). A simulation investigation, inspired by experiments comparing the genetic variation among Drosophila buzzatii breeding sites (Santos et al. 1989; Thomas and Barker 1990; Quezada-Diaz 1993), is carried out to evaluate the magnitude of heterozygote deficiency as a function of the allele frequencies, the strength of selection, and the number of females ovipositing on a niche. Finally, empirical studies to test the likelihood that the niche-variation hypothesis could explain the observed deficiency of heterozygotes are suggested.

Levene (1953) considered a model of selection and extreme migration (i.e., there is a single pool of mating individuals who mate at random) in which the population is subdivided into several discrete units (niches). Two alleles, \( A_1 \) and \( A_2 \), with frequencies \( p \) and \( q = 1 - p \), respectively, were considered. The genotypes are distributed randomly among the spatially isolated patches with different environments, where they become subject to selection such that the fitnesses in the \( i \)th \((i = 1, 2, \ldots, s)\) subpopulation are \( w_{11,i} \), \( 1 \), and \( w_{22,i} \) for \( A_1A_1 \), \( A_1A_2 \), and \( A_2A_2 \) genotypes, respectively. After selection is completed, the proportion of the mating pool that subpopulation \( i \) contributes is \( c_i \) (\( \Sigma c_i = 1 \)). Under this model, it is well known that the sufficient conditions for a protected polymorphism (i.e., the property of persistence of an allele even when initially rare) are

\[
\sum_i c_i \left[ \frac{c_i}{w_{11,i}} \right]^{-1} < 1 > \sum_i c_i \left[ \frac{c_i}{w_{22,i}} \right]^{-1}.
\] (1)

The precise nature of polymorphism may not be determined, and there may be several stable equilibrium states, oscillatory behavior or even unpredictable dynamics (see Karlin 1982, pp. 66–67).

The conditions in (1) require that the weighted harmonic mean of the heterozygote fitnesses exceeds the weighted harmonic means of both homozygote fitnesses. It follows that none of the following relationships for all or some \( i \) violate these conditions for a protected polymorphism:

\[
w_{11,i}w_{22,i} < 1, \quad (2A)
\]

\[
w_{11,i}w_{22,i} = 1, \quad (2B)
\]

\[
w_{11,i}w_{22,i} > 1. \quad (2C)
\]

What equations 2 mean is that the fixation index in the \( i \)th subpopulation after selection, given by Nei (1977) as

\[
F_{IS} = \frac{P_i - p_i^2}{p_i(1 - p_i)},
\] (3)

where \( P_i \) is the frequency of homozygote \( A_iA_i \) in niche \( i \), can be negative, zero, or positive, respectively (Lewontin and Cockerham 1959). Also, the fixation index in the entire population,

\[
F_{IT} = \frac{\bar{p} - \bar{p}^2}{\bar{p}(1 - \bar{p})},
\] (4)

where \( \bar{P} = \Sigma_i P_i \), can be negative, zero, or positive depending on the selection regimes within the niches. The possibility of a positive \( F_{IT} \) index under Levene's model is easily illustrated when relative fitness values form a geometric progres-
sion in opposite directions in the subpopulations. The genotype frequencies in the $i$th niche after selection are in Hardy-Weinberg proportions (Li 1959), and the excess of homozygotes in the mating pool is proportional to the variance in gene frequencies among the subpopulations, that is, a mix of Hardy-Weinberg populations resulting in a Wahlund effect is observed.

Let us consider the situation in table 1. After selection, the frequency of genotype $A_1A_1$ (a similar result is obtained for genotype $A_2A_2$) in the mating pool is (e.g., Crow and Kimura 1970, pp. 54–55)

$$P = \rho^2 + V_p,$$

(5)

where

$$\rho = \frac{1}{2} \left( \frac{p}{p + qw} + \frac{pw}{pw + q} \right),$$

$$V_p = \frac{1}{4} \left( \frac{p}{p + qw} - \frac{pw}{pw + q} \right)^2.$$

Because $F_{ST}$ equals zero in all subpopulations,

$$F_{IT} = F_{ST} = \frac{V_p}{\rho(1 - \rho)}. \quad (6)$$

The extension to $k > 2$ alleles is difficult because (1) the conditions for simultaneous $A_1-, A_2-, \ldots, A_k-$ protection are not known (Karlin 1982, p. 67), and (2) Wright’s (1943, 1951) formula $1 - F_{IT} = (1 - F_{IS})(1 - F_{ST})$ is no longer independent of the form of genetic differentiation (see Nei 1965, 1977).

When excess heterozygosity is observed in samples from natural populations, basic selectionist theories on the maintenance of polymorphisms by overdominance (Zouros and Foltz 1987) are usually advanced to account for the result. However, when heterozygote deficiencies at a variety of loci are noticed, explanations such as the Wahlund effect, inbreeding, and null alleles are often proposed, even though the reproductive biology of the species under study militates against these causative agents. For instance, in marine bivalves, frequent occurrences of heterozygote deficiencies occur at allozyme loci (Fujio et al. 1983; Zouros and Foltz 1984) coupled with a positive relationship between multiple-locus heterozygosity and several fitness related traits (Singh and Zouros 1978; Zouros et al. 1980; Koehn and Gaffney 1984; Rodhouse et al. 1986; Koehn et al. 1988). Although high fecundity, random external fertilization, and extensive larval dispersal are characteristic features of most marine bi-

<table>
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<th>$w_{12}$</th>
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<td>1/w</td>
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</tr>
<tr>
<td>2</td>
<td>1/2</td>
<td>w</td>
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</table>

Harmonic mean $2w/(1 + w^2)$, Arithmetic mean $(1 + w^2)/2w$

Values that make the chances of closely related individuals occurring in the same locality very remote, partial inbreeding has been suggested as an explanation for those observations (Charlesworth 1991). Similarly, flies of the genus Drosophila exemplify the colonizing lifestyle and high dispersal rates have been reported (Johnson and Heed 1976; Jones et al. 1981; Coyne et al. 1982; Barker et al. 1989). Nonetheless, inbreeding has also been suggested to account for the often-observed deficiency of heterozygotes at some enzyme loci in cactophilic Drosophila (Thomas and Barker 1990).

Members of the mulleri subgroup of the repleta group of Drosophila feed and breed exclusively in decaying cactus tissue. One member of the subgroup, D. buzzatti, has spread from South America to the Madeira and Canary islands, countries of the Mediterranean basin, Africa, and Australia in close association with its host Opuntia (Barker and Mulley 1976; Fontdevila et al. 1981). The decaying Opuntia cladodes (rots) sustain a yeast community (Starmer and Phaff 1983; Starmer et al. 1987; Barker et al. 1987; Peris et al. 1994) and constitute a discrete, ephemeral and patchy resource upon which a limited (about ten) number of parents breed (Santos et al. 1989; Thomas and Barker 1990). Under a neutral model of genetic differentiation, a general deficiency of heterozygotes is not expected unless more than one round of drift takes place; that is, unless the flies emerging from a rotting cladode tend to stay and to mate rather than to disperse. A within-rot excess of heterozygotes ($F_{IS} < 0$) was found in a thoroughly studied Spanish population (Carmoneras) for both gene arrangements (Santos et al. 1989) and allozyme markers (Quezada-Diaz 1993). This is to be expected in a large, random mating population in which there are founder events associated with the colonization of Opuntia rots (Robertson 1965; Rasmussen 1979). This
excess was still significant for both the gene arrangements on the second chromosome and those polymorphic enzyme loci in linkage disequilibria with the inversions (viz. Esterase-2 and Aldehyde oxidase; Quezada-Díaz 1993; see also Knibb et al. 1987) when the whole population was considered \( \left( F_{IT} < 0 \right) \), which strongly argues for differential viability among karyotypes (see also Ruiz et al. 1986; Hasson et al. 1991). However, the expectation of negative \( F_{IS} \) values was violated in Australian populations, in which an overall deficiency of heterozygotes is usually observed (Thomas and Barker 1990; see also Barker 1981). This is specially true for the two enzyme loci referred to above and Esterase-1, whose alleles are also strongly associated with the inversions on the second chromosome (Knibb et al. 1987). Thomas and Barker (1990) concluded, from an analysis of population structure, that inbreeding because of local mating of genetically related newly emerged adults from Opuntia rots is the most likely interpretation. Some difficulties exist with this hypothesis: (1) The effect of inbreeding is expected to be the same for all loci, and this is inconsistent with the data from Australian populations, in which locus-specific inbreeding coefficients are usually found (Barker et al. 1986a; Thomas and Barker 1990); (2) even though the flies stay and mate in their natal rot, within-rot deficiency of heterozygotes is not expected if there is local random mating, but a slight excess is expected if few individuals emerge from a rot (Kirby 1975, pp. 35–37). In addition, Quezada-Díaz et al. (1992), working at Carboneras, have recently found that wild females and males randomly engaged in copulation with respect to rot of origin, which means that newly emerged adults tend to disperse rather than to remain in their natal rot.

Ignoring founder events and selection for fertility, the population structure of D. buzzatii can be characterized by the Levene (1953) migration pattern. Zygotes are assumed to be settled at random into each of the breeding sites; that is, neither homing (Deakin 1966) nor genetically based oviposition-behavior differences exist. This last assumption is surely open to controversy (cf. Barker et al. 1986b; Santos et al. 1989; Barker 1992; Peris et al. 1994), but it will be accepted here because it is not crucial for the point to be made. In addition, Rausher (1984) has shown that genotypic-specific oviposition behavior (assuming within-habitat equal viabilities for the different genotypes) will lead to Hardy-Weinberg proportions at equilibrium. Cactophilic Drosophila are coarse grained with respect to their larval niches, and it is likely that larval viabilities are responsible for a substantial amount of the polymorphism in these species. Thus, Ruiz et al. (1986) have detected strong selection acting on the second-chromosome gene arrangements of D. buzzatii, with viabilities in the range 0.738–3.071 (i.e., selection coefficients as large as 0.75). Microspatial heterogeneity in yeast microbiota at the level of individual rots (Barker et al. 1987; Barker 1990; Peris et al. 1994) may be a major factor promoting diversifying selection. Coupled with the large selective differences reported above, the maintenance of polymorphism by environmental heterogeneity is a plausible explanation for D. buzzatii (Maynard Smith and Hoekstra 1980). Furthermore, Prout and Barker (1989) found indirect evidence of larval crowding in natural rots; thus, it is possible that fly numbers are regulated within each rot. In summary, the hypothesis that multiple niche selection is contributing to the observed heterozygote deficiency in some populations of D. buzzatii is worth exploring.

Simulations

I considered a large, random mating population subdivided into a number \( (s = 40) \) of breeding sites. Two situations were analyzed. (1) Each site is colonized by infinite adults (Levene's model), and (2) the more realistic case of several females ovipositing on a breeding site. Viability selection at a diallelic locus was simulated on a diploid population with the restriction that both alleles are protected (see below). Parenthetically, I am assuming that conditions (1) for a protected polymorphism are independent of the number of parents breeding on each subpopulation, which obviously may not be true. Given that a general deficiency of heterozygotes will be observed only when there is not overdominance within each subpopulation [a particularly relevant situation included in (2A)], only those cases where relationships (2B) or (2C) are met in all niches were investigated. Homozygote \( A_A \), was assumed to be the most fit genotype in half of the niches. Under (2B) and for each initial condition (gene frequency and number of breeding females), 50 fitness matrices were generated with one element independently and uniformly distributed over (1, 2). Figure 1 shows the distribution of the selection coefficients against the unfavorable homozygote within each niche. The average (mini-
maximum, maximum) harmonic means of homozygote fitnesses in the resulting matrices were \( w_{11} = 0.9204 \) (0.8512, 0.9913) and \( w_{22} = 0.9076 \) (0.8454, 0.9730). The genotype frequencies in the adult population after selection were obtained as

\[
T = \frac{1}{40} \sum_{i=1}^{40} \frac{1}{\text{tr}(G_i W_i)} G_i W_i, \tag{7}
\]

where \( G_i \) and \( W_i \) are, respectively, the 3 \times 3 diagonal matrices of input genotypes and fitness values in niche \( f \) and \( tr \) means trace. The relative size of the \( i \)th subpopulation, \( c_i \), was assumed to be \( 1/s \). This particular case is relevant because methods to estimate \( F \)-statistics usually ignore population size differences (Nei 1977; Nei and Chesser 1983).

To simulate (2C), the homozygote fitnesses in the 50 matrices were increased by 5%, which results in a 10% reduction of heterozygote fitness relative to the product of the fitnesses of the two homozygotes in each niche. Conditions (1) still hold in 39 out of 50 matrices, with average (minimum, maximum) harmonic means \( w_{11} = 0.9656 \) (0.9283, 0.9999), and \( w_{22} = 0.9515 \) (0.8986, 0.9946).

\( F \)-statistics were calculated following Nei (1977). All calculations were performed in double precision on a 386 PC-compatible with a mathematical coprocessor. The PC-MATLAB (Moler et al. 1987) interactive matrix algebra program and the statistical package CSS:STATISTICA™ (1991) were used for computations.

**Numerical Results**

Tables 2 and 3 give the results obtained from the simulations under relationships (2B) and (2C), respectively. When the number of females ovipositing on a breeding site was infinite (i.e., no sampling effect existed), the magnitude of heterozygote deficiency in the overall population after selection was a direct function of the allele frequencies and the relationship among the three fitness values. \( F_{IT} \) ranged from 0.0010 to 0.0972 when all simulation results are considered. The important point is that \( F_{IT} \) estimates obtained by Thomas and Barker (1990) in some Australian populations for those allozyme loci that show a consistent heterozygote deficiency are included within these values. Because the strength of selection in the simulations was always lower than in nature (see above), the niche-variation hypothesis could help to explain their observations.

Even when the frequency of the allele \( A_1 \) is low \((p = 0.1)\), the effect of sampling on the fixation index \( F_{IT} \) may be meaningful (tables 2, 3).

The magnitude of the genetic differentiation among breeding sites \((F_{ST})\) may also be substantial under Levene's model. To appreciate the effect of within-niche differential selection on population structure, we can compare the values in tables 2 and 3 when there are no founder events in the colonization of breeding sites with the \( F_{ST} \) values estimated for 29 insect species (including Diptera, Lepidoptera, Coleoptera, Hemiptera, and Hymenoptera) when considered on a broad geographic scale (McCaulay and Eanes 1987, p. 199). These estimates vary from 0.003 for *Prosimulium fuscum* to 0.380 for *Rhytidoponera confusa*. The average \( F_{ST} \) value for *Drosophila* species is 0.054. The average (minimum, maximum) value obtained in the simulations was 0.035 (0.011, 0.059).

\( F_{IS} \) fixation indices were always negative when five females contributed progeny to a niche. In these cases, an estimation of the effective number of breeding parents \((N_e)\) can be obtained by taking \( F_{IS} = -1/(2N_e - 1) \) (last column in tables 2 and 3; see Kirby 1975). The estimates vary as a function of the selection regime. Santos et al. (1989) estimate that \( N_e = 10 \), from the \( F_{IS} \) fixation index of the fourth-chromosome inversion polymorphism, in which no statistical indications of fitness differences among karyotypes were detected (Ruiz et al. 1986). However, Thomas and Barker (1990) observed positive \( F_{IS} \) values, and \( N_e \) was estimated from the genetic variation among rots \((F_{ST})\). As can be easily deduced from...
Table 2.  F-statistics (average, minimum, and maximum) for a diallelic locus under protected polymorphism in a subdivided population with Levene’s migration pattern. The number of breeding parents in each niche was set to $N = \infty$ or $N = 10$ (random sampling). Multiplicative fitnesses were assumed with the restriction: $w_{11,i} < 2 > w_{22,i}$. $N^*$ is the estimated number of parents from $F_{IS} = -1/(2N^* - 1)$.

<table>
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<th>Population frequency ($p$)</th>
<th>Zygotic input</th>
<th>$(\rho)^*$</th>
<th>$p^\dagger$</th>
<th>$p^2$</th>
<th>$(\rho^2)^\ddagger$</th>
<th>$F_{IS}$</th>
<th>$F_{IT}$</th>
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* Average gene frequency after selection in the 50 simulations.
† Average frequency of homozygotes over the 40 niches with an equal weight in the 50 simulations.
‡ Average of $p^2$ over the 40 niches in the 50 simulations.
Table 3. $F$-statistics (average, minimum, and maximum) for a diallelic locus under protected polymorphism in a subdivided population with Levene's migration pattern. The number of breeding parents in each niche was set to $N = \infty$ or $N = 10$ (random sampling). Within-niche fitnesses fit the relationship: $w_{11,i}w_{22,i} > 1$. $N^*$ is the estimated number of parents from $F_{IS} = -1/(2N^* - 1)$.

<table>
<thead>
<tr>
<th>Population frequency ($p$)</th>
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<tr>
<td>0.5</td>
<td>infinite</td>
<td>0.5019</td>
<td>0.2691</td>
<td>0.2519</td>
<td>0.2636</td>
<td>0.0233</td>
<td>0.0688</td>
<td>0.0465</td>
<td></td>
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<tr>
<td></td>
<td>sampling</td>
<td>0.5058</td>
<td>0.2695</td>
<td>0.2559</td>
<td>0.2750</td>
<td>-0.0236</td>
<td>0.0547</td>
<td>0.0765</td>
<td>(22)</td>
</tr>
</tbody>
</table>

* Average gene frequency after selection in the 39 simulations.
† Average frequency of homozygotes over the 40 niches with an equal weight in the 39 simulations.
‡ Average of $p^2$ over the 40 niches in the 39 simulations.
tables 2 and 3, their estimate of ten individuals contributing gametes to each rot may be highly biased if selection is affecting the genetic variation. In any case, the maximum $F_{IS}$ value obtained in the simulations was 0.024, which is lower than those values observed by Thomas and Barker (1990).

It should be pointed out that the selection coefficients generated for the simulations (fig. 1) are sensible when applied to inversion polymorphisms (Dobzhansky 1970; Crumpacker et al. 1977; Anderson et al. 1979; Ruiz et al. 1986; Hasson et al. 1991), but the data obtained by Thomas and Barker (1990) are for allozyme loci where the magnitude of selection is expected to be much lower. As previously discussed, a strong linkage disequilibrium exists between those loci displaying the heterozygote deficiencies and the second-chromosome inversions. In this case, the extent of the heterozygote deficiency is a function of the degree of linkage. Let us consider again the situation in table 1 and assume that marker locus $M_6$ with alleles $M_1$ and $M_2$ at frequencies $r$ and $s = 1 - r$, respectively, is in linkage disequilibrium with the selected locus $A$. It is readily obvious that the frequency of genotype $M_1M_1$ in the mating pool after selection is

$$P(M_1M_1) = r^2 + rD(1 - w)(\frac{1}{p + qw} - \frac{1}{pw + q})$$

$$+ D^2(\frac{1}{\bar{v}}_1 + \frac{1}{\bar{v}}_2)(\frac{1}{1 - w})^2$$

where $D$ is the corresponding gametic association measured by the determinant of the gamete frequency matrix (Lewontin and Kojima 1960); $\bar{v}_1 = (p + qw)^2/w$, and $\bar{v}_2 = (pw + q)^2/w$ are, respectively, the average fitnesses in niches 1 and 2. A nontrivial equilibrium point for locus $A$ is $p = q = \frac{1}{2}$, and it is easy to show that the excess of genotype $M_1M_1$ at this point equals $16D^2V_\rho$.

In some populations of D. buzzatii, an almost complete association exists between Est-1 and Est-2 alleles and second-chromosome inversions. This is specially true for the rare cosmopolitan $2jz^2$ and $2jq^2$, which are usually fixed for one allozyme allele. In the case of the two common cosmopolitan inversions, $2st$ and $2j$, several alleles can be found but in very different frequencies (Knibb et al. 1987; Quezada-Díaz 1993; Betrán et al. 1994). For instance, allele $Est-1^b$ is almost fixed within $2j$, whereas in $2st$ it has intermediate frequencies (Knibb et al. 1987). Clearly, the behavior of allozyme loci on chromosome 2 cannot be considered in isolation from the inversion complex, and the strength of within-rot linkage disequilibria could even increase because of the breeding structure of D. buzzatii. If a few parents breed on a rot, strong disequilibria are generated even when unlinked loci on the same chromosome are considered (Quezada-Díaz 1993).

In the foregoing discussion, I have assumed that population dynamics in Spain and Australia are the same, which obviously may not be true. However, the alternative that inbreeding is really responsible for the observed deficiency of heterozygotes in Australia is not convincing (see above). The disparate results obtained in Spain and Australia may not reflect differences in population structure but in host species (Opuntia ficus-indica at Carboneras and Opuntia stricta in Australia), yeast communities (cf. Barker et al. 1987; Peris et al. 1994), rotting process (the phytophagous moth, Cactoblastis cactorum, is absent from Spain), and genetic background (e.g., the gene arrangement $2jq^2$, relatively frequent in Spain, has not been recorded in Australia). The results in tables 2 and 3 suggest that the Levene model might apply to those situations in which heterozygote deficiencies are detected, but the biology of the species militates against inbreeding and Wahlund effect. However, the real problem is to evaluate the likelihood of the “Levene effect” in nature. An informative experimental approach in D. buzzatii could be the artificial seeding of eggs, obtained from genetically marked laboratory strains, into several Opuntia rots in nature. The estimation of egg-to-adult viability fitness component from the emerged flies would give us an idea about the genotype-environment interaction and the relationships among homozygote and heterozygote fitnesses within the rots.

The main problem is that more than two gene arrangements are usually found on the second chromosome in nature and up to eight alleles at the Est-2 locus (Fontdevila et al. 1981, 1982; Knibb et al. 1987). Nevertheless, some insight can be gained into the properties of multiallelic diversifying selection by using the matrices of input genotypes in the rots and the matrices of estimated fitnesses for each genotype.

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**LITERATURE CITED**


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