Buildup of a Pathogen Subpopulation Resistant to a Systemic Fungicide Under Various Control Strategies: A Flexible Simulation Model

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The buildup of fungal subpopulations resistant to systemic fungicides is a well-known problem in plant disease control (2,4,9). It has been suggested (4) that the use of a systemic fungicide in a mixture with a second fungicide that has a different mode of action (usually a protectant) would delay the buildup of such resistant subpopulations. Limited experimental data, if any, are available to support this suggestion.

Skylakakis (10) recently presented a mathematical model, in which the relation between relative parasitic fitness and apparent infection rate (as developed by MacKenzie [8]) were used to assess the relative effects of simultaneous or alternate applications of a systemic and a protectant fungicide on the buildup of the resistant subpopulation of a pathogen. Skylakakis's (10) model is based on two main assumptions: that the activity of the protectant and systemic fungicides is additive and that there is no competition either between or within the two subpopulations for disease-free susceptible host sites.

In contrast to Skylakakis (10), our model assumes that the effects of the systemic and protectant fungicides in a mixture on the sensitive subpopulation of a pathogen may be additive, partially additive, or not additive, and that the two subpopulations of the pathogen compete among and between themselves for disease-free susceptible host sites.

THE MODEL

The model is based on the following assumptions:

1. The systemic fungicide is not mutagenic. A subpopulation b, resistant to the systemic, exists in nature.
2. There is no import of inoculum from other fields.
3. The apparent infection rates (r) of the two subpopulations are equal in the absence of fungicides.
4. The efficacy of the protectant fungicide is equal against both the sensitive (a) and the resistant (b) subpopulations.
5. Tolerance to the systemic is absolute in the resistant subpopulation b. The systemic is highly effective against the sensitive subpopulation a.
6. The additive action of the protectant in a mixture towards the sensitive subpopulation a is either zero (complete overlapping action between the two fungicides) or greater than zero (the mixture is more efficient in controlling subpopulation a than the systemic alone).
7. There is no redistribution of the protectant fungicide.

Let r represent the apparent infection rate (sensu Vanderplank [11]) of the two subpopulations in the absence of fungicides. The increases with time of the two subpopulations in the absence of fungicide application are described in the equations:

$$da/dt = r \cdot a\,[1-(a+b)] \quad (1)$$

$$db/dt = r \cdot b[1-(a+b)] \quad (2)$$

in which a = percentage leaf area infected with the sensitive subpopulation, and b = percentage leaf area infected with the resistant subpopulation.

In the presence of a systemic fungicide the increase of the sensitive subpopulation a is described in the equation:

$$da/dt = r \cdot C_s \cdot D_s \cdot a[1-(a+b)] + r \cdot a(1-C_s) \cdot [1-(a+b)] \quad (3)$$

in which C_s = percentage leaf area covered by the systemic fungicide (the pattern of change in C_s with time is given in Fig. 1), D_s = proportion of the systemic fungicide rendered inactive by weathering (the pattern of change in D_s is given in Fig. 1 insert).

The increase of the sensitive subpopulation a in the presence of the protectant fungicide is described in the equation:

$$da/dt = r \cdot C_p \cdot D_p \cdot a \cdot [1-(a+b)] + r \cdot a \cdot (1-C_p) \cdot [1-(a+b)] \quad (4)$$

in which C_p = percentage leaf area covered by the protectant fungicide (the pattern of change in C_p with time is given in Fig. 1), and D_p = proportion of the protectant fungicide rendered inactive by weathering (the pattern of change in D_p is given in Fig. 1 insert).

The increase of the resistant subpopulation b in the presence of the protectant fungicide is described in the equation:

$$db/dt = r \cdot C_p \cdot D_p \cdot b \cdot [1-(a+b)] + r \cdot b \cdot (1-C_p) \cdot [1-(a+b)]. \quad (5)$$

The increase of subpopulation b in the presence of the systemic fungicide is described by equation 2 (see assumption 5).

In the presence of a fungicide mixture (each fungicide at a full strength) the increase of subpopulation a follows one of two possibilities depending on whether there is additive action between the two fungicides composing the mixture: with no additive action the increase in subpopulation a is given in equation 3, which means a total overlapping action between the two fungicides or; with an additive action the increase in subpopulation a is given in the equation:

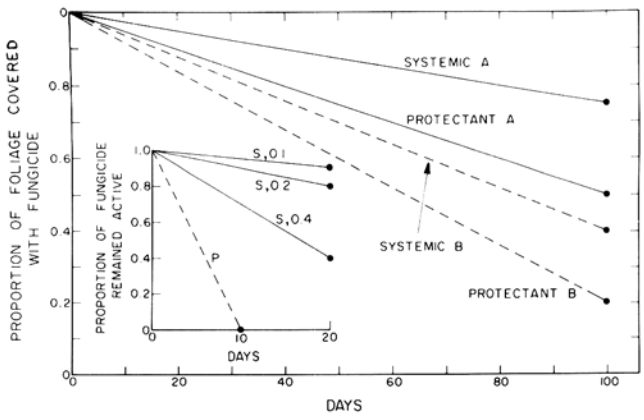

Fig. 1. Pattern of change in proportion of foliage covered with fungicides during the growing season in a theoretical model. Solid lines = treatment A, dashed lines = treatment B (see Table 2). Insert: pattern of change in proportion of protectant (P) and systemic (S) fungicides remaining active after increasing days of weathering between sprays. Changes are linear for simplicity of computation in the model.

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$$da/dt = r \cdot C_s \cdot D_s \cdot a[1-(a+b)] + r \cdot a(1-C_s) \cdot [1-(a+b)]$$
$$-\left\{ r \cdot a \cdot [1-(a+b)] - A(r \cdot C_p \cdot D_p \cdot a[1-(a+b)] + r \cdot a \cdot (1-C_p) \cdot [1-(a+b)]) \right\} \quad (6)$$

in which A = percentage additive action of the protectant. This means that the increase in a in the presence of a mixture possessing an additive action is equal to the increase of subpopulation a in the presence of a systemic fungicide (equation 3) minus the partial effect of the protectant fungicide on the increase of a (equation $1 - A$. equation 4).

APPLICATION OF THE MODEL

Simulations of the model were done by numeric integration of the corresponding difference equations using the CSMP III computer language of IBM (6). In all simulations, it was assumed that:

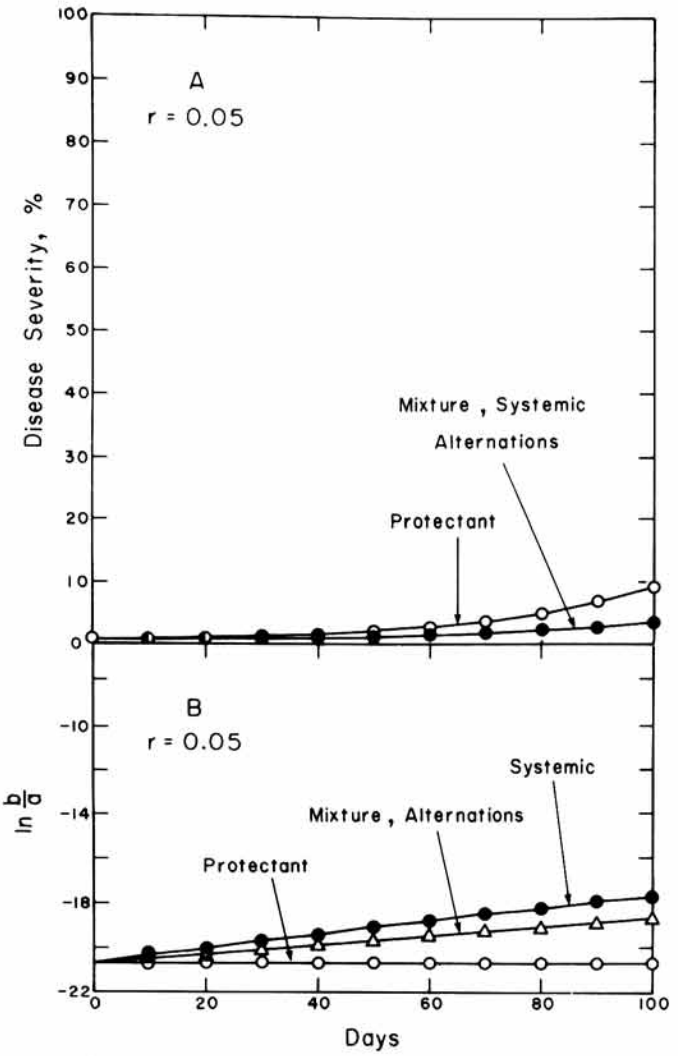

Fig. 2 A, Calculated percentage of infected leaf area in a crop managed with four types of fungicidal control strategies. **B,** Patterns of changes of the ratio (expressed as its natural logarithm) between subpopulation b (resistant to a systemic fungicide) and subpopulation a (sensitive to the systemic fungicide) as affected by fungicidal strategy employed. Apparent infection rate = 0.05. The protectant is assumed to have no additive effect in mixtures with the systemic. Note that $\alpha = 0$ (α is defined as ln b/a mixture—ln b/a alternations). Disease severity at time $0 = 5 \times 10^{-4}$. Initial frequency of $b = 5 \times 10^{-12}$. Coverage with the systemic changes from 0.99 at day 0 to 0.75 at day 100, and with the protectant from 0.99 to 0.5 at day 0 and 100, respectively. Weathering was assumed to linearly reduce activity of the systemic to 0% in 20 days and of the protectant to 0 in 10 days.

1) Epidemics began with 0.5% infected leaf area.
2) The growing season was of 100 days.
3) Periodic sprays with the systemic, the mixture, or the protectant fungicides were applied at 20-, 20-, and 10-day intervals, respectively, whereas with alternations − 20 days lapsed between sprays of systemic and protectant and 10 days between the protectant and the systemic.
4) The first spray was at day 0, and the total number of sprays per season were: 10 for protectant alone, five for the systemic alone or for the mixture, and seven for the alternations (four with the systemic and three with the protectant).

For each fungicidal control strategy, model simulations were done with three apparent infection rates and three initial levels of the resistant subpopulation. For the fungicide mixture and alternations, model simulations were done also with three rates of weathering of the systemic, and two levels of coverage with either fungicide.

Effects of the following parameters on the rate of increase of the resistant subpopulation b were taken into consideration: initial proportion of b; apparent infection rate; dynamic changes in fungicides coverage and weathering; additive action of the protectant fungicide; and fungicidal control strategy. Model applications were done to study the effects of these parameters on: the pattern of disease increase during a 100-day growing period under four fungicidal control strategies and the time-course change in the proportion of subpopulations a and b of the pathogen. Our measure to quantitate the buildup of the resistant subpopulation b, which reflects the selection pressure of the systemic fungicide, is the natural logarithm (ln) of the ratio between the percentage of infected leaf area caused by subpopulation b (resistant), and the percentage of infected leaf area caused by subpopulation a (sensitive). Our measure to assess superiority of mixture applications over alternations regarding the frequency of b was the difference between their respective ln ratios (α = ln b/a mixture − ln b/a alternations). Negative values of α indicate superiority of the mixture over alternations; positive values indicate the reverse.

RESULTS

The effect of apparent infection rate, *r*. Figs. 2, 3, and 4 represent simulations of disease increase with time and the change in the ratio between the resistant and susceptible subpopulations at apparent infection rates of 0.05 (Fig. 2), 0.2 (Fig. 3), and 0.4 (Fig. 4). In these simulations there was assumed to be no additive effect of fungicides in the mixtures.

At $r = 0.05$, disease progressed exponentially from 0.5% to about 9.5% during a 100-day period in plants treated with a protectant fungicide (Fig. 2A). Ln b/a during that period remained at the initial level (Fig. 2B). Periodic applications of a systemic fungicide, either mixed or in alternations with a protectant, reduced disease development, which reached a final severity of about 3% (Fig. 2A), but increased the proportion of subpopulation b in the population from an initial value of ln b/a of −21 to about −17.5 in plants treated with a systemic fungicide and to −19 in plants treated with either the mixture, or alternations (Fig. 2B).

With $r = 0.2$, disease progressed at a much faster rate under all treatments. By the 50th day of the epidemic about 50% of the foliage treated with the protectant fungicide was infected, as compared to 10% of foliage treated with fungicidal combinations containing a systemic fungicide. Minor differences in final disease severity were recorded between treatments at the end of the growing period (Fig. 3A). The relative proportion of subpopulation b showed considerable variation according to the control strategy employed. With the sole use of a protectant, ln b/a did not increase, but with the use of a systemic it increased almost linearly during the growing period, reaching a level of about −11. The increase in ln b/a was slower when a combination of systemic and protectant was employed, with a minor advantage to mixtures over alternations (Fig. 3B).

With $r = 0.4$, disease was devastating in all treatments, but more so with the sole use of a protectant (disease severity of 65% at 30

days, Fig. 4A). The proportion of b in the population showed a dramatic increase in plants treated with a systemic alone ($\ln b/a$ reaching a value of -9 at 100 days). It also increased considerably in plants treated with fungicide alternations ($\ln b/a = -12$ in 100 days) and mixtures ($\ln b/a = -14$), but remained low ($\ln b/a = -21$) in plants treated with the protectant (Fig. 4B).

The effect of additive action of a protectant in a mixture, A. The computed data presented in Figs. 2, 3, and 4 are based on the assumption that there is a complete overlapping action between the systemic and the protectant in a mixture regarding the sensitive subpopulation a (additive action = $A = 0$). This means that the mixture was equally as effective against genotype a as was the systemic alone. Because no experimental data regarding additive action are available in the literature, we incorporated into our model various degrees of additive action (Table 1), assuming that it may occur in reality. An additive action of 0.1, 0.5, and 0.9 means that the protectant in a mixture performs additional controlling effect towards subpopulation a of 10, 50, and 90%, respectively, relative to its controlling effect when not mixed (see equation 6). Results in Table 1 indicate that additive action affects disease development and buildup of the resistant subpopulation b in opposite directions. While additive action decreased disease development, increasing levels of additive action increased the proportion of b in the population. For example, the proportion of b following the use of a systemic alone was similar to that with a mixture possessing a 50% additive action ($\ln b/a = -11.1$ versus -11.3 at 100 days), and with a mixture possessing 90% of additive action the proportion of b was higher ($\ln b/a = -9$).

Dynamic changes in coverage of plant surfaces with fungicides, C_s and C_p. Plant growth and canopy structure affects deposition

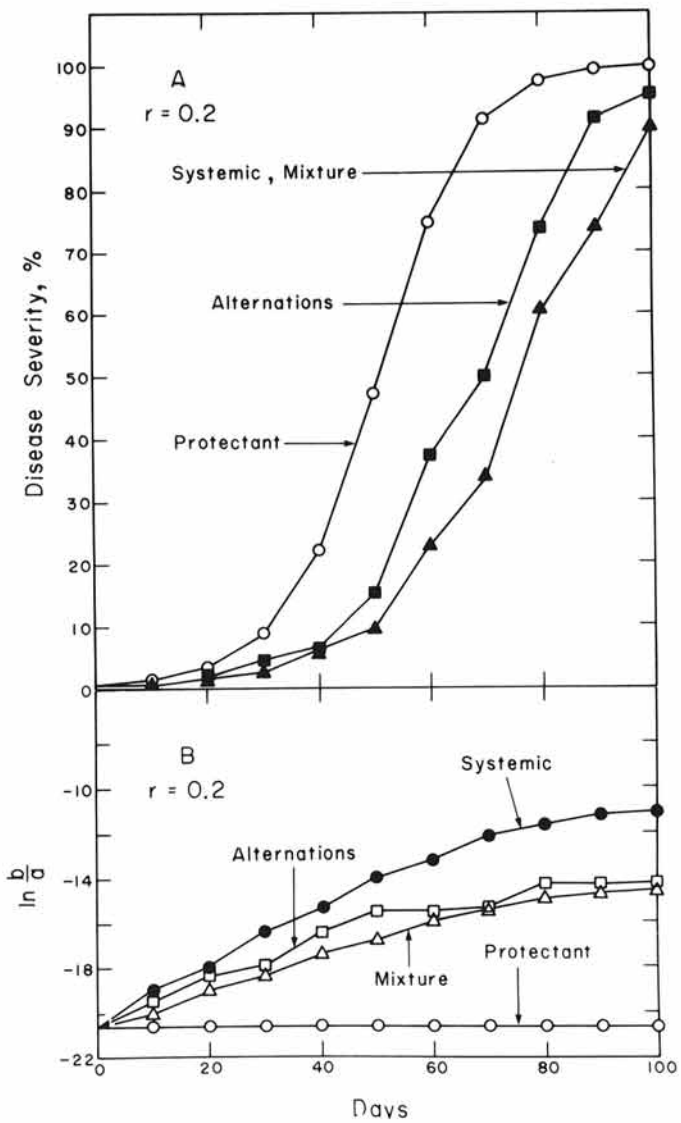

Fig. 3. A, Calculated percentage of infected leaf area in a crop managed with four types of fungicidal control strategies. **B,** Patterns of changes of the ratio (expressed as its natural logarithm) between subpopulation b (resistant to a systemic fungicide) and subpopulation a (sensitive to the systemic fungicide) as affected by the fungicidal strategy employed. Apparent infection rate = 0.2. The protectant is assumed to have no additive effect in mixtures with the systemic. Note that α ranged between -0.1 and -0.9 (α is defined as in b/a mixture$-\ln b/a$ alternations). Disease severity at time $0 = 5 \times 10^{-4}$. Initial frequency of $b = 5 \times 10^{-12}$. Coverage with the systemic changes from 0.99 at day 0 to 0.75 at day 100, and with the protectant from 0.99 to 0.5 at day 0 and 100, respectively. Weathering was assumed to linearly reduce activity of the systemic to 0% in 20 days and of the protectant to 0 in 10 days.

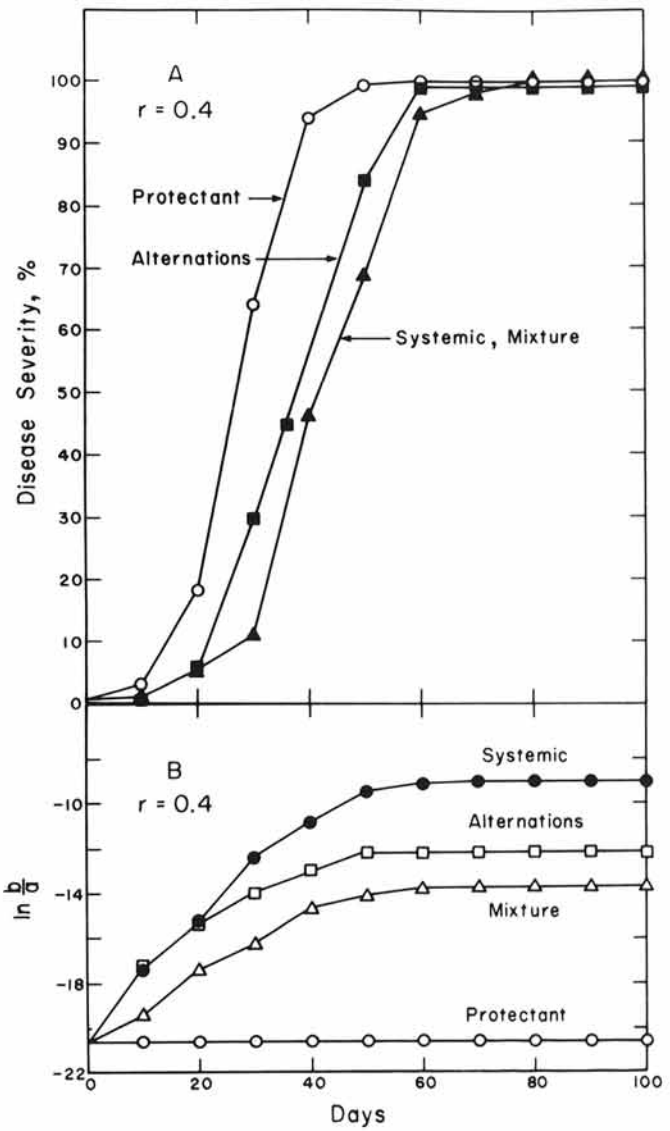

Fig. 4. A, Calculated percentage of infected leaf area in a crop managed with four types of fungicidal control strategies. **B,** Patterns of changes of the ratio (expressed as its natural logarithm) between subpopulation b (resistant to a systemic fungicide) and subpopulation a (sensitive to the systemic fungicide) as affected by the fungicidal strategy employed. Apparent infection rate = 0.4. The protectant is assumed to have no additive effect in mixtures with the systemic. Note that α ranged between -0.8 and -1.1 (α is defined as $\ln b/a$ mixture$-\ln b/a$ alternations). Disease severity at time $0 = 5 \times 10^{-4}$. Initial frequency of $b = 5 \times 10^{-12}$. Coverage with the systemic changes from 0.99 at day 0 to 0.75 at day 100, and with the protectant from 0.99 to 0.5 at day 0 and 100, respectively. Weathering was assumed to linearly reduce activity of the systemic to 0% in 20 days and of the protectant to 0% in 10 days.

and translocation of fungicides (1). In Table 2 a comparison is given between two control strategies with two plant coverage treatments. In treatment A, coverage with the systemic changes during the growing season from 0.99 at day 0 to 0.75 at day 100, and coverage with the protectant from 0.99 to 0.5. In treatment B, coverages change from 0.99 to 0.4, and 0.99 to 0.2 for the systemic and the protectant, respectively (Fig. 1). Incorporating these variables into the model shows that under either control strategy, disease development was lower and proportion of subpopulation *b* higher in treatment A than in treatment B (Table 2).

Dynamic changes in activity of fungicide because of weathering, D_s and D_p. Weathering and loss of fungicides due to washing, etc. are common phenomena in nature. Various degrees of fungicide weathering were incorporated into the model to assess their effect on disease development and on buildup of *b*. In Table 3, we assumed that the rate of weathering of the systemic between sprays (20 days) was 60, 20, and 10% so that the amount left active was 40, 80, and 90%, respectively (Fig. 1, inset). Weathering of the protectant was considered 100% (0% left active) in a 10-day period (Fig. 1, inset). Increasing rates of weathering resulted in increased disease development, but it also reduced rates of the buildup of the resistant genotype *b* relative to *a*. These contrasting processes occurred with the use of either a mixture or alternations. The mixture was superior to alternations in suppressing *b* except in two instances with low rates of weathering in which alternations gave slightly lower values of ln *b*/*a* towards the end of the growing season.

The effect of initial level of subpopulation *b*. The effect of varying initial levels of the resistant subpopulation *b* at three different apparent infection rates on the final proportion of subpopulation *b* is presented in Table 4. When the initial level of *b* was low, eg, 5×10^{-12} (disease severity = 0.05%, the proportion of the resistant subpopulation = 5×10^{-9}, ln *b*/*a* = −20.7) the sole use of the systemic resulted, at the end of a 100-day growing period, in final proportions of foliage infected with *b* of 6.8×10^{-10}, 1.3×10^{-5}, and 1.2×10^{-4} at *r* values of 0.05, 0.2, and 0.4, respectively. This means that in one growing season the resistant subpopulation increased by a factor of about 1.4×10^{2}, 2.6×10^{6}, and 2.4×10^{7} at *r* values of 0.05, 0.2, and 0.4, respectively. The increase in the resistant subpopulation *b* was smaller when alternations or a

TABLE 1. Frequency of the resistant subpopulation *b* of a plant pathogenic fungus, proportion of diseased tissue (*a* + *b*), and values of α in plants treated with fungicide mixtures with various degrees of additive action toward the sensitive subpopulation *a*

	Additive action of the protectant towards the sensitive genotype[a]											
	0			0.1			0.5			0.9		
Time (days)	ln *b*/*a*	Disease severity (%)	α	ln *b*/*a*	Disease severity (%)	α	ln *b*/*a*	Disease severity (%)	α	ln *b*/*a*	Disease severity (%)	α
10	−20.1	6.7×10^{-3}	−1.1	−20.0	5.9×10^{-3}	−1.0	−19.6	3.8×10^{-3}	−0.6	−19.1	2.4×10^{-3}	−0.1
50	−16.8	9.6×10^{-2}	−1.2	−16.5	7.3×10^{-2}	−0.9	−15.3	2.4×10^{-2}	+0.3	−14.1	7.8×10^{-3}	+1.5
100	−14.6	0.90	−0.3	−13.9	0.86	+0.4	−11.3	0.52	+3.0	−9.0	0.17	+5.3

[a] ln *b*/*a* at time 0 = −20.7. Disease severity at time 0 = 5×10^{-4}, *r* = 0.2. Initial frequency of *b* = 5×10^{-12}. Coverage with the systemic changes from 0.99 at day 0 to 0.75 at day 100, and with the protectant from 0.99 to 0.5 at day 0 and 100, respectively. Weathering of the systemic fungicide = 0.6 in 20 days. Weathering of the protectant fungicide = 1.0 (complete) in 10 days. The value of α = ln *b*/*a* mixture − ln *b*/*a* alternations represents the relative superiority (negative values) or inferiority (positive values) of mixtures compared with alternations in delaying the buildup of fungicide resistance relative to sensitivity in the pathogen population.

TABLE 2. Frequency of the resistant subpopulation *b* of a plant pathogenic fungus, proportion of diseased tissue (*a* + *b*), and values of α in plants treated with two fungicides each having two different rates of change in coverage of the foliage over time

	Treatment A[a]					Treatment B[b]				
	Mixture		Alternations			Mixture		Alternations		
Time (days)	ln *b*/*a*	Disease severity (%)	ln *b*/*a*	Disease severity (%)	α	ln *b*/*a*	Disease severity (%)	ln *b*/*a*	Disease severity (%)	α
10	−20.1	6.7×10^{-3}	−19.0	6.5×10^{-3}	−1.1	−20.2	6.9×10^{-3}	−19.1	6.9×10^{-3}	−1.0
50	−16.8	9.6×10^{-2}	−15.6	9.5×10^{-2}	−1.2	−17.3	0.17	−16.0	0.22	−1.3
100	−14.6	0.90	−14.3	0.90	−0.3	−16.3	0.99	−15.4	0.99	−0.9

[a] Treatment A: $C_s = 0.99 \rightarrow 0.75$; $C_p = 0.99 \rightarrow 0.5$. Treatment B: $C_s = 0.99 \rightarrow 0.4$; $C_p = 0.99 \rightarrow 0.2$.
[b] ln *b*/*a* at time 0 = 20.7. Disease severity at time 0 = $5 \times 10^{-4} \cdot r = 0.2$. Initial frequency of *b* = 5×10^{-12}. Weathering of the systemic = 0.6 in 20 days, and of the protectant = 1.0 in 10 days. α = ln *b*/*a* mixture − ln *b*/*a* alternations. The protectant is assumed to have no additive effect in mixtures with the systemic.

TABLE 3. Frequency of the resistant subpopulation *b* of a plant pathogenic fungus, proportion of diseased tissue (*a* + *b*), and values of α in plants treated with two fungicides with which the systemic exhibits three rates of weathering

	Rate of weathering of the systemic fungicide in 20 days[a]														
	60%[b]					20%					10%				
	Mixture		Alternations			Mixture		Alternations			Mixture		Alternations		
Time (days)	ln *b*/*a*	Disease severity (%)	ln *b*/*a*	Disease severity (%)	α	ln *b*/*a*	Disease severity (%)	ln *b*/*a*	Disease severity (%)	α	ln *b*/*a*	Disease severity (%)	ln *b*/*a*	Disease severity (%)	α
10	−20.1	6.7×10^{-3}	−19.0	6.5×10^{-3}	−1.1	−19.9	5.7×10^{-3}	−18.8	5.3×10^{-3}	−1.1	−19.9	5.4×10^{-3}	−18.8	5.3×10^{-3}	−1.1
50	−16.8	9.6×10^{-2}	−15.6	9.5×10^{-2}	−1.2	−15.2	2.2×10^{-2}	−13.1	3.9×10^{-2}	−2.1	−14.8	1.5×10^{-2}	−13.6	2.8×10^{-2}	−1.2
100	−14.6	0.90	−14.3	0.90	−0.3	−9.9	0.26	−10.9	0.68	+1.0	−8.9	0.13	−10.0	0.55	+1.1

[a] The protectant fungicide shows complete weathering (100%) in 10 days.
[b] Percentage systemic fungicide lost in 20 days after application. Note: ln *b*/*a* at time 0 = −20.7. Disease severity at time 0 = $5 \times 10^{-4} \cdot r = 0.2$. Initial frequency of b = 5×10^{-12}. Coverage with the systemic changes from 0.99 at day 0 to 0.75 at day 100, and with the protectant from 0.99 to 0.5 at days 0 and 100, respectively. α = ln *b*/*a* mixture − ln *b*/*a* alternations. The proctectant is assumed to have no additive effect in mixtures with the systemic.

TABLE 4. Final levels of a fungicide-resistant subpopulation of a plant pathogenic fungus and superiority of mixture over alternations (α) at the end of a 100-day growing season as influenced by initial level of b, apparent infection rate r, and fungicidal control strategy

			Fungicidal control strategy								
			Protectant		Systemic		Alternations		Mixture		
Initial b	$\ln b/a$	Apparent infection rate, (r)	Disease severity (%)	$\ln b/a$	Disease severity (%)	$\ln b/a$	Disease severity (%)	$\ln b/a$	Disease severity (%)	$\ln b/a$	α
5×10^{-12}	−20.7	0.05	8.6×10^{-11}	−20.7	6.8×10^{-10}	−17.6	3.6×10^{-10}	−18.4	2.4×10^{-10}	−18.7	−0.3
		0.2	9.9×10^{-10}	−20.7	1.3×10^{-5}	−11.1	6.1×10^{-7}	−14.2	4.0×10^{-7}	−14.6	−0.4
		0.4	9.9×10^{-10}	−20.7	1.2×10^{-4}	−9.1	4.9×10^{-6}	−12.2	1.0×10^{-6}	−13.7	−1.5
5×10^{-9}	−13.8	0.05	8.6×10^{-8}	−13.8	6.8×10^{-4}	−10.7	6.8×10^{-7}	−11.5	2.4×10^{-7}	−11.7	−0.2
		0.2	9.9×10^{-7}	−13.8	1.3×10^{-2}	−4.1	6.1×10^{-4}	−7.3	4.1×10^{-4}	−7.7	−0.4
		0.4	9.9×10^{-7}	−13.8	9.1×10^{-2}	−2.3	3.1×10^{-2}	−3.4	1.0×10^{-3}	−6.8	−3.4
5×10^{-6}	−6.9	0.05	8.6×10^{-5}	−6.9	6.8×10^{-4}	−3.8	3.6×10^{-4}	−4.7	2.4×10^{-4}	−4.9	−0.2
		0.2	2.9×10^{-4}	−6.9	0.73	1.0	0.31	−0.7	0.24	−1.0	−0.3
		0.4	9.9×10^{-4}	−6.9	0.84	1.7	0.54	0.2	0.38	−0.5	−0.7

[a]The protectant is assumed to have no additive effect in mixtures with the systemic.

mixture were used (but was still appreciably high) and almost negligible when a protectant fungicide was applied. A similar trend occurred, but at a higher magnitude, when the initial levels of b were higher. Thus, when initial levels of b were 5×10^{-9} and 5×10^{-6} and $r = 0.2$, the final proportion of b in plants treated with the systemic alone reached 1.3% ($\ln b/a = -4.1$) and 73% ($\ln b/a = 1.0$) of the total population of the pathogen, respectively, whereas in plants treated with a protectant the level of b did not exceed the values of 0.0001 and 0.003%, respectively.

If we assume that survivability (overwintering, for example) of the two subpopulations is equal, it is possible to predict from Table 4 the final proportion of b at the end of the second and third consecutive growing seasons. Consider, for example, that a mixture is used at $r = 0.4$; at the end of season 1, the ratio $\ln b/a = -13.7$. Season 2 starts with 0.5% foliage affected with initial level of b of 5×10^{-9} ($\ln b/a = -13.8$) and ends with 1% of the foliage affected by b ($\ln b/a = -6.8$). Season 3 starts with 0.5% of foliage affected with initial level of b of 5×10^{-6} ($\ln b/a = -6.9$) and ends with 38.2% of the foliage affected by the resistant subpopulation b.

TABLE 5. Differences among the models of Kable and Jeffery (7), Skylakakis (10) and Levy et al for effects of control strategies in the use of fungicides

Model features	Kable and Jeffery	Skylakakis	Levy et al
Time step	discrete	continuous	continuous
Spray coverage	included, static	not included	included, dynamic
Latent period	not included	included	not included
Competition between and within the two subpopulations	not included	not included	included
Fungicides decay	not included	not included	included, dynamic
Degree of resistance to the systemic	partial	partial	complete
Additive action of the protectant in a mixture	included	included	optional

DISCUSSION

The model presented in this paper describes disease progress and changes in frequencies of foliage affected by a fungicide-sensitive subpopulation and a fungicide-resistant subpopulation of a pathogen, during a growing season and in subsequent seasons, under various control strategies. The model also assesses the superiority (α) of mixture applications. The unique characteristic of this model is that it uses an absolute measure of percentage of infected leaf area for either the sensitive or the resistant subpopulations. The model is flexible enough to permit alterations in the parameters and variables. It allows the user to plan his own strategy in using the fungicide-at-risk for disease control by choosing whether he cares for a better control, for delaying the buildup of the resistant genotype, or for a compromise between the two.

Computer simulations of the model show that treatments with a systemic, either alone or in combination with a protectant, reduce disease development, but increase the frequency of the resistant genotype. The resistant genotype can attain a relative frequency greater than 50% ($b > a$, $\ln b/a > 0$) in the pathogen population within three growing seasons (15 sprays) of use of a systemic or of alternations. Such predominance of the resistant genotype may occur in one growing season if its initial level is high (5×10^{-6}) and $r \geq 0.2$.

This modeling exercise shows that the optimal fungicide application strategy (mixture or alternations) which suppress the development of fungicide-resistant genotypes in a pathogen population depends on a number of factors that might play a role in the field: initial frequency of the resistant genotype (which ranges in various fungi between 10^{-4} to 10^{-12}) (3); apparent infection rate (which reflects fitness and environmental conditions); plant coverage with fungicides (which depends on plant growth, spray practices, and fungicide redistribution) (1); rate of fungicide weathering (which depends on fungicide characteristics and environment, mainly rainfall) (1); and additive action of the protectant fungicide mixed with a systemic towards the sensitive genotype of the pathogen.

All of the simulation runs with nine combinations of initial frequency of a resistant genotype b and apparent infection rates showed that mixture application was superior ($\alpha < 0$) to alternations in delaying the buildup of the resistant genotype when there was no additive action in mixtures and fungicide weathering was rapid. Suppression of b was stronger (α more negative) with high r values, probably because of greater competition exerted by the sensitive genotype a.

Superiority of the mixture over alternation of fungicides was evident also when two ranges of coverage (both less than complete) with fungicides were tested, thus confirming the results of Kable and Jeffery (7) who found that "when spray coverage is less than complete, the efficacy of mixtures in delaying resistant buildup increases much faster than the efficacy of alternations, and mixtures are always preferable when coverage is $\leqslant$90%."

Computer simulations in these studies predict that with low rates of fungicidal weathering, however, alternate applications will be superior to mixed applications toward the end of the growing season when the proportion of the diseased tissue ($a + b$) was higher with alternations than with a mixture. Special attention should be given to fungicidal mixtures which possess additive action. An

additive action implies that a mixture has a better controlling effect on the sensitive genotype than the systemic alone in spite of the fact that the systemic translocates and persists better in the host than the protectant does. Simulation runs with increasing levels of additive action resulted in increased superiority of alternations over mixture which was associated with decreasing proportions of diseased tissue. Mixtures possessing additive action were inferior even to the systemic alone regarding the buildup of b.

As stated by Jeffery and Kable (7), "An ideal model may be a continuous process in which the selection pressure for the alternative organisms varies, depending on how recently the last spray was applied." The model presented in this paper fulfills such a requirement; it includes a dynamic change in both coverage and persistance of the fungicides.

In contrast to Skylakakis (10), who used a relationship valid for only the logarithmic stage of an epidemic, our model uses a logistic growth curve which takes into consideration the competition for disease-free host sites both within and between the two subpopulations. Basic differences between our model and those of Skylakakis (10), Kable and Jeffery (5,7) are listed in Table 5.

Although empirical validation of our model is required, the limited data available from our work in Israel seems to be consistent with its predictions. With *Pseudoperonospora cubensis* in cucumbers, it took about 2 yr of selection pressure of metalaxyl for resistant populations to predominate (9), and with *Phytophthora infestans* predominance of metalaxyl-resistant populations occurred within 4 wk, probably due to a high initial level of the resistant subpopulation and a high r value (2).

Conclusion. This model shows that a resistant genotype builds up at a faster rate when a systemic fungicide is applied alone, but will be delayed when alternative applications of a systemic and a protectant are given. Mixtures delay the buildup more than alternations except when the systemic degrades very slowly, or when the two fungicides in a mixture provide better control of the sensitive genotype than the systemic alone.

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