A Simple Model of Selection for Fungicide Resistance in Plant Pathogen Populations

K. M. Chin

20, Jalan Tembaga, 11600 Pulau Pinang, Malaysia.
I am indebted to J. A. Barrett for useful suggestions in the preparation of this manuscript.
Accepted for publication 22 September 1986.

ABSTRACT

Chin, K. M. 1987. A simple model of selection for fungicide resistance in plant pathogen populations. Phytopathology 77:666-669.

A simple model is proposed for studying changes in pathogen populations in response to selection by fungicide and for estimating pathogen fitness. Its implications are discussed in relation to other current models of fungicide resistance. Simulations indicate that the outcome of selection is largely dependent on a fine balance between the relative fitnesses of sensitive and resistant populations and the proportion of host plants treated with the fungicide. Analysis of data on selection by benomyl on *Pyricularia oryzae* populations indicates that resistance to the fungicide is likely to increase rapidly with moderate use. The model may be extended to describe host selection for increased virulence in pathogen populations. Apart from those that are discontinuously expressed (e.g., adult plant resistance), host resistances may be regarded as behaving like systemic fungicides with maximum persistence. Strategies for limiting the development of resistant pathogen genotypes are discussed.

The use of fungicides and host resistance against disease is often complicated by shifts in pathogen populations. These changes tend to restore the mean fitness of the populations to levels existing before the introduction of the chemical or resistance genes into the cropping system, thus resulting in the apparent failure of the control measure.

Several strategies have been proposed to prevent or delay pathogen evolution leading to the negation of imposed measures of disease control. These include the use of durable resistance (10) and systems of resistance gene management that confer durability (4,24). In the case of fungicides, use of chemicals that are apparently beyond metabolic adaptation by the pathogen, systems of application (alternating, mixing, etc.) that may result in disruptive selection of the pathogen (5,7,12,19,23), and methods integrating host resistance and fungicides have been suggested (3,21).

In all of these methods, it is essential to measure the fitness of pathogen genotypes in order to determine the fate of the corresponding control measures. In recent years, "fitness, which is one of the most fundamental variables of population genetics, has been recognized as important in plant pathology in several contexts" (8). Following pioneering work by Leonard (15), MacKenzie (16) introduced the concept of relating parasitic fitness to the Vanderplankian r (apparent rate of infection [20]). This concept was subsequently clarified by Groth and Barrett (8), improved upon by Skylakakis (17), and modeled generally by Barrett (2). Some recent models (e.g., that of Kable and Jeffery [12]) have not considered fitness values.

This paper presents a modification of an early model by J. A. Barrett (*personal communication*), relates it to current models of selection for fungicide insensitivity, and discusses its implications. Unlike MacKenzie's model (16), which is limited to host areas that are either completely treated or untreated with fungicides, this model takes into account the proportions of treated and untreated areas and may therefore be more relevant to practical strategies of disease management.

THE MODEL

Consider two pathogen genotypes that are sensitive (S) and resistant (R) to a given fungicide. The fitness matrix of the genotypes on treated (T) and untreated (U) areas of a susceptible host may be described as follows:

	$U(\theta)$	$T(1-\theta)$
$S(\beta)$	1	0
$R(\alpha)$	$1-s$	$1-s$

in which s represents the selection coefficient against the resistant genotype in the absence of the fungicide. For simplicity, an equal selection coefficient is assumed on the treated host and the sensitive genotype fails completely against the fungicide.

If the initial frequencies of S and R are β_0 and α_0, respectively, and the proportion of $U = \theta$, then after one cycle of selection:

$$\text{frequency of } S(\beta_1) = \beta_0\theta / (\alpha_0 W + \beta_0\theta)$$

$$\text{frequency of } R(\alpha_1) = \alpha_0 W / (\alpha_0 W + \beta_0\theta)$$

in which $W = 1 - s$ is the relative fitness of R, and

$$\alpha_2 = \alpha_1 W / (\alpha_1 W + \beta_1\theta)$$

$$= \alpha_0 W^2 / (\alpha_0 W + \beta_0\theta) / [\alpha_0 W^2 / (\alpha_0 W + \beta_0\theta) + \beta_0\theta^2 / (\alpha_0 W + \beta_0\theta)]$$

$$= \alpha_0 W^2 / (\alpha_0 W^2 + \beta_0\theta^2).$$

By induction

$$\alpha_t = \alpha_0 W^t / (\alpha_0 W^t + \beta_0\theta^t) \quad (1)$$

$$\beta_t = \beta_0\theta^t / (\alpha_0 W^t + \beta_0\theta^t). \quad (2)$$

From equations 1 and 2,

$$\alpha_t / \beta_t = \alpha_0 W^t / \beta_0\theta^t \quad (3)$$

$$W^t = \alpha_t\beta_0\theta^t / \alpha_0\beta_t$$

$$\ln W = (1/t)(\ln \alpha_t\beta_0 / \alpha_0\beta_t) + \ln\theta. \quad (4)$$

On the treated host alone (i.e., $\theta = 1$), equation 4 becomes:

$$\ln W = (1/t) \ln \alpha_t\beta_0 / \alpha_0\beta_t$$

$$= (1/t) \ln \alpha_t(1-\alpha_0) / \alpha_0(1-\alpha_t)$$

$$= (1/t)[\ln \alpha_t/(1-\alpha_t) - \ln \alpha_0/(1-\alpha_0)] \quad (5)$$

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. § 1734 solely to indicate this fact.

which is identical to the model by MacKenzie (16)

$$q/p = q_0/p_0 \exp (r_1 - r_2)t$$

in which p_0 and p are initial and final proportions, respectively, of a pathogen race x; q_0 and q the initial and final proportions, respectively, of a second, more fit race y after time t; and r_1 and r_2 are the apparent infection rates of x and y. Since

$$\ln W = r_1 - r_2$$

(where W is the relative fitness of the less fit race),

$$q/p = q_0/p_0 (W^t).$$

This may be rearranged to give

$$\ln W = 1/t [\ln q/(1-q) - \ln q_0/(1-q_0)]$$

which is identical to equation 5.

IMPLICATIONS OF THE MODEL

Equation 3 suggests that the outcome of selection depends on (i) the initial frequencies of S and R; (ii) the fitness of resistant genotypes relative to sensitive genotypes; (iii) the proportion of treated plants; and (iv) the number of pathogen generations. The equation for the change in frequency of R after one pathogen generation is given by:

$$\Delta\alpha = \alpha_1 - \alpha = [\alpha W - \alpha(\alpha W + \beta\theta)]/(\alpha W + \beta\theta)$$

$$= \alpha\beta(W - \theta)/(\alpha W + \beta\theta).$$

At equilibrium, $\Delta\alpha = 0$, and $W = \theta$ ($\alpha = 0$ and $\alpha = 1$ are trivial solutions). The stability of the equilibrium is given by the solution of:

$$\partial\Delta\alpha/\partial\alpha = (W - \theta)(\beta^2\theta - \alpha^2 W) / [\alpha(W - \theta) + \theta].$$

At equilibrium, $W - \theta = 0$, and $\partial\Delta\alpha/\partial\alpha = 0$. The equilibrium is therefore neutral and the genotypic frequencies remain unchanged irrespective of their actual values when $W = \theta$. If $W > \theta$, then $\Delta\alpha > 0$, and the frequency of R increases until it is fixed in the pathogen population; there is no internal equilibrium. If $W < \theta$, then $\Delta\alpha < 0$, and the frequency of R declines until it is lost from the population.

Changes in frequency of *R* with time. In this series of simulations (Fig. 1), the value of W is set at 0.8 and changes in the frequency of R (α) are plotted against time for different values of θ. When $\theta = W = 0.8$, the value of α_t is constant with time. When $\theta < W$ (i.e., the untreated area is less than the relative fitness of the R genotype), then α increases with time and R is ultimately fixed in the pathogen population.

With $\theta = 0.5$ (i.e., 50% of area treated), the frequency of R increases from 0.1 to 0.54 in five generations. Corresponding values are 0.1 to 0.99 if $\theta = 0.2$ (i.e., 80% of area treated). The model demonstrates the rapidity with which the pathogen population can respond to extensive fungicide applications if the resistant genotypes have a high level of relative fitness.

Changes in frequency of *R* with increase in $1 - \theta$ (treated area). Figure 2 illustrates the final frequencies of R (α_t) attained after 10 cycles of simulated selection on different proportions of treated host and with three levels of selection coefficient, 0.2, 0.5, and 0.8. In each case, α_t increases above the initial level $\alpha = 0.1$ as soon as the treated area ($1 - \theta$) exceeds the selection coefficient.

When the area treated is small, resistant genotypes need to be very fit (high W) to survive. After 10 generations, R is virtually undetectable when the treated area is < 0.3 if W is < 0.5 (Fig. 2). Even if pathogen genotypes are very fit ($W = 0.8$), they increase relatively slowly with increases in the proportion of treated area. For example, an increase of $1 - \theta$ from 0.2 to 0.3 increases α_t from 0.10 to 0.30 in 10 cycles of selection when $s = 0.2$.

When the area treated is large ($1 - \theta > 0.8$), even resistant genotypes that are considerably less fit than sensitive genotypes (e.g., $W = 0.2$) are preferred. Small increases in the treated area above the selection coefficient result in the rapid selection of R genotypes. For example, even poor genotypes ($W = 0.2$) are capable of increasing from 0.1 to 0.99 for an increase in treated area of 0.8 to 0.9 (Fig. 2).

APPLICATION OF THE MODEL

The model may be used to determine selection coefficients against fungicide resistant genotypes. For example, Chin (3) studied the effects of selection by benomyl on a natural population of *Pyricularia oryzae* (Cav.). Seedlings of susceptible rice cultivar Mahsuri were sown in seed boxes measuring $60 \times 36 \times 8$ cm at the rate of 600 seeds per box. In treated boxes, half the plants in each box were treated 7 days after sowing by spraying alternate rows of plants with benomyl at 250 ppm. Untreated boxes were sprayed with distilled water. The plants were then exposed to natural

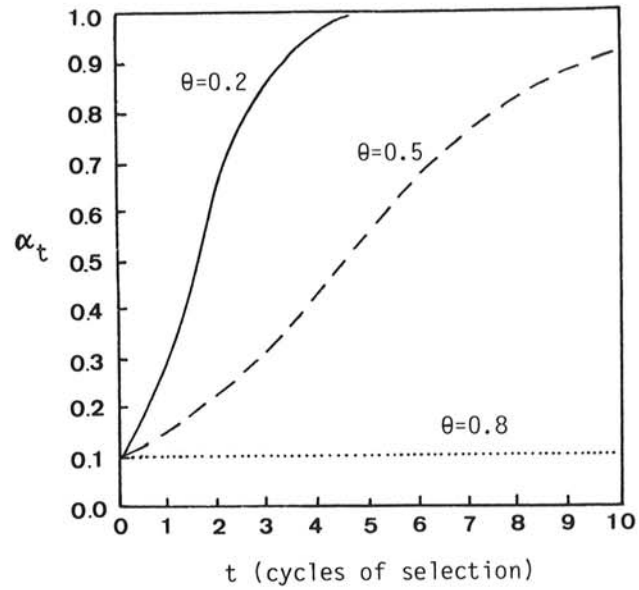

Fig. 1. Changes in frequency (α) of resistant genotype R with time (t) for different proportions (θ) of host areas not treated with fungicide; fitness of R fixed at 0.8.

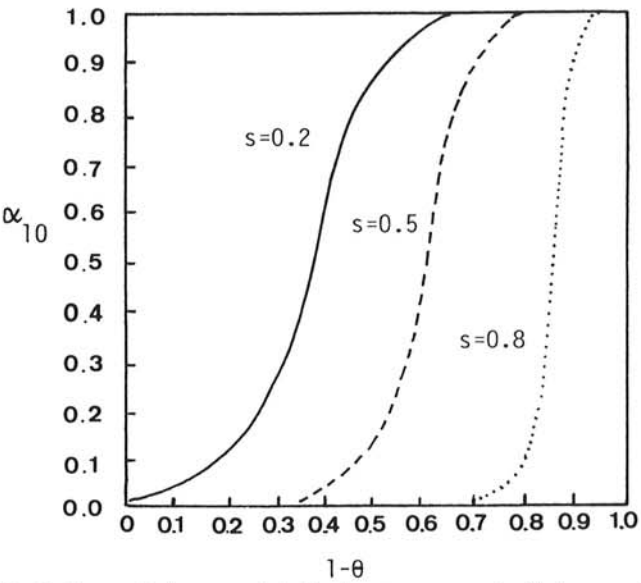

Fig. 2. Changes in frequency (α) of resistant genotype R with increases in proportion ($1 - \theta$) of hosts treated with fungicide, for different selection coefficient (s) against R, following 10 cycles of selection.

infection in disease nurseries for 3 days. Following incubation in a clean greenhouse for a further 3 days, spores from 50 lesions in each box were isolated, multiplied on agar culture, and reinoculated on fresh trays of seedlings identical to the original treatments. Spores produced from the second inoculation had therefore undergone two cycles of selection and were tested for insensitivity by germination tests on agar plates containing benomyl at 3.2 ppm.

The frequency of resistant genotypes increased from 0.115 to 0.295 after two selection cycles. As half of the plants were not treated with benomyl, $\theta = 0.5$. Substituting into equation 4,

$$\ln W = \tfrac{1}{2} \ln (0.295)(0.885)/(0.115)(0.705) + \ln 0.5$$

$$= -0.108$$

$$W = 0.897$$

$$s = 0.103.$$

(Alternatively, when s is small, $\ln W \sim -s$ and $s = 0.108$.)

Since the selection coefficient against the resistant genotype is small, benomyl resistance is likely to increase rapidly in response to moderate use of the fungicide. For example, if 30% of the plants in an area are treated with benomyl, then the frequency of the resistant genotype may increase from 0.1 to 0.57 in 10 cycles of selection.

DISCUSSION

The model presented is simple because it does not include competition between pathogen genotypes for available infection sites at the later phase of an epidemic. Also, aspects of fitness other than parasitic fitness affect survival of the pathogen in nature. The model may, however, be particularly useful in wet tropical areas where environmental variations are less severe and where parasitic fitness may be the most important component of biological fitness of plant pathogens.

The model assumes random distribution of spores over an area and the absence of age structure on the population. For example, Barrett (1) has considered that the proportion of spores ($1 - \phi$) that lands on the same plant and causes self-infection may affect the outcome of selection of pathogen races in multilines and cultivar mixtures. High proportions of spores that are randomly distributed ($\phi = 0.9 - 0.95$), as detected by Leonard (14) for oat stem rust and by Kiyosawa and Shiyomi (13) for blast, suggest that simple models may be a good approximation for these pathogens. Further, the model suggests that whereas selection in the pathogen population for resistance to fungicides may generally be related directly to the proportion ($1 - \theta$) of treated crop and the fitness (W) of resistant phenotypes, interactions between the two factors may be complex.

Chemicals that select for resistant genotypes of low fitness (W) values are likely to be more durable than those that do not. Persistency and systemicity of a compound also affect the rate of selection for resistance through their effects on $1 - \theta$. For example, if the compound is nonsystemic, $1 - \theta$ is in practice likely to be smaller than the proportion of crop treated because of incomplete protection of susceptible tissue. If the compound has poor persistence, $1 - \theta$ may be expected to decrease rapidly with time. Fungicides that lack persistence and are not systemic are therefore likely to be more durable in effectiveness than compounds that have these qualities, since selection for resistance is reduced. A similar opinion has been expressed by Wolfe (23).

Strategies for fungicide use that are intended to increase durability operate in a similar manner by reducing the extent or duration of exposure of the fungal population to the toxicant. Examples include limiting fungicide usage until disease exceeds economic threshold levels, alternating use of fungicides with different modes of action, or use on alternate crops when there are two or more crop seasons a year (6,25).

Fungicide mixtures have been advocated as presenting a more complex problem for pathogens to overcome than single fungicides. They may also have a synergistic effect (18). Wolfe (22) suggested the use of heterogeneous mixtures (different plants receiving different fungicides) because homogeneous mixtures (all plants receiving the same mixture) present a uniform environment for selecting resistant genotypes. Heterogeneous mixtures, particularly those whose components vary in persistence, may allow sensitive genotypes to compete more successfully with resistant genotypes. Urech and Staub (19), however, considered prepacked mixtures to be the only practical strategy for delaying or preventing the development of resistance.

The model may be extended to follow selection for increased virulence by substituting susceptible and resistant hosts for U and T and nonvirulent and virulent pathogen phenotypes for S and R. The outcome of selection then depends on the initial frequencies of virulent and nonvirulent phenotypes of the pathogen, the proportion of resistant hosts, and the number of pathogen generations in a manner similar to that discussed for the fungicide resistance model. A similar model for host resistance has been presented earlier by Groth and Person (9).

Some host resistances may be considered to behave like systemic fungicides with maximum persistence, and selection for virulence may be expected to be intense. Other hosts that exhibit different degrees of resistance at different growth stages (e.g., adult resistance or susceptibility) may be more durable because selection for increased virulences occurs only in limited periods of time. Examples include adult resistance of some varieties of wheat and barley to rusts and powdery mildew. Rice cultivars that are susceptible to foliar blast but resistant to neck blast may be more durable in resistance than cultivars that are resistant to both phases of the disease.

Although it seems probable that cultivars possessing discontinuously expressed resistance are more durable than those that do not, other as yet unidentified factors may also be important in conferring durability. For example, attention has been drawn to the greater durability of resistance of the wheat cultivar Capelle-Deprez to *Puccinia striiformis* (West.) compared with that of other cultivars that possess a similar pattern of seedling susceptibility and adult plant resistance (11).

The mean fitness of pathogen populations may be further reduced by integrating fungicide use with host resistance. Wolfe (22) considered that a combination of intermediate resistance with low levels of fungicide application would provide adequate protection while extending the durability of both control measures. In controlled experiments, adaptation of *Pyricularia oryzae* to either resistance of the rice host or benomyl application was delayed by a combination of both measures (3).

LITERATURE CITED

1. Barrett, J. A. 1980. Pathogen evolution in multilines and variety mixtures. Z. Pflanzenkr. Pflanzenschutz 87:383-396.
2. Barrett, J. A. 1983. Estimating relative fitness in plant parasites: Some general problems. Phytopathology 73:510-512.
3. Chin, K. M. 1984. Response of *Pyricularia oryzae* populations to integrated disease management. Pages 183-190 in: Proc. Int. Semin. Integr. Pest Manage. Kuala Lumpur, Malaysia.
4. Chin, K. M., and Wolfe, M. S. 1984. Selection on *Erysiphe graminis* in pure and mixed stands of barley. Plant Pathol. 33:535-546.
5. Dekker, J. 1976. Acquired resistance to fungicides. Annu. Rev. Phytopathol. 14:405-428.
6. Dekker, J. 1977. Resistance. Pages 176-197 in: Systemic Fungicides. R. W. Marsh, ed. Longman: London.
7. Georgopoulos, S. G. 1977. Pathogens become resistant to chemicals. Pages 237-245 in: Plant Diseases, an Advanced Treatise. Vol. I. J. G. Horsfall and E. B. Cowling, eds. Academic Press, New York.
8. Groth, J. V., and Barrett, J. A. 1980. Estimating parasitic fitness: A reply. Phytopathology 70:840-842.
9. Groth, J. V., and Person, C. O. 1977. Genetic interdependence of host and parasite in epidemics. Ann. N.Y. Acad. Sci. 287:97-106.
10. Johnson, R. 1979. The concept of durable resistance. Phytopathology 69:198-199.
11. Johnson, R. 1981. Durable resistance: Definition of, genetic control, and attainment in plant breeding. Phytopathology 71:567-568.

12. Kable, P. F., and Jeffery, H. 1980. Selection for tolerance in organisms exposed to sprays of biocide mixtures: A theoretical model. Phytopathology 70:8-12.
13. Kiyosawa, S., and Shiyomi, M. 1976. Simulation of the process of breakdown of disease resistant varieties. Ikushugaku Zasshi 26:339-352.
14. Leonard, K. J. 1969. Factors affecting rate of stem rust increase in mixed plantings of susceptible and resistant oat varieties. Phytopathology 59:1845-1850.
15. Leonard, K. J. 1969. Selection in heterogeneous populations of *Puccinia graminis* f. sp. *avenae*. Phytopathology 59:1851-1857.
16. MacKenzie, D. R. 1978. Estimating parasitic fitness. Phytopathology 68:9-13, 1108 (erratum).
17. Skylakakis, G. 1980. Estimating parasitic fitness of plant pathogenic fungi: A theoretical contribution. Phytopathology 70:696-698.
18. Uesugi, Y., Katagiri, M., and Noda, O. 1974. Negatively correlated cross resistance and synergism between phosphorimidates and phosphorothiolates in their fungicide actions on rice blast fungi. Agric. Biol. Chem. 38:907-912.
19. Urech, P. A., and Staub, T. 1985. The resistance strategy for acylanine fungicides. Bull. OEPP 15:8.
20. Vanderplank, J. E. 1963. Plant Diseases: Epidemics and Control. Academic Press, New York. 349 pp.
21. Wolfe, M. S. 1975. Pathogen response to fungicide use. Pages 813-822 in: Proc. Br. Insectic. Fungic. Conf., 8th. British Crop Protection Council.
22. Wolfe, M. S. 1981. Integrated use of fungicides and host resistance for stable disease control. Philos. Trans. R. Soc. London Ser. B 295:175-184.
23. Wolfe, M. S. 1982. Dynamics of the pathogen population in relation to fungicide resistance. Pages 139-149 in: Fungicide Resistance in Crop Protection. J. Dekker and S. G. Georgopoulos, eds. Centre for Agricultural Publishing and Documentation, Wageningen. 265 pp.
24. Wolfe, M. S., and Barrett, J. A. 1980. Can we lead the pathogen astray? Plant Dis. 64:148-155.
25. Wolfe, M. S., and Dinoor, A. 1973. The problem of fungicide tolerance in the field. Pages 11-19 in: Proc. Br. Insectic. Fungic. Conf., 7th. British Crop Protection Council.