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Preserving genes: a model of the maintenance of genetic variation in a metapopulation under frequency-dependent selection

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Summary

Understanding how genetic variability is maintained in natural populations is of both theoretical and practical interest. In particular, the subdivision of populations into demes linked by low levels of migration has been suggested to play an important role. But the maintenance of genetic variation in populations is also often linked to the maintenance of sexual reproduction: any force that acts to maintain sex should also act to maintain variation. One theory for the maintenance of sex, the Red Queen, states that sex and variation are maintained by antagonistic coevolutionary interactions – especially those between hosts and their harmful parasites – that give rise to negative frequency-dependent selection. In this paper I present a model to examine the relationships between population subdivision, negative frequency-dependent selection due to parasites, the maintenance of sex, and the preservation of alleles from fixation. The results show strong interactions between migration rates, negative frequency-dependent selection, and the maintenance of variability for sexual and asexual populations.

1. Introduction

(i) *A statement of the problem*

Natural populations show extensive genetic variation among individuals. Population geneticists and conservation biologists alike have long debated what maintains this variation (see, for example: Haldane, 1949; Clarke, 1979; Karlin & Campbell, 1981; Takahata & Nei, 1990; Frank, 1991; Pimm, 1991; Golding, 1991). Both groups have focused on understanding the effects of habitat fragmentation – or population subdivision – on the genetic structure of populations (for example, Mather, 1955, see Slatkin, 1985 for review). But biologists often link the maintenance of variation in populations to the maintenance of sexual reproduction (see, for example, Bell, 1985). Some theories of the maintenance of sexual reproduction cannot confer an advantage for sex if populations are not genetically variable (Kondrashov, 1993); an hypothesis for sex that requires the existence of variation is more plausible if it can also be shown to maintain variation. In this paper I present an individual-based simulation model with which I examine the relationship between population subdivision, and the maintenance of sex and variation in the context of the theory of sex known as the Red Queen. As natural populations of asexuals seem to show high levels of clonal diversity, I will also consider the maintenance of variation in populations of asexuals. Before presenting the model and the results, I give a brief outline of the Red Queen and introduce two notions that are important in the consideration of the maintenance of genetic variation in a metapopulation: asynchrony and gene storage.

(ii) *The Red Queen*

In general terms, the Red Queen proposes that sex and variation are maintained by antagonistic coevolutionary interactions, whether between competitors (Glesener & Tilman, 1978), between predators and prey, or between parasites and hosts (Bell, 1982; Bell, 1985). Parasites, harmful parasites in particular, are thought to be most likely to bring about the time-lagged, negative frequency-dependent selection (see Clarke, 1979; Hutson & Law, 1981) that promotes variation (Haldane, 1949) and brings an advantage to sex (Hamilton, 1980). Recent models, whether verbal or mathematical, have concentrated on parasites as the force that maintains sex and variation (see, for example, Jayakar, 1970; Jaenike, 1978; Hamilton, 1980; Bremermann, 1980; Tooby, 1982; Hamilton, 1986; Seger, 1988; Seger & Hamilton, 1988; Hamilton

et al. 1990; Hamilton, 1993). The most complex models have shown that parasites are able to maintain sexual reproduction under stringent conditions that have been identified as hostile to sex (see Hamilton *et al.* 1990; Hamilton, 1993). These complex models have not been assessed for whether parasites maintain variation, yet a genetically variable population is necessary for sex to be an advantage under the Red Queen (Bell, 1985; Kondrashov, 1993).

(iii) *Migration and asynchrony*

Several authors have asserted that, in theory, a metapopulation could remain stable because of asynchronous cycling among demes linked by migration (Maynard Smith, 1974; Hamilton, 1986; Reeve, 1990; Taylor, 1990; Frank, 1991; Ruxton, 1994). For example, if one population is near extinction and a second is not, then the extinction can be prevented or reversed by immigration. Asynchrony usually refers to different demes having different population densities, but it can also be used to mean that demes have different gene frequencies.

In antagonistic coevolutionary interactions asynchrony can arise in at least two ways (Frank, 1991). First, the pursuing species and the pursued species enter a limit cycle. In different demes, limit cycles are at different phases, leading to asynchrony (Frank, 1991). Secondly, asynchrony can arise from local extinction followed by recolonization of patches (Frank, 1991). Other factors also help to maintain asynchrony. In general, the more demes in the metapopulation, the more likely the system as a whole is to maintain all of its demes and alleles (Taylor, 1990). Low levels of migration usually facilitate asynchrony (Taylor, 1990; Frank, 1991), and the pattern of migration also has an effect (Taylor, 1990; Frank, 1991).

As mentioned above, the extinction and recolonization of populations and patches by species can also be thought of in terms of extinction and reappearance of genotypes (or alleles) within populations and patches. Although the dynamics of a multilocus model may be too complicated for a single host genotype to be described as participating in a limit cycle with the corresponding parasite genotypes, the host alleles may cycle with respect to parasite alleles at least in an irregular 'pseudostochastic' fashion even when the dynamics of the population are fully determined (see Hamilton, 1993). In such cycles, alleles may become locally extinct. If demes are asynchronous, low and intermediate levels of migration should serve to reintroduce an allele to a deme where it has been lost.

(iv) *Gene storage*

Even in the absence of selection, 'gene storage' – the preservation of alleles from fixation (or loss) in a metapopulation (Hamilton, 1993) – is expected to arise in subdivided populations whose demes are linked by low levels of migration. This follows from classical neutral-allele theory (Wright, 1951; Kimura & Crow, 1963; Wright, 1965), which shows that due to random fluctuations, small finite populations in the absence of selection tend to become increasingly homozygous – that is, they lose genetic variability – even if they have completely random mating. But if demes do occasionally exchange migrants, loss of variability will be reduced (Wright, 1951; Kimura & Crow, 1963; Crow & Kimura, 1970). Thus, in a metapopulation of small, finite populations, genetic variability of the whole metapopulation will be maintained – despite local increases in homogeneity – because different demes will fix at different alleles. However, again, variability can only be restored to demes where it has been lost through crossing with other subpopulations. Thus, low levels of migration could lead to the maintenance of more genetic variability than would be found either in a single large population or in several small, completely isolated ones.

In a stronger form, gene storage may arise in subdivided populations whose demes are undergoing asynchronous fluctuations in gene frequencies due to host-parasite coevolution (Hamilton, 1993). In such situations, Hamilton (1993) proposes that the asynchrony of gene frequencies among the demes allows migration to reintroduce an allele to a subpopulation from which it has been lost. I suggest, more generally, that migration between asynchronous populations can preserve alleles by preventing their loss in the first place.

(v) *Asexuals and gene storage*

Classical population genetics theory tends to deal with idealized populations of diploid sexuals, and the arguments presented above apply to sexuals. I argue here that the situation for asexuals may be somewhat different. I propose that for asexuals asynchrony may preserve not just genes but whole genotypes at the metapopulation level; thus for asexuals, migration may have a much more important counter-fixation effect than it does for sexuals which are also able to bring back lost or rare genotypes by recombination. For asexual individuals, genomic diversity (or in the diploid case, heterozygosity) is not reduced in each generation as it would be for sexuals. But as one clone comes to predominate in a population, the genetic variability of the population will decline.

However, Lively (1992) and Howard & Lively (1994) have suggested that the high and fluctuating selection pressures mediated by parasites, rather than eliminating asexuals completely (for discussion of why parasites are thought to eliminate asexuals, see Ladle *et al.* 1993), may select for clonal diversity in asexuals. High asynchrony may benefit asexual individuals such

that by moving from one deme where they are common to another where they are rare, they may be able to escape from parasites. In some cases, I suggest that asynchrony may be more beneficial to an aggregate of asexuals than to sexuals by allowing a sort of clone storage that would not happen otherwise. The effect of gene-storage, or in this asexual case, genotype-storage, may simply be to slow down the complete loss of genotypes due to random genetic drift. Or, in some cases, genotype storage may allow asexuals to persist even in the face of frequency-dependent selection from parasites.

Bearing this background in mind, I will now examine the effects of migration – and therefore of gene storage and asynchrony – on the maintenance of genetic variation in a metapopulation in a multi-locus model. I consider four cases separately: (1) a sexual metapopulation in the absence of selection; (2) a sexual metapopulation subject to time-lagged, negative frequency-dependent selection mediated by parasites; (3) an asexual metapopulation in the absence of selection; (4) an asexual metapopulation subject to time-lagged, negative frequency-dependent selection mediated by parasites. The cases without selection serve two purposes. First, they allow the model itself to be tested against expected theoretical values. Secondly, as some gene preservation is expected in the absence of selection, the results set a baseline from which to judge the effects of selection on populations of sexuals and of asexuals.

2. Methods

(i) *The model*

The model is an individual-based simulation model. It extends that of Hamilton *et al.* (1990) by incorporating an explicit metapopulation, and as a consequence, migration between demes. It is also similar to that described in Ladle *et al.* (1993).

The metapopulation consists of a number of demes of constant, equal size. In this model, each of ten demes contains one hundred individuals of a haploid, iteroparous host species and one hundred individuals of each of six haploid, shorter-lived, but again iteroparous parasite species.

The following events occur each year in every deme:

1. *Infection.* Individuals of each species of parasite have two virulence loci, each with two possible alleles; each parasite locus for virulence has a corresponding host locus for resistance (a simplified gene-for-gene system). Therefore, each host individual has twelve corresponding resistance loci, also with two possible alleles. Each host is randomly assigned one parasite of each species. The number of 'matches' between host and parasite alleles is counted, giving a 'match score' for each host and parasite individual.

2. *Selection.* Parasites are selected for virulence; hosts are selected for resistance. Parasites with a high match score are more virulent. Hosts with a high match score are less resistant. Soft-truncation selection occurs according to death rates specified below.

3. *Death.* 90% of parasites and 10% of hosts in each deme are killed off each year, in order of least virulent or least resistant respectively. Survivors have their match scores reset to zero: the next score will depend on the next pairing.

4. *Reproduction.* Individuals are randomly chosen to reproduce until enough offspring have been produced to bring the demes back to their constant size. Parasites are asexual only, and reproduce by cloning. They are able to reproduce in their first year. All hosts have a thirteen year juvenile period in which they are unable to reproduce (Hamilton *et al.* 1990); this gives, as a measure of generation time (from the formula given by Hamilton *et al.* 1990), a mean age at reproduction of 23. Host populations are either all sexual or all asexual. Asexual hosts reproduce by cloning. Sexual hosts are assumed to be non-self-fertile hermaphrodites. Adult parents are sampled at random, and without replacement, from their deme. Asexuals reproduce immediately, passing on a copy of their entire genome. Sexuals mate in pairs and together produce only one offspring, a procedure that provides the two-fold cost of sex.

5. *Recombination.* All host loci are unlinked. Pairs of loci in parasites are fully linked due to the absence of sex.

6. *Mutation.* Hosts have no mutation at any time; parasites have a mutation rate of 0·01 (in either direction) per locus.

7. *Migration.* An equal number of migrants from each deme is randomly chosen to form a 'migrant cloud'. Following Wright's (1951) island model, the distance between demes is treated as unimportant; the probability of going to any deme, including returning to the deme of origin, is the same. Except by chance, hosts and parasites do not migrate together. As migration rate is the parameter of interest, I examined a number of different values for hosts and parasites: 0, $\frac{1}{32}$, $\frac{1}{4}$, $\frac{1}{2}$, 1, 2, 4, 32, 100 for each, giving 81 combinations in all. In the last state of course, there is effectively no metapopulation. In the runs without selection, hosts and parasites have no effect on each other, so only the nine values of host migration need be examined. Where migration is less than 1, it has a random chance of occurring that is equal to the value of the fraction in question. For example, a migration rate of $\frac{1}{32}$ means that each year the chance that migration takes place is $\frac{1}{32} = 0{\cdot}031\,25$. On average, migration should happen once every 32 years. Owing to the constraint that population sizes must stay constant, migration occurs in all ponds at the same time. However, if more than one species has a fractional migration rate, the chance of migration is determined separately for each species.

The simulation begins with host populations of reproductive age and the full complement of parasite species. Each randomly-generated deme begins with

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equal frequencies of all resistance and virulence alleles. One run lasts for 1000 years. During the runs, and especially during the last 50 years, various indices (described below; see Table 1) are calculated.

(ii) *Theoretical expectations and indices of interest*

For the next sections, the following notation is useful. The frequency of an allele at a given locus in deme j and year k is denoted by q_{jk}. The mean gene frequency across years, y, for a particular deme is denoted by $q_{j.}$ and the mean gene frequency across demes, d, for a particular year is denoted by $q_{.k}$. The variance of the gene frequency across demes in a particular year k is

$$\mathrm{var}_k(q_{jk}) = \frac{\sum_{j=1}^{d}(q_{jk}-q_{.k})^2}{d}.$$

(iii) *Variance of gene-frequency distributions*

In the absence of selection, populations that exchange migrants will start to homogenize when the product of the migration rate and the effective population number exceeds a certain value. As the migration rate increases, the gene frequency distribution of the metapopulation (measured for each gene, in each pond, and in each year for the last 50) is expected to pass from a U-shaped distribution, through a flat distribution, to a bell-shaped distribution. For haploids under the island model, the flat distribution should occur when $N_e m = 1$, the U-shaped distribution when $N_e m < 1$, and the bell-shaped distribution when $N_e m > 1$, where N_e is the effective population number (Wright, 1951; Crow & Kimura, 1970). For a flat distribution, the variance will be $\frac{1}{12}$, and for a completely polarized distribution, the variance will be $\frac{1}{4}$. The variance can be standardized to run between 0 and 1 by dividing by $\frac{1}{4}$. Then, the flat distribution occurs at $\frac{1}{3}$ (see Table 1). Note that because the variance is calculated by considering the values of every locus in every pond in each year for the last 50,

$$\text{variance} = \frac{\sum_{i=1}^{L}\sum_{j=1}^{d}\sum_{k=1}^{y}(q_{ijk}-\bar{q})^2}{L\,dk},$$

where L is the number of loci and $\bar{q}$ is the mean calculated for every locus, in every pond, for every year of the last 50, the index will be completely polarized both when every deme is fixed at each locus and when the metapopulation as a whole is fixed at each locus.

Given that the critical value for migration to give a flat distribution, $1/N_e$, is likely to be quite small, in the absence of selection populations should exchange migrants only rarely if the U-shaped distribution is to be maintained across the metapopulation (Wright, 1951; Crow & Kimura, 1970).

(iv) *Effective population number*

For a metapopulation with demes that are stable in space and time, the effective population number is very close to what it would be if the population were panmictic (Ewens, 1979). Thus, the effective population number for the current model can be calculated from Felsenstein's (1971) formula for the effective population number for a haploid population with overlapping generations:

$$N_{eI} = N_{eV} = \frac{N_1 T}{1+\sum_{i=1}^{\infty} r_{i+1}^2\left(\frac{1}{l_{i+1}}-\frac{1}{l_i}\right)},$$

where N_{eI} is the inbreeding effective number, N_{eV} is the variance effective number, N_1 is the number of offspring born per time interval, T is the generation time, r_i is the fraction of reproduction that takes place on or after age i, and l_i is the probability of surviving to age i. For this model, $N_{eI} = 0{\cdot}31\,697N$, where N is the actual population size, and $T = 22{\cdot}223$, which agrees with the generation time calculated earlier. Thus, the flat distribution should occur at $m = 1/N_e$, or $m = 3{\cdot}15$ migrants per generation. As the generation time is 22·23, the flat distribution should occur at approximately 1 migrant every 7 years – that is, between the migration rates $\frac{1}{32}$ and $\frac{1}{4}$.

(v) *Measuring divergence*

The variance of the gene frequency distributions can also be used for a related index that will show how much demes differ from each other: Wright's F_{ST} (Wright, 1951; Wright, 1965; Wright, 1969). In my notation, for a given year, k:

$$F_{STk} = \frac{\mathrm{var}_k(q_{jk})}{q_{.k}(1-q_{.k})}.$$

F_{ST} varies between 0 and 1 (see Table 1). As there is no *a priori* reason to suppose that any of the genes should be behaving differently from each other, and to reduce the chance that the index will become undefined, for each year the index is combined over all genes as follows:

$$F^*_{ST} = \frac{\sum_{i=1}^{L}\mathrm{var}_k(q_{jk})}{\sum_{i=1}^{L}q_{.k}(1-q_{.k})},$$

where L is the number of loci. Finally, the mean value of the index over the last 50 years is calculated.

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Table 1. *Properties of the indices*

Index	Range	Special Values	Meaning
Variance	[0, 1]	$\frac{1}{3}$	Flat distribution. In the absence of selection, this value should occur at a migration rate of 1/7; index $> \frac{1}{3}$ = U-shaped, index $< \frac{1}{3}$ = bell-shaped
Divergence	[0, 1], undefined	1	Demes differentiated
		0	Demes identical
		Undefined	1 genotype present in the metapopulation
Asynchrony	[0, 1·1], undefined	1	Theoretical Expectation in the absence of selection. Index > 1 = asynchrony (Maximum reached when $SSY = 0$ and $SSI \neq 0$). Index < 1 = synchrony (Minimum reached when $SSY \neq 0$ and $SSI = 0$). Index undefined when $SSI = SSY = 0$
Gene Storage	Population Size 100 Maximum −0·6931 Minimum −2·3174 Population Size 1000 Maximum −0·6931 Minimum −3·4554	—	The larger the index, the further all alleles are from fixation; the smaller the index, the closer the approach to fixation

(vi) *Measuring asynchrony*

In the papers that discuss asynchrony, none describe how it is measured (see, for example, Reeve, 1990; Taylor, 1990; Frank, 1991). Perhaps this is because in those models, dealing with only two – or at the most, four – interacting types, the asynchrony is self-evident. However, for this model, an index of asynchrony is a necessity.

A good index for the asynchrony, A, of a single gene, q, would be:

$$A = \frac{SSI}{SSI+SSY},$$

where SSI is the sum of squares interaction term from a 2-way ANOVA, and SSY is the change over time (Sokal & Rohlf, 1981). So, by the preceding notation,

$$SST = \sum_{j=1}^{d}\sum_{k=1}^{y} q_{jk}^2 - \frac{\left(\sum_{j=1}^{d}\sum_{k=1}^{y} q_{jk}\right)^2}{dy},$$

$$SSD = \frac{\sum_{j=1}^{d}\left(\sum_{k=1}^{y} q_{jk}\right)^2}{y} - \frac{\left(\sum_{j=1}^{d}\sum_{k=1}^{y} q_{jk}\right)^2}{dy},$$

$$SSY = \frac{\sum_{k=1}^{y}\left(\sum_{j=1}^{d} q_{jk}\right)^2}{d} - \frac{\left(\sum_{j=1}^{d}\sum_{k=1}^{y} q_{jk}\right)^2}{dy},$$

$$SSI = SST - SSD - SSY.$$

This index varies between 0 and 1. In the case where all genes are fixed for all of the time that asynchrony is measured, the index will be undefined. In the absence of selection, and under 100% migration, $(SSI/SSI+SSY)$ reduces to $((d-1)/d)$ (Weatherburn, 1961). Hence, multiplying by the inverse, $(d/(d-1))$, gives an index that is independent of the number of demes; further, in the case of 100% migration and no selection, the standard value is 1, a value which will be found empirically to hold approximately for all other migration rates in the absence of selection. When the index is adjusted in this manner, it varies between 0 and $(d/(d-1))$ (see Table 1). Thus, values greater than 1 indicate more asynchrony than expected in the absence of selection; values less than 1 indicate more synchrony than expected.

For the last 50 years of a run, asynchrony is calculated for each gene from the gene frequencies in each pond and each year. To reach an index of asynchrony for all the genes, A^*, the components of asynchrony for each gene are combined in a similar manner to the divergence index:

$$A^* = \left(\frac{\sum_{i=1}^{L} SSI}{\sum_{i=1}^{L}(SSI+SSY)}\right)\left(\frac{d}{d-1}\right),$$

where L is the number of loci. This combined index will only be undefined when every pond consists of a single genotype that is stable over time.

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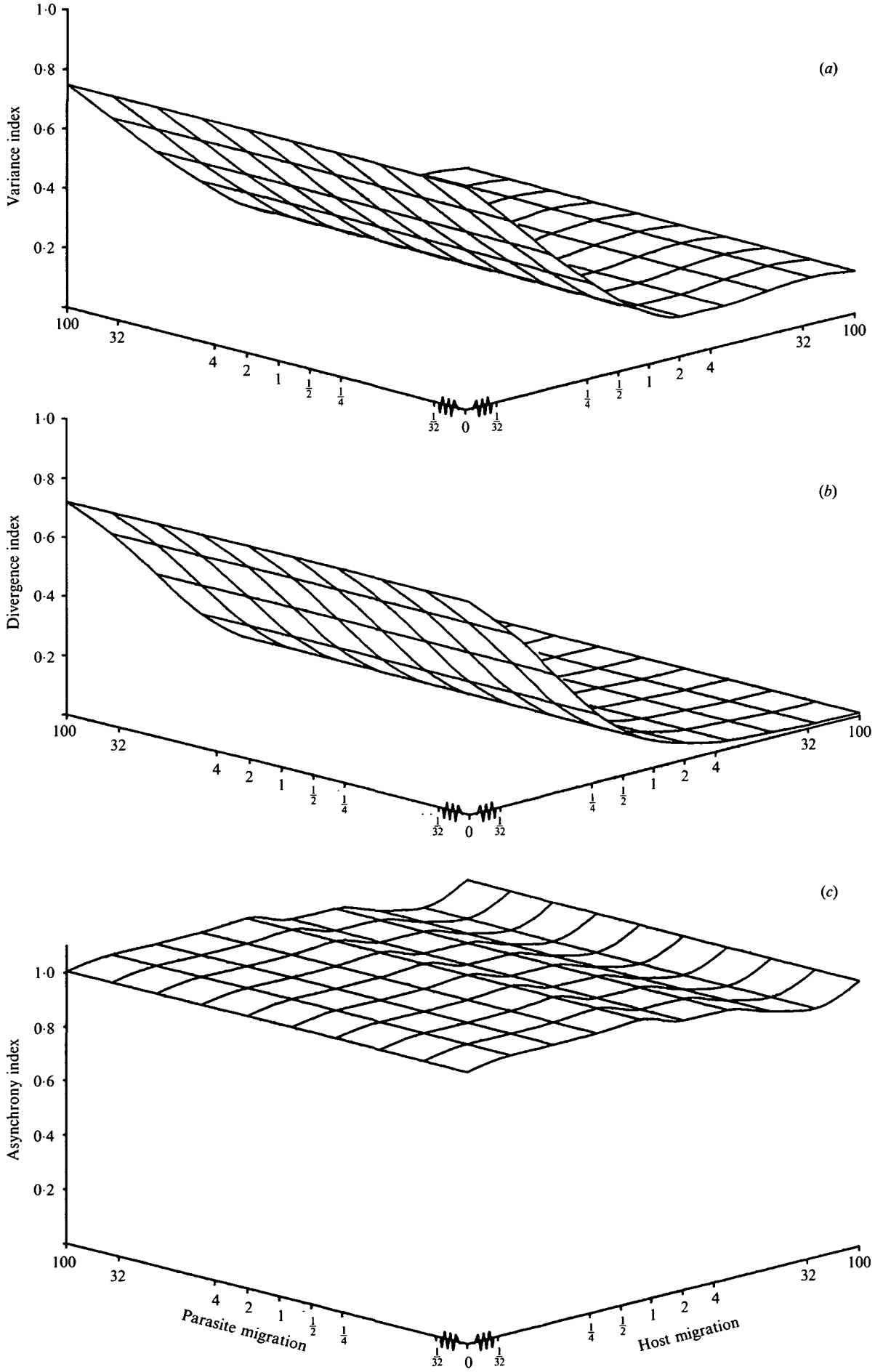

Fig. 1(*a–c*). For legend see facing page.

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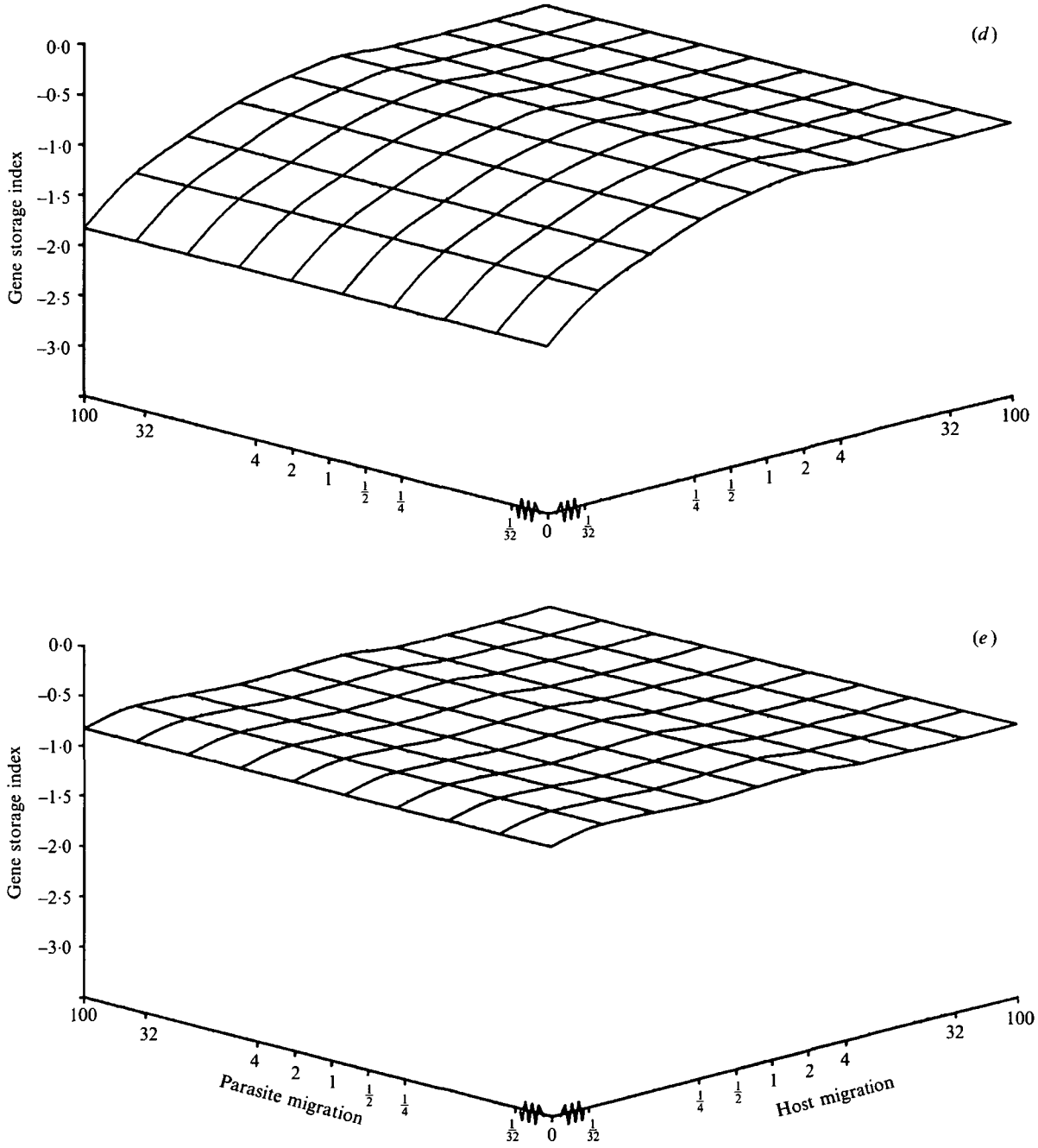

Fig. 1(*a*). The variance index for a sexual or an asexual host population in the absence of selection; (*b*) the divergence index for a sexual or an asexual host population in the absence of selection; (*c*) the asynchrony index for a sexual or an asexual host population in the absence of selection; (*d*) the values of the gene storage index for the last year of a run, measured after migration and averaged across demes, for a sexual or an asexual host population in the absence of selection; (*e*) the values of the gene storage index for the last year of a run, measured after migration in the metapopulation as a whole, for a sexual or an asexual host population in the absence of selection.

(vii) *Gene storage: measuring the effect of migration*

To measure the effect of migration on gene storage, an index of gene storage must be measured before and after migration. One way to measure gene storage is to indicate the distance from the boundary – that is, from fixation – of the gene frequency space for each allele at each locus. This can be done as follows. If n_i is the number of individuals carrying allele i and N is the population size, then $p_i' = ((n_i+1)/(N+2))$. In any year, the index for any deme (counting both alleles at each locus) would be:

$$\frac{\sum_{i=1}^{2L} \ln p_i'}{2L},$$

where L is the number of loci. This index can also be thought of as the log of the geometric mean frequency of all alleles, both within and across loci.

The gene storage index needs to be measured at two

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points each year: before migration and after migration. Further, the index can be calculated for each deme and for the metapopulation as a whole (that is, treated as if it is a single deme). If migration does have a gene-protective effect, the values of the pre-migration gene storage index should be smaller (closer to the boundary) than the values of the post-migration gene storage index (closer to the centre of the gene-frequency space) (see Table 1).

Two questions arise: does migration protect genes? and if it does, how much? To see the first, I perform a sign test to see whether the difference between the post-migration gene storage index and the pre-migration gene storage index is greater than zero (migration helps) significantly more often than it is less than zero (migration hurts). To see the second, I look at the magnitude of the difference between the gene storage index measured pre- and post-migration. As ponds are not independent, the index is averaged across ponds before looking at either of these effects. In runs where migration happens every year, only the last 50 years are considered; in cases where migration took place less frequently, the last 50 years where migration occurred are considered; in the case of $\frac{1}{32}$ migrants/year, migration should not have occurred as many as 50 times, so every instance of migration is considered in the analysis.

Finally, the extent to which the metapopulation as whole has preserved genes in a run can be seen by comparing the last value of the gene storage index averaged across demes with the last value of the gene storage index measured in the metapopulation as a whole.

3. Results

All of the figures show host and parasite migration rates taken to $\log_2$ along the x and y axes. Because the limit as the migration rate approaches zero may not be the same as zero migration, and because $\log_2(0)$ is undefined, this parameter value is offset from the rest.

(i) *Sexual and asexual populations in the absence of selection*

Sexual and asexual populations in the absence of selection conform well to theoretical expectation and give rise to nearly identical results. This may seem puzzling. However, if only the random sampling of alleles at a single locus is under consideration, any recombination with other loci is irrelevant, and sexual and asexual populations should give the same results. Therefore, I discuss the two cases together and show only one set of graphs for both.

The variance index (Fig. 1*a*) shifts from a maximum value of around 0·75, through the critical value of $\frac{1}{3}$, to a minimum value of 0·15. As predicted, the critical value occurs between the migration rates of $\frac{1}{32}$ and $\frac{1}{4}$, although as expected, it occurs nearer to $\frac{1}{4}$.

The divergence index (Fig. 1*b*) also conforms to expectation, with 0 migrants/year giving rise to a high value of the index, reflecting that each deme is panmictic but different from the others. Panmixis of the entire metapopulation gives a very small divergence index. Between the two extremes, the index declines monotonically.

As mentioned above, the theoretical expectation for the value of the asynchrony index in the absence of selection is 1. Again, the model conforms well to theoretical expectations with almost all levels of migration giving rise to an asynchrony that is very close to 1 (Fig. 1*c*).

When migration takes place, it has a highly significant effect on gene preservation. At low levels of migration, even when alleles are being lost from demes (Fig. 1*d*, left-hand edge), the metapopulation as a whole is not in immediate danger of losing genetic variation (Fig. 1*e*, left-hand edge). Migration even has a significant preservative effect – albeit not as significant – in the panmictic case (although clearly over a very long time all diversity will be lost). This makes sense: each year all the demes undergo random changes. Migration acts to remove any local differentiation. Unsurprisingly, the magnitude of the effect of migration decreases with increasing migration (from a maximum value of approximately 0·3 at a migration rate of $\frac{1}{32}$ to a minimum value of approximately 0·01 at panmixis), reflecting that the demes become more similar to each other as migration increases.

(ii) *Sexual populations under frequency-dependent selection*

Parasites have a strong effect on sexual populations. They eliminate almost all polarized gene-frequency distributions – indeed, the variance index is in general well below the critical value of $\frac{1}{3}$ – and substantially reduce the chance of local losses of alleles even in the absence of host migration (Fig. 2*a*). However, where hosts do not migrate, or only migrate at low levels, and where parasites are essentially panmictic, parasites slightly increase the chance of local fixation above what it is in the absence of selection – an area I shall refer to as 'the danger area' (Fig. 2*a*, left-hand corner; compare with Fig. 1*a*). In the danger area variability is lost from demes. But even here, variation is never in danger of being lost from the entire metapopulation. As host migration increases, the variance index quickly falls below $\frac{1}{3}$.

The divergence index is low everywhere except in the danger area (Fig. 2*b*); even though it is low to start with at zero host and zero parasite migration, it declines further as both host and parasite migration increase.

Asynchrony does not often arise in a sexual metapopulation (Fig. 2*c*). Although the dynamics of the index seem to be complex, it is possible to make

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some generalizations. As host migration increases above 2 migrants/year the asynchrony index rapidly drops well below the theoretical expectation of 1 in the absence of selection. In fact, as migration increases, the trend becomes one towards high synchrony. The highest asynchronies – and the majority of cases where the index is greater than 1 – occur along the first part of the diagonal of equal host and parasite migration where migration rates are low but not zero: if host and parasite migration are low and nearly equal, asynchrony may arise. This shows that despite the fact that all demes are near the centre of the gene-frequency space (see below), parasites force the gene frequencies to fluctuate in different directions. The only other area where the asynchrony index is above 1 is in the danger area (Fig. 2*c*, left corner).

In general, all the demes are always near the centre of the gene-frequency space (Fig. 2*d*). Again, the only exception occurs in the danger area (Fig. 2*d*, left corner). Even when neither hosts nor parasites migrate (Fig. 2*d*, front corner), demes are not in any danger of losing variability. Moreover, the metapopulation as a whole is never in danger of losing any alleles (Fig. 2*e*). Even though all demes are already near the centre of the gene-frequency space, migration still has a significant effect on preserving genes. However, the magnitude of the effect of migration is 0·01 or less (except in the danger area where it is approximately 0·3), reflecting that demes are not differentiated from each other.

(iii) *Asexual populations under frequency-dependent selection*

Asexual populations under frequency-dependent selection show behaviours that differ substantially from either sexual populations under similar selection pressures or asexual populations in the absence of selection. However, the differences can largely be explained.

In general, the variance index for asexual populations under selection reaches a high or maximum value both with little migration and with total migration (Fig. 3*a*) – a situation not previously encountered. The only exception to this pattern is when parasites have a migration rate of 32 migrants/year. In between the extremes of migration, the variance index drops well below the critical value of $\frac{1}{3}$ and sometimes reaches lower values than in the absence of selection (compare with Fig. 1*a*).

When each pond contains only a single genotype, but the metapopulation maintains some diversity, the divergence index is almost exactly 1 (Fig. 3*b*, left-hand edge). When the entire metapopulation contains only one genotype, the index is undefined. The divergence index declines with increasing host migration, becoming very small, or undefined, at 100% migration. Where the divergence index is very small, the total genetic diversity has become very low; in sexual populations under 100% migration the divergence is of the same order of magnitude, but this does not signal loss of diversity – just loss of differentiation between the demes.

The asynchrony index becomes undefined wherever all ponds are fixed at all genes for the last 50 years – that is, either when each deme consists of a single clone, or when the entire metapopulation consists of a single clone (Fig. 3*c*, and inset). However, when host and parasite migration are both low, the asynchrony index often rises above 1, suggesting that asexuals give rise to asynchrony more readily than sexuals (compare Fig. 2*c*). When host migration is high and genetic diversity is low but not completely eliminated, the asynchrony index becomes very small – an order of magnitude smaller than that which arises for sexual populations under selection. This signals the almost complete synchrony with which genes are moving. In these cases an approach to total fixation is imminent. In fact, asexuals rarely gave rise to the levels of intermediate synchrony that sexuals did – in general, the index is either above or close to 1, very small, or undefined.

For asexuals, migration has a strong gene – or really genotype – storage effect; the only exception comes when the number of different clones is already low. In this case, migration may have no effect or, by removing some of the only remaining genetic variation, may be detrimental. Thus, host migration is effective as long as it is low or intermediate (Fig. 3*d*, *e*). The magnitude of the effect of migration is largest when the overall gene-frequency distributions are polarized (around 0·7) – the magnitude is larger when the demes are starting to lose, or have already lost, variability. As long as migration is effective, the magnitude of the effect is always at least ten times larger than for sexual populations under selection.

Thus, asexuals under selection show true gene storage. At either extreme of host migration, parasites rapidly eliminate genetic diversity. However, when no hosts migrate, each deme maintains only one clone, but the clones are different from each other and the metapopulation as a whole remains diverse; when all hosts migrate, the entire metapopulation loses genotypes, and is often reduced to consisting of a few or even a single clone. Intermediate levels of host migration, however, allow genetic diversity to be maintained, both within demes and within the entire metapopulation. In some cases more genetic diversity is maintained than in the absence of selection.

4. Discussion

The analysis of individual-based simulation models is always problematic (Hamilton, 1993; Judson, 1994). However, the model produces results – in the absence of selection – that are consistent with theoretical expectations, and the results under each set of parameters are consistent with each other.

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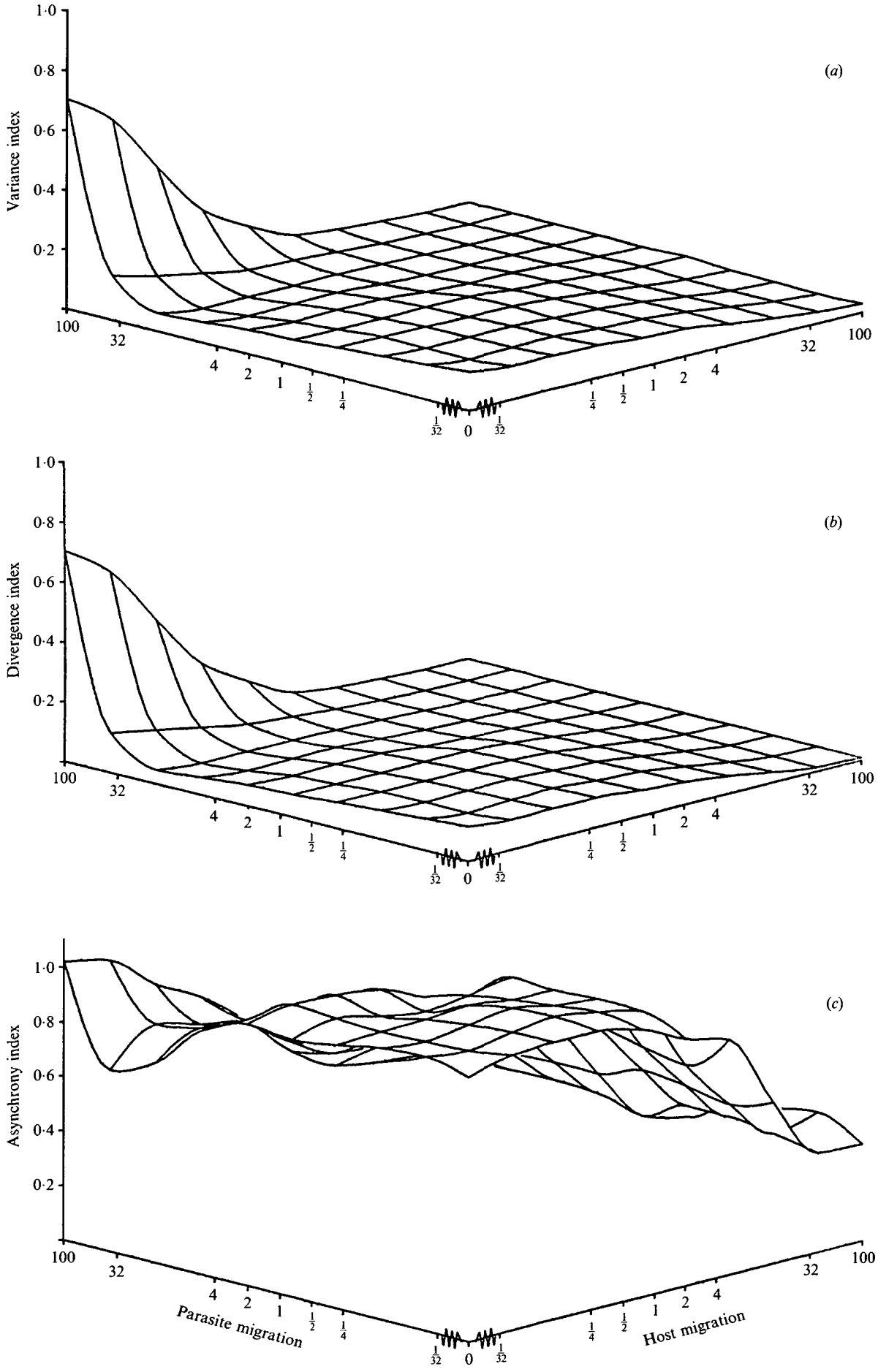

Fig. 2(*a–c*). For legend see facing page.

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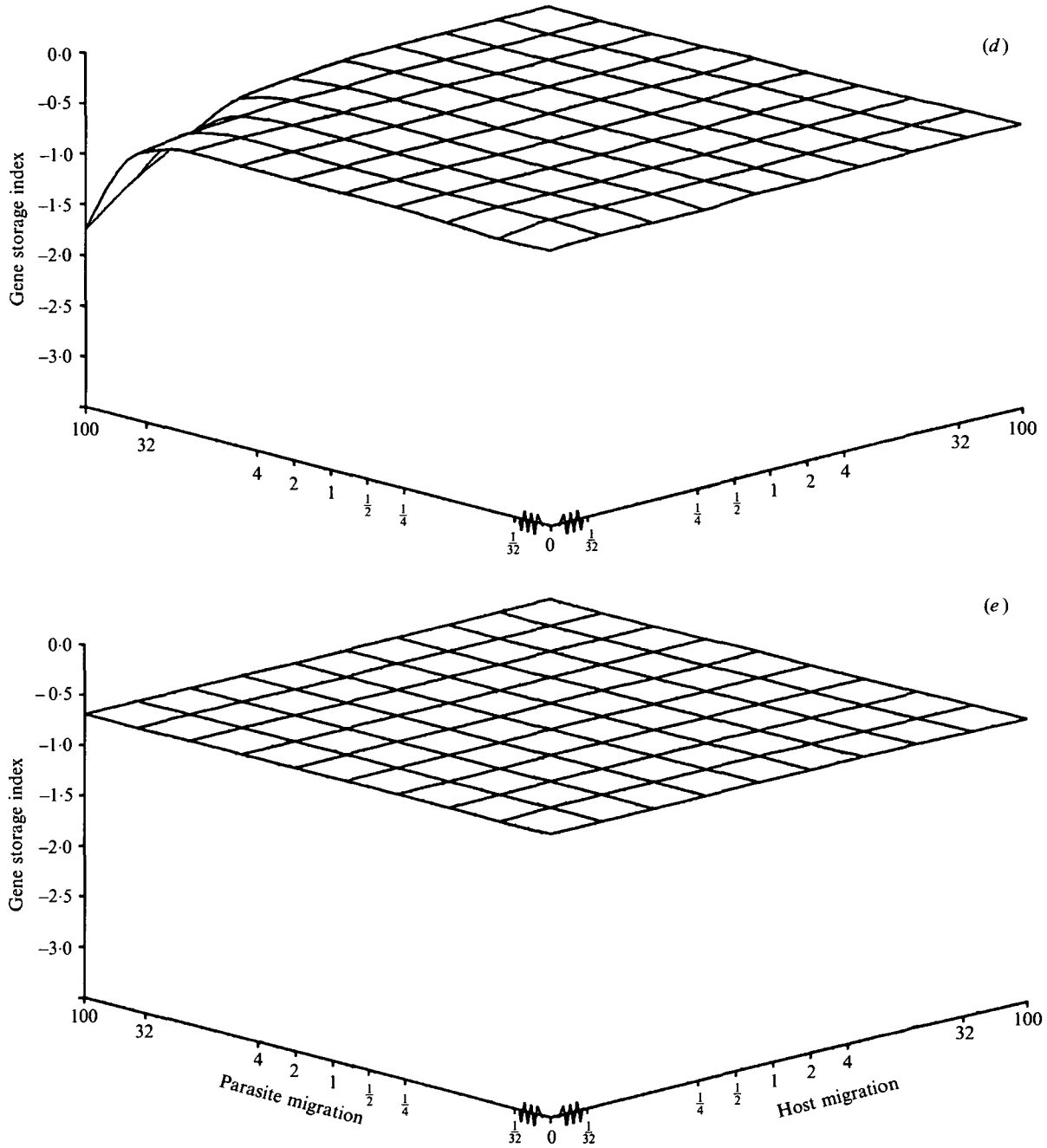

Fig. 2(*a*). The variance index for a sexual host population under selection; (*b*) the divergence index for a sexual host population under selection; (*c*) the asynchrony index for a sexual host population under selection; (*d*) the values of the gene storage index for the last year of a run, measured after migration and averaged across demes, for a sexual host population under selection; (*e*) the values of the gene storage index for the last year of a run, measured after migration in the metapopulation as a whole, for a sexual host population under selection.

Sexual and asexual metapopulations in the absence of selection show similar, expected, behaviours. When selection is introduced, however, populations of sexuals and asexuals behave rather differently, with populations of asexuals showing much more extreme behaviours. In asexual metapopulations, genetic variation can only be maintained in the presence of selection if the levels of migration are low or intermediate; sexual populations under selection are generally highly effective at maintaining genetic diversity regardless of the migration rate. For sexuals, even on the few occasions where genetic diversity is being lost from demes, genetic diversity at the level of the metapopulation is never in danger.

As long as the metapopulation has reasonable levels of genetic diversity, migration always helps to reduce the chance of the local loss of alleles. However, in the case of sexuals, selection plays such a strong role at preserving variation that migration does not usually reintroduce alleles that have been lost locally (since none have been lost); each year it simply nudges each deme slightly more towards the centre of the gene frequency space. For asexuals, gene storage does occur – that is, migration does sometimes serve to

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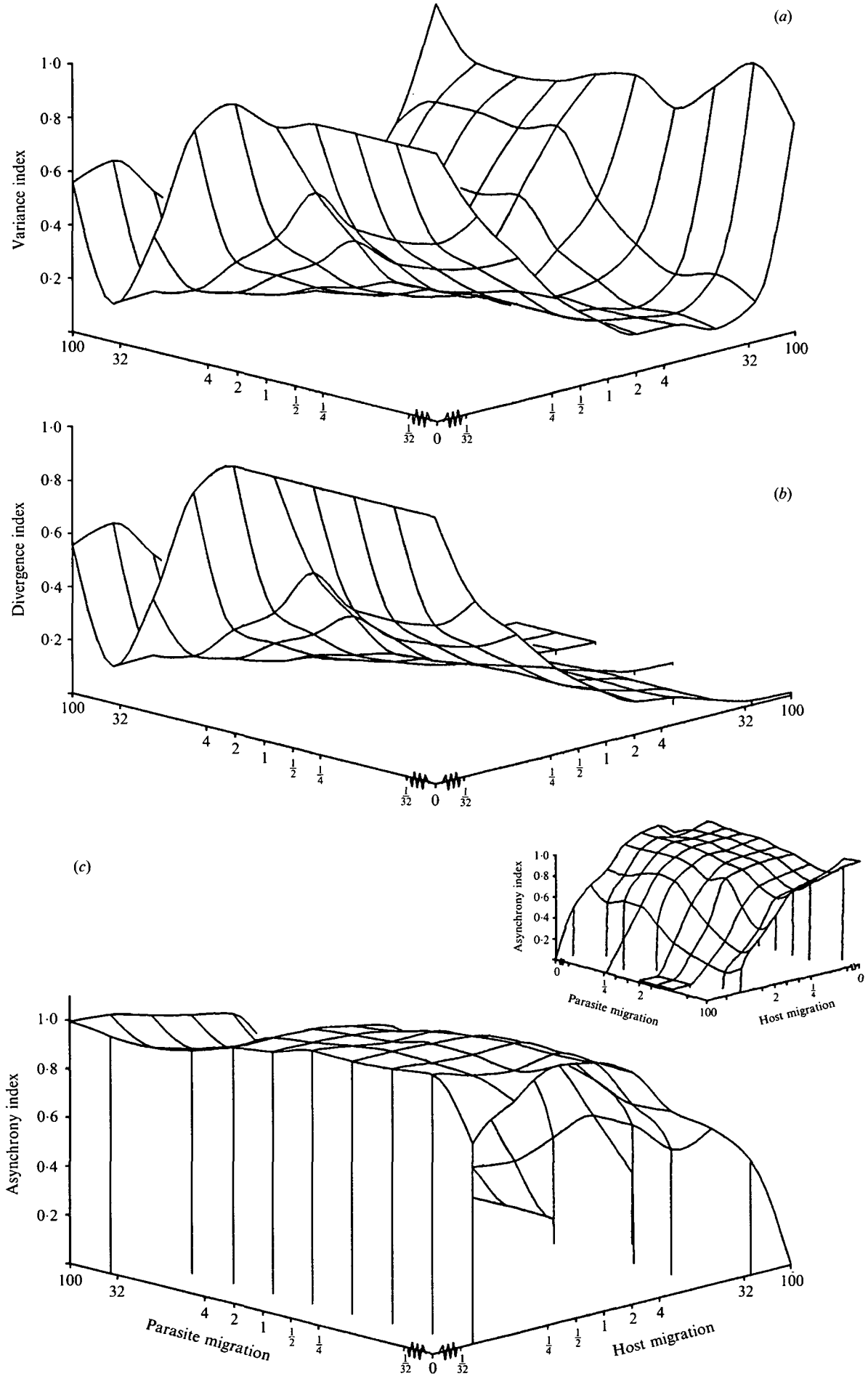

Fig. 3(*a–c*). For legend see facing page.

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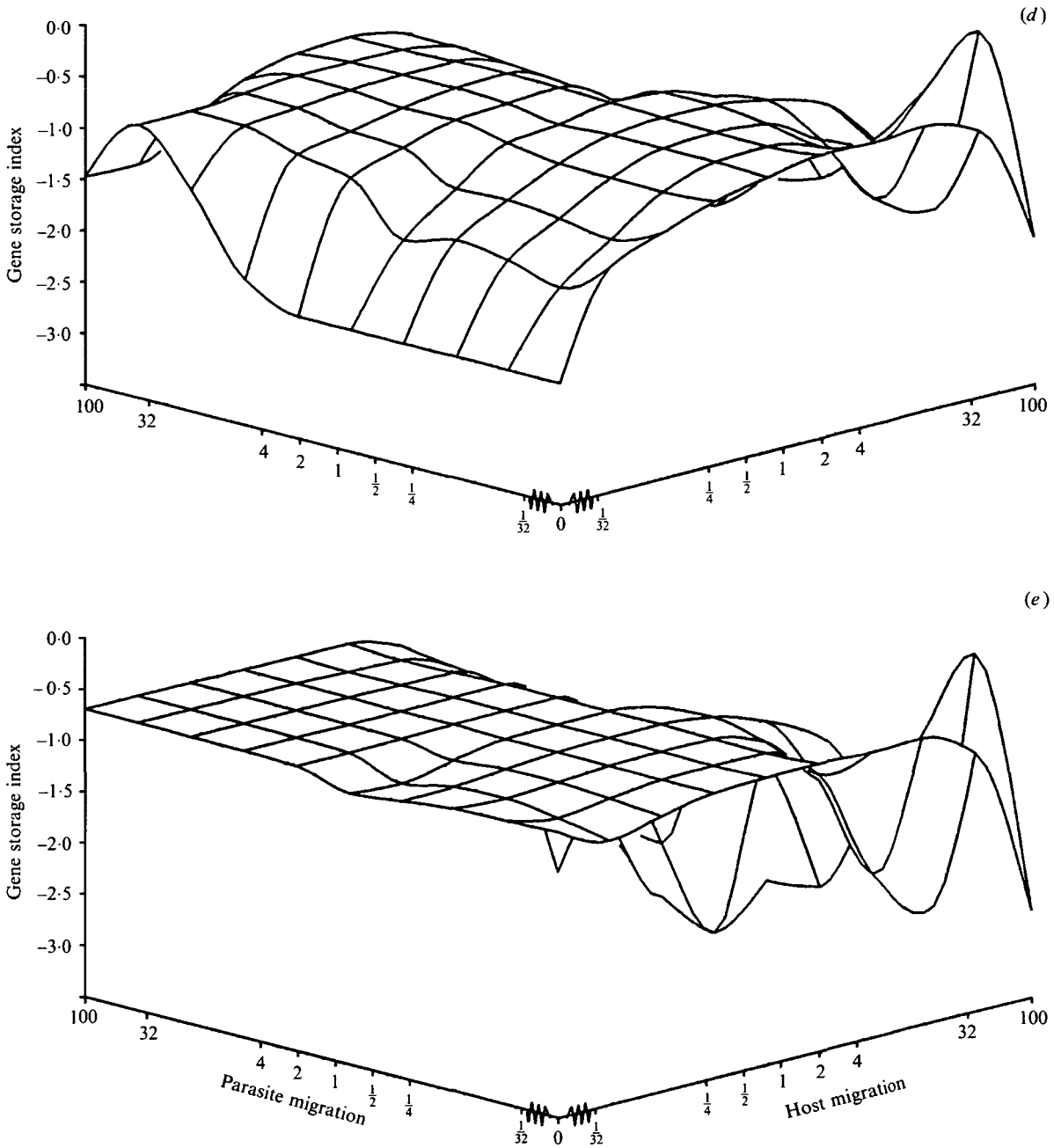

Fig. 3(*a*). The variance index for an asexual host population under selection; (*b*) the divergence index for an asexual host population under selection; (*c*) the asynchrony index for an asexual host population under selection. Note that the inset has the axes reversed such that the front corner shows a migration rate of 100 migrants per deme per year for both hosts and parasites; (*d*) the values of the gene storage index for the last year of a run, measured after migration and averaged across demes, for an asexual host population under selection; (*e*) the values of the gene storage index for the last year of a run, measured after migration in the metapopulation as a whole, for an asexual host population under selection.

reintroduce alleles that have been lost locally (with the proviso that alleles have not already been lost from the entire metapopulation). For sexual populations 'gene preservation' is a more accurate description than 'gene storage'. The difference is that 'gene storage' means that alleles are lost from a deme, but remain in another (in storage), and are eventually reintroduced to the deme from which they have been lost: low levels of migration maintain more genetic diversity than either total isolation of small sub-populations or panmixis of a single, large population. 'Gene preservation' means that alleles are not being lost locally but always remain in a deme.

This result could be due to the lack of linkage between genes; introducing some degree of linkage might increase the importance of migration for sexuals. In particular, Hamilton (1993) suggests that low recombination rates could give rise to gene storage rather than the gene preservation found here.

Generally, in the simulation as a whole, the variance

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index is lower for sexual populations than is expected in the absence of selection; for asexual populations, it is higher than expected, resulting in gene storage where the metapopulation remains diverse. For asexuals, low and intermediate levels of migration often give rise to asynchrony and divergence of subpopulations. These effects in turn allow migration to have a larger impact. Sexual populations under selection are so good at maintaining genetic diversity that divergence among subpopulations is low, and even when asynchrony arises, the effect of migration is small. Sexual and asexual metapopulations in the absence of selection do not give rise to asynchrony; indeed, their stochastic 'asynchrony' is treated as a standard. In the absence of selection, increasing migration rates lead to increased homogeneity among demes. As migration rates approach panmixis the metapopulation as a whole has a higher probability of eventually losing alleles (see also Wright, 1951; Kimura and Crow, 1963).

The dynamics of the asynchrony index are complex. For a sexual metapopulation under selection, asynchrony arises if host and parasite migration are low and nearly equal; high migration rates lead to synchrony. For an asexual metapopulation under selection, asynchrony plays an important role in the maintenance of genetic variation. But because both sexual and asexual metapopulations under selection can give rise to asynchrony, asynchrony is not correlated with the success of sex (see Ladle *et al.* 1993). This is an interesting, and unexpected, result.

The four indices together give a fairly complete picture of the dynamics of the model. Although within groups of runs (for example, all runs where host migration was zero) the indices are consistent – for example, the divergence index declines with increasing migration – across sets of runs, the indices behave quite differently. For example, similar variance indices can have rather different divergences or asynchronies. When the metapopulation as a whole is losing diversity, the divergence index is low, the asynchrony index is very small, and the variance index approaches 1. If the variance index approaches 1 but the divergence index is high and the asynchrony index is high, the demes are losing genetic diversity but the metapopulation is not. This effect can also be seen through the behaviour of the gene storage index. The best predictor of the magnitude of the effect that migration will have is a high variance index and a high divergence index.

In an infinite population, mutation and migration are formally equivalent (Wright, 1969). In a finite population, however, they are not; migration is the more realistic notion to consider. But using small populations and not considering mutation introduces an asymmetry between sexuals and asexuals: the total number of possible host genotypes is 2^{12} but the total population size is 1000. As long as alleles have not been lost from the metapopulation, sexuals have the potential to form all possible genotypes during the course of the simulation. Asexuals, on the other hand, are limited to the genotypes present at the start of a run, and once a genotype has been lost from the metapopulation it can never return. However, this just gives a more conservative estimate of the conditions under which populations of asexuals may maintain variation.

One important difficulty with individual-based models is knowing how long they should be run for, and assessing what would happen if the run continued for longer (Judson, 1994). The analysis presented here allows predictions to be made about the future behaviour of populations under selection. For example, sexual populations under selection do not (except in the danger area) come close to losing alleles; all alleles are preserved in the middle of the gene-frequency space. In this case, the strength of the effect of parasites is such that I am fully confident that regardless of how many years the simulation were allowed to run for, genetic variability would never be lost.

In this model, sexuals rarely, if ever, lose alleles, whereas asexuals can only maintain genetic diversity under particular conditions. This result differs from that of Frank (1993), where asexuals in general maintained higher levels of genic diversity, and where sexuals were more likely than asexuals to lose alleles. However, the only large empirical study looking at genetic diversity of sexual and asexual populations supports the notion that sexuals are more readily able to maintain diversity (Groth & Roelfs, 1982).

Both Frank's (1993) model and my own are island models of migration (Wright, 1951). Frank (1993) points out that this is a conservative model; models such as the stepping-stone model where migration occurs only between neighbouring demes are more likely to give rise to local differentiation. In my model, sexual populations do not differentiate as much as asexual populations because sexual populations generally manage to maintain all alleles.

Another important underlying assumption of my model, and a significant difference from Frank (1993), is that the metapopulation is demographically stable – that is, the demes do not go through cycles of extinction and recolonization. When metapopulations are stable, immigration clearly has more of a role to play in the genetics rather than in the population dynamics (Gilpin, 1987); in unstable, or 'winking' metapopulations, genetic variability is likely to decline quite quickly and may lead to almost total loss (Gilpin, 1987, 1991). This could be the main reason for the difference between my results and those of Frank (1993). At a regional level, stable metapopulations are considered to enhance the preservation of genetic variance either because different alleles fix in different demes, or because the local selection pressures may be different (Wright, 1951, 1969; Gilpin, 1987), or both. In the latter situation,

migration rates can be higher than expected without homogenizing the demes (Wright, 1969). In my model, both effects come into play separately. When the rates of migration are low and the variance index is high, the metapopulation has greater variability due to fixation of alleles; when the variance index is low, the metapopulation has greater variability due to differences in the local parasite pressures. For sexual populations, the forces of frequency-dependent selection are usually sufficient to maintain genetic variation even in small subpopulations: for sexual populations under this selection, geographical structure usually makes little difference. However, as I have shown, for asexuals under selection, population subdivision linked by limited migration plays a crucial role in maintaining more variability than could be maintained in a single, large population.

Genetic variability has been observed in most natural populations of animals and plants, and negative frequency-dependent selection has been proposed as a likely cause (Clarke, 1979). The results of my model show that negative frequency-dependent selection can, except in the danger area, be a strong force in the maintenance of genetic variability for sexual populations and that stability of gene frequencies is not a precondition. For asexual populations, negative frequency-dependent selection can maintain a high level of genetic variability under more restricted conditions. Natural populations of asexuals often do show high levels of clonal diversity (see, for example, Parker, 1979; Levin, 1988; Browne & Hoopes, 1990; Carter & Robinson, 1993; Castagnone-Sereno *et al.* 1993; Lively & Apanius, in press); some authors have suggested that this diversity could be due to negative frequency-dependent selection (Levin, 1988; Lively & Apanius, in press). Indeed, ecological heterogeneity has been found to be important for species diversity; it is also likely to be good for clonal diversity (Parker, 1979). In my model, clonal diversity is only maintained when the parasite pressures in the different sub-populations are different from each other. In other words, local adaptation of demes linked by migration is crucial for the maintenance of asexuality. Anecdotal evidence suggests that asexual organisms do have life histories similar to the ones described in this model (for a discussion, see Ladle *et al.* 1993).

In conservation biology, it is sometimes argued that genetic variability should be conserved for its own sake (Lande & Barrowclough, 1987). This view is controversial (see, for example, Allendorf & Leary, 1986; Ledig, 1986; Lande; 1988; Pimm, 1991). Some large natural populations do not have high levels of genetic variability. For example, beavers (Ellegren *et al.* 1993), cheetahs (Menotti-Raymond & O'Brien, 1993), lions and elephant seals (Pimm, 1991) all seem to have low levels of genetic diversity despite having large population sizes. On the other hand, otters and rhinos have small population sizes but seem to maintain high levels of genetic variability (Pimm, 1991). Further, some have argued that habitat fragmentation and environmental stochasticity are more important concerns and pose more of a threat to the survival of a species than loss of genetic variability *per se* (Gilpin, 1987; Pimm, 1991). However, loss of genetic variability has been suggested to have played a role in the decimation of native American populations by the previously unknown diseases introduced by the arrival of European settlers (Black, 1992). Others have argued that for many birds and mammals, the levels of migration between groups should be sufficient to homogenize the populations and counter the local loss of heterozygosity that arises in isolated populations (Ralls *et al.* 1986). Further, the subdivision of a population has been hypothesized to prevent the spread of disease (Dobson & May, 1986).

The effects of habitat fragmentation and of environmental accident can be reduced by migration between subpopulations (Pimm, 1991), with demes connected by migration maintaining more species than totally isolated subpopulations (Kruess & Tscharntke, 1994). Migration can save species from extinction – this is known as the rescue effect (Brown & Kodric-Brown, 1977; Pimm, 1991). As I have shown, particularly for asexuals, migration may also play a significant role in gene preservation as long as variability remains in the metapopulation. Thus, although conservation biologists may not wish to focus on the maintenance of genetic variability alone, ensuring that some migration can take place between demes – either by keeping habitats connected with corridors or by artificially moving individual organisms between isolated populations – may have an important role in any programme of conservation.

Unfortunately, although extensive theoretical support has been given to the importance of spatial dynamics for the maintenance of species (Kareiva, 1990) and for the maintenance of variation within a species (Frank, 1991), little experimental work has been done. Models of the type presented here should help to point the way towards understanding some of the processes that preserve genes in natural populations.

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