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Intense selection in an age-structured population

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In a population with overlapping generations, intense selection can perturb the age distribution and thus affect the rate of increase of an advantageous allele. We found that the age-specific nature of intense selection, such as that generated by many diseases, can affect the outcome of selection on loci, such as those conferring disease resistance. We also found that the temporal dynamics of selection alter the speed of evolution, particularly when selection is intense, and even more so when it is age-specific. We relate our model and results to selection for disease resistance, although the results have broader implications for inferences about past selection pressures in general.

Keywords: age structure; disease resistance; population genetics; temporal dynamics; virulence

1. INTRODUCTION

Most population genetic models ignore age structure, even when they are applied to humans and other species with overlapping generations. This simplification is justified when selection is weak, because selection in an age-structured system can be adequately approximated by a model that ignores age structure, provided that selection coefficients are correctly related to genotype-dependent Malthusian parameters (Charlesworth 1994). If selection is strong, however, age structure can no longer be ignored because significant changes in allele frequency can occur during perturbations and before a new stable age distribution is established. Therefore, we explored the effect of age structure on the spread of a selected allele.

Disease is an important source of intense selection within host populations (Haldane 1949). Disease also plays a major role in shaping age-specific patterns of human mortality (Anderson & May 1991), since diseases tend to affect age classes differentially. For example, the average age of infection is 2–5 years for measles and 10–14 years for scarlet fever (Anderson & May 1991). Sexually transmitted diseases such as acquired immunodeficiency syndrome (AIDS), syphilis and gonorrhoea predominantly affect reproductive age classes. By contrast, bubonic plague is less age specific (Russell 1948; Twigg 1984). Diseases also vary considerably in their virulence, defined as the level of infection-induced host mortality (Galvani 2003). For example, the case fatality rate is *ca.* 90% for ebola (Oldstone 1998), 3% for the Spanish influenza pandemic strain (Reid *et al.* 1999), 30% for smallpox (Fenner *et al.* 1988) and 15% for severe acute respiratory syndrome (SARS) (Galvani *et al.* 2003). These high levels of mortality can generate strong selection in favour of host genotypes resistant to infection. We relate our model of intense selection in an age-structured population to the selection for a resistance genotype generated by disease mortality.

Perturbations in age structure are likely to be affected by the temporal pattern of selection. Indeed, different diseases exhibit a wide range of patterns (Anderson & May 1991; Bauch & Earn 2003). Before vaccination, epidemics of measles occurred every 1–2 years (Bauch & Earn 2003), poliomyelitis every 3–5 years (Anderson & May 1991) and diphtheria every 4–6 years (Anderson & May 1991). Bubonic plague was stochastically intermittent (Twigg 1984), while influenza epidemics occur annually, with sporadic pandemics (Ferguson *et al.* 2003). Additionally, malaria is endemic in some countries, implying that its infection rate is roughly constant over time. Therefore, we also explored the effect of the temporal dynamics of selection on the spread of an allele in an age-structured population by comparing continuous and periodic selection. We found that the difference between populations with and without age structure is greatest when selection is periodic. Thus, it can be important to take into account both the periodicity and the age specificity of selection, particularly when developing models of the population genetics of disease resistance.

2. MODEL STRUCTURE

(a) *No age structure*

For a rare dominant allele, A, the rate of increase in frequency is determined by the relative fitnesses of the common (aa) homozygote and the Aa heterozygote. In the absence of disease, these two genotypes are assumed to have the same fitness. In the presence of disease, the mortality rate of susceptible aa individuals is increased by a factor $1 - s$ relative to Aa individuals. We will refer to s as the selection intensity in favour of A.

Let p_t be the frequency of A in generation t. In the absence of the disease, p_t will not change. In the presence of the disease, the change in p_t is approximated by

$$p_{t+1} = (1 + s)\, p_t. \tag{2.1}$$

If disease mortality occurs every generation, then the per-generation rate of increase of p_t would be $(1 + s)$. If the disease is present during only a fraction γ of T generations, the per-generation rate of increase in p_t is $(1 + s)^{\gamma}$, independent of which generations the disease affects. After T generations, $p_T = (1 + s)^{\gamma T} p_0$, provided that A remains in low frequency. We will characterize the results in populations with overlapping generations by computing values of p_T in comparable models with and without age structure.

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(b) *Overlapping generations: demography*

We assumed that, before exposure to the disease, an age-structured population had reached a stable age distribution determined by its mortality. The age-structured population was divided into 55 (k) age classes, each of 1 year. The probability of a female surviving from age 0 to age x is l_x ($l_0 = 1$), α_x is the annual probability of survival at age x and the number of female offspring born to a female of age x is m_x. The table of l_x and m_x that we used was based on estimates from the human population in nineteenth century France (Coale & Demeny 1983; Preston *et al.* 2001). Age classes were allowed to differ in the extent to which they are affected by disease.

(c) *Disease*

The virulence (σ) of a disease is defined by the level of mortality that it causes. It was assumed that the resistance allele A is dominant and confers complete resistance. Therefore, disease is assumed to kill a proportion σ of susceptible hosts while both heterozygotes and resistant homozygotes are fully protected. While there is evidence that disease resistance often entails a cost, in most cases the cost would be subsumed into the selection coefficient for the resistance allele.

We assessed the effect of age-specific selection on the rise in the frequency of the favoured allele A. Age-specific diseases were assumed to target hosts over a 5 year range (e.g. 5–10 years). The proportion of individuals in the targeted age class at a stable age distribution is w. Thus, the initial proportion of individuals that are under selection is w. When comparing this age-specific selection with selection in a population without age structure, we assumed that a proportion w of individuals were also targeted in the population without age structure.

(d) *Model of mating*

Unless otherwise stated, each system was initiated with $p_0 = 5 \times 10^{-5}$, equivalent to one copy of the resistance allele in 10 000 diploid individuals. We define $\check{s}$ as the selection intensity per 25 years (approximately one generation, t) acting on A, averaged over the entire 350 years simulated (i.e. over 14 total generations, T). It is calculated from the change in p:

$$\check{s} = \frac{\ln(p_T - p_0)}{T}. \tag{2.2}$$

The final proportion of the resistant allele at the end of the simulation is p_T. R is defined as the ratio of p_T in a population with age structure to p_T from a population without age structure. When $R > 1$, A is more frequent than would be expected if age structure were ignored. When $R < 1$, A is less frequent in an age-structured population than expected in a population without age structure.

We assumed that the sex ratio is equal within all age classes, which is equivalent to assuming that the life tables are the same for males and females. Mating was random with respect to genotype within each age class, such that offspring are produced according to Hardy–Weinberg ratios based on p and $q = 1 - p$ in each age class.

(e) *Numerical model*

To explore the impact of the inter-epidemic period of a disease, we employed a discrete-time model, with a time-step, i, of 1 year. The number of females in age class x at time-step i is $f_{x,i}$. Changes in the number of susceptible homozygotes (z), heterozygotes (h) and resistant homozygotes (r) in age class 0 during one time-step are given by:

$$z_{0,i+1} = (1 - \sigma_1)\alpha_1 \sum_{x=1}^{k} q_{x,i}^2 m_x f_{x,i}, \tag{2.3}$$

$$h_{0,i+1} = \alpha_1 \sum_{x=1}^{k} 2\,p_{x,i} q_{x,i} m_x f_{x,i}, \tag{2.4}$$

$$r_{0,i+1} = \alpha_1 \sum_{x=1}^{k} p_{x,i}^2 m_x f_{x,i}. \tag{2.5}$$

Changes in the numbers of z, h and r in age classes 1–54 are given by:

$$z_{x,i+1} = (1 - \sigma_x)\alpha_x z_{x,i}, \tag{2.6}$$

$$h_{x,i+1} = \alpha_x h_{x,i}, \tag{2.7}$$

$$r_{x,i+1} = \alpha_x r_{x,i}. \tag{2.8}$$

The population dynamics of the system without age structure are defined by:

$$z_{i+1} = (1 - \sigma) q_i^2 g, \tag{2.9}$$

$$h_{i+1} = 2\,p_i q_i g, \tag{2.10}$$

$$r_{x,i+1} = p_i^2 g, \tag{2.11}$$

where g is the growth rate of the population and was assumed to be equal to that of the age-structured population at stable age distribution, as determined by the survival and fecundity probabilities.

3. RESULTS

(a) *Analytical results*

The size of each age class at the stable age distribution is proportional to $l_x\lambda^{-x}$ where λ is the dominant eigenvalue that determines the exponential rate of increase of population size. The dominant eigenvalue is the (unique) positive solution to

$$1 = \sum_{x=0}^{k} l_x m_x \lambda^{-x-1}, \tag{3.1}$$

derived from Pollard's model of population growth (Pollard 1973). It is convenient to define the proportion of individuals in each age class (u_x), and hence the stable age distribution, as follows:

$$u_x = \frac{l_x \lambda^{-x}}{\sum_{y=0}^{k} (y + 1) m_y l_y \lambda^{-y-1}}. \tag{3.2}$$

With this choice, when a population is at a stable age distribution, the sum of the reproductive values of all individuals over all age classes is the total population size. The reproductive value of an individual of age x is

$$v_x = \sum_{y=x}^{k} \frac{l_y}{l_x} m_y \lambda^{x-y-1}, \tag{3.3}$$

and, given the definition of u_x in equation (3.2),

$$\sum_{x=0}^{k} u_x v_x = 1. \tag{3.4}$$

For any initial age distribution, the population size at the stable age distribution is determined by u_x and v_x:

$$N_{x,t} \approx C u_x \lambda^t, \tag{3.5}$$

where

$$C = \sum_{x=0}^{k} N_{x,0} v_x. \tag{3.6}$$

Initially, A is sufficiently rare that, to a first approximation, AA individuals can be ignored. The effect of the disease on the individuals is an increase in mortality resulting in a new life table $\tilde{l}_x$. Because we assumed that A confers complete and genetically dominant resistance, Aa heterozygotes are unaffected by the disease and have the same life table as before the epidemic, l_x.

To find the rate of increase in A, let $N_{x,t}$ be the number of aa homozygotes at generation t and let $n_{x,t}$ be the number of Aa heterozygotes. Ignoring the AA homozygotes and using the deterministic theory of selection in an age-structured population (Charlesworth 1994), we can find the number of newborn heterozygotes in generation $t + 1$:

$$n_{0,t+1} = \frac{1}{2} \sum_{x=0}^{k} [n_{x,t} \Pr(\mathrm{aa}) + N_{x,t} \Pr(\mathrm{Aa})] m_x, \tag{3.7}$$

where Pr(aa) is the probability that the father has genotype aa, and Pr(Aa) is the probability that the father has genotype Aa.

Because we have assumed that mating occurs only between individuals in the same age class, $\Pr(\mathrm{aa}) = N_{x,t}/(N_{x,t} + n_{x,t})$ and $\Pr(\mathrm{Aa}) = n_{x,t}/(N_{x,t} + n_{x,t})$. Retaining only terms in the first power of $n_{x,t}$, we obtain

$$n_{0,t+1} = \sum_{x=0}^{k} n_{x,t} m_x, \tag{3.8}$$

where $n_{x,t} = l_x n_{0,t-x}$. This result indicates that the population of Aa females behaves as if it is an autonomous population with life table l_x and fertility schedule m_x. Because we assumed that the heterozygotes are unaffected by the epidemic, the population of heterozygotes will retain the stable age distribution given by equation (3.2) and continue to grow exponentially at rate λ after $t = 0$.

In generation t,

$$p_t = \frac{\sum_{x=0}^{k} n_{x,t}}{2 \sum_{x=0}^{k} N_{x,t}}. \tag{3.9}$$

At $t = 0$, both the aa and Aa individuals are assumed to be in the stable age distribution, so

$$p_0 = \frac{n_0 \sum_{x=0}^{k} u_x}{2N_0 \sum_{x=0}^{k} u_x} = \frac{n_0}{2N_0}. \tag{3.10}$$

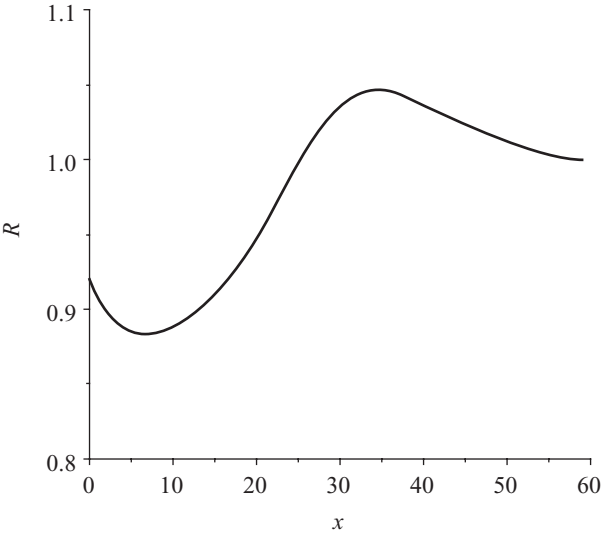

Figure 1. Dependence of R, defined by equation (3.13), on the age x at which survivorship is reduced by 50%. The life table and fecundity schedule were for France in 1801 (Coale & Demeny 1983; Preston *et al.* 2001).

After a new stable age distribution is established for the aa individuals, but while A is still at low frequency,

$$p_t = \frac{n_0 \sum_{x=0}^{k} u_x}{2C \sum_{x=0}^{k} \tilde{u}_x} \left(\frac{\lambda}{\tilde{\lambda}}\right)^t = \tilde{p}_0 (1 + s)^t, \tag{3.11}$$

where s is defined as the per-generation selection intensity,

$$s = \left(\frac{\lambda}{\tilde{\lambda}}\right) - 1, \tag{3.12}$$

and $\tilde{p}_0$ is a constant.

If there were no age structure, then for $t > 0$, the frequency of A while it is rare is given by equation (2.1). Equation (3.11) has this form but the coefficient differs because of the adjustment of the aa population to the new life table. The long-term effect of this adjustment is summarized by the ratio

$$R = \frac{\tilde{p}_0}{p_0} = \frac{1}{\sum_{x=0}^{k} u_x \tilde{v}_x} \frac{\sum_{x=0}^{k} u_x}{\sum_{x=0}^{k} \tilde{u}_x}. \tag{3.13}$$

There appears to be no simple dependence of R on the parameters: R may be either greater or less than 1. To illustrate the dependence of R on the age dependence of the disease, we considered the l_x and m_x values for France in 1801 (Coale & Demeny 1983; Preston *et al.* 2001). We assumed that the disease reduced survivorship of individuals of age x by 50% but left all other survivorship rates unchanged. To find the effect of a mortality increase in a single age class, we computed R from equation (3.13) as a function of x. The results are shown in figure 1. Selection for resistance to diseases that affect the earliest age classes is weaker than expected ($R < 1$), whereas selection

for resistance to diseases that affect intermediate age classes is slightly stronger than expected ($R > 1$).

If a disease affects hosts independently of host age, the influence of age structure is much weaker. For the life table used for figure 1, a 50% decrease in the survivorship of any age class before first reproduction ($x \leqslant 16$) reduces λ from 1.0429 to 1.0207. The values of R in all cases are less than 0.92 (see figure 1). By contrast, if the survivorship of each age class is reduced by 97.8%, λ is still reduced from 1.0429 to 1.0207. With this change in the life table, however, R is 0.999. These results were typical for other life tables as well.

Our results are closely related to the concept of population momentum, introduced by Keyfitz (1971). Keyfitz showed that if, in a growing population, birth rates of all age classes are reduced by a factor that makes the dominant eigenvalue 1, population growth will not immediately cease but will continue until the new stable age distribution is attained, at which time population growth ceases. Tognetti considered the effect of an instantaneous increase in age-specific mortality and showed that the ultimate population size could not be easily predicted (Tognetti 1976*a*,*b*). Once the stable age distribution is reached, the population size can be larger or smaller than the initial population depending on which age classes are affected. The results derived here can be regarded as a generalization of Tognetti's predictions. The difference is that we did not restrict the population growth rate to be unity, and we were concerned with the relative sizes of two groups (the Aa and aa individuals) once the aa population reached the new stable age distribution.

(b) *Numerical analysis*

We used numerical analysis to examine the trends of the response to selection for resistance over many years, and thus to consider the impact of disease periodicity on selection. We compared selection resulting from a disease that causes continuous mortality, such as malaria in Africa, with that from a disease responsible for periodic mortality, such as poliomyelitis or bubonic plague. In the periodic case, it was assumed that there are year-long epidemics, with inter-epidemic periods of 5 years, as was the case for poliomyelitis before vaccination (Anderson & May 1991), over a period of 350 years. This gave a total of 58 years of disease and 292 years without disease. In the continuous case, the period of disease lasted for 58 years and was then followed by a period of 292 years without disease. Thus, both the total duration of the disease periods and the total duration of periods without disease were the same irrespective of disease periodicity. The point at which the block of 58 years of continuous disease occurred within the 350 years made negligible quantitative difference.

(i) *Age-independent disease*

Age structuring reduced selection intensity, particularly at high levels of virulence, when disease mortality was independent of host age (figure 2). For $\sigma = 0.2$–0.9, the resulting selection intensity ($\breve{s}$) resulting from continuous disease mortality was at least 20% higher when age structure was ignored.

In the absence of age structure, p remained constant after an epidemic ended and thus selection lifted (figure 3). Consequently, time under selection was additive, such that p depended only on the cumulative duration and intensity of the disease. Thus in the absence of age structure, disease periodicity was not important. However, in the presence of age structure, periodicity did influence the intensity of selection (figure 3). We found that this discrepancy between temporal patterns increased with greater disease virulence, with a continuous epidemic resulting in lower selection intensity (and hence lower frequency of the favoured allele) than when the epidemic was periodic (figures 2 and 3).

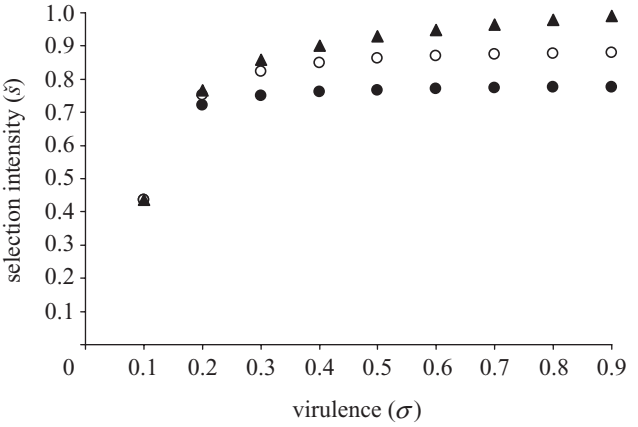

Figure 2. Increase in selection intensity ($\breve{s}$) at different levels of virulence (σ): continuous (filled circles); periodic (open circles) and no age structure (filled triangles). Disease mortality is independent of host age.

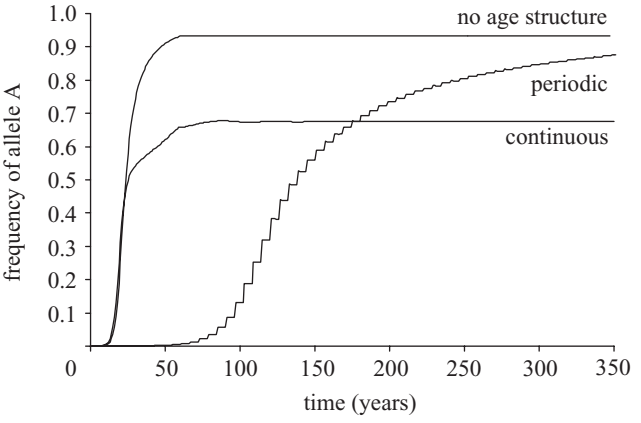

Figure 3. An example of the increasing frequency of allele A (p) over time. Disease mortality is independent of host age. Virulence (σ) = 0.4.

(ii) *Age-dependent disease*

The value of R (the ratio of the proportion of resistant alleles reached by the end of the simulation in the age-structured system to that in a system without age structure) varied with the age specificity of the disease (figure 4; where $\sigma = 50\%$). Diseases that affected hosts with high reproductive potential resulted in $R > 1$. For example, R was highest (over 12 for a periodic disease and over 6 for a continuous disease) when the disease targeted the most fecund hosts (between the ages of 20 and 25 years). Diseases that affected hosts with lower reproductive potential (older than 35 years) generated $R < 1$.

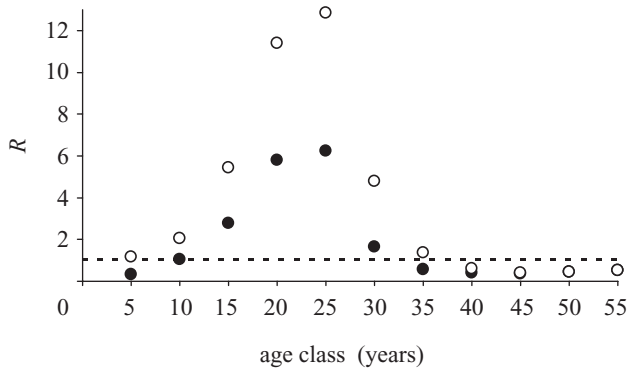

Figure 4. Dependence of R (dashed line: $R = 1$) on the age specificity of disease mortality for continuous (filled circles) and periodic (open circles) dynamics. Here, virulence (σ) = 0.5.

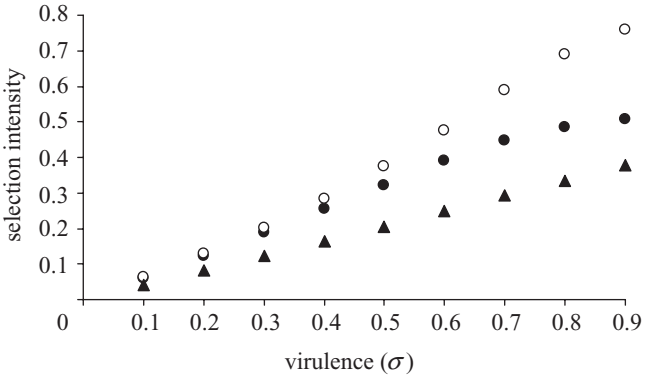

Figure 5. Increase in selection intensity with virulence for populations without age structure (filled triangles) and for age-structured populations under continuous (filled circles) and periodic (open circles) disease mortality. Here, the disease targets individuals from 20 to 25 years of age in the age-structured model, or the equivalent proportion in the non-age-structured model.

For diseases that affected young children, R was also less than 1. There is a delay before the children begin reproducing, thus slowing selection relative to a population without age structure, consistent with figure 1. Periodic disease resulted in a higher R than did the same number of years of disease over a continuous period. Disease can devastate a targeted age class, leaving a smaller target for selection to affect. In the periodic case, the targeted age class was able to build up during the inter-epidemic period before it was subjected to another pulse of selection.

The effects of both age structuring and periodicity became increasingly pronounced with greater virulence for a disease that targeted reproductive hosts aged between 20 and 25 years, such as a sexually transmitted disease (figure 5), consistent with figure 2. For example, when $\sigma = 90\%$, the resulting selection intensity ($\hat{s}$) for a periodic epidemic in an age-structured population was over twice that generated without age structuring.

4. DISCUSSION

Deciphering the dynamics of diseases that have shaped the population genetics of resistance loci requires an understanding of the effects of age structure, the age specificity of disease mortality and the periodicity of epidemiological dynamics. We found that, when selection was intense, the response to selection for resistance depended in a complex way on the age dependence and periodicity of disease mortality. Age structure tended to reduce selection intensity when disease mortality was independent of host age. Age structure also reduced the intensity of selection for resistance to diseases, such as cancer, that affected older hosts. The relationship was reversed for diseases that affected reproductive ages, such as sexually transmitted diseases. Although we discuss our results in terms of a disease generating selection for a resistance allele, these results have broader relevance for any form of intense selection. Our results highlight the importance of using an age-structured framework when modelling the population genetics of intense selection, particularly if selection is age-specific and periodic.

Several factors contribute to the effects of age structure. First, age-specific mortality caused by a disease reduces the population growth rate in proportion to the effect on reproductive value. Second, if the disease mortality is age-specific, shifts in age distribution can alter the proportion of the population that is under selection, given that other age classes do not contribute to selection for resistance. Third, there may be a delay between the time of the selection pressure and the reproductive propagation of changes in allele frequency. Fourth, age-specific mortality generates varying degrees of deviation from Hardy–Weinberg ratios between age classes.

(a) *Effects of age-specific mortality*

Both our analytical and our numerical results for a single time-step indicated that there is a lag in the response to selection for resistance to childhood diseases. This lag occurs because the change in p brought about by a childhood disease is not magnified in the population through reproduction until the first cohort that has experienced the disease reaches reproductive maturity. This lag reduces the response to selection for resistance. Diseases that affect the elderly will also result in slower selection than in a population without age structure, because the reproductive consequences of this selection are minimal. However, when a disease affects intermediate age classes with large reproductive values, selection is more effective in increasing the frequency of resistance alleles than when a disease affects the youngest or oldest age classes.

(b) *Periodicity of disease mortality*

Periodicity can have a considerable effect on the intensity of selection for resistance in an age-structured population. Continuous disease tended to result in lower selection intensity than a periodic disease for both age-dependent and age-independent diseases. The effect of periodicity is generated by changes in the age distribution and by deviation from Hardy–Weinberg proportions among newborns. In this context, population momentum has a specific meaning. In an age-structured population, age structure continues to change even after selection ceases. During periods between epidemics, the age structure begins to return to its disease-free equilibrium, until the next epidemic pulse. These displacements from age-

structure equilibrium can influence the selection intensity acting on resistance alleles. High virulence and associated mortality caused significant destabilization of the age structure, resulting in a trend of greater deviation from Hardy–Weinberg proportions when disease mortality was continuous than when it was periodic, as virulence increases.

The pronounced effect that age specificity of disease mortality can have on the response to selection indicates the importance of employing an age-structured model when exploring the population genetics of resistance to virulent diseases. Models that ignore age structuring and disease periodicity may either considerably overestimate or underestimate the intensity of selection and hence the virulence of the disease, depending on the periodicity and age specificity of the disease. For example, if a disease affects individuals predominantly in the reproductive age classes, age structure can increase selection intensity substantially. Magnified over numerous generations, this can generate enormous discrepancies in allele frequency.

In some cases, it is possible to infer when an allele arose by mutation and consequently to estimate the average selection intensity in favour of that allele since its origin. For example, Stephens *et al.* (1998) estimated that the Δ32 allele at the CCR5 locus arose *ca*. 700 years ago, and concluded that it is necessary to assume an average selection coefficient in favour of Δ32 of 0.2–0.3 to account for its current average frequency of 10% in European populations when non-overlapping generations were assumed. Our results show that, to achieve an effective selection coefficient of this magnitude, predictions of the actual reduction in mortality of carriers of Δ32 may be altered considerably once the effects of age structure and the properties of particular diseases are taken into account (Galvani & Slatkin 2003).

Future research could consider the epidemiological feedback caused by evolution. The spread of a resistance allele through a population would reduce transmissibility, resulting in lower levels of disease prevalence. Consequently, it is expected that the risk of infection for a susceptible host would fall, as would the selection intensity for disease resistance, thereby slowing down the increase in the frequency of the resistance allele over time.

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