THE ROYAL SOCIETY

doi 10.1098/rspb.2000.1267

Host–parasite coevolution in a multilocus gene-for-gene system

Akira Sasaki

Department of Biology, Faculty of Science, Kyushu University, Fukuoka 812-8581, Japan (asasascb@mbox.nc.kyushu-u.ac.jp)

This paper examines a mathematical model for the coevolution of parasite virulence and host resistance under a multilocus gene-for-gene interaction. The degrees of parasite virulence and host resistance show coevolutionary cycles for sufficiently small costs of virulence and resistance. Besides these coevolutionary cycles of a longer period, multilocus genotype frequencies show complex fluctuations over shorter periods. All multilocus genotypes are maintained within host and parasite classes having the same number of resistant/virulent alleles and their frequencies fluctuate with approximately equally displaced phases. If either the cost of virulence or the number of resistance loci is larger then a threshold, the host maintains the static polymorphism of singly (or doubly or more, depending on the cost of resistance) resistant genotypes and the parasite remains universally avirulent. In other words, host polymorphism can prevent the invasion of any virulent strain in the parasite. Thus, although assuming an empirically common type of asymmetrical gene-for-gene interaction, both host and parasite populations can maintain polymorphism in each locus and retain complex fluctuations. Implications for the red queen hypothesis of the evolution of sex and the control of multiple drug resistance are discussed.

Keywords: gene for gene; red queen; resistance; virulence; coevolution

1. INTRODUCTION

A genotype-specific interaction between host resistance and parasite virulence, which is called gene-for-gene interaction, is widely observed in plants and their microbial parasites (Flor 1956; Burdon 1987). Studies on crop plant–fungus pathogen systems have revealed that, when breeders introduce resistant races of host plants, emergence and rapid spread of a virulent parasite occurs which overcomes the resistance. These observations suggest a continuous coevolutionary change in both host and parasite. The spread of a resistant genotype capable of escaping a currently prevalent parasite will be challenged by a new parasite strain that harbours a virulent gene which is capable of overcoming that resistance. Similarly, a host with a new resistant gene, possibly at another locus, will be able to restore resistance against the same parasite.

Besides its practical importance in agriculture and biological control, gene-for-gene interaction has played a key role in mathematical models of host–parasite coevolution. The models reveal a robust tendency towards protected polymorphism and sustained cycles of host and parasite genotypes, which in turn favour higher rates of mutation, recombination and sexual reproduction (e.g. Hamilton 1980; Hamilton *et al*. 1990; Frank 1993; Haraguchi & Sasaki 1996). Previous gene-for-gene models have assumed symmetrical interactions (matching genotype interaction) between host and parasite genotypes. This assumption has been challenged by empirical studies which have revealed great asymmetry in the gene-for-gene system (Parker 1994): some parasite genotypes have a broader host range than others. Therefore, it is often the case that a generalist parasite (super-race) predominates locally and exploits all existing host genotypes (e.g. Espiau *et al*. 1998). Parker (1994) argued that, under this empirically common type of gene-for-gene interaction, cycles in genotype frequencies are less likely and, hence, the evolution of sex is barely explained by host–parasite interactions. In this paper, I explore the consequences of the coevolution of host resistance and parasite virulence while taking into account the asymmetrical nature and multilocus inheritance of gene-for-gene systems. It will be shown that a multilocus interaction restores genetic diversity and complex sustained cycles of host and parasite genotypes in an empirically common type of gene-for-gene interaction.

The present model naturally embeds two selective forces that drive the coevolutionary process of host resistance and parasite virulence in a gene-for-gene system. The first is selection favouring greater degrees of resistance and virulence as quantitative traits, which results in an escalation in both the number of resistance genes in the host and the number of virulence genes in the parasite. The dynamics therefore have an aspect of the evolutionary arms race of quantitative traits (Rosenzweig *et al*. 1987; Saloniemi 1993; Frank 1994; Dieckmann *et al*. 1995; Doebeli 1996, 1997; Abrams & Matsuda 1997; Sasaki & Godfray 1999). The second is frequency-dependent selection between genotypes which favours new combinations of genes (Hamilton 1980; Hamilton *et al*. 1990; Frank 1993; Haraguchi & Sasaki 1996).

2. COEVOLUTIONARY DYNAMICS OF MUTILOCUS GENE-FOR-GENE SYSTEMS

The simplest model of gene-for-gene interactions assumes haploid, single-locus inheritance in host resistance and parasite virulence (e.g. Jayakar 1970) (see Seger & Hamilton (1988) for the matching genotype versions). The host has either a resistant (R) or susceptible (S) allele in the resistance locus, while the parasite has either a virulent (V) or avirulent (A) allele at the corresponding locus. The resistance only takes effect when the resistant host is attacked by an avirulent parasite. Assuming random encounter of the host and parasite,

Received 25 January 2000 *Accepted* 4 August 2000

we can write the respective fitnesses of the host and parasite genotypes as

$$w_{\mathrm{H}}(S) = \exp(-\beta_{\mathrm{H}}), \tag{1}$$

$$w_{\mathrm{H}}(R) = \exp(-\beta_{\mathrm{H}}p - c_{\mathrm{H}}), \tag{2}$$

$$w_{\mathrm{P}}(A) = \exp(-\beta_{\mathrm{P}}(1-q) \tag{3}$$

and

$$w_{\mathrm{P}}(V) = \exp(\beta_{\mathrm{P}} - c_{\mathrm{P}}), \tag{4}$$

where β_{H} and β_{P} are the fitness loss of a host and the fitness gain of a parasite by a successful infection, respectively and c_{H} and c_{P} are the costs of resistance and virulence, respectively. The frequencies of the resistant allele in the host (q) and the virulent allele in the parasite (p) change as

$$q' = w_{\mathrm{H}}(R)q/\bar{w}_{\mathrm{H}} \tag{5}$$

and

$$p' = w_{\mathrm{P}}(V)p/\bar{w}_{\mathrm{P}}, \tag{6}$$

where $\bar{w}_{\mathrm{H}} = w_{\mathrm{H}}(S)(1-q) + w_{\mathrm{H}}(R)q$ and $\bar{w}_{\mathrm{P}} = w_{\mathrm{P}}(A)(1-p) + w_{\mathrm{P}}(V)p$ are the mean fitnesses of the host and parasite, respectively. At internal equilibrium the respective frequencies are

$$\hat{q} = c_{\mathrm{P}}/\beta_{\mathrm{P}} \tag{7}$$

and

$$\hat{p} = 1 - c_{\mathrm{H}}/\beta_{\mathrm{P}}. \tag{8}$$

The internal equilibrium in equations (7) and (8) is always unstable, thereby leading to a cycle that approaches the monomorphic boundary in gene frequency space (i.e. the trajectory converges to the 'heteroclinic cycle' that connects four monomorphic corners in gene frequency space) (see Hofbauer & Sigmund 1988). A metapopulation structure is able to keep the trajectory away from the boundary and yield a stable limit cycle or more chaotic but sustained trajectory in each deme (Sasaki *et al.* 2001). One of the main objectives of the paper is to determine whether the multilocus interaction can also promote polymorphism in each locus.

An extension of the multilocus system is straightforward by noting how each locus contributes to the overall resistance reaction when they are combined. Resistance occurs if there is at least one combination of resistant/avirulent alleles in a corresponding locus of the host and parasite genotypes. Let us consider the n resistance loci of a host with two alleles at each locus, i.e. 1 (resistant) and 0 (susceptible) and the corresponding n virulence loci of a parasite with two alleles at each locus, i.e. 1 (virulent) and 0 (avirulent). The host multilocus genotype for resistance and parasite multilocus genotype for virulence can be denoted by the binary numbers $s = s_1, s_2, \ldots, s_n$ and $t = t_1, t_2, \ldots, t_n$ with n digits, where each digit (s_i and t_i) describes the allelic state of resistance and virulence in the corresponding locus. A host genotype s is (partially) resistant to a parasite genotype t if there is at least one resistant allele that is not masked by a corresponding parasite virulence gene (i.e. when for some i, $s_i = 1$ and $t_i = 0$). In order to simplify the notation we indicate that $s \leqslant t$ if $t_i = 1$ for any i with $s_i = 1$ (i.e. when all resistant alleles in host genotype s are neutralized by corresponding parasite t's virulence genes).

The mean parasite load of the host genotype, i.e. the probability of being infected when the host randomly encounters the parasite genotype, is then $\sum_{t \geqslant s} p(t)$, i.e. the sum of the parasite frequencies that can infect host genotype s. The fitness of host genotype s is assumed to decrease with the mean parasite load and to decrease with the number ($|s| = \sum_i s_i$) of resistance genes due to the cost of resistance, i.e.

$$w_{\mathrm{H}}(s) = \exp\left\{-|s|c_{\mathrm{H}} - \beta_{\mathrm{H}} \sum_{t \geq s} p(t)\right\}, \tag{9}$$

where c_{H} is the cost incurred per resistance gene and β_{H} is the selection intensity for a unit increase in the mean parasite load. Similarly, the fitness of parasite genotype t is assumed to increase with the mean host availability, i.e.

$$w_{\mathrm{P}}(t) = \exp\left\{-|t|c_{\mathrm{P}} + \beta_{\mathrm{P}} \sum_{s \leq t} q(s)\right\}, \tag{10}$$

where c_{P} is the cost incurred per virulence gene in the parasite, β_{P} is the selection intensity for a unit increase in the mean host availability and $q(s)$ is the frequency of host genotype s. The frequencies then change by selection as

$$q(s)' = w_{\mathrm{H}}(s)q(s)/\bar{w}_{\mathrm{H}} \tag{11}$$

and

$$p(t)' = w_{\mathrm{P}}(t)p(t)/\bar{w}_{\mathrm{P}}, \tag{12}$$

where $\bar{w} = \sum_s w_{\mathrm{H}}(s)q(s)$ and $\bar{w}_{\mathrm{P}} = \sum_t w_{\mathrm{P}}(t)p(t)$ are the mean fitnesses of the host and parasite, respectively. Small recurrent mutations between alleles at each locus complete the change in one generation in the host and parasite. Both populations are infinite.

In general, having one resistance may not be sufficient for preventing exploitation by the parasite completely. In order to incorporate partial resistance, we assume that each effective resistance gene reduces the probability of successful infection to $\sigma (0 < \sigma < 1)$ and that resistance at different loci acts multiplicatively. Let $r(s, t)$ be the number of effective resistance genes of host genotype s when attacked by parasite genotype t:

$$\begin{aligned} r(s, t) &= \{\text{number of loci with } s_i = 1 \text{ and } t_i = 0\} \\ &= \sum_{i=1}^{n} s_i(1 - t_i). \end{aligned} \tag{13}$$

The probability of successful infection (Q) when host genotype s encounters parasite genotype t is $Q(s, t) = \sigma^{r(s,t)}$. For example, when $s = 01101$ and $t = 01000$ there are two positions where the host has a resistant allele and the parasite has an avirulent allele and, hence, $r(s, t) = 2$ and the probability of infection for this host and parasite pair is then σ^2. The mean parasite load for host genotype s and the mean host availability of parasite genotype t are then expressed as $\sum_t \sigma^{r(s,t)} p(t)$ and $\sum_s \sigma^{r(s,t)} q(s)$, respectively. The genotypic fitnesses of the host and parasite with partial resistance ($\sigma > 0$) are then, respectively,

$$w_{\mathrm{H}}(s) = \exp\left\{-|s|c_{\mathrm{H}} - \beta_{\mathrm{H}} \sum_{t} \sigma^{r(s,t)} p(t)\right\} \tag{14}$$

and

$$w_{\mathrm{P}}(t) = \exp\left\{-|t|c_{\mathrm{P}} + \beta_{\mathrm{P}} \sum_{s} \sigma^{r(s,t)} q(s)\right\}. \tag{15}$$

In the following analysis, the more general fitness schemes in equations (14) and (15) are used in place of equations (9) and (10). The results of the simpler but more intuitively appealing model in equations (9) and (10) can be obtained by simply setting $\sigma = 0$ for the results obtained in § 3.

3. RESULTS

(a) *Coevolutionary cycle*

Figure 1 shows typical coevolutionary trajectories for the number of host resistance genes and the number of parasite virulence genes for the case of five resistance loci in the host and five corresponding virulence loci in the parasite. The trajectories shown in figure 1*c*,*d* demonstrate that the mean numbers of resistance genes and virulence genes cycle endlessly. According to the stability analysis of static coevolutionary equilibrium (see below), this pattern should be found in a wide range of parameters as long as the costs of resistance and virulence are not very high (figure 2). Extensive simulations for various values of $c_{\mathrm{H}}/\beta_{\mathrm{H}}$ and $c_{\mathrm{P}}/\beta_{\mathrm{P}}$ confirmed the prediction summarized in figure 2.

Why a degrees of resistance and virulence cycle? In order to describe the evolutionary cycles shown in figure 1*d*, for example, let us start at a point where the majority of parasites have one avirulent and four virulent alleles and the majority of hosts have one resistance allele and four susceptibility alleles.

(i) This quasi-equilibrium is broken by the spread of a parasite super-race, the genotype of which has virulence alleles at all loci (escalation against resistance).
(ii) The predominance of the parasite super-race then precludes the spread of any new resistance gene and the host genotype without any resistance subsequently spreads because of the cost of resistance (no resistance is the best against the parasite super-race).
(iii) Once the majority of hosts become universally susceptible, a gradual decline in the number of virulence genes then occurs in the parasite population because no costly virulent genes are needed for exploiting the susceptible host (virulence does not improve infectivity).
(iv) This lays the basis for the next phase during which there is a spread of resistant genotypes in the host (some resistance helps against avirulent parasites). The coevolutionary trajectory then returns to the starting point of the cycle.

(b) *Static equilibrium*

Static coevolutionary equilibria can occur with either no host resistance or no virulence in the parasite if the costs of resistance and virulence are sufficiently large. Indeed, it can be shown that no resistance and avirulence is evolutionary stable if the cost of resistance (c_{H}) relative to the selection intensity (β_{H}) for the parasite load ($c_{\mathrm{H}}/\beta_{\mathrm{H}}$) is larger than $1-\sigma$, i.e.

$$c_{\mathrm{H}}/\beta_{\mathrm{H}} > 1 - \sigma. \tag{16}$$

This simply means that the fitness gain ($\beta_{\mathrm{H}}(1-\sigma)$) of a singly resistant mutant by reducing the parasite load must be smaller than the cost of resistance, otherwise the mutant can invade the susceptible population. The evolutionary stability of an avirulent parasite automatically follows as there is no advantage for virulence genes against universally susceptible hosts. Single resistance and avirulence is evolutionarily stable if the relative cost of resistance is in between two thresholds, i.e.

$$\sigma(1-\sigma) < c_{\mathrm{H}}/\beta_{\mathrm{H}} < 1 - \sigma, \tag{17}$$

and if the frequencies of single-resistance genotypes are all smaller than the threshold, i.e.

$$q(1\underbrace{0\ldots0}_{n-1}),\ q(01\underbrace{0\ldots0}_{n-2}),\ \ldots,\ q(\underbrace{0\ldots0}_{n-1}1) < c_{\mathrm{P}}/\beta_{\mathrm{P}}(1-\sigma). \tag{18}$$

Under the conditions in equation (17) a singly resistant host population can prevent the invasion of the universally susceptible host (right inequality) and that of a doubly resistant host (left inequality). The condition in equation (18) is necessary in order to protect an avirulent parasite population from being invaded by a singly or even more virulent parasite. Indeed, if the frequency of any of the singly resistant host genotypes exceeds the threshold, the parasite genotype which can exploit the overabundant host is allowed to invade. Equation (18) defines a surface of equilibria—any combination of frequencies of singly resistant genotypes stays the same as long as none exceeds the threshold. The threshold in turn depends on the cost of virulence (c_{P}) relative to the selection intensity (β_{P}) for host availability. The stability of this equilibrium therefore requires the genotypic polymorphism of all the single-resistance genotypes, which differ only in the locus harbouring the resistance allele. More specifically, if the relative cost of virulence $c_{\mathrm{P}}/\beta_{\mathrm{P}}$ satisfies

$$c_{\mathrm{P}}/\beta_{\mathrm{P}} > (1-\sigma)/n, \tag{19}$$

a combination of single-resistance genotype frequencies exists that makes the equilibrium in equation (18) stable. At the stability boundary, all the single-resistance genotypes must be segregating with the same frequency, i.e. $(1-\sigma)/n$.

Asymptotic states of the coevolutionary trajectories for the various relative costs of resistance ($c_{\mathrm{H}}/\beta_{\mathrm{H}}$) and virulence ($c_{\mathrm{P}}/\beta_{\mathrm{P}}$) are summarized in figure 2. The coevolutionary outcome depends only on the relative costs of resistance and virulence ($c_{\mathrm{H}}/\beta_{\mathrm{H}}$ and $c_{\mathrm{P}}/\beta_{\mathrm{P}}$, respectively), with the thresholds dividing the different final outcomes depending on the number of loci (n). Evolutionary cycles occur for relatively small costs of resistance and virulence. A static host polymorphism for single resistance that prevents the evolution of a virulent parasite is stable when the relative cost of virulence is above the threshold (equation (19)), which is more easily attained when the number of loci increases. In general, the static coevolutionary

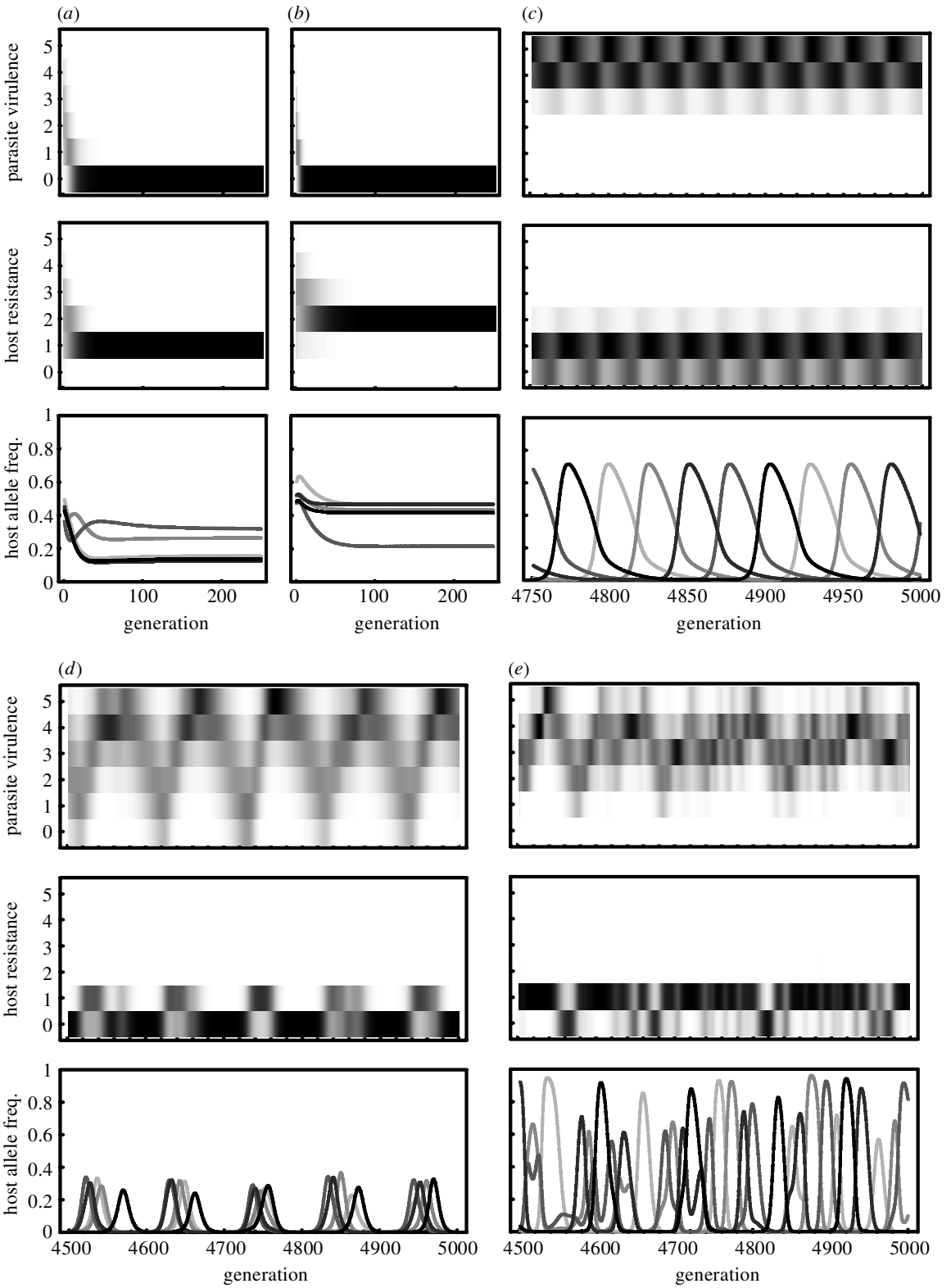

Figure 1. Evolutionary trajectories for the number of resistant genes in hosts and the number of virulence genes in parasites. The upper and middle panels show the time change in the frequency distributions for the number of virulence alleles in a parasite and the number of resistance alleles in a host with darker grades indicating higher frequencies. The lower panel shows the change in frequency of the host resistance alleles at each locus, where different shades of grey are given for different loci. The are five resistance and virulence loci ($n = 5$) and, hence, there are six classes (from zero to five) for the number of virulence and resistance genes. $\sigma = 0.2$ and $\beta_H = \beta_P = 1$. (*a*) The trajectory converging to static equilibrium with single-resistance polymorphism in the host and avirulence in the parasite ($c_H = c_P = 0.3$). (*b*) The trajectory converging to static equilibrium with double-resistance polymorphism in the host and avirulence in the parasite ($c_H = 0.1$ and $c_P = 0.5$). (*c–e*) The trajectories in which the degrees of host resistance and parasite virulence cycle endlessly: (*c*) $c_H = c_P = 0.1$, (*d*) $c_H = 0.3$ and $c_P = 0.04$ and (*e*) $c_H = 0.3$ and $c_P = 0.12$. The population sizes were assumed to be infinite and the recurrent mutation rate in each locus was 2×10^5 per generation in both the host and parasite.

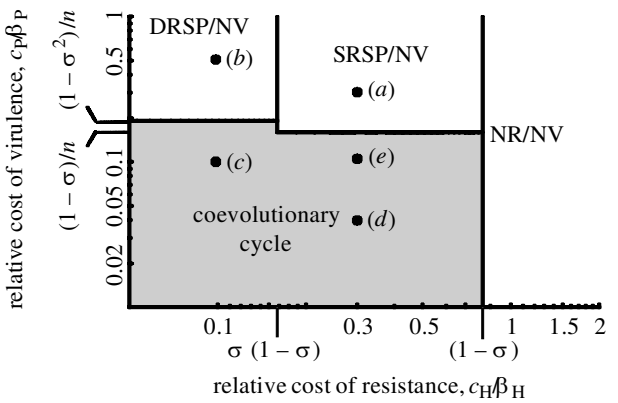

Figure 2. Phase diagram for the coevolutionary dynamics. The coevolutionary outcome of the model in parameter space of the relative cost of resistance c_H/β_H and the relative cost of virulence c_P/β_P. The lines indicate the threshold relative costs that divide qualitatively different final states as predicted from the evolutionary stability analysis of static equilibria. Dots with italic letters are the values used in figure 1*a–e*. NR/NV, no resistance in the host and no virulence (avirulence) in the parasite; SRSP/NV, single-resistance static polymorphism in the host and avirulence in the parasite; DRSP/NV, double-resistance static polymorphism in the host and avirulence in the parasite. The degrees of host resistance and parasite virulence cycle indefinitely in the shaded region. The lines dividing the regions are given by equations (16), (17), (19) and (20). The parameters used to draw the diagram presented here are $\sigma = 0.2$ and $n = 5$.

equilibrium with the polymorphism of host genotypes with n resistance alleles at different loci and avirulent parasite is stable if

$$\sigma^n(1-\sigma) < c_H/\beta_H < \sigma^{n-1}(1-\sigma) \tag{20}$$

and

$$c_P/\beta_P > (1-\sigma^n)/n. \tag{21}$$

The existence of the avirulence equilibrium raises the possibility that we may be able to minimize parasitic damage by carefully mixing a large number of different genotypes with a few resistance alleles rather than by constructing a multiple-resistance genotype. Possible implications concerning this idea will be discussed in § 4.

(c) *Parasite super-race: a bet hedger*

The mean number of parasite virulent genes within the evolutionary cycles of host resistance and parasite virulence is often larger than the mean number of host resistance genes (see figure 1*c–e*). For example, the mean number of resistance genes in the host population is at most one in the trajectories illustrated in figure 1*c–e*, while the mean number of virulence genes in the parasite population is raised up to five. At first glance the parasite virulence seems unnecessarily high because one corresponding virulence gene is sufficient for infecting a singly resistant host. This paradox can be explained through the polymorphism and asynchronous cycles in the frequencies of host resistance genotype (see the bottom panels of figure 1*c–e*) which retain the same number of resistance genes at different loci. The frequencies of host genotypes possessing the same number of resistance genes but at different loci fluctuate with approximately the same period but with different phases. This creates a fluctuating selection coefficient for each virulent gene of a parasite. The super-race of parasite thus enjoy an advantage as a bet hedger (e.g. Seger & Brockmann 1987); an unpredictable and changing host environment favours a costly generalist parasite rather than the coexistence of several strains of specialist parasites.

4. DISCUSSION

The most important contribution of this model to the theory of host–parasite coevolution and the red queen hypothesis for the evolution of sex (Jayaker 1970; Jeanike 1978; Bremermann 1980; Hamilton 1980; Seger & Hamilton 1988; Hamilton *et al*. 1990; Frank 1993) is that both genetic diversity in host and parasite genotypes and the complex cycles of their frequencies are promoted under the asymmetrical gene-for-gene system often found in nature (but see also Parker 1994, 1996; Frank 1996*a*,*b*). This is to say that, although it was assumed in this paper that gene-for-gene interaction is extremely asymmetrical, gene-for-gene interaction can still promote genetic polymorphism and cycles in genotype frequencies. The process considered here is doubly cyclic—it is a combination of evolutionary cycles in the degree of host resistance and parasite virulence and asynchronous cycles in genotype frequencies under potential combinatorial diversity in multilocus inheritance. Whether the sustained asynchronous cycles and the protected multilocus polymorphism yield a sufficient short-term advantage for sex and recombination is an important question which is still to be explored.

The cost of resistance and virulence is necessary in ensuring that gene-for-gene interaction allows protected polymorphism of both resistance and virulence genotypes. Otherwise the best genotypes (those with all resistant genes and those with all virulent genes) will establish themselves in both the host and parasite populations. The fact that the virulence of a pathogen declines after a reduction in resistance in a host (which is historically called 'stabilizing selection') is attributed to selection against unnecessary virulent genes (i.e. to the cost of virulence). However, it is difficult to measure the cost of virulence directly (Burdon 1987). The cost of resistance in the gene-for-gene system is even more difficult to detect and is considered to be small except for a few cases (Bergelson & Purrington 1996). However, it should be noted that the cost of resistance may be condition dependent, as is the case for the significant cost of encapsulation (resistance) against parasitoids in *Drosophila* under starvation conditions (Kraaijeveld & Godfray 1997).

Gene-for-gene and matching genotype interactions often produce cycles in host and parasite genotypic frequencies, but the population tends to converge to a heteroclinic cycle whereby the population is often found in a monomorphic corner of frequency space. A breakthrough occurs when a new favourable genotype emerges, which then leads the population into another corner (Seger & Hamilton 1988). Indeed, population genetic models for gene-for-gene (matching genotype) interactions do not indicate promotion of genetic diversity (Takahata & Nei 1990; Frank 1993). This leads incidentally

to rejection of the hypothesis of parasite adaptation as the factor responsible for major histocompatibility complex polymorphism (see Takahata & Nei 1990). However, a relatively small rate of migration or mutation has been found to restore diversity and enhance the persistence of multiple alleles in the matching genotype model (Seger & Hamilton 1988). Metapopulation structure and asynchrony between demes are other factors that promote genetic diversity in a gene-for-gene system (Keeling & Rand 1995; Burdon & Thrall 1999; Lively 1999; Sasaki *et al*. 2001). We have shown that multilocus gene-for-gene interaction promotes genetic polymorphism in host resistance loci. How well the dynamics of host–parasite coevolution account for the observed degrees of genetic diversity in a finite population is still open to question.

From the perspective of virulence management, one consequence of the model is of potential practical importance. The model reveals a wide parameter region in which polymorphism of host resistance can prevent the spread of any virulent strain of parasite and this maintains a disease-free host population. This requires that the cost of virulence exceed a certain threshold, but the threshold can be lowered by increasing the number of resistant genotypes maintained in the population. Hence, for any degree of cost of virulence, it is theoretically possible to protect the population from disease by retaining sufficient numbers of resistant varieties. This strategy requires that none of the genotype frequencies exceed the threshold; failure to achieve this leaves the way open for spread of the corresponding virulent parasite. In addition, if the same variety tends to be spatially clustered, local spread of a virulent strain might occur. Despite these potential difficulties in control, the principle has far more prospects than the use of multiple resistance which has invariably failed.

The emergence of multiple drug resistance in infectious bacteria is still a serious problem in public health. The emergence of drug resistance in human infectious bacteria can be compared with the emergence of virulent pathogens in plant–fungi gene-for-gene systems. Multiple drug resistance in bacteria therefore corresponds to the superrace of pathogen in gene-for-gene coevolution. It is preferable to use a variety of separate antibiotics in the prevention of epidemics rather than using multiple drugs in the same patient. A similar principle would also apply to the emergence of resistant biotypes in pest control.

The author thanks Bill Hamilton, Austin Burt, David Krakauer and Tetsukazu Yahara for discussions.

REFERENCES

Abrams, P. A. & Matsuda, H. 1997 Fitness minimization and dynamic instability as a consequence of predator–prey coevolution. *Evol. Ecol.* **11**, 1–20.

Bergelson, J. & Purrington, C. B. 1996 Surveying patterns in the cost of resistance in plants. *Am. Nat.* **148**, 536–558.

Bremermann, H. J. 1980 Sex and polymorphism and strategies in host–pathogen interactions. *J. Theor. Biol.* **87**, 331–334.

Burdon, J. J. 1987 *Diseases and plant population biology*. Cambridge University Press.

Burdon, J. J. & Thrall, P. H. 1999 Spatial and temporal patterns in coevolving plant and pathogen associations. *Am. Nat.* **153**, S16–S33.

Dieckmann, U., Marrow, P. & Law, R. 1995 Evolutionary cycling in predator–prey interactions: population dynamics and the red queen. *J. Theor. Biol.* **176**, 91–102.

Doebeli, M. 1996 Quantitative genetics and population dynamics. *Evolution* **50**, 532–546.

Doebeli, M. 1997 Genetic variation and the persistence of predator–prey interactions in the Nicholson–Bailey model. *J. Theor. Biol.* **188**, 109–120.

Espiau, C., Riviere, D., Burdon, J. J., Gartner, S., Daclinat, B., Hasan, S. & Chaboudez, P. 1998 Host–pathogen diversity in a wild system: *Chondrilla juncea–Puccinia chondrillina*. *Oecologia* **113**, 133–139.

Flor, H. H. 1956 The complementary genetics systems in flax and flax rust. *Adv. Genet.* **8**, 29–54.

Frank, S. A. 1993 Coevolutionary genetics of plants and pathogens. *Evol. Ecol.* **7**, 45–75.

Frank, S. A. 1994 Coevolutionary genetics of hosts and parasites with quantitative inheritance. *Evol. Ecol.* **8**, 74–94.

Frank, S. A. 1996*a* Statistical properties of polymorphism in host–parasite genetics. *Evol. Ecol.* **10**, 307–317.

Frank, S. A. 1996*b* Problems inferring the specificity of plant–pathogen genetics—reply. *Evol. Ecol.* **10**, 323–325.

Hamilton, W. D. 1980 Sex vs non-sex vs parasite. *Oikos* **35**, 282–290.

Hamilton, W. D., Axelrod, R. & Tanese, R. 1990 Sexual reproduction as an adaptation to resist parasites (a review). *Proc. Natl Acad. Sci. USA* **87**, 3566–3573.

Haraguchi, Y. & Sasaki, A. 1996 Host–parasite arms race in mutation modifications: indefinite escalation despite a heavy load? *J. Theor. Biol.* **183**, 121–137.

Hofbauer, J. & Sigmund, K. 1988 *The theory of evolution and dynamical systems*. Cambridge University Press.

Jayaker, S. D. 1970 A mathematical model for interaction of gene frequencies in a parasite and its host. *Theor. Popul. Biol.* **1**, 140–164.

Jeanike, J. 1978 An hypothesis to account for the maintenance of the sex within populations. *Evol. Theory* **3**, 191–194.

Keeling, M. J. & Rand, D. A. 1995 A spatial mechanism for the evolution and maintenance of sexual reproduction. *Oikos* **74**, 414–424.

Kraaijeveld, A. R. & Godfray, H. C. J. 1997 Trade-off between parasitoid resistance and larval competitive ability in *Drosophila melanogaster*. *Nature* **389**, 278–290.

Lively, C. M. 1999 Migration, virulence, and the geographical mosaic of adaptation by parasites. *Am. Nat.* **153**, S34–S47.

Parker, M. A. 1994 Pathogens and sex in plants. *Evol. Ecol.* **8**, 560–584.

Parker, M. A. 1996 The nature of plant–parasite specificity—comment. *Evol. Ecol.* **10**, 319–322.

Rosenzweig, M. L., Brown, J. S. & Vincent, T. L. 1987 Red queens and ESS: the coevolution of evolutionary rates. *Evol. Ecol.* **1**, 59–94.

Saloniemi, I. 1993 A coevolutionary predator–prey model with quantitative characters. *Am. Nat.* **141**, 880–896.

Sasaki, A. & Godfray, H. C. J. 1999 A model for the coevolution of resistance and virulence in coupled host–parasitoid interactions. *Proc. R. Soc. Lond.* B **266**, 455–463.

Sasaki, A., Hamilton, W. D. & Ubeda, F. 2001 Clone mixtures and a pacemaker: new facets of Red-Queen theory and ecology. (In preparation.)

Seger, J. & Brockmann, H. J. 1987 What is bet-hedging? *Oxf. Surv. Evol. Biol.* **4**, 182–211.

Seger, J. & Hamilton, W. D. 1988 Parasite and sex. In *The evolution of sex* (ed. R. E. Michod & B. R. Levin), pp. 176–193. Sunderland, MA: Sinauer Associates, Inc.

Takahata, N. & Nei, M. 1990 Frequency-dependent selection and polymorphism of major histocompatibility complex loci. *Genetics* **124**, 967–978.