International Institute for
Applied Systems Analysis
Schlossplatz 1
A-2361 Laxenburg, Austria

Tel: +43 2236 807 342
Fax: +43 2236 71313
E-mail: publications@iiasa.ac.at
Web: www.iiasa.ac.at

Interim Report **IR-05-068**

Epidemiology and Disease-Control Under Gene-for-Gene Plant-Pathogen Interaction

Akiko Ohtsuki (iwanaga@bio-math10.biology.kyushu-u.ac.jp)
Akira Sasaki (asasascb@mbox.nc.kyushu-u.ac.jp)

Approved by

Ulf Dieckmann
Program Leader, ADN

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Contents

Epidemiology and disease-control under gene-for-gene plant-pathogen interaction

Akiko Ohtsuki*[1] & Akira Sasaki[1]

[1]Department of Biology, Faculty of Science
Kyushu University Graduate Schools, Fukuoka 812-8581, JAPAN

* The author of correspondence: iwanaga@bio-math10.biology.kyushu-u.ac.jp

Abstract

An introduction of disease-resistant variety of a crop plant often leads to the development of a virulent race in pathogen species that restores the pathogenicity to the resistant crop. This often makes disease control of crop plants extremely difficult. In this paper, we theoretically explore the optimal 'multiline' control, which makes use of several different resistant varieties, that minimizes the expected degree of crop damages caused by epidemic outbreaks of the pathogen. We examine both single-locus and two-locus gene-for-gene (GFG) systems for the compatibility relationship between host genotypes and pathogen genotypes, in which host haplotype has either susceptible or resistant allele in each resistance locus, and the pathogen haplotype has either avirulent or virulent allele in the corresponding virulence locus. We then study the optimal planting strategy of host resistant genotypes based on standard epidemiological dynamics with pathogen spore stages. The most striking result of our single locus GFG model is that there exists an intermediate optimum mixing ratio for the susceptible and resistant crops that maximizes the final yield, in spite of the fact that the susceptible crop has no use to fight against either avirulent or virulent race of the pathogen. The intermediate mixture is optimum except when the initial pathogen spore population in the season consists exclusively of the virulent race. The optimal proportion of resistant crops is approximately $1/R_0$, where R_0 is the basic reproductive ratio of pathogen — the rest (the vast majority if R_0 is large) of crops should be the susceptible genotype. By mixing susceptible and resistant crops, we can force the pathogen races to compete with each other for their available hosts. This competition between avirulent and virulent races prevents the fatal outbreak of the virulent race (the super-race) that can infect all the host genotypes. In the two-locus GFG control, there again exists the optimal mixing ratio for the fraction of universally susceptible genotype and the *total* fraction of various resistant genotypes, with the ratio close to $1/R_0$.

Keywords : coevolution, gene-for-gene, resistance, virulence

1 Introduction

Plants have physical and chemical defense mechanisms against their pathogens. In addition to general, nonspecific defense mechanisms called 'field resistances', plant hosts have race-specific defense system induced by the recognition of a certain strain of pathogen that infected the plant cells. Viral, bacterial, and fungal infections of a plant induce hypersensitive response (HR) by the infected and surrounding cells, thereby preventing the infected pathogens from spreading in the tissue (Goodman & Novacky, 1994). The hypersensitive response is triggered by the recognition of pathogen-derived elicitor molecules (avirulent gene product). The plant resistance gene refers to the gene encoding an receptor or a signal transduction enzyme responsible for the recognition of the elicitor molecule of a specific species or race of pathogens. A plant that lacks such resistance genes is called susceptible. This plant resistance is often defeated by the emergence of a pathogen race that lacks or modifies the elicitor molecule targeted by the resistance gene product. Such pathogens, called the virulent race, can infect the resistant host plant, as well as the susceptible one. This race-specific defense mechanism is called the gene-for-gene system (Flor, 1956; Thompson & Burdon, 1992)

There is a great amount of literature on the disease management under gene-for-gene interaction of plants and pathogens. As suggested by mathematical study on rust diseases (Leonard, 1969), cultivar mixtures of crops has been recognized as one of the most promising strategies to lessen the damage caused by the epidemics in crop plants (Browning & Frey, 1969; Wolfe, 1985; Mundt, 2002). Many experimental studies demonstrated the efficiency of multiline (cultivar mixture) controls as well. For example, the severity of blast disease and the percent diseased plants in the mixtures of rice cultivar were less than that observed in the single line plantings (Nakajima *et al.*, 1996). According to the experiments on the bacterial infection of bell peppers, the yield in susceptible and resistant mixture tended to be higher than that of pure stands of either susceptible or resistance genotype (Kousik *et al.*, 1996). The study on the fungal infections in experimental rice field (Zhu *et al.*, 2000) revealed that the mixture of different resistant genotypes contributed to reduce the total number of infections. It is also postulated that an increased resistance diversity in host plant may slow down the adaptation of the pathogen to resistance genes (Garrett & Mundt, 1999).

In spite of these potential benefits, the host diversification in resistance in the cultivar

mixture often promotes the diversity of pathogen virulence genotypes (DiLeone & Mundt, 1994; Muller *et al.*, 1996), offsetting the advantage of resistance diversity. The introductions of multiple resistance in various crop plants did not improve the situation either, because they usually ended up with the development of pathogen super-races that can infect all the resistant varieties of crop plant (Burdon 1987, Thompson & Burdon 1992 for review; see Sasaki 2000, 2002 for the theoretical aspects of coevolutionary dynamics with a multilocus gene-for-gene system). Thus it is necessary to develop a model that can assess the effect of mixing various resistance variety in the face of the risk of development of virulent races in the pathogen, which is the primary objective of the present paper.

The gene-for-gene interaction between host and pathogen genotypes has attracted great attentions in theoretical biology (e.g., in the subjects of the maintenance of polymorphism (Gillespie, 1975), the coevolutionary cycles (Hamilton, 1980; Frank, 1993; Sasaki, 2000), the evolution of sex (Hamilton, 1980; May & Anderson, 1983; Hamilton *et al.*, 1990; Parker, 1994), and the spatio-temporal pattern of polymorphism (Damgaard, 1999; Sasaki *et al.*, 2002)). However, quite little is understood theoretically on the optimal disease control in crop plants under the gene-for-gene interaction between host and pathogen genotypes. The optimal drug control of human diseases has been studies intensively, which, for example, focus on the time to the development of drug-resistant strain and multiple drug-resistant strain of pathogen (Anderson & May, 1991; Nowak & May, 2000). However, this problem of the optimal therapy *after* the infection of a patient is quite different from the optimal planting strategy of resistant crops (optimal prophylactic control) we examine here. The decision for the proportion of resistant varieties to be planted must be made prior to the season for the pathogen outbreaks. This is the reason why we obtain the results quite different from the conventional wisdom of the drug therapy. For example, our model reveals that there is an optimal mixture of susceptible and resistant crops that maximizes the final yields. In drug control, by contrast, there is no such intermediate optimum for the intensity of drug, and there is no optimal mixture for multiple drugs either (see Nowak and May (2000) for review).

In this paper, we address the optimal planting strategy to maximize the final crop yield under the threat of pathogen infection and the threat of the development of a virulent race. Our analysis is based on the epidemiological dynamics with multiple host resistance genotypes and pathogen virulence genotypes. We ask, for example, what is the optimal mixing ratio of resistant genotypes to minimize the total damage by pathogen infection.

2 Disease-control under gene-for-gene interaction

We first introduce the plant-pathogen epidemiological dynamics with the spore stage of pathogen, and study the total final yield expected under a single crop variety and a single compatible pathogen race. In section 2.2, the optimal disease control strategy (the optimal mixing ratio of susceptible and resistant variety, and the optimal total crop density) is studied under the single locus di-allelic gene-for-gene system (i.e. with two host genotypes and two pathogen genotypes).

2.1 Crop plant and fungal infection: Final yields

We consider a crop plant and its fungal pathogen that can be transmitted by free-living spores (Anderson & May, 1981). Let X, Y, and W be the numbers of uninfected plants, infected plants, and the pathogen spores. We denote the transmission rate of fungal pathogen by β, the mortality of infected plants by α, the number of pathogen spore production from an infected plant in a unit time interval by λ, and the decay rate of spores by μ. To estimate the impact of pathogen outbreak in crop plants, we examine the final yields $X(T)$, the number of plants that have not experienced pathogen infection until the time T of harvesting. We obtain the final yields as a function of the initial crop density $X(0) = H$, and the epidemiological parameters. We assume that initially no plant is infected ($Y(0) = 0$), and the spore density $W(0) = \delta$ in the beginning of breeding season is sufficiently small. The epidemiological dynamics of the crop plant-pathogen system are then

$$\frac{dX}{dt} = -\beta XW, \tag{1a}$$

$$\frac{dY}{dt} = \beta XW - \alpha Y, \tag{1b}$$

$$\frac{dW}{dt} = \lambda Y - \mu W, \tag{1c}$$

Let $\phi = X(T)/H$ be the fraction of plants that have never experienced infection until the harvesting time T. If the basic reproductive ratio of pathogen is not too small, the final yield $X(T)$ is well approximated by that in the limit of $T \to \infty$. In Appendix A, we derive the implicit equation with which $\phi = X(\infty)/H$ is determined:

$$\phi = \exp\left[-\frac{\beta\lambda H}{\alpha\mu}(1-\phi)\right], \tag{2}$$

(Gillespie, 1975; May & Anderson, 1983). The pathogen outbreak occurs if the initial crop density H exceeds the threshold $H_c = \alpha\mu/\beta\lambda$. If H exceeds H_c, a part of plants experience infection during the breeding season. Because the efficiency of infection increases as the initial crop density increases, the fraction of plants that remain uninfected during the breeding season decreases as the initial crop density is increased past the threshold. Thus, the final yields $X(\infty) = H\phi$ is a one-humped function of the initial crop density H, and is maximized at an intermediate initial crop density $H = H_c$ (Fig. 1).

2.2 Resistant plants and virulent pathogens: Optimal multiline control under gene-for-gene interaction

Now we consider the introduction of the resistant crop variety to prevent the pathogen from prevailing in the crop fields which the crops are planted over the epidemic threshold density. It is clear that, if we ignore the development of virulent pathogen races, the maximum use of resistant variety is the best strategy to increase the final yields. However, the development of virulent pathogen races within (or shortly after) the year of the introduction of new resistant crop variety is the rule rather than the exception. It will be shown below that if we take into account the development of virulent races, the mixture of susceptible and resistant plants is better than replacing all crops by resistant variety. We here examine the optimal fraction of resistant variety in the total crop under the possibility of the development of virulent races in pathogens.

We assume the gene-for-gene interaction (Flor, 1956) for the compatibility between two host genotypes (susceptible and resistant) and two pathogen genotypes (avirulent and virulent). Let X_0 and X_1 be the densities of uninfected susceptible and resistant hosts, Y_0 and Y_1 be the densities of hosts infected by avirulent and virulent pathogen races, and W_0 and W_1 be the densities of avirulent and virulent pathogen spores. The extended version of

model (1) incorporating resistant host plant and virulent pathogen is then

$$\begin{aligned}
\frac{dX_0}{dt} &= -\beta X_0(W_0 + W_1), && \text{(3a)}\\
\frac{dX_1}{dt} &= -\beta X_1 W_1, && \text{(3b)}\\
\frac{dY_0}{dt} &= \beta X_0 W_0 - \alpha Y_0, && \text{(3c)}\\
\frac{dY_1}{dt} &= \beta(X_0 + X_1)W_1 - \alpha Y_1, && \text{(3d)}\\
\frac{dW_0}{dt} &= \lambda Y_0 - \mu W_0, && \text{(3e)}\\
\frac{dW_1}{dt} &= \lambda Y_1 - \mu W_1, && \text{(3f)}
\end{aligned}$$

where we assume, for simplicity, that the transmission rate β, the mortality of infected host α, the spore production rate λ, and the spore dilution rate μ are independent of the host or the pathogen genotypes (Fig. 2).

Now we examine the total final yields $X_0(T) + X_1(T)$ as a function of the initial crop densities of susceptible and resistant hosts ($X_0(0) = H_0$ and $X_1(0) = H_1$), and of the initial densities of avirulent and virulent pathogen spores ($W_0(0) = \delta_0$ and $W_1(0) = \delta_1$). As before, we assume that no host is infected in the beginning of the breeding season ($t = 0$), that the initial densities of pathogens spores (δ_i's) are sufficiently small, and that the pathogen outbreak occurs before the harvesting time T so that we can approximate the final yields $X_0(T) + X_1(T)$ by $X_0(\infty) + X_1(\infty)$. The initial frequency of pathogen spore genotypes ($\delta_i/(\delta_0 + \delta_1)$, $i = 0, 1$) should mainly depend on the outbreak in the previous year. For example, if the infection by the virulent race prevailed in the previous year, we expect that $\delta_1/\delta_0 \gg 1$. The main purpose of the analysis of the model (3) is to find out the optimal planting strategy of susceptible and resistant crop varieties as a function of δ_0 and δ_1.

2.2.1 Sequential outbreaks: Avirulent-race outbreak followed by virulent-race outbreak

The analysis of the optimal planting strategy is greatly simplified if the initial frequency of pathogen genotypes is strongly biased towards the excess of avirulent race ($\delta_1/\delta_0^\sigma \ll 1$), where $\sigma = \zeta_1/\zeta_0 > 1$ is the ratio of initial rate of increase of virulent race to that of avirulent race. It is interesting to note that the initial excess of avirulent frequency ($\delta_1/\delta_0 \ll 1$) is

not sufficient for this order of outbreaks to occur. This is because the virulent race having a larger rate of initial exponential growth than the avirulent race (due to its wider host range) eventually catches up the forgoing avirulent race. More precise condition for that the outbreaks occurs in the avirulent-virulent order is derived in Appendix B as

$$\delta_1 < {\delta_0}^{\sigma}, \tag{4}$$

where $\sigma = \zeta_1/\zeta_0$ is the ratio of the initial rate of increase of virulent race to that of avirulent race. See Appendix B for detail. Suppose for example that the resistant variety is newly introduced in the year, and therefore the pathogen spores consist exclusively of avirulent genotype in the beginning of the season. We then expect that the spread of the avirulent race precedes that of the virulent race. By contrast, the outbreak of virulent pathogen may come first if the virulent race prevailed in the previous year.

The final crop yields as a function of the planting strategy (H_0, H_1) of susceptible and resistant varieties is then easily analyzed. Consider first the case where the initial spore density of virulent race is sufficiently smaller than that of avirulent race ($\delta_1/\delta_0^{\sigma} \ll 1$). In this case the outbreaks of avirulent pathogen precedes that of the virulent pathogen. After the outbreak of avirulent pathogen race, the density $\tilde{H}_0$ of susceptible hosts that remain uninfected is given by $\tilde{H}_0 = H_0\phi_0$ where

$$\phi_0 = \exp\left[-\frac{\beta\lambda}{\alpha\mu}H_0(1-\phi_0)\right]. \tag{5}$$

This is the same as (2) with $H_0 = H$ and $\phi_0 = \phi$, and hence the density of susceptible hosts that remain uninfected after the outbreak of avirulent pathogen race is a unimodal function of the initial density H_0 of susceptible plants, with the maximum attained near the threshold $H_c = \alpha\mu/\beta\lambda$ (Fig. 1). The next epidemic occurs by the spread of virulent pathogen race, which can equally infect the susceptible and the resistant plants. As the 'initial' host density for the virulent pathogen is $\tilde{H}_0 + H_1$, the fraction ϕ_1 of hosts that remain uninfected after the second outbreak by the virulent race satisfies

$$\phi_1 = \exp\left[-\frac{\beta\lambda}{\alpha\mu}(\tilde{H}_0 + H_1)(1-\phi_1)\right]. \tag{6}$$

The total yields of the season when the pathogen outbreak occurs in the order of avirulent $\rightarrow$ virulent is then

$$Y_{AV} = (\tilde{H}_0 + H_1)\phi_1 = (H_0\phi_0 + H_1)\phi_1. \tag{7}$$

Now we examine how the total final yields changes by changing the total crop density, $H = H_0 + H_1$, and the fraction of resistant crop in the beginning of the season, $p = H_1/H$.

Figure 3 shows the final total yields Y_{AV} as a function of p. The whole range of the fraction of resistant crops p is divided by its two thresholds. The first threshold for p is derived in Appendix C as

$$p_1^* = \frac{1 - R_0 e^{1-R_0}}{R_0 \left(1 - e^{1-R_0}\right)} \sim \begin{cases} 1/R_0, & (R_0 \to \infty), \\ (R_0 - 1), & (R_0 \to +1). \end{cases} \tag{8}$$

where $R_0 = \beta\lambda H/\alpha\mu$ is the basic reproductive ratio of pathogen. If p is less than p_1^*, the second outbreak by the virulent race will not occur because the density of uninfected hosts remained after the avirulent race outbreak becomes smaller than the epidemiological threshold for the virulent race. The second threshold is defined as

$$p_2^* = 1 - \frac{1}{R_0}, \tag{9}$$

(see Appendix C). If $p > p_2^*$, there will be no outbreak by avirulent race because the density of susceptible hosts is below the epidemiological threshold. If the fraction of resistant crop is in between the two thresholds, $p_1^* < p < p_2^*$, there will be two outbreaks, first by avirulent race and second by virulent race, in a season. The final yields as a function of p is demonstrated in Fig. 3.

As is illustrated in Fig. 3, the final yield first increases by increasing the fraction of resistant crop, attains the maximum at $p = p_1^*$, and start decreasing when p is increased past p_1^*. When p exceeds the second threshold p_2*, the final yields becomes independent of the fraction of resistant crops, because all infections are due to virulent race.

When we plot the final yields in the parameter space of H and p, there are two ridges of high final yields — one is for the total crop density at $H = H_c = \alpha\mu/\beta\lambda$, and the another for the optimal fraction

$$p = p_1^* = \frac{1 - (H/H_c)e^{1-H/H_c}}{(H/Hc)(1 - e^{1-H/H_c})} \tag{10}$$

of resistant crop for a given total host density H ($> H_c$) (Fig. 4).

We next examine the case $\delta_1/\delta_0^\sigma \gg 1$ where the outbreak due to the virulent race occurs earlier in the season than that due to avirulent race. Note that only difference between virulent and avirulent races assumed in the present model is that virulent race has a broader host range (the resistance makes no sense for the virulent race but is perfectly effective against the avirulent race). Therefore, if virulent races can no longer spread after the outbreak due to the shortage of uninfected hosts, there is no chance for avirulent race to

spread in the host population. Hence there will be no outbreak by avirulent race if virulent race epidemic comes first. The final yield Y_{VA} for this case is therefore independent of the fraction of resistant crops, and is given by

$$Y_{VA} = H\phi, \tag{11}$$

where ϕ is the root of (2). Thus, if the virulent pathogen race prevailed in the previous year, and is its early appearance expected, planting the resistant crop has no effect. One should just adjust the total crop density around H_c to maximize the final yields.

2.2.2 Simultaneous outbreaks of avirulent and virulent races

If the initial spore densities of avirulent and virulent pathogens are comparable, the above analysis for the sequential outbreaks must fail. The final yields numerically obtained from (3) are plotted against the fraction p of the resistant crops for various values of relative frequencies of avirulent to virulent pathogens (Fig. 3b). Clearly from the figure, there exists the optimum fraction of resistant crops that maximizes the final yields, as suggested from the analysis of sequential outbreaks in the last two sections. The optimal fraction is close to p_1^* for sufficiently small δ_1/δ_0^σ (and the final yield curve approaches to Y_{AV} as δ_1/δ_0^σ becomes small). The final yield becomes less sensitive to p as δ_1/δ_0^σ increases, but still an intermediate p is the optimum. The final yield curve approaches to Y_{VA} as δ_1/δ_0^σ is increased further.

The reason why the mixture of susceptible and resistant crops are better than the exclusive use of resistant crops lies in the strong nonlinearity in the epidemiological cultivation curve (Fig. 1). The total impact by infectious disease is smaller if the host with a given density is subdivided into varieties and exposed to different compatibility genotypes of pathogen, than if a single host genotype of the same density is exposed to a single compatible pathogen genotype.

One may think that, under the presence of a super-race of pathogen, the host resistance diversity is of no use. This is correct in our model in the sense that, if the initial spore population consists exclusively of the virulent race (which is the super-race in the single locus gene-for-gene system), then the final yield is independent of the fraction of resistant crops. This is, however, not generally correct, if the initial spore population consists of the mixture of avirulent and virulent genotypes (and is the most notably incorrect if it consists

exclusively of avirulent race). Using both susceptible and resistant crops can then greatly improve the final yields from using resistant or susceptible crops only.

3 Disease control under multilocus GFG system

Here we extend the model to the haploid multilocus gene-for-gene system. We consider n resistant loci of host, each having either resistant (1) or susceptible (0) allele. Hence the host genotype is expressed as a binary number ($i = i_1 i_2 \cdots i_n$, with $i_k \in \{0, 1\}$). We also consider the corresponding n virulence loci of pathogen, each having either virulent (1) or avirulent (0) allele. The pathogen genotype is also expressed as a binary number ($j = j_1 j_2 \cdots j_n$, with $j_k \in \{0, 1\}$).

A pathogen genotype is called *compatible* with a host genotype if the infection occurs normally between the pair of genotypes. Under the multilocus gene-for-gene relationship assumed here, the pathogen is compatible if it has no avirulent allele that may invoke the hypersensitive response in the infected host. This is equivalent to say that host i and pathogen j are compatible if, for every avirulent allele $j_k = 0$ the pathogen might have, the host has susceptible allele $i_k = 0$ in the corresponding locus. It is convenient to define the compatibility index $c(i, j)$ of multi-locus gene-for-gene system ($c = 1$ if compatible, $c = 0$ if incompatible) between the host genotype $i = i_1 i_2 \cdots i_n$ and the pathogen genotype $j = j_1 j_2 \cdots j_n$:

$$c(i, j) = \prod_{k=1}^{n} [1 - i_k(1 - j_k)] = \prod_{k=1}^{n} [(1 - i_k) + i_k j_k]. \tag{12}$$

The middle part of (12) can be read as "there is no such locus in which host has resistant allele and pathogen has avirulent allele (there is no such k with which $i_k = 1$ and $j_k = 0$; hence, $1 - i_k(1 - j_k) = 1$ for all k)". The right hand side gives an alternative expression, which specifies the condition as "in every locus, either host has susceptible allele ($i_k = 0$) or host has resistant allele but pathogen has virulent allele ($i_k = 1$ and $j_k = 1$), for host i and pathogen j to be compatible". The compatibility relationship in two locus gene-for-gene system is illustrated in Table 1.

The epidemiological dynamics of the multilocus gene-for-gene system can be described as the differential equations for X_i (the density of uninfected host genotype i), Y_i (the density

of hosts of any genotype infected by pathogen genotype i), and W_i (the spore density of pathogen genotype i) for every n-locus resistance genotype of host and virulence genotype of pathogen ($i \in \{0,1\}^n$):

$$\frac{dX_i}{dt} = -X_i \sum_{j\in\{0,1\}^n} \beta c(i,j) W_j, \tag{13a}$$

$$\frac{dY_i}{dt} = W_i \sum_{j\in\{0,1\}^n} \beta c(j,i) X_j - \alpha Y_i, \tag{13b}$$

$$\frac{dW_i}{dt} = \lambda Y_i - \mu W_i, \tag{13c}$$

where $c(i,j)$ is the compatibility index defined above. β, α, λ, μ are the transmission rate, the mortality of infected hosts, the spore production rate from an infected host, and the decay rate of a spore, as defined in the single locus model. The objective function of the model which is to be maximized is the final yield

$$Y_f = \sum_{i\in\{0,1\}^n} X_i(T). \tag{14}$$

We seek the initial planting densities $X_i(0) = H_i$, for given initial densities of pathogen spores $W_i(0) = \delta_i$, that maximizes Y_f. All hosts are assumed to be uninfected in the beginning of the season: $Y_i(0) = 0$. The harvesting time T is assumed to be sufficiently longer than the growth period of any of the pathogen genotypes (though some would never actually increase if the compatible host density is low).

In this paper we concentrate on the two locus case ($n = 2$). There are therefore 4 genotypes of host: universally susceptible (00), singly resistant (01 and 10), and doubly resistant (11). There are correspondingly 4 genotypes of pathogen: universally avirulent (00), singly virulent (01 and 10), and doubly virulent (11). The last pathogen genotype is the super-race, which can infect all the host genotypes.

3.1 Optimal multiline control

3.1.1 sequential outbreak: universally avirulent → singly virulent → super-race

As in the single locus gene-for-gene model, we study the optimal fractions of host resistant genotypes that maximizes the total final yield Y_f. We here focus on the case where the

initial pathogen spore population primarily consist of the universally avirulent race (00), which might be the most commonly faced situation in practice just after the introduction of resistant variety. The expected order of outbreaks in the breeding season would be: first outbreak of the universally avirulent race, followed by the second outbreak of the single step mutants (or the singly virulent races 01 and 10), and then by the final outbreak of the two step mutant (or the super-race 11). This is indeed the case if the initial spore densities of singly virulent race is sufficiently smaller than that of the universally avirulent race, and if the initial spore density of the super-race is further smaller. An analytical condition for this order of emergence to occur is obtained in Appendix B, by assuming that the initial densities of the singly virulent races are the same and that the initial planting densities of singly resistant hosts are the same. The condition in terms of the initial spore densities δ_{00} of universally avirulent race 00, δ_{01} and δ_{10} of the singly virulent races 01 and 10 ($\delta_{01} = \delta_{10}$ by assumption), and δ_{11} of the super-race 11 is

$$\delta_{01} < {\delta_{00}}^{\zeta_{01}/\zeta_{00}}, \qquad \text{and} \tag{15a}$$

$$\delta_{11} < {\delta_{00}}^{(\zeta_{11}\zeta'_{01}-\zeta'_{11}\zeta_{01})/\zeta_{00}\zeta'_{01}} {\delta_{01}}^{\zeta'_{11}/\zeta'_{01}} \tag{15b}$$

where ζ_{00}, ζ_{01}, ζ_{11} are the initial growth rates of the universally avirulent race, the singly virulent race, and the super-race, respectively, before the first outbreak, and ζ'_{00}, ζ'_{01}, and ζ'_{11} are the corresponding quantities after the first epidemic by the universally avirulent race but before the second epidemic by the singly virulent races (see Appendix B for detail).

Figure 5a-b shows how the final yield (14) depends on the total fraction of resistant genotypes ($p = (H_{01} + H_{10} + H_{11})/H$, where $H = H_{00} + H_{01} + H_{10} + H_{11}$ is the total initial crop density) and the relative proportion of doubly resistant among all resistant genotypes ($q = H_{11}/(H_{01}+H_{10}+H_{11})$). Here we assume the same initial density for two singly resistant genotypes: $H_{01} = H_{10}$. Then, because of the symmetry of the model and initial conditions (recall that we have assumed $\delta_{01} = \delta_{10}$ as well), $X_{01}(t) = X_{10}(t)$, $Y_{01}(t) = Y_{10}(t)$, and $W_{01}(t) = W_{10}(t)$ follow for all t.

According to the analysis in Appendix D, we found that there are two ridges for the maximum final yields in the parameter space of p (the fraction of resistant, either singly or doubly resistant, crops) and the relative fraction q of doubly resistant crop among the resistant crops (Fig. 5c). The first ridge for the final yields is defined as

$$p = p_1^* = \frac{1 - R_0 e^{1-R_0}}{R_0\left(1 - e^{1-R_0}\right)}. \tag{16}$$

This optimal is independent of q, and is the same as the optimal fraction of resistant crops in the single locus gene-for-gene system. Therefore, the optimal fraction of resistant crops increases approximately as $p_1^* \approx R_0 - 1$ as the basic reproductive ratio $R_0 = \beta\lambda H/\alpha\mu$ of the pathogen increases past 1, attains its maximum ($p_{max} = 0.23$) around $R_0 = 2.8$, and then declines with R_0 as $p_1^* \sim 1/R_0$ ($R_0 \to \infty$).

The second ridge for the maximum final yields is on Γ_3 and Γ_4 which are the epidemic thresholds for the super-race after the second outbreak took place:

$$q = \begin{cases} b(p), & (p < 1 - 1/R_0) \\ \dfrac{1/R_0 - (1-p)e^{1-R_0} - pe^{(1-R_0)/2}}{p(1 - e^{(1-R_0)/2})}, & (p > 1 - 1/R_0) \end{cases} \tag{17}$$

where $q = b(p)$ is the branch of the curve $B(p, q) = 0$ where $B(p, q)$ is defined in (D14) of Appendix D. This ridge corresponds to the strategy of using resistant crop rather extensively (i.e., p is sufficiently large), but limit the use of doubly resistant crop at the fraction (17), which is approximately $1/R_0$ for large R_0. As shown in Fig. 5a-b, the maximum final yields obtained from the direct numerical simulation of (13) with the initial spore densities $\delta_{00} = 0.1$, $\delta_{01} = \delta_{10} = 10^{-4}$, $\delta_{11} = 10^{-12}$ agrees very well with the predicted results ((16) and (17)) of the ordered outbreak approximation.

An important result of two-locus gene-for-gene system is that the maximum final yields is obtained when p and q are adjusted on the epidemiological threshold for the super-race of pathogen, and independent of the impact of preceding outbreaks by the other races. In other words, preventing the last outbreak in the breeding season caused by the super-race is primarily important in maximizing the final crop.

3.1.2 Other order of outbreak

So far, we have assumed that the initial spore densities of the singly virulent races is sufficiently smaller than that of the universally avirulent race, and that of the super-race is even smaller (exact condition is given by (15)), so that the outbreaks in the season occurs in the order of avirulent → singly virulent → super-race. Here we briefly summarize the results when this assumption on the order of outbreaks is violated. We focus on the cases where, in the beginning of the season, only one of the races is abundant, and the frequencies of

the other races decrease with their genetic distances from the abundant type (as expected if they are derived by mutation from the abundant type). There are therefore two important cases which haven't yet been analyzed: (i) one of the singly virulent race is common in the beginning of the season, and (ii) the super-race is common in the beginning.

(i) Suppose that the race 01 is the most abundant in the beginning of the season, and the abundance of the initial spores of the races satisfies $01 > 00, 11 > 10$. The first outbreak then occurs by the race 01. The next outbreak by the super-race may follow later in the season. However no other races can spread in the host population. The problem is therefore equivalent to the single locus gene-for-gene case obtained in the previous section. The optimal planting strategy is therefore to use the host genotype 10 and 11 in the proportion of p_1^* defined in (8), and use the other genotypes, 00 and 01, in the proportion of $1 - p_1^*$. The relative proportion of 10 to 11, or 00 to 01 does not affect the results, because either 10 or 11 is resistant to the pathogen race 01, and the other host genotypes are susceptible to the race. Exactly the same result holds when the race 10, rather than 01, is common.

(ii) If the super-race is common in the beginning of the season, there is no way to reduce the impact of epidemic. The final yields is independent of the relative proportion of host genotypes, and depends only on the total host density. Only possible strategy is to adjust the total host density to the epidemiological threshold.

4 Discussion

We have analyzed in this paper the optimal disease control in crop plants under the threat of pathogen infection and the development of virulent race that overrides the disease-resistance. The most important and unexpected result of our model is that there exists an intermediate optimum for the fraction of resistant crops that maximizes the final yields. This seems to be counter-intuitive at first glance because there is no advantage of using susceptible crop itself to fight against either avirulent or virulent race of pathogen. By mixing susceptible and resistant crops, however, we can force the pathogen races to compete with each other for their available hosts. Exclusive use of the resistant hosts would completely eliminate the threat of the avirulent race epidemic, but it provides the virulent race a great chance of

infecting densely planted hosts with full efficiency. The less we use the resistant hosts, the more intense is the inter-race resource competition in the pathogen, thereby reducing the transmission efficiency of either of races and hence reducing the total number of infections. On the other hand, if we use susceptible crops exclusively, either of races can fully exploit the host without any difficulty. Hence there is an optimum mixture.

The optimal fraction of resistant crops in single locus gene-for-gene system is determined by the basic reproductive ratio R_0 of the pathogen. If R_0 is only slightly larger than 1, its threshold for the epidemics, the optimal fraction of resistant crop is approximately $R_0 - 1$. The optimal fraction increases by increasing R_0 past 1, and attains its maximum, ($p^*_{max} = 23\%$) and then declines for large R_0 as $p^* \sim 1/R_0$. Therefore if there is a high risk of the development of virulent pathogen that can infect the resistant host in the season, the fraction of resistant crop should never exceed about 1/4 for any pathogen having a basic reproductive ratio greater than 1.

As mentioned earlier, the reason why the mixture of susceptible and resistant crops are better than the exclusive use of resistant crops can be explained by the strong nonlinearity in the epidemiological cultivation curve (Fig. 1). The total impact by infectious disease is smaller if the host with a given density is subdivided into varieties and exposed to different compatibility genotypes of pathogen, than if a single host genotype of the same density is exposed to a single compatible pathogen genotype.

As the optimal fraction of resistant crops, and its importance as well, depends on the initial spore frequencies, the estimation of the initial abundances of the spore genotype is primality important in making the optimal planting strategy.

The analysis of disease-control in two-locus gene-for-gene system reveals that the pooled fraction of various resistant genotypes is the major determinant of the final crop yield. As analogous to the single-locus gene-for-gene problem, the final yield is maximized by setting this proportion near $1/R_0$. By setting so, the population can escape the outbreak by doubly virulent race, though all susceptible and singly resistant crops are to be cultivated before the outbreak of doubly virulent pathogen. We should note that, though this simple guideline for two-locus problem remains true, there can be another optimal planting strategy which make use of more resistant crops, but keeps the relative fraction of doubly resistant crops sufficiently small (of the order of $1/R_0$).

We ignored the cost of virulence in our analyses of the optimum planting strategy under the gene-for-gene interaction. The cost of virulence is hard to detect in the field (see, for example, Parlevliet 1981). The classical work by Leonard (Leonard, 1969), for example, showed 10-50% fitness reduction of the virulent race of oat stem rust relative to its avirulent counterpart on susceptible oat variety. Reports on the selection against unnecessary virulent genes are ubiquitous (Alexander *et al.*, 1985; Burdon, 1987). We therefore numerically examined the optimal planting strategies by introducing the cost of virulence as a reduced spore production rate λ', but failed to show any significant difference – we again obtained the optimum intermediate proportions of resistant cultivars though they are slightly changed by the cost. This conclusion, however, depends on that we focus on the optimum disease control in one year. As we discuss in the next paragraph, the cost of virulence would influence the initial genotype frequencies in the next year after an outbreak, thereby affecting the optimal planting strategy in the next year. We should also emphasize that the costs of pathogen virulence and host resistance play critical role in the maintenance of genetic diversity in host-pathogen gene-for-gene dynamics (Burdon, 1987; Mundt, 2002; Sasaki, 2000).

Our analysis is based on the single year optimization of the final yield, as mentioned above. However, the strategy adopted in the previous year would strongly influence the optimal strategy in the next year, because the planting in the previous year should affect the initial composition of pathogen spore genotypes. The dynamical optimization approach would be needed to take into account this between-year correlation. For example, in some parameter region of our two-locus gene-for-gene control problem (Fig. 5), the use of doubly resistant crops is equally effective as that of the singly resistant crops if the total fraction of resistant crops is kept at the optimal level of the single year. However, doing so would make the disease control in the next year extremely difficult, because the crop fields would then face the outbreak of doubly virulent race (the super-race) at the very early stage of the season.

In this paper, we defined the yields as the number of plants that have not experienced pathogen infection until the time of harvesting. In other words, we assume that the infected crops contribute nothing to the yields. We can however translate the variables from the number of individuals to biomass. With this translation uninfected tissue of a plant suffering from pathogens infection can also be includes in yields. We also assumed that the multiple infections do not occur when more than two type of pathogen races coexist in a field. This has negligible effect unless there is strong interaction between co-infected pathogens such as

the cross protection.

We have ignored the spatial structure of epidemiological dynamics. When we use different resistant crop varieties, the spatial scale of each monocultural stand would be quite important in determining the effectiveness of multiline control (the control strategy that makes use of the mixture of resistant crops), as is suggested by the field study of *Puccinia* infection in the rice fields (Zhu *et al.*, 2000) and of bean rust and maize rust epidemics (Mundt & Leonard, 1986), and the simulation study (Van den Bosch *et al.*, 1990). Zhu *et al.* (2000) found that the multiline effect in protecting rice fields from the fungal infection was greater if the different resistant varieties are planted in a larger scale, than when they are spatially mixed together in a fine scale. It is challenging to extend our analysis developed in this paper to the spatially structured model, where the spatial arrangement of resistant variety in the fields is to be optimized to protect crops from the pathogen infection. The optimal spatial distance between different resistant varieties would then be found as a function of the pathogen spore dispersal range.

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Appendix A: The final yield

Here we derive the fraction, $\phi = X(\infty)/H$, of crop plants that have never experienced infection during an epidemic outbreak. In obtaining ϕ, we assume that the initial densities of the host crop, the infected crop and the pathogen spore are given by

$$X(0) = H, \qquad Y(0) = 0, \qquad W(0) = \delta,$$

where δ is a small positive constant. Integrating both sides of (1a), (1b) and (1c) in the text, we have

$$X(\infty) - X(0) = H(\phi - 1) = -\beta \int_0^\infty X(t)W(t)\,dt, \tag{A1a}$$

$$Y(\infty) - Y(0) = 0 = \beta \int_0^\infty X(t)W(t)\,dt - \alpha \int_0^\infty Y(t)\,dt, \tag{A1b}$$

$$W(\infty) - W(0) = -\delta = \lambda \int_0^\infty Y(t)\,dt - \mu \int_0^\infty W(t)\,dt. \tag{A1c}$$

Dividing both sides of (1a) by $X(t)$, and integrating the resultants, we have

$$\int_0^\infty \frac{1}{X}\frac{dX}{dt} = \log\frac{X(\infty)}{X(0)} = \log\phi = -\beta \int_0^\infty W(t)\,dt. \tag{A2}$$

Combining (A1c) and (A2),

$$\begin{aligned} \phi &= X(\infty)/H = \exp\left[-\beta \int_0^\infty W(t)\,dt\right] \\ &= \exp\left[-\frac{\beta\lambda}{\mu}\int_0^\infty Y(t)\,dt - \frac{\beta\delta}{\mu}\right] \\ &= \exp\left[-\frac{\beta\lambda}{\mu}\int_0^\infty Y(t)\,dt\right](1 + O(\delta)). \end{aligned} \tag{A3}$$

We also have from (A1a) and (A1b),

$$1 - \phi = 1 - \frac{X(\infty)}{H} = \frac{\beta}{H}\int_0^\infty X(t)W(t)\,dt = \frac{\alpha}{H}\int_0^\infty Y(t)\,dt \tag{A4}$$

From (A3) and (A4), we thus obtain ϕ as

$$\begin{aligned} \phi &= (1 + O(\delta))\exp\left[-\frac{\beta\lambda}{\mu}\int_0^\infty Y(t)\,dt\right] \\ &= (1 + O(\delta))\exp\left[-\frac{\beta\lambda}{\mu}\frac{H}{\alpha}(1-\phi)\right] \\ &\to \exp\left[-\frac{\beta\lambda H}{\mu\alpha}(1-\phi)\right], \quad (\delta \to 0) \end{aligned} \tag{A5}$$

(Gillespie, 1975; May & Anderson, 1983). This complete the derivation of (2) in the text.

Appendix B: Condition for the order of outbreak

Here we define an approximate condition under which, with a given initial spore densities, δ_0, and δ_1 of avirulent and virulent races, the epidemic occurs in the order of avirulnet-virulent races. That the initial spore density of the avirulent race is greater than that of the virulent race is not sufficient for this to occur, because the virulent race has a broader host range and hence a greater growth rate in the field where both the susceptible and the resistant hosts are planted. In the beginning of the season, the densities of hosts infected by either of strains and the spore densities are small, and we obtain an asymptotic form for W_i from the system with respect to Y_i's and W_i's:

$$W_i \sim \delta_i e^{\zeta_i t}, \qquad (i = 0, 1), \tag{B1}$$

where $\zeta_0 = Z(H_0)$, $\zeta_1 = Z(H_0 + H_1)$, with

$$Z(H) = [\sqrt{(\alpha+\mu)^2 + 4(\beta\lambda H - \alpha\mu)} - (\alpha+\mu)]/2, \tag{B2}$$

are the dominant eigenvalues for the linearlized dynamics of (Y_0, W_0) and (Y_1, W_1). We call that the ordered outbreak occurs if, at the time t_0 the avirulent spore density reaches the order of magnitude of 1, the virulent spore density is still sufficiently small. As $t_0 \sim -(1/\zeta_0)\log\delta_0$, this condition becomes $W_1(t_0) = \delta_1 \exp(t_0) \ll 1$, or

$$\delta_1^{1/\zeta_1} \ll \delta_0^{1/\zeta_0}. \tag{B3}$$

This complete the derivation of (4) in the text.

In the two locus gene-for-gene model, there are 4 pathogen genotypes: the universally avirulent race 00, the singly virulent races 01 and 10, and the super-race 11, whose initial spore densities are denoted by δ_{00}, δ_{01}, δ_{10}, and δ_{11}. We then ask what's the condition for that epidemic occurs in the order of the universally avirulent race $\rightarrow$ the singly virulent races $\rightarrow$ the super-race, for a given crop density H_{00} of the universally susceptible hosts 00, H_{01} and H_{10} of the singly resistant hosts 01 and 10, and H_{11} of the doubly resistant hosts 11. For simplicity, we assume that the initial spore densities of singly virulent races, and the density of the singly resistant hosts are the same: $\delta_{01} = \delta_{10}$ and $H_{01} = H_{10}$. A condition for that the epidemic caused by 00 occurs earlier than that of 01 or 10 is, as in the single locus case,

$$W_{01}(t_0) = W_{10}(t_0) \sim \delta_{01}\exp(\zeta_{01}t_0) < 1, \qquad \text{with } t_0 \sim -\frac{1}{\zeta_{00}}\log\delta_{00} \tag{B4}$$

where $\zeta_{00} = Z(H_{00})$, $\zeta_{01} = Z(H_{00} + H_{01})$ are the initial asymptotic growth rate of the pathogen races 00 and 01. This yields the condition

$$\delta_{01} < {\delta_{00}}^{\zeta_{01}/\zeta_{00}} \tag{B5}$$

After a sufficient time is passed since the epidemic caused by the universally avirulent pathogen ($t > t_0$), the universally susceptible hosts that remain uninfected approaches $H_{00}\phi_{00}$. Then, the next epidemic caused by singly virulent races occurs around the time t_1 is obtained from

$$W_{01}(t_1) \sim W_{01}(t_0)\exp(\zeta'_{01}(t_1 - t_0)) = \delta_{01}\exp(\zeta_{01}t_0 + \zeta'_{01}(t_1 - t_0)) = 1$$

or

$$t_1 \sim t_0\left(1 - \frac{\zeta_{01}}{\zeta'_{01}}\right) - \frac{1}{\zeta'_{01}}\log\delta_{01} \tag{B6}$$

where $\zeta'_{01} = Z(H_{00}\phi_{00} + H_{01})$ is the asymptotic growth rate of the singly virulent race 01 after the first epidemic. Here, ϕ_{00} is the fraction of universally susceptible hosts that remain uninfected after the first outbreak and is the same as ϕ_0 defined as (5) in the text. The density of super-race spores in the phase between the first and the second epidemic is

$$W_{11}(t) \sim W_{11}(t_0)e^{\zeta'_{11}(t-t_0)} \sim \delta_{11}e^{\zeta_{11}t_0 + \zeta'_{11}(t-t_0)} \tag{B7}$$

where $\zeta_{11} = Z(H_{00} + H_{01} + H_{10} + H_{11})$ and $\zeta'_{11} = Z(H_{00}\phi_{00} + H_{01} + H_{10} + H_{11})$. Thus the condition for that, at the time of the second outbreak caused by the singly virulent races, the super-race density is still sufficiently small is

$$\log\delta_{11} < \frac{\zeta_{11}\zeta'_{01} - \zeta'_{11}\zeta_{01}}{\zeta_{00}\zeta'_{01}}\log\delta_{00} + \frac{\zeta'_{11}}{\zeta'_{01}}\log\delta_{01}. \tag{B8}$$

This completes the derivation of (15) in the text.

Appendix C: Threshold fractions of resistant crops in one-locus GFG system

We here derive the threshold fractions p_1^* and p_2^* of the resistant crops (Equation (8) and (9) in the text) in the case that the outbreak of avirulent pathogen occurs first, which is followed by that of the virulent pathogen (i.e., $\delta_1/\delta_0^\sigma \ll 1$ in Appendix B). We substitute $H_0 = H(1-p)$, $H_1 = Hp$ and $R_0 = \beta\lambda H/\alpha\mu$ into (5) and (6) in the text to have

$$F(\phi_0) \equiv \phi_0 - \exp\left[-R_0(1-p)(1-\phi_0)\right] = 0, \tag{C1}$$

$$G(\phi_0,\phi_1) \equiv \phi_1 - \exp\left[-R_0\{(1-p)\phi_0 + p\}(1-\phi_1)\right] = 0. \tag{C2}$$

If the fraction of resistant crop p is less than a threshold p_1^*, there is an epidemic by avirulent pathogen (i.e. $0 < \exists\phi_0 < 1; F(\phi_0) = 0$), but there is no outbreak by virulent pathogen (i.e. $\phi_1 = 1$ is the only root of $G(\phi_0,\phi_1) = 0$, where ϕ_0 is the root of $F(\phi_0) = 0$). If, however, p exceeds p_1^*, there is also an epidemic by virulent pathogen (i.e. another root ϕ_1 of $G(\phi_0,\phi_1) = 0$ with $0 < \phi_1 < 1$ bifurcates from $\phi_1 = 1$ at $p = p_1^*$). Therefore, if p is right on the threshold, we must have

$$\frac{\partial G}{\partial \phi_1}(\phi_0, 1) = 0, \qquad \text{and} \qquad F(\phi_0) = 0. \tag{C3}$$

Thus we have

$$\frac{\partial G}{\partial \phi_1}(\phi_0, 1) = 1 - R_0\left\{(1-p)\phi_0 + p\right\} = 0, \tag{C4}$$

which yields

$$p = \frac{1/R_0 - \phi_0}{1-\phi_0}. \tag{C5}$$

Substituting this into $F(\phi_0) = 0$, ϕ_0 at the bifurcation point is explicitly obtained as

$$\begin{aligned} \phi_0 &= \exp\left[-R_0(1-p)(1-\phi_0)\right] \\ &= \exp\left[-R_0(1-p) + (1-pR_0)\right] = e^{1-R_0}. \end{aligned} \tag{C6}$$

Substituting (C6) into (C5) then yields

$$p = p_1^* = \frac{1 - R_0 e^{1-R_0}}{R_0(1-e^{1-R_0})}. \tag{C7}$$

Thus Equation (8) in the text is derived.

The second threshold p_2^* is obtained in the same vein. For p above p_2^*, there is no epidemic by avirulent pathogen because the density of susceptible host genotype is below the threshold. At $p = p_2^*$, therefore, we must have $F'(1) = 0$, or

$$\frac{dF}{d\phi_0}(1) = 1 - R_0(1-p) = 0, \tag{C8}$$

and hence

$$p = p_2^* = 1 - \frac{1}{R_0}, \tag{C9}$$

which is Equation (9) in the text. This completes the derivation of the threshold fractions p_1^* and p_2^* of resistant crops in the single locus gene-for-gene system.

Appendix D: Sequential outbreak under multi-locus GFG system

In this Appendix, we derive the final yields in two locus GFG system as a function of the total fraction p of resistant crops and the relative fraction q of doubly resistant crops, assuming sequential outbreaks of pathogen races. We here denote by H_{00}, H_{01}, H_{10} and H_{11} the names and their initial crop densities of the host resistant genotype `00`, `01`, `10` and `11`, respectively. We also denote by P_{00}, P_{01}, P_{10} and P_{11} the pathogen virulence genotypes `00`, `01`, `10` and `11` (Table 2).

We analyze the model assuming that the outbreak of an avirulent pathogen (P_{00}) occurs first, which is then followed by the synchronized outbreaks of singly virulent pathogens (P_{01} and P_{10}) , and then by that of the doubly virulent pathogen (P_{11}). We then obtain the total final yield as a function of the fraction of susceptible and resistant crop varieties.

The final yield is obtained as functions of the total fraction of all resistant host p and the relative proportion of doubly resistant among all resistant genotypes q. After the outbreak by avirulent race P_{00}, the density of susceptible hosts $\tilde{H_{00}}$ that remain uninfected is given by $\tilde{H_{00}} = H_{00}\phi_{00}$ where

$$\phi_{00} = \exp\left[-\frac{\beta\lambda}{\alpha\mu}H_{00}(1-\phi_{00})\right]. \tag{D1}$$

This and (D2)-(D5) below follows by integration of both sides of (13), as described in Appendix A. We denote ϕ_i as the fraction of hosts that remain uninfected after the outbreak of pathogen race P_i (see Table 2). The next phase is the outbreak by singly virulent pathogen P_{01} and P_{10}, which can infect either susceptible or singly resistant crops (i.e. P_{01} can infect susceptible (00) and a singly resistant genotype (01), and P_{10} can infect susceptible (00) and another singly resistant genotype (10)). We assume for simplicity that the initial densities of two singly resistant genotypes are the same, $H_{01} = H_{10}$, and that two singly virulent pathogen races have the same infection rate and the same initial spore densities. Then, the densities of two singly resistant hosts that remain uninfected after the second outbreak are the same $\tilde{\tilde{H_{01}}} = \tilde{\tilde{H_{10}}}$, where $\tilde{\tilde{H_{01}}} = H_{01}\phi_{01}$, $\tilde{\tilde{H_{10}}} = H_{10}\phi_{10}$ with $\phi_{01} = \phi_{10}$. The susceptible host $\tilde{H_{00}}$ which survived the avirulent pathogen infection can be infected either of two singly virulent races. The density of susceptible hosts that remain uninfected again after the second outbreak is then $\tilde{\tilde{H_{00}}} = \tilde{H_{00}}\phi_{01+10}$. These fractions ϕ_{01}, ϕ_{10}, and ϕ_{01+10} of survivors during

the second outbreak are obtained from

$$\phi_{01} = \phi_{10} = \exp\left[-\frac{\beta\lambda}{\alpha\mu}\left\{\frac{\tilde{H_{00}}(1-\phi_{01+10})}{2} + H_{01}(1-\phi_{01})\right\}\right], \quad \text{(D2)}$$

$$\phi_{01+10} = \exp\left[-\frac{\beta\lambda}{\alpha\mu}\left\{\tilde{H_{00}}(1-\phi_{01+10}) + 2H_{01}(1-\phi_{01})\right\}\right]. \quad \text{(D3)}$$

It follows from (D2) and (D3) that $\phi_{01+10} = \phi_{01}\phi_{10} = {\phi_{01}}^2$. The third and the last phase is the outbreak by doubly virulent pathogen P_3 which can infect all the crop varieties. The density of uninfected susceptible host $\hat{H_{00}}$, singly resistant hosts $\hat{H_{01}}$ and $\hat{H_{10}}$, and doubly resistant host $\hat{H_{11}}$ after the third outbreak are given by $\hat{H_{00}} = \tilde{\tilde{H}}_{00}\phi_{11}$, $\hat{H_{01}} = \tilde{\tilde{H}}_{01}\phi_{11}$, $\hat{H_{10}} = \tilde{\tilde{H}}_{10}\phi_{11}$ and $\hat{H_{11}} = H_{11}\phi_{11}$, where ϕ_{11} is obtained from

$$\phi_{11} = \exp\left[-\frac{\beta\lambda}{\alpha\mu}(\tilde{\tilde{H}}_{00} + \tilde{\tilde{H}}_{01} + \tilde{\tilde{H}}_{10} + H_{11})(1-\phi_{11})\right]. \quad \text{(D4)}$$

The total yield of the season when the outbreak occurs on the order of avirulent, singly virulent, doubly virulent is then

$$\begin{aligned} Y_f &= (\hat{H_{00}} + \hat{H_{01}} + \hat{H_{10}} + H_{11})\phi_{11} \\ &= \{\phi_{00}\phi_{01+10}H_{00} + \phi_{01}(H_{01} + H_{10}) + H_{11}\}\,\phi_{11}. \end{aligned} \quad \text{(D5)}$$

Figure 5a, b show the simulation result of the final total yield Y_f and the analytically obtained result of threshold for outbreaks of pathogens as a function of $p = (H_{01} + H_{10} + H_{11})/H$ and $q = H_{11}/(H_{01} + H_{10} + H_{11})$, in sequential outbreak case. The final yield depends mostly on the total fraction p of the resistant crop genotypes and we found that this maximum corresponds to the epidemiological thresholds for doubly virulent pathogen. Below, we obtain epidemiological thresholds in the parameter space of p and q.

To obtain these thresholds, we here describe initial densities of crops as the functions of p and q : $H_{00} = H(1-p)$, $H_{01} = H_{10} = Hp(1-q)/2$, and $H_{11} = Hpq$ where H is the total initial density of crop. We define the functions F, G, and K from (D1)-(D4) :

$$F(\phi_{00}) = \phi_{00} - \exp\left[-R_0(1-p)(1-\phi_{00})\right] \quad \text{(D6)}$$

$$G(\phi_{01}) = \phi_{01} - \exp\left[-\frac{R_0}{2}\{(1-p)\phi_{00}(1-{\phi_{01}}^2) + p(1-q)(1-\phi_{01})\}\right] \quad \text{(D7)}$$

$$K(\phi_{11}) = \phi_{11} - \exp\left[-R_0\{(1-p)\phi_{00}{\phi_{01}}^2 + p(1-q)\phi_{01} + pq\}\right] \quad \text{(D8)}$$

where $R_0 = \beta\lambda H/\alpha\mu$ and we used ${\phi_{01}}^2 = \phi_{01+10}$. The solutions of $F(\phi_{00}) = 0$, $G(\phi_{01}) = 0$ and $K(\phi_{11}) = 0$ define ϕ_{00}, ϕ_{01} ,ϕ_{01+10}, and ϕ_{11}, the fractions of crops that remain uninfected after each phase of outbreak.

The whole parameter region ((p, q) with $0 \leq p \leq 1$ and $0 \leq q \leq 1$) is divided into 7 sectors by 6 epidemiological thresholds (for the outbreak of each pathogen strain) (Fig. 5c). For example, the sector denoted by `oxo` indicates that there are the outbreaks in the 1st phase (by avirulent) and the 3rd phase (by the super-race), but is not in the 2nd phase (by the singly virulent races). In the following, we obtain the 6 thresholds that separates each pair of neighboring sectors in Fig 5c.

The first threshold, `o--/x--`, corresponds to the boundary of the sectors `x--` and `o--`, where `-` denotes either `o` or `x`:

`x--/o--` This is the threshold for the outbreak of avirulent race P_{00} in the first phase. At this threshold, a new root satisfying $0 < \phi_{00} < 1$ of $F(\phi_{00}) = 0$ bifurcates from $\phi_{00} = 1$. Thus the threshold is obtained from $F'(1) = 0$, namely,

$$p = p_0^* = 1 - 1/R_0. \tag{D9}$$

This is the same as the threshold p_2^* for avirulent race outbreak in single locus system (C9).

`xx-/xo-` The epidemiological threshold for the singly virulent races, given that no outbreak occurred in the 1st phase ($\phi_{00} = 1$). The threshold, Γ_1, is obtained from $G'(1)|_{\phi_{00}=1} = 0$, as

$$\Gamma_1 : \qquad q = 2(1 - 1/R_0)(1/p) - 1. \tag{D10}$$

`ox-/oo-` The same epidemiological threshold as above, but now the assumption is that the 1st outbreak took place. This threshold, Γ_2, is obtained from $F(\phi_{00}) = 0$ and $G'(1) = 0$, as

$$\Gamma_2 : \qquad \frac{2R_0 + p(1-q)}{2(p-1)} = \exp\left[2R_0\left\{(p-1) - R_0 - \frac{p(1-q)}{2}\right\}\right]. \tag{D11}$$

`xxx/xxo` The epidemiological threshold for the super-race, given that there was no preceding outbreaks before the 3rd phase. This threshold is obtained from $K'(1)|_{\phi_{00},\phi_{01}=1} = 0$, and is equivalent to $R_0 = 1$. (This threshold doesn't appear in the Fig. 5)

`xox/xoo` The same epidemiological threshold as above, but now the assumption is that the 2nd outbreak took place. This threshold is obtained from $\phi_{00} = 1$, $G(\phi_{01}) = 0$ and $K'(1) = 0$, or

$$\Gamma_3 : \qquad q = \frac{(1-p)e^{1-R_0} + p\,e^{(1-R_0)/2} - 1/R_0}{p(e^{(1-R_0)/2} - 1)}. \tag{D12}$$

`oxx/oxo` The epidemiological threshold for the super-race, as above two, but now the assumption is that the 1st outbreak occurred (but the 2nd does not). The threshold is given by $F(\phi_{00}) = 0$, $\phi_{01} = 1$ and $K'(1) = 0$, or

$$p = p_1^* = \frac{1 - R_0 e^{1-R_0}}{R_0 \left(1 - e^{1-R_0}\right)}. \tag{D13}$$

This is the same as the optimal fraction of resistant crops in the single locus gene-for-gene system (C7).

`oox/ooo` The epidemilogical threshold for the super-race, once again, but now the outbreaks occurred in either of preceding phases. The threshold is then obtained from $F(\phi_{00}) = 0$, $G(\phi_{01}) = 0$, and $K'(1) = 0$. This yields

$$B(p,q) \quad = \quad \hat{\phi}_{01}(p,q) - \exp\left[\frac{1}{2}\left(1 - pR_0 + \frac{R_0 e^{1-R_0}(1-p)}{\hat{\phi}_{01}(p,q)^2}\right)\right], \tag{D14}$$

$$\text{with} \quad \hat{\phi}_{01}(p,q) = \frac{1/R_0 - pq - (1-p)e^{1-R_0}}{p(1-q)},$$

The implicitly defined curve $B(p,q) = 0$ gives the threshold Γ_4.

This completes the derivation of 6 thresholds in Fig. 5c. It is then easy to see that the final yields Y_f is maximized when (p,q) are on the thresholds Γ_3, $p = p_1^*$, or Γ_4 (with the maximum value H/R_0.

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Caption of Table

Table 1. Compatibility table for two-locus gene-for-gene system. + indicates that infection occurs.

Table 2. The fraction of each host genotypes (from H_{00} to H_{11}) that remain uninfected after the outbreak by pathogen races (from P_{00} to P_{01}).

Figure Legends

Figure 1. Final yields after pathogen outbreak. The density of plants remain uninfected at $T \to \infty$ ($X(\infty) = H\phi$ where ϕ is defined by (2)) is plotted against the initial crop density H. The threshold crop density for the spread of pathogen is $H_c = \alpha\mu/\beta\lambda = 5$.

Figure 2. Single locus gene-for-gene dynamics with spore stage of pathogen. See text for detail.

Figure 3. The final total yield as a function of the fraction p of resistant crops. **a)** shows the final yield Y_{AV} when the outbreak of avirulent pathogen race well precedes the outbreak of virulent pathogen race (corresponding to $\delta_1/\delta_0^\sigma \ll 1$). The final yield is maximized at $p = p_1^* \approx H_c/H$, and is constant for $p > p_2^* = 1 - H_c/H$, where H is the total crop density and $H_c = \alpha\mu/\beta\lambda$. The maximum yield approximately equals to H_c. In figure **b)**, the total crop density is fixed at $H = 4$. The red and blue curves correspond to the final yields for the sequential outbreaks. The red curve: Y_{AV} for the avirulent-first case ($\delta_1/\delta_0^\sigma \ll 1$); the blue broken curve: Y_{VA} for the virulent-first case ($\delta_1/\delta_0^\sigma \gg 1$). The black curves are the final yields obtained numerically from (3) with different values of δ_1/δ_0^σ ($\delta_1/\delta_0^\sigma = 0.002, 0.01, 0.076, 0.791$ at the optimal fraction $p = p_1^*$, from top to bottom). The threshold crop density: $H_c = \alpha\mu/\beta\lambda = 1$.

Figure 4. The contours for the total final yield Y_{AV} for the sequential outbreaks (avirulent followed by virulent race). There are two ridges of high final yield (red region) — one for the total crop density at $H = H_c = 1$, and the other for the optimal fraction $p = p_1^* \approx H_c/H$ (the broken curve) of resistant crop in the region $H > H_c$. The hatched curve represents the second threshold fraction p_2^*.

Figure 5. The contours for the total final yield under two locus gene-for-gene system. The total yield is plotted as a function of the total fraction of resistant crops $p = (H_{01} + H_{10} + H_{11})/H$ (horizontal axis) and the relative fraction of doubly resitant among all resistant crops $q = H_{11}/(H_{01} + H_{10} + H_{11})$ (vertical axis). **a)-b)** show the result of numerical simulations with analytically obtained dashed lines which show the threshold for outbreaks of pathogens. **a)** The threshold density: $H_c = \beta\lambda/\alpha\mu = 1$, the total density: $H = 5$. **b)** The threshold density: $H_c = \beta\lambda/\alpha\mu = 1$, the total density: $H = 10$. The yiled is maximized when p is adjusted to $H_c/H = 1/R_0$, i.e., for $p = 0.2$ in a) and $p = 0.1$ in b) and on the thresholds Γ_3, Γ_4. The panels **c)** show the regions of outbreaks of pathogens as a function of p and q, analytically obtained from the sequential outbreak approximation when $H = 5$. The whole p-q parameter space is divided into 7 sectors according to whether or not the outbreak at each of 3 stages takes place and their borders define the thresholds ($p = p_0^*$, $p = p_1^*$, Γ_1, Γ_2, Γ_3 and Γ_4). The left, center, and right symbol in each

region respectively indicates whether or not the first (by avirulent), the second (by singly virulent) and the third (by doubly virulent) outbreak occurs (`o` for having outbreak and `x` for not).

Table 1:

Host genotype \ Pathogen genotype	00	01	10	11
00	+	+	+	+
01	−	+	−	+
10	−	−	+	+
11	−	−	−	+

Table 2:

	H_{00}	H_{01}	H_{10}	H_{11}
P_{00}	ϕ_{00}	$-$	$-$	$-$
P_{01}, P_{10}	ϕ_{01+10}	ϕ_{01}	ϕ_{10}	$-$
P_{11}	ϕ_{11}	ϕ_{11}	ϕ_{11}	ϕ_{11}

Figure 1:

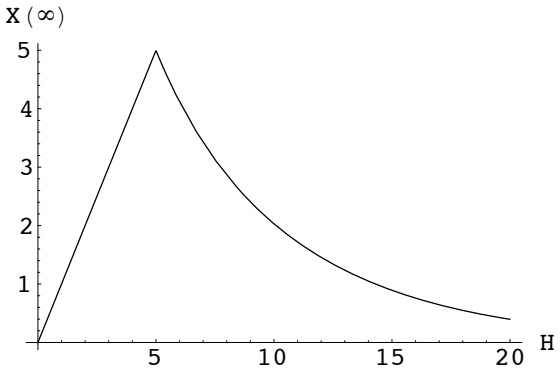


Figure 2:

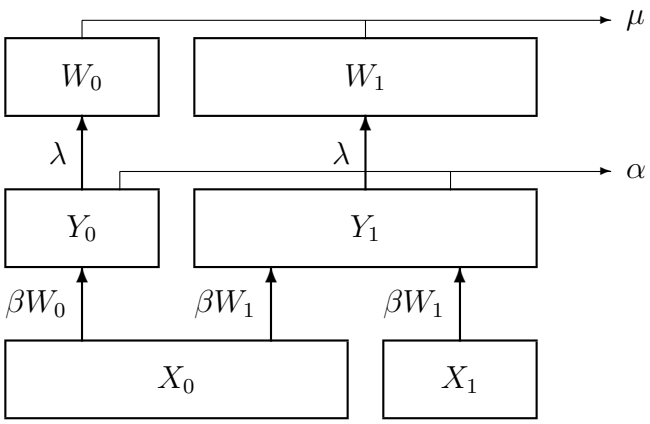


Figure 3:

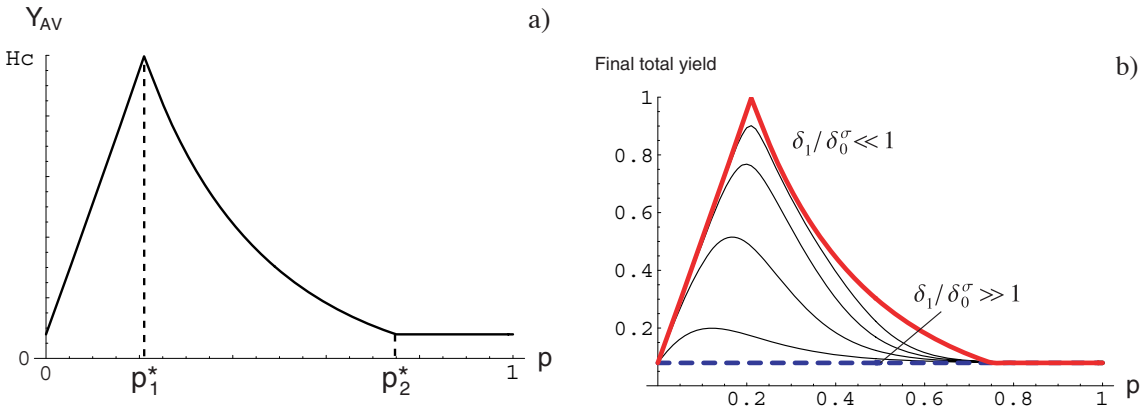

a)
Y_{AV}
Hc
0
0
p_1^*
p_2^*
1
p
b)
Final total yield
1
0.8
0.6
0.4
0.2
$\delta_1/\delta_0^\sigma \ll 1$
$\delta_1/\delta_0^\sigma \gg 1$
0.2
0.4
0.6
0.8
1
p

Figure 4:

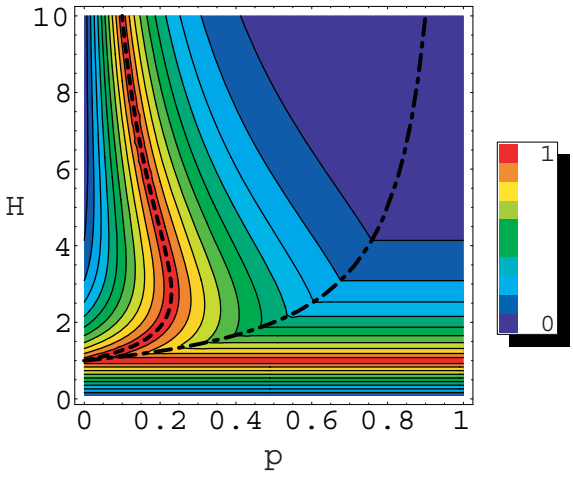
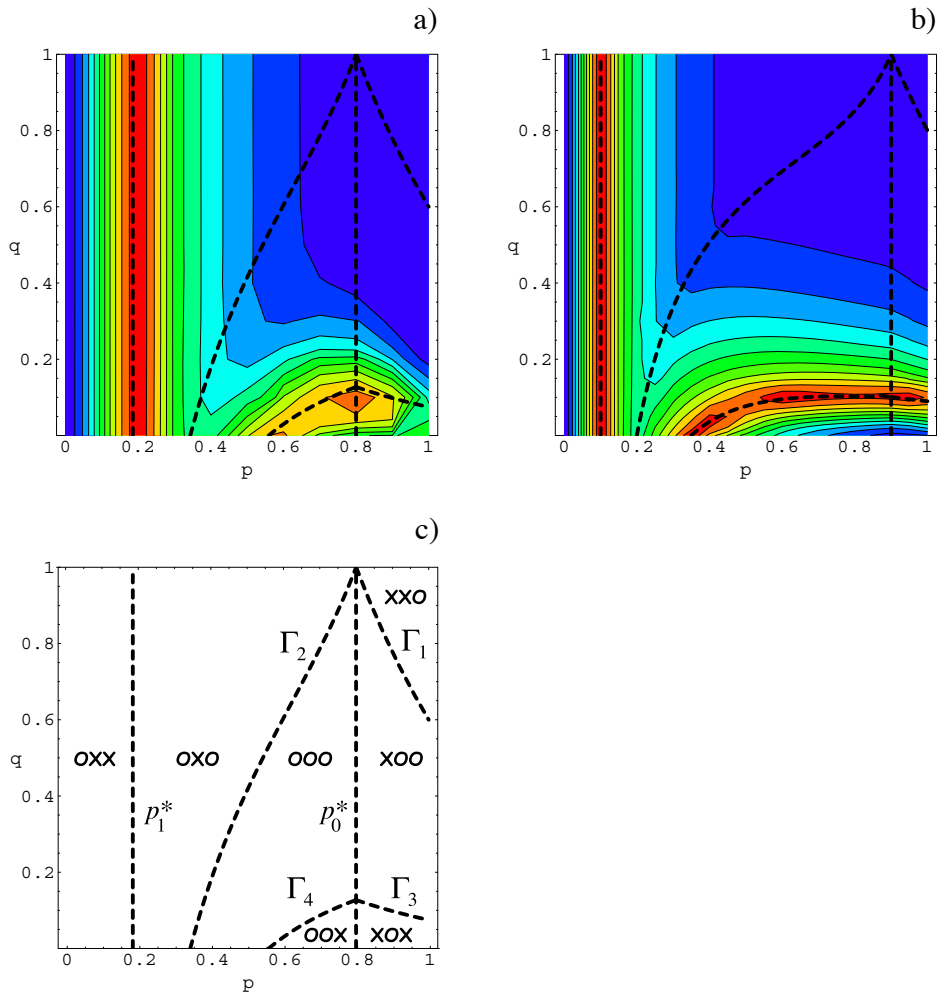


Figure 5:


a)
b)
c)
q
p
0
0.2
0.4
0.6
0.8
1
OXX
OXO
OOO
XOO
XXO
OOX
XOX
Γ_1
Γ_2
Γ_3
Γ_4
p_1^*
p_0^*