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THE ROYAL SOCIETY

The effects of host heterogeneity on pathogen population structure

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We have shown that among pathogens, populations may self-organize into strains with non-overlapping repertoires of antigenic variants as a consequence of strong immune selection operating on polymorphic antigens. Recently, we have also demonstrated that over a wide range of intermediate levels of immune selection, pathogens may still be structured into discrete strains, but different sets of non-overlapping pathogen types will replace each other in a cyclical or chaotic manner. These models assume that the ranking of antigens in terms of the strength of the induced immune response is the same for every host. However, host immune responses may be restricted by the genotype of the individual. To explore this issue, a mathematical model was constructed under the assumption that a proportion of the host population responds principally to a variable antigen while the remainder of the population responds principally to a conserved antigen. The results of this analysis indicate that discrete strain structure (DSS) will be maintained even with a high frequency of hosts that do not respond in a variant-specific manner. Furthermore, the range of the immune selection pressure over which DSS prevails is increased (and the region of cyclical or chaotic behaviour reduced) by the inclusion of hosts that respond in a cross-reactive rather than a variant-specific manner.

Keywords: strains; host heterogeneity; pathogen diversity; chaos; immune selection

1. INTRODUCTION

The simplest models of infectious disease systems assume that hosts and pathogens are homogeneous in terms of their response to the process of infection. In other words, all hosts have an equal probability of becoming immune and/or developing disease and/or transmitting the infection. Similarly, all pathogens are assumed to elicit the same degree of immunity and have the same level of virulence. However, it is becoming increasingly clear with the application of molecular typing methods that a considerable amount of diversity exists among pathogens and hosts, particularly among the pathogen genes that are involved in provoking an immune response in the host, and the host genes that are involved in responding to infectious agents.

The integration of population genetics with basic epidemiological principles can provide some insights into the coevolution of hosts and parasites within these complex systems (May & Anderson 1983). We have developed mathematical models to try and understand the evolution of diversity of pathogens under immune selection by the host. These models suggest that the epidemiology of an infectious agent will be influenced by the antigens that elicit the strongest immune responses. If these antigens are conserved between all pathogen strains, the latter will compete strongly with each other by removing from each other their only available resource: susceptible hosts. Consequently, pathogens with strong, conserved, antigenic determinants will tend to evolve towards single-strain systems, with the most successful parasite type outcompeting the others. By contrast, where the strongest immune responses are directed against polymorphic antigens, it can be shown that the pathogen population will self-organize into strains with non-overlapping repertoires of antigenic variants (Gupta *et al*. 1996). These will function as independently transmitted strains with limited levels of interaction. Recently, we have also demonstrated that over a wide range of intermediate levels of immune selection, pathogens may still be structured into discrete strains, but different sets of non-overlapping pathogen types will replace each other in a cyclical or chaotic manner (Gupta *et al*. 1998).

These models assume that the ranking of antigens in terms of the strength of the induced immune response is the same for every host. However, host immune responses may be restricted by the genotype of the individual, such as the human leucocyte antigen (HLA) type. Here, we discuss the consequences of heterogeneity in host response for the population structure of pathogens. In particular, we address the case where a proportion of the host population responds principally to a variable antigen, while the remainder of the population responds principally to a conserved antigen.

2. SINGLE-LOCUS STRAIN SYSTEMS

Pathogen strains may be defined by variation at a single locus where the latter encodes a polymorphic antigen. We consider two parasite types, x and y, representing specific epitopes recognized by hosts of

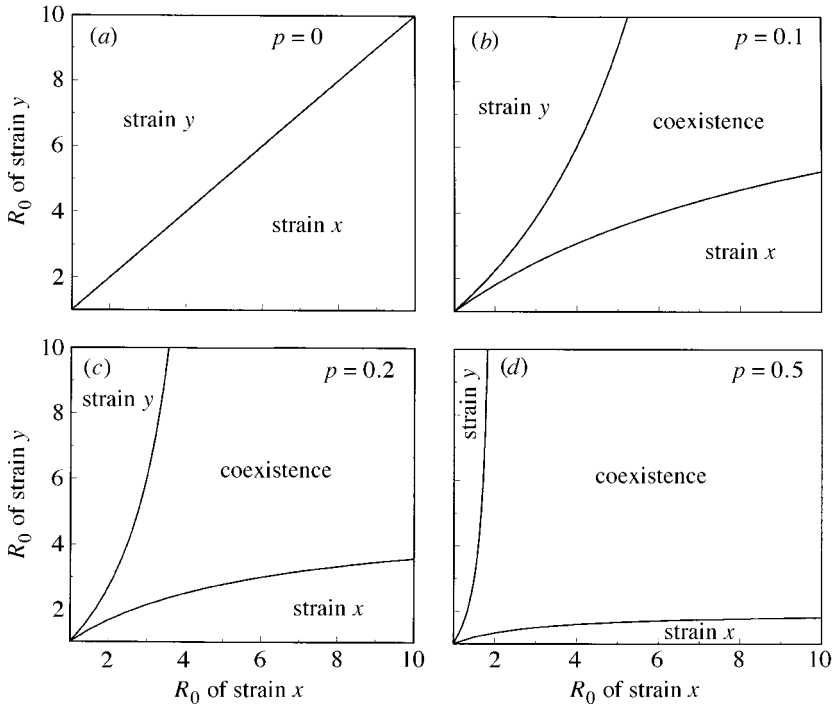

Figure 1. The range of R_0s of strains x and y over which coexistence can occur, for different frequencies of host genotype A (p).

genotype A. We assume that the immune responses developed by hosts of genotype A to x and y are non-cross-reactive. Thus within hosts of genotype A, the proportion immune to strain 'i' will be given by

$$\frac{dz_i^A}{dt} = h_i\lambda_i(1 - z_i^A) - \mu z_i^A, \tag{1}$$

where λ_i is the force of infection with strain i and h_i represents the fraction of individuals that become immune upon exposure to strain i. We assume, for simplicity, that immunity is lifelong. The changes with time in the proportion that are infectious with a given strain, y_i^A, is given by

$$\frac{dy_i^A}{dt} = \lambda_i(1 - z_i^A) - (\sigma + \mu)y_i^A, \tag{2}$$

where σ is the rate of loss of infectiousness.

Let us now consider a second host genotype B, which primarily recognizes a different antigen or epitope, encoded by another locus. We assume that the antigenic determinant recognized by B is conserved between strains. As a result, hosts of genotype B will respond to infection by either x or y in a cross-reactive manner. The proportion immune to either parasite strain in hosts of genotype B may thus be represented by a single variable z^B, whose dynamics may be characterized by the equation

$$\frac{dz^B}{dt} = h\sum\lambda_i(1 - z^B) - \mu z^B, \tag{3}$$

where λ_i is the force of infection with strain i and h represents the fraction of individuals that become immune upon exposure to any strain. The proportion that are infectious with a given strain is given by

$$\frac{dy_i^B}{dt} = \lambda_i(1 - z^B) - (\sigma + \mu)y_i^B. \tag{4}$$

The two host populations are coupled together by the force of infection λ_i of strain i, which may be written as $\beta_i(py_i^A + (1-p)y_i^B)$, where p is the proportionate contribution of hosts of genotype A to the pool of infectious agents. In general, p can be assumed to be equal to the frequency of genotype A in the host population. Thus, when $p = 1$, we recover the situation where immunity is entirely strain-specific; and conversely, when $p = 0$, we recover the situation where immunity is entirely cross-protective. The basic reproductive rate (R_0) of strain i is given by β_i/σ. The latter defines the average number of secondary cases generated by a primary case of infection in a totally susceptible population, and is a fundamental measure of the transmission success of a pathogen strain within a given community (Anderson & May 1991).

The criteria for coexistence of strains is defined by the relative proportions of hosts of genotype A and B, as well as the associated probabilities of developing a protective immune response. For particular values of the latter, the region of strain coexistence may be mapped according to the frequency of the host genotypes, as shown in figure 1. When the host population is entirely composed of individuals with genotype B, the strains are not able to coexist, the strain with the lower R_0 being driven extinct through competitive exclusion (figure 1*a*), unless the R_0 values are identical, as previously shown (Gupta *et al.* 1994). There is a significant change in the chance of persistence when the occurrence of genotype A is increased even slightly (figure 1*b*). More specifically, coexistence is permitted provided that the difference between the R_0 values, relative to the absolute values of R_0, is sufficiently small. High R_0 values will permit coexistence even if there is a large difference between the R_0 values of the two strains.

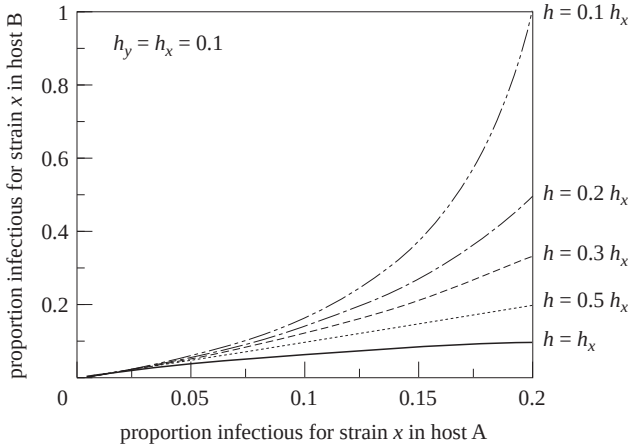

Figure 2. The relationship between proportions infectious in hosts of genotype A and B, respectively, for different ratios of rate of development of strain-specific versus cross-reactive immunity.

Even a small proportion of genotype A is sufficient to provide adequate niche space in which both the strains can coexist. With increasing proportions of genotype A, the range of R_0 values over which the two strains can coexist widens, as shown in figure 1*c*,*d*. This trend continues, culminating when the proportion of genotype A reaches unity and the strains can coexist over any range of R_0 values. It may be demonstrated analytically (see Appendix A) that the frequency of genotype A defines the range of coexistence of strains in the following manner:

$$p > \frac{R_0^x - R_0^y}{(R_0^x - 1)R_0^y}. \qquad (5)$$

In this respect, the frequency of genotype A functions exactly as the coefficient of cross-immunity described in Gupta *et al*. (1994), where the latter is a measure of the degree to which the transmission of a second strain is inhibited by immunity to the first in a homogeneous host population.

Levels of infection with strains x and y in the two subpopulations will be dictated by the rates of development of immunity (or equivalently the duration of immunity) as well as host genotype frequency. However, where the strains are equivalent in terms of induction of immunity, the relationship between the proportions that are infectious at equilibrium in the different populations is given by

$$\frac{1}{y_i^{\mathrm{A}}} - \frac{1}{y_i^{\mathrm{B}}} = \frac{\sigma}{\mu}(h_i - nh), \qquad (6)$$

where n refers to the number of strains involved.

Figure 2 illustrates this relationship for different ratios of h:h_i in the two-strain case ($h_x = h_y = 0.1$ in this example). The lowest line ($h = h_x$) indicates that if the probability of mounting a protective immune response is constant between hosts, the equilibrium level of infection with either strain will always be lower in subpopulation B than in subpopulation A. This result arises because a single infection in a host of genotype A will only give protection against one of the two strains, but will give protection against both strains in hosts of B. Consequently, a lower level of infection for population B will be reached when the probability of developing immunity is half of that of population A (equilibrium solutions become identical when $h = 0.5h_x$, as shown by the dotted line in figure 2). A significant difference in the proportions that are infectious for a given strain in the two subpopulations only emerges when the rate of acquisition of immunity in subgroup B is very low in comparison with subgroup A. More complex patterns may emerge when the rates of development of immunity to the two strains are different, as these will be dictated by competition between the two strains within genotype B. However, the general point holds that levels of infection with strains x and y in hosts for whom x and y are not epitopes will only be lower than in hosts that respond in an epitope-specific manner provided that the epitope-specific responses are very much more protective than the non-epitope-specific response. Figure 3 shows the expected proportions that are infectious for the two strains within host genotypes A and B, as a function of the level of cross-specific immunity (h) generated within B to either strain. In figure 3*a*, genotype A-specific host immune responses against epitopes defining strains x and y are not strongly protective, with x being the weaker of the two. If the overall non-epitope-specific response in hosts of genotype B is similar in magnitude to the anti-x response in genotype A, levels of infection will be lower in hosts of genotype B. Significant differences emerge when the anti-x response is ten times as strong. When strain-specific protection is strong, as in figure 3*b*, the difference in the proportions that are infectious are much smaller for an equivalent reduction in protection among hosts of genotype B. This raises important questions regarding the use of strain-stratified infection-prevalence data to detect a protective effect among host genes, which we will address in § 4.

3. MULTILOCUS STRAIN SYSTEMS

We now consider the situation where the principal target of the immune response in hosts of genotype A is defined by more than one locus. Each combination of alleles at the different loci thus constitutes a strain. For example, in the case where there are two immunologically dominant loci, each with two alleles or variants, the four possible types of strains are *ay*, *ax*, *bx* and *by*, where *a* and *b* are alleles at one locus, and *x* and *y* are alleles at the second locus. In the single-locus case, the different strains do not interfere with each other immunologically as the immune response within the host is allele-specific and hence entirely strain-specific (each allele defines a strain). In the multilocus case, by contrast, allele-specific responses can cause significant immunological interference between strains, as a host exposed to *ax* will have protective anti-*a* and anti-*x* responses that will confer a degree of cross-protection, γ, against any other strain with these alleles (i.e. *ay* and *bx*). Only strains that do not share any alleles will not interfere with each others' transmission (i.e. $\gamma = 0$ for that particular pair), since the immune responses directed against one strain, say *ax*, will be ineffective against the other, say *by*, since neither anti-*a* nor anti-*x* responses will recognize either *b* or *y*. For strains that do share alleles, cross-protection may range

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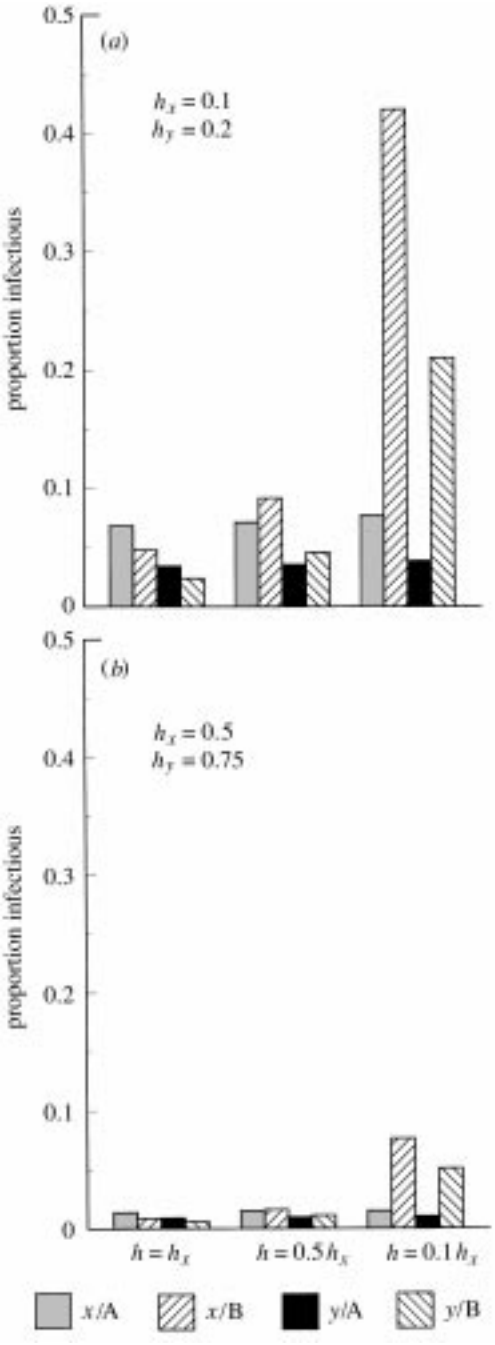

Figure 3. Comparison of the proportions that are infectious for strains x and y in hosts of genotype A and B, respectively, where the rates of development of strain-specific immunity are (*a*) weak, and (*b*) strong.

from none to complete protection ($0<\gamma<1$). The dynamics of these multilocus genotypes (where strain i is defined by n loci) with hosts of genotype A may be described by the following set of equations:

$$\frac{dz_i^A}{dt} = \lambda_i(1 - z_i^A) - \mu z_i^A, \tag{7}$$

$$\frac{dw_i^A}{dt} = \sum \lambda_j(1 - w_i^A) - \mu w_i^A, \tag{8}$$

$$\frac{dy_i^A}{dt} = \lambda_i[(1 - w_i^A) + (1 - \gamma)(w_i^A - z_i^A)] - \sigma y_i^A. \tag{9}$$

Here, w_i represents those individuals that are immune to any strain j that shares alleles (at the relevant polymorphic loci) with strain i. This subset $\{j\}$ includes strain i itself. Individuals that have not been infected either by i or any strain sharing alleles with i, i.e. $(1 - w_i)$, are completely susceptible to strain i. However, those that have been exposed to a strain sharing alleles with i, but not exposed to strain i itself, i.e. $(w_i - z_i)$, will become infectious with a probability $1 - \gamma$ when they are infected by strain i. We assume, for simplicity, that the probability of becoming immune (h_i) is unity in hosts of genotype A for all strains.

Analysis of this model in the case where the host population is genetically homogeneous (consisting entirely of genotype A) reveals that provided the degree of cross-protection is high, the pathogen population will be organized into discrete non-overlapping (or discordant) combinations of alleles, with one such set existing at a far greater frequency than the others. The pathogen population may exhibit such a discrete strain structure (DSS) despite frequent recombination (Gupta *et al*. 1996). However, for this pattern to emerge and be stable over time, the intensity of acquired immunity to a specific variant antigen (encoded by a given allele) within the host population, must considerably reduce the fitness of all genotypes possessing that allele. This is reflected in the analytical result that a stable DSS will only occur if the level of cross-protection exceeds an upper threshold, $\gamma_T = 1 - 1/(2R_0)$. Conversely, beyond a lower threshold γ_L, no strain structure (NSS) exists. Between these two thresholds, pathogens may exist as a set of strains that exhibit cyclical or chaotic fluctuations in frequency over time (Gupta *et al*. 1998). They may still be organized by immune selection into discordant groups of variants, but the frequency of each group may fluctuate widely over time, either in a cyclical or a chaotic manner.

By introducing host heterogeneity into this system, we define two clear boundaries. At one extreme, where the population consists entirely of genotype B, competitive exclusion will work to reduce the system to a single strain of the highest R_0 (May & Anderson 1983; Bremermann & Thieme 1989; Gupta *et al*. 1994). At the other extreme, where the population consists entirely of genotype A, the transitions between NSS, chaotic or cyclical strain structure (CSS) and DSS will essentially be defined by the degree of cross-protection or the strength of the immune response directed against the variable antigens.

The first clear effect of introducing a proportion of individuals that react in a cross-reactive rather than a variant-specific manner is a reduction in the magnitude of cross-protection required for stable DSS to occur. As shown in figure 4, for a range of R_0 values, the threshold drops with increasing frequency of genotype B. Thus, rather than disrupting strain structure, the effect of increased competition among all strains would appear to stabilize it. Figure 5 charts the transition between CSS and DSS in a two-locus two-allele system where all four strains have basic reproductive rates in the region of 4, and the degree of cross-protection afforded by sharing alleles is 0.85. In the absence of genotype B, strain abundance exhibits a cyclical pattern with each non-overlapping subset of strains dominating for a given period. Introducing a proportion of individuals of genotype B causes the period of these oscillations to increase as evidenced by figure 5*b*. Eventually, the proportion of B in the population exceeds a threshold beyond which no oscillation occurs. In practical

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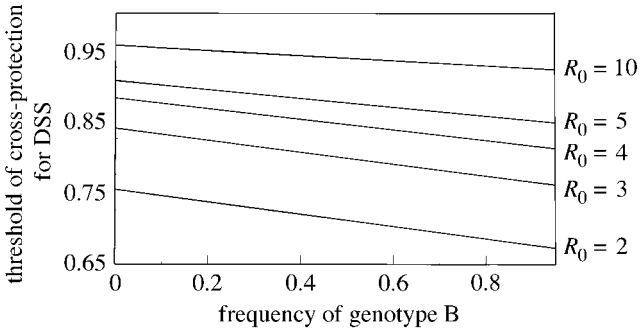

Figure 4. The threshold of the magnitude of cross-protection required for the establishment of stable DSS declines with increasing frequency of hosts of genotype B for a range of values of R_0.

terms, such a transition will have been achieved earlier, as the very low levels of infection involved in the long cycles are likely to lead to the elimination of the rarer strains due to stochastic effects.

In the situation where the strains do not differ significantly in R_0, the effects of cross-immunity (operating between all strains) will be less marked than cross-protection (operating between strains that share alleles), since competitive exclusion through cross-immunity will only occur provided there are differences in R_0 of the interacting strains. By contrast, the competitive exclusion of antigenically related strains through cross-protection will occur even when the strains have identical R_0s. Thus, even at extremely low frequencies of host genotype A, strain structure will occur among pathogen populations where the different strain combinations have similar R_0s. This may be expected to be the case in non-clonal populations where the genetic factors influencing transmission are likely to have the same random distribution in each strain. Figure 6*a–d* charts the effect of increasing the frequency of genotype B in a system of four strains (designated *ay*, *ax*, *bx* and *by*) with identical R_0 ($R_0 = 4$ in this example) and complete cross-protection. Under these circumstances, DSS will occur even at very high frequencies of genotype B. The effects of increasing the frequency of genotype B are twofold: (i) to delay the process of bifurcation towards strain structure, and (ii) to depress the equilbrium frequencies of the dominant pathogen genotypes (shown in this example as *ax* and *by*) due to immunological interference mediated by cross-immunity. When there is no cross-immunity (i.e. $p = 1$), the dominant pathogen strains do not interfere with each other's transmission, and the proportions that are immune to either type in the population are given by $1 - 1/R_0$, which is equal to what they would achieve in each other's absence.

Figure 6*e–f* shows the consequences of increasing the frequency of genotype B under the more realistic scenario where the strains do not have identical R_0s. As there are fundamental asymmetries between strains, bifurcation towards strain structure occurs very rapidly under all initial conditions. The effects of immunological interference between the dominant strains are different from the situation with identical R_0s in that the strain with the higher R_0 (*ax* in this example) maintains its equilibrium frequency as the frequency of host genotype B increases, progressively suppressing the frequency of the other dominant strain (*by*). However, unless the strain has a very high relative R_0, the total suppression of the discordant type only occurs at very high frequencies of B, as shown in figure 6*h*. The threshold frequency for the elimination of the discordant strain (and associated loss of strain structure) is given by the same expression as equation (5) where the R_0s are the basic reproductive rates of the dominant discordant strains.

Figure 7 links the sequential suppression of the pathogen genotypes to the loss of complexity in the dynamics of the system. In this example, the strains all differ in R_0, and the degree of cross-protection associated with sharing of alleles is 0.85. In the absence of hosts of genotype B, this leads to a complex cyclical regime with different combinations of strains dominating at different times, as shown in figure 7*a*. Introducing a proportion of hosts of genotype B leads to a simpler cyclical regime where the strain with the highest R_0 (represented by the unbroken line) dominates in conjunction with its discordant partner. It is clear in this example (figure 7*b*) that the subdominant strain of lower R_0 has been eliminated due to the additional element of competition between discordant strains arising from cross-immunity. A further increase in the frequency of genotype B causes the eventual elimination of the other subdominant strain, with the associated loss of cyclical behaviour. Meanwhile, the equilibrium level of the dominant strain of lower R_0 begins to decline; from equation (5) it can be calculated that it will be excluded from the system when the frequency of B reaches 90%.

4. DISCUSSION

Host–pathogen interactions occur at several levels. Those that may be deconstructed into a single host gene responding to a single pathogen gene can be represented by simple models involving several pathogen strains that may interact due to cross-immunity. We have introduced host heterogeneity into this system by dividing the population such that certain host genotypes respond in a strain-specific manner, while others respond in a strain-transcending manner. This may occur because the nature of the immune response directed against the relevant epitopes is specific in one case and cross-reactive in the other. Alternatively, one set of hosts may respond principally to these epitopes, while the other set responds to a conserved epitope. The equilibrium frequencies of the strains (as defined by the single locus) are determined in this case by the proportion of each host genotype in the population. The conditions for coexistence of strains are very stringent when the vast majority are hosts that respond in a non-strain-specific manner; conversely, there are no boundaries to coexistence when the majority of hosts respond in a strain-specific fashion. An important conclusion of this theoretical exercise is that even a small fraction of the latter can cause a significant expansion in the range of coexistence between strains of different transmissibilities.

The precise frequencies of the different strains within the different types of hosts will depend on their relative ability to mount a protective immune response. Of interest here is the observation that where host genes confer strain-specific protection, this will not be evident in the levels of infection within different hosts unless the magnitude of strain-specific protection is very much

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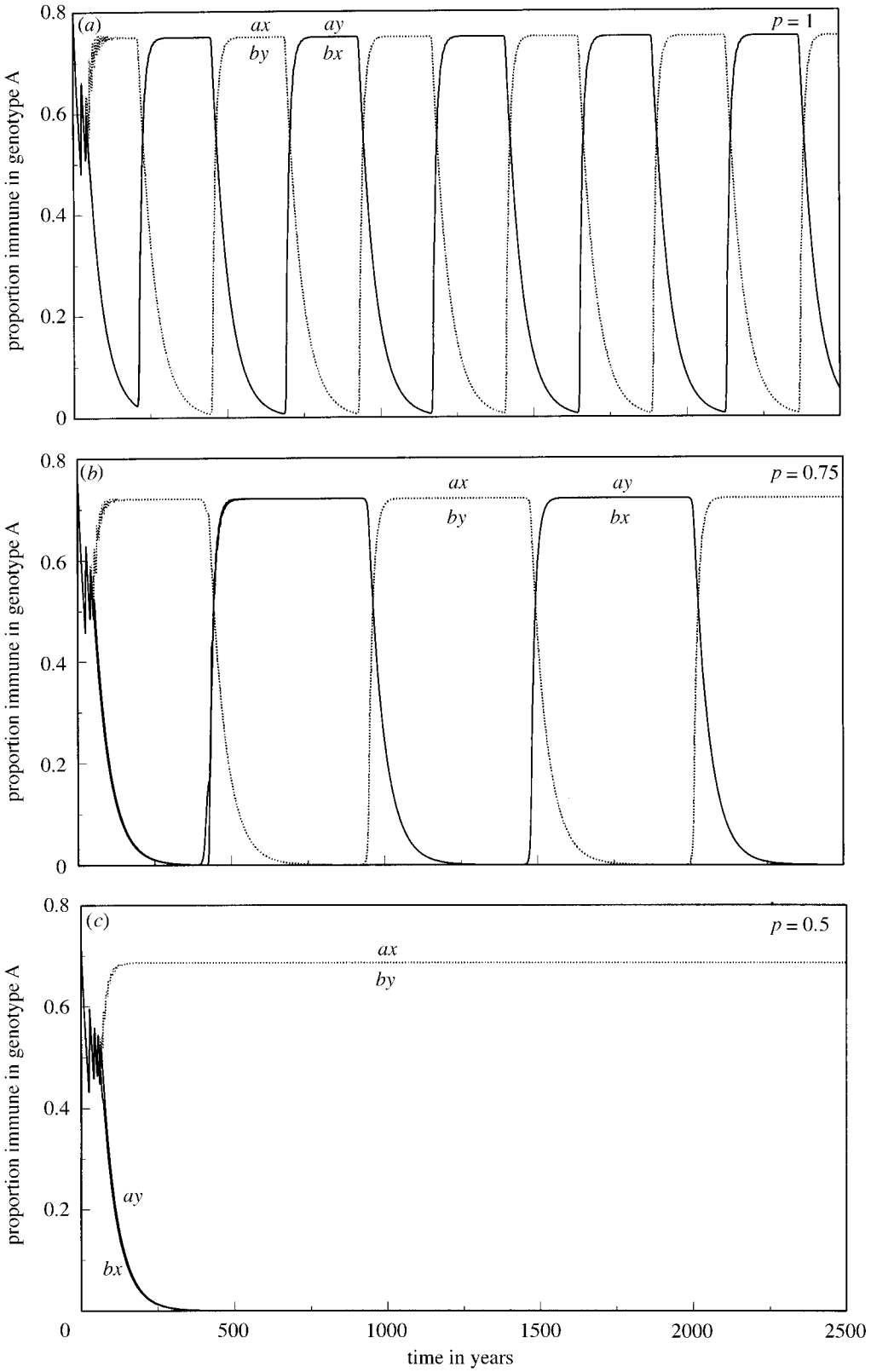

Figure 5. The dynamics of a two-locus two-allele system for different values of the frequency of host genotype A (p). The solid and dotted lines represent each pair of non-overlapping types ($R_0 = 4, \gamma = 0.85, \sigma = 10$).

greater than that afforded by other genes. Roughly speaking, the magnitude of strain-specific protection must be at least n times that of 'strain-transcending' protection where n is the number of different strains involved. Furthermore, differences between levels of infection will tend to decline if the overall protective effect is stronger, and may become difficult to detect in studies of limited sample size. Caution must therefore be exercised in the interpretation of field data on frequencies of infection by different strains within different host genotypes. A small difference does not imply that strain-specific protection is weak. More importantly, a negative association is not an indication of an inability to mount an immune response, but may simply result from extreme

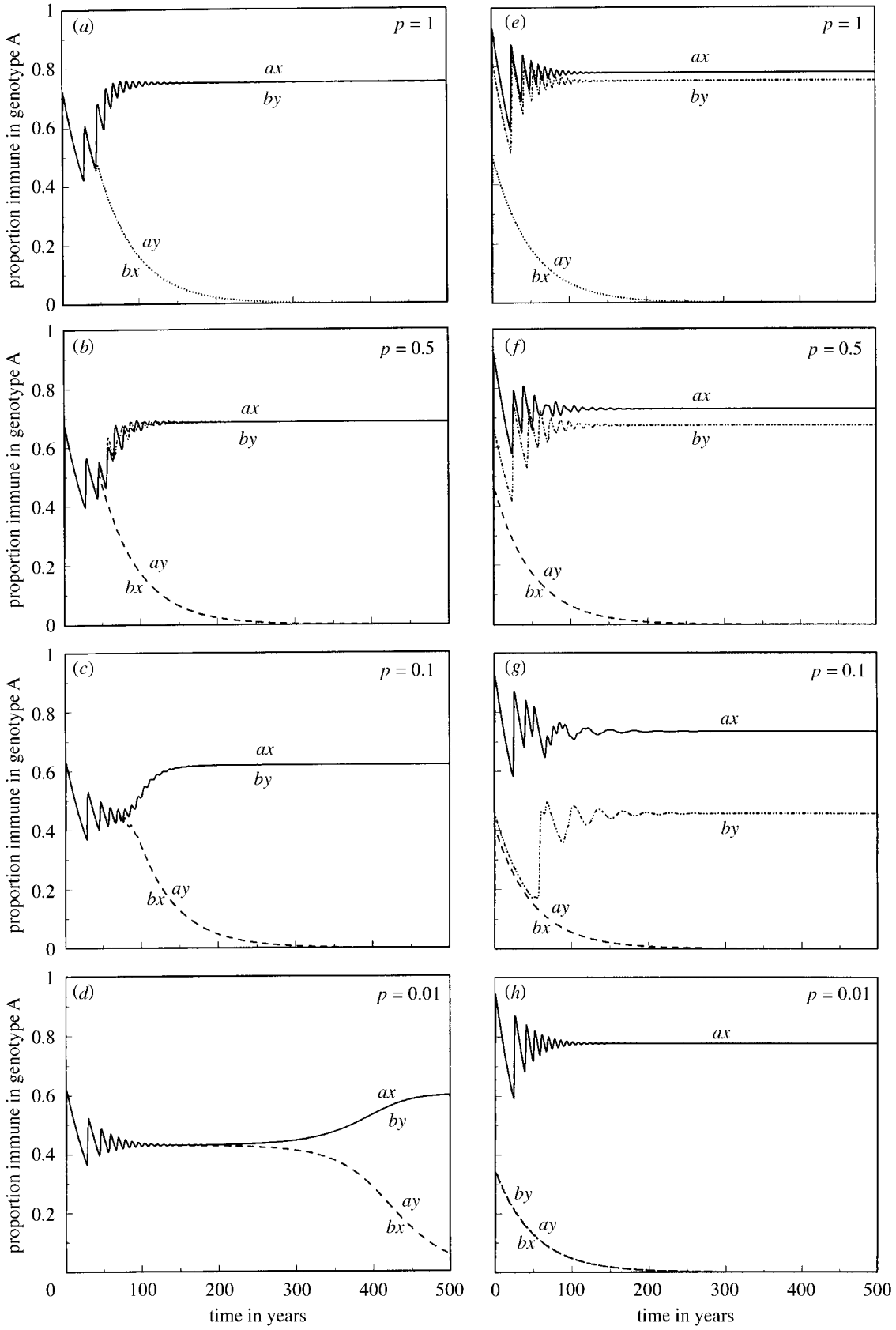

Figure 6. The effect of increasing the frequency of genotype B in a two-locus two-allele system with complete cross-protection. In (*a*)–(*d*), all $R_0 = 4$, while in (*e*)–(*h*), all $R_0 = 4$, except for strain *ax* ($R_0 = 4.5$).

strain specificity of the protective response. A recent study by Gilbert *et al.* (1998) provides an illustration of different distributions of *Plasmodium falciparum* strains among hosts with and without the HLA class-I-type recognizing the polymorphic epitope, on the basis of which the strains are defined. In this particular case, the population structure is also strongly influenced by a positive interaction between the strains mediated by altered peptide ligand (APL) antagonism whereby the HLA class-I-restricted cytotoxic T lymphocytes are able to induce non-responsiveness in

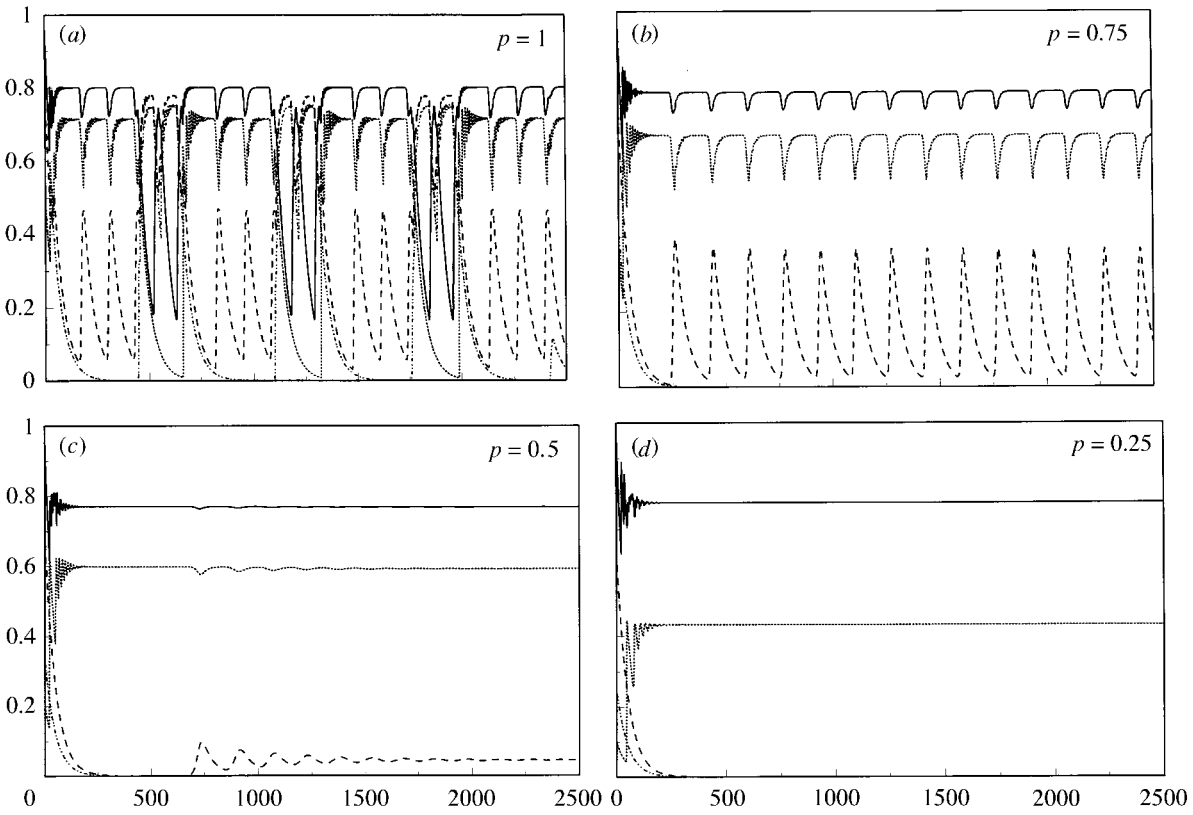

Figure 7. The effect of increasing the frequency of genotype B in a two-locus two-allele system with partial cross-protection, and significant differences in R_0 ($R_0 = 5$, 4.5, 4 and 3.5) among the different strains.

each other. The advantage that this provides to the parasites can cause levels of infection to be higher in hosts that respond specifically, even when the degree of strain-specific protection is very high (Gilbert *et al*. 1998). These exercises underscore the importance of analysing field data in the context of output from simple mathematical models incorporating the specific immunological mechanisms involved in the host–pathogen interaction.

In § 3 of the paper we considered the effects of host heterogeneity on the structure of multilocus strain systems, where interaction between different pathogen types can occur either as a result of sharing of variants (cross-protection) among hosts that react in a variant-specific manner, as well as due to cross-immunity among hosts that react in a non-variant-specific manner. We have shown previously that high levels of cross-protection in homogeneous host populations can lead to the maintenance of DSS. The analyses presented in this paper show that DSS will be maintained even with a high frequency of hosts that do not respond in a variant-specific manner. This is because the suppression of the subdominant strains will be reinforced by immunological interference amongst themselves due to cross-immunity as well as through the sharing of variants with the dominant strains. Immunological interference will also occur among the dominant strains, leading to the suppression and eventual elimination of the strain with lower R_0. However, the latter eventuality is only likely to be observed when the frequency of hosts that respond in a specific manner has fallen to very low levels, unless there is a vast difference in the reproductive rates. Thus, within a normal range of variation of R_0, the existence of a large subpopulation of hosts that respond cross-reactively rather than in a variant-specific manner will tend to reinforce the organization of these variants into discrete non-overlapping units.

The increased suppression of the subdominant strains also has another important effect on the dynamics of the system. We have shown previously that beyond a certain threshold of cross-protection, stable DSS is replaced by cyclical or chaotic behaviour (CSS). The increased suppression of the subdominant strains due to cross-immunity increases the asymmetries between the dominant and subdominant groups, causing the threshold of DSS to drop. In other words, the relative dominance of the subgroups is reinforced by cross-immunity, and can only be in tension at lower values of cross-protection. In particular, the elimination of a subdominant type (as shown in the example in figure 7) can lead to considerable loss of complexity in the dynamics of the system. Thus, broadly speaking, the range over which DSS prevails is increased by the inclusion of hosts responding in a cross-reactive rather than a variant specific manner.

Analyses of both single- and multilocus systems indicate that the structure of a pathogen population is primarily dictated by whether a certain proportion of the host population is responding in a variant-specific manner. Even when this proportion is small, coexistence of strains differing in R_0 may be permitted, provided they do not share variants of the polymorphic antigens. The stable coexistence of discrete non-overlapping strains is reinforced by competitive exclusion among the strains

whose repertoires overlap with the dominant types. The validation of these results requires a multistage experimental design. The first of these steps involves the identification of host-restricted strain-specific immune responses, such as may be performed by identifying the epitopes dominantly recognized by different host genotypes. Parasite strain-specific class I major histocompatibility complex (MHC) restriction has been reported, as previously discussed, by Gilbert *et al*. (1998) with reference to *P. falciparum* infection in humans. Studies of bovine cytotoxic T-cell (CTL) responses to *Theileria parva* indicate that the strain specificity of the immune response is determined by the phenotype of restricting class I MHC (Goddeeris *et al*. 1990). The role of these CTLs in strain-specific protection against infection has been demonstrated by challenge studies in cattle (Morrison *et al*. 1987). More importantly, these experiments also indicate that infection with a given *T. parva* strain can induce a cross-reactive (and cross-protective), rather than a strain-specific, CTL response in some individuals (Taracha *et al*. 1995). These observations open the way towards testing some of our model predictions in the field by analysing strain distribution in the context of the genetic composition of the host population within a given transmission system.

APPENDIX A

For the system described by equations (1)–(4), the total proportion infected by strain i in the host population as a whole, y_i^{T}, is given at equilibrium by

$$[p(1-z_i^*)+(1-p)(1-z^*)]\beta_i y_i^{\mathrm{T}} = \sigma y_i^{\mathrm{T}}. \qquad (\mathrm{A}1a)$$

Hence

$$p(1-z_i^*)+(1-p)(1-z^*) = \frac{1}{R_{0i}}, \qquad (\mathrm{A}1b)$$

and similarly, for strain j,

$$p(1-z_j^*)+(1-p)(1-z^*) = \frac{1}{R_{0j}}. \qquad (\mathrm{A}1c)$$

Consequently,

$$p(z_j^*-z_i^*) = \frac{1}{R_{0i}} - \frac{1}{R_{0j}}. \qquad (\mathrm{A}1d)$$

By substituting the solution $(1-1/R_{0i}, 0)$ into equation (1*d*), we get

$$p > \frac{R_0^1 - R_0^2}{(R_0^1 - 1)R_0^2}. \qquad (\mathrm{A}1e)$$

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