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Optimal rotation of insecticides to prevent the evolution of resistance in a structured environment

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Abstract

Several strategies have been used in insecticide resistance management to prevent the evolution of resistance, but the spatial aspects of insecticide application are crucially important among these strategies. Here, we consider a structured environment that consists of on-farm and off-farm fields where crops are planted periodically in on-farm fields during cultivation periods. We define the basic reproduction rate (R_0) of resistance as the expected number of offspring of a resistant individual divided by that of a susceptible individual under the condition that the proportion of resistance is extremely small; it is measured as the quantity per cycle of the cultivation period. We calculate $\log_e(R_0)$ using realistic dose-survival curves under a given fitness cost of resistance genes. The evolution of resistance occurs if and only if the $\log_e(R_0)$ value is larger than 0. Then, we propose a procedure for calculating the optimal design of rotational spraying that prevents the evolution of resistance, that is, the evolutionary stable strategy (ESS) for farmers, satisfying the mortality required for managing the abundance of insects. We consider the following controllable factors in calculating the optimal design: the dose of insecticide, the number of sprays, the number of different types of insecticides and potentially, the size of on-farm fields.

KEYWORDS

basic reproduction rate, dose-survival curves, evolutionary stable strategy for farmers, insecticide resistance management, on-farm/off-farm fields

1 | INTRODUCTION

Humans have developed a variety of chemicals to control harmful organisms, including insects, fungi and bacteria, that threaten food production as well as human health. The repeated evolution of resistance against these chemicals, however, is reducing our potential to find new chemicals for insecticides. Global climate change may further accelerate the evolution of resistance by increasing the amount of insecticide that is used against the increased abundance of insects (Maino, Umina, & Hoffmann, 2018; Yamamura, Yokozawa, Nishimori, Ueda, & Yokosuka, 2006). We should prolong the "useful life" of chemicals by implementing pre-emptive insecticide resistance management (IRM) strategies (Dusfour et al., 2019; Suzuki, 2012a; Suzuki, 2012b). Two strategies have been compared for many years after Coyne (1951): that is, mixture use of chemicals and rotational use of chemicals. Coyne (1951) recommended the rotational use of chemicals, claiming that the mixture use advocated by

manufacturers for fly-control measures in those days may "result in the development of fly-strains resistant to both insecticides at once." Sixty years later, REX Consortium (2013) reviewed the effects of these strategies from both theoretical and empirical studies. They showed that theoretical studies favored using a mixture of chemicals but that empirical studies yielded no such conclusion. On the other hand, the Insecticide Resistance Action Committee (IRAC) recommends the rotation-based resistance management program (Sparks & Nauen, 2015; Yamamoto, 2017). The mode of action (MoA) classification of types of insecticides, which is required for constructing the design of rotation, is provided on the IRAC website (http://www.irac-online.org/).

The spatial aspects of insecticide application are crucially important. Using a mixture of different types of insecticides corresponds to a special case of rotational use where the interval between the consecutive use of two types of insecticides approaches zero. Hence, mixture use and rotational use will yield no difference if the insecticide acts independently and if no spatial structure exists. The influence of spatial structure has been intensively discussed in the context of the high-dose/refuge (HDR) strategy for the management of Bt crops, which are genetically engineered crops for producing Bt toxins against insects (Huang, Andow, & Buschman, 2011; Ives & Andow, 2002). This strategy relies on the existence of "refuges," in which no insecticide is applied. Another use of spatial structure is seen in the "mosaic" application of insecticides, where we apply different insecticides continuously in the different spatial areas of the fields instead of providing refuges where no insecticide is applied (REX Consortium, 2013). In this paper, we consider a structured environment that consists of on-farm and off-farm fields (Figure 1a). Crops are planted periodically in on-farm fields during the cultivation period. Off-farm fields theoretically correspond to refuges in the HDR strategy, but off-farm fields rather correspond to the background fields that are given before creating the cultivation fields. HDR strategy considers controlling the size of refuges either for natural refuges or artificial refuges, while the size of background fields may be less controllable.

We utilize the basic reproduction rate to calculate the condition for the evolution of resistance. The basic

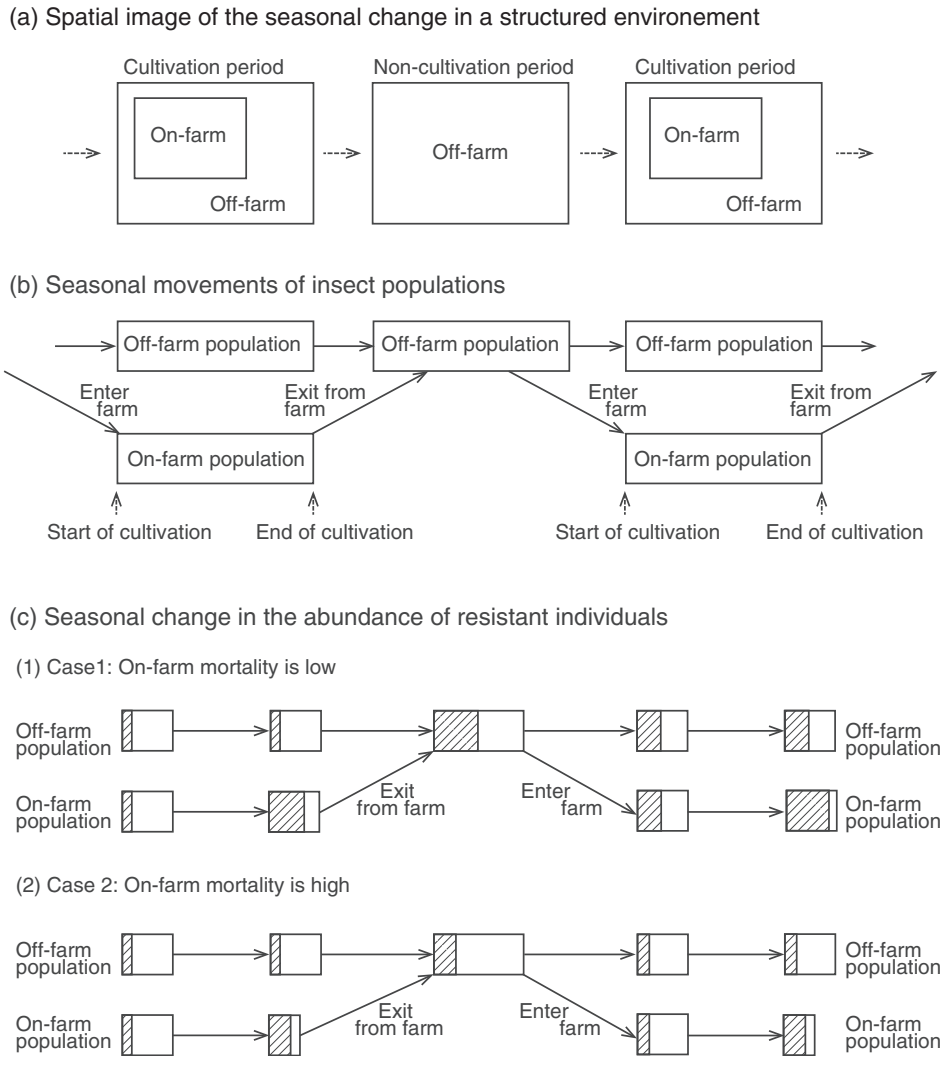

FIGURE 1 Schematic illustration of the mechanism for suppressing the evolution of resistance. (a) Spatial image of a structured environment. On-farm fields arise periodically in a structured environment. (b) Seasonal movements of individuals across on-farm and off-farm fields. The population is divided into two subpopulations at the beginning of the cultivation period. Natural selection for resistance occurs only for on-farm populations. (c) Seasonal change in the number of resistant individuals. Hatched rectangles indicate the abundance of resistant individuals. Open rectangles indicate the abundance of susceptible individuals. The global evolution of resistance is suppressed when on-farm mortality is sufficiently large, although the proportion of resistance increases locally during the on-farm period. Cultivation periods should be interpreted as generation periods if the insect species disperses at the end of each generation across on-farm and off-farm fields

reproduction number or the basic reproduction rate (usually denoted by R_0) is frequently used in epidemiological models to judge the condition where diseases invade epidemiological systems. The concept of R_0 has become somewhat popular in 2020 due to the prevalence of COVID-19. It was originally defined as "the expected number of secondary cases produced, in a completely susceptible population, by a typical infected individual during its entire period of infectiousness" (Diekmann, Heesterbeek, & Metz, 1990). R_0 denotes "R under condition 0" in the sense that it indicates the reproduction rate when the density of infected individuals is nearly zero. Several modifications of R_0 can be used to define the basic reproduction rate, depending on the system. Yamamura (1998) calculated the basic reproduction rate of the rice stripe virus disease per year, which is transmitted by the small brown planthopper *Laodelphax striatellus* (Fallén), to elucidate the required strength of control against the small brown planthopper, for eliminating the disease. Yamamura (2020) calculated the basic reproduction rate of the *Plum pox virus* (PPV) per infected Japanese plum tree to elucidate the required control area in which the host trees are removed to eradicate PPV. We apply a similar procedure here. We propose a procedure to calculate the optimal design of rotational spraying that prevents the evolution of resistance, that is, the evolutionary stable strategy (ESS) for farmers, satisfying the mortality required for managing the abundance of insects. We consider the following controllable factors in calculating the optimal design: the dose of insecticide, the number of sprays, the number of different types of insecticides and potentially, the size of on-farm fields. We first consider a situation in which the phenotype of the resistance gene is always resistant to insecticides. It corresponds to haploid insects that reproduce asexually or diploid insects in which the resistance gene is completely dominant. Then, we next show that the theory is approximately applicable to general genetic systems where the resistance gene is recessive or incompletely dominant.

2 | MODEL

2.1 | Effect of structured environments

We consider a structured environment as illustrated in Figure 1a; we assume that cultivation farms emerge periodically in fields, constructing a structured environment. The insect population is divided into two subpopulations, an off-farm population and an on-farm population, at the beginning of the cultivation period, as illustrated in Figure 1b. Each population repeats one or more generations within the cultivation period. Then, the two populations are mixed at the end of each cultivation period.

Figure 1c illustrates how the evolution of resistance can be suppressed in a structured environment. The proportion of resistance increases in the on-farm population due to the use of insecticides, as illustrated by the increase in the proportion of the hatched area in the on-farm population during the cultivation period. Let us compare two cases: (a) the mortality of the on-farm population is low and (b) the mortality of the on-farm population is high. If we can reduce the overall survival rate of the on-farm population, then the absolute number of resistant individuals becomes smaller, as indicated by the smaller hatched area of the on-farm population in Case 2 in Figure 1c, although the proportion of resistant individuals becomes larger within the on-farm population. Consequently, in Case 2, the proportion of resistance becomes smaller in the mixed population at the beginning of the non-cultivation period. That is, the global evolution of resistance over the entire field is suppressed, although the local evolution of resistance occurs within the on-farm population during the cultivation period.

Control measures other than insecticides are effective in reducing the frequency of sprays. Such a decrease in the frequency of sprays may suppress the evolution of resistance. However, even if the frequency of sprays is kept at the same, control measures other than insecticides are obviously effective in suppressing the evolution of resistance, as indicated in Figure 1c. If we can remove whole crops just after harvesting them, for example, then we may be able to suppress the evolution of resistance by killing the resistant individuals in the on-farm populations. If we cannot use such non-insecticide measures, then additional insecticides should be used to increase the mortality of on-farm populations. However, the selection pressure for the local evolution of resistance becomes stronger if we use additional insecticides, and hence, we should carefully explore the conditions to suppress the global evolution of resistance if we rely on additional insecticides.

2.2 | Basic reproduction rate of resistance

We consider the basic reproduction rate (R_0) of the proportion of resistance, that is referred to as the "basic reproduction rate of resistance" for simplicity. The reproduction rate of a proportion, under the condition that the proportion is extremely small, is generally given by the reproduction rate of numerator divided by the reproduction rate of denominator. Hence, we can define the

basic reproduction rate of resistance as the expected number of offspring of a resistant individual divided by that of a susceptible individual under the condition that the proportion of resistance is extremely small; it is measured as the quantity per cultivation period cycle, including one cultivation period and one non-cultivation period. The evolution of resistance occurs if and only if $\log_e(R_0) > 0$; the evolution is suppressed if and only if $\log_e(R_0) \le 0$. This criterion of evolution is closely related to the ESS. An ESS is defined as a phenotype such that, if almost all individuals have that phenotype, no alternative phenotype can invade the population (Maynard Smith, 1989, p. 126). Most classical literature discussed the ESS as a strategy for selfish genes, while we discuss the ESS as a strategy for farmers.

We first consider a situation in which the phenotype of the resistance gene is always resistant to insecticides. Let q be the proportion of individuals that remain on off-farm fields at the beginning of the cultivation period. Then, the proportion of the on-farm population is given by $1-q$ at the beginning of the cultivation period. The rate of increase in the on-farm population may be larger than that of the off-farm population because on-farm fields may provide dense monoculture of host plants and a smaller number of natural enemies for insects. Let ρ be the relative increase rate of the on-farm population in a condition without insecticides, as compared to the increase rate of the off-farm population. Then, the potential abundance of the on-farm population without insecticides is given by $(1-q)\rho$ while that of the off-farm population is given by q. Let us further define $\theta = q/[(1-q)\rho]$. The parameter θ is interpreted as follows:

$$\theta = \frac{\text{Potential abundance of the off-farm population}}{\text{Potential abundance of the on-farm population}}. \quad (1)$$

Let $s_i(x_i)$ be the survival proportion of susceptible insects when we used the ith type of insecticide of a logarithmic dose x_i in the field. Let $r_i(x_i)$ be the survival proportion of resistant insects when we used the ith type of insecticide of a logarithmic dose x_i. We focus on the basic reproduction rate of the resistance against the Type 1 insecticide. We assume that no cross-resistance occurs between the different types of insecticides. Let n be the total number of sprays in a cultivation period, and k be the number of sprays of insecticide Type 1 during the cultivation period. The survival rate of resistant individuals in a cultivation period is proportional to the multiplication of the survival rate over n sprays, that is, $(r_1(x_1))^k \prod s_i(x_i)$ where Π indicates the multiplication of survival rates over $n-k$ sprays for $i \neq 1$. Similarly, the survival rate of susceptible individuals in a cultivation period is proportional to $(s_1(x_1))^k \prod s_i(x_i)$. The potential abundance of the on-farm population without insecticides is given by $(1-q)\rho \times (\text{constant})$ at the end of the cultivation period, while the abundance of the off-farm population is given by $q \times (\text{constant})$ at the end of the cultivation period. Then, by summing these two quantities after incorporating the on-farm mortality due to insecticides, the total abundance of resistant individuals at the end of the cultivation period is given by $\left[(1-q)\rho\,(r_1(x_1))^k \prod s_i(x_i) + q\right] \times (\text{constant}) \times$ (proportion of resistance at the beginning of the cultivation period). Hence, the reproduction rate of resistant individuals is proportional to $(r_1(x_1))^k \prod s_i(x_i) + \theta$ at the end of the cultivation period, by the definition of θ. Similarly, the reproduction rate of susceptible individuals is proportional to $(s_1(x_1))^k \prod s_i(x_i) + \theta$ at the end of the cultivation period. The basic reproduction rate of the proportion of resistance is given by the ratio of these two quantities.

We further consider the difference in the reproduction rate between resistant individuals and susceptible individuals; resistant individuals sometimes have a smaller reproduction rate because of the fitness cost required for maintaining their resistance systems (e.g., Okuma et al., 2017; Shirai, Tanaka, Miyasono, & Kuno, 1998). We define the cost for resistance by

$$C = \frac{\begin{array}{c}\text{Increase rate of susceptible individuals}\\ \text{per cycle of cultivation period without insecticides}\end{array}}{\begin{array}{c}\text{Increase rate of resistant individuals}\\ \text{per cycle of cultivation period without insecticides}\end{array}}. \quad (2)$$

We have $C \ge 1$ and hence, we have $\log_e(C) \ge 0$. Then, we can express the logarithm of the basic reproduction rate by

$$\log_e(R_0) = \log_e\left[(r_1(x_1))^k \prod^{n-k} (s_i(x_i)) + \theta\right] - \log_e\left[(s_1(x_1))^k \prod^{n-k} (s_i(x_i)) + \theta\right] - \log_e(C). \quad (3)$$

The evolution of resistance occurs if and only if $\log_e(R_0) > 0$.

2.3 | Various designs of spraying

We can consider various spraying designs, such as those indicated in Figure 2. Spray designs can be categorized using several axes. We call the design "uniform" if the same pattern of spraying is used for all cultivation periods, while we can call the design "aggregated" if the sprays of a

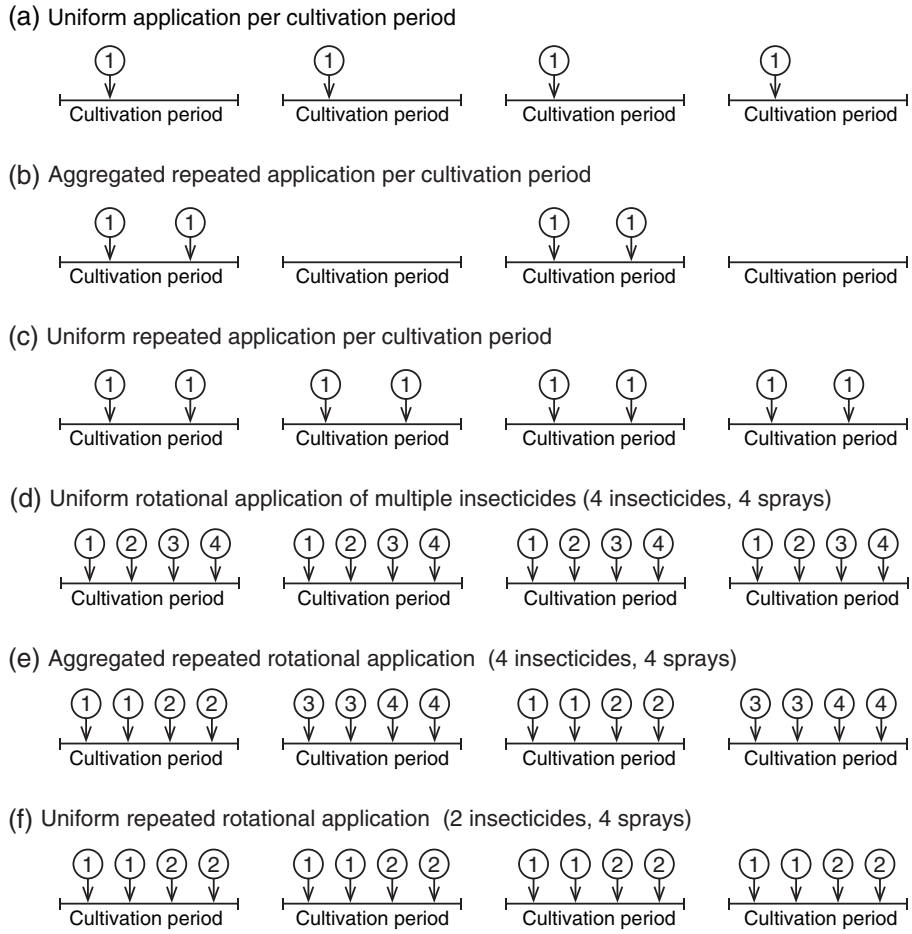

FIGURE 2 Examples of temporal arrangements of sprays. Arrows indicate the time of spraying. The different numbers inside the circles indicate the type of insecticide. (a), (b) and (c) correspond to the designs using a single type of insecticide while (d), (e) and (f) correspond to the designs using multiple types of insecticides. The corresponding models are as follows. (a) $n=k=1$ in Equation (3) or (4); (b) $n=k=2$ in Equation (4); (c) $n=k=2$ in Equation (3); (d) $n=4,k=1$ in Equation (3) or (4); (e) $n=4,k=2$ in Equation (4); (f) $n=4,k=2$ in Equation (3)

specific type of insecticide are aggregated in some cultivation periods. We call the design "repeated" if the same type of insecticide is used twice (or more) in the same cultivation period, while we call the design "rotational" if two or more types of insecticides are used in the same cultivation period. The meaning of the term "rotation" used in our paper is somewhat different from that used by IRAC (Sparks & Nauen, 2015). We will later explain about why we should adopt this modified definition.

Figure 2a shows the basic pattern of spraying, where insecticide Type 1 is sprayed once in each cultivation period. Figure 2b shows an aggregated design of spraying. The average number of sprays of the Type 1 insecticide was kept the same as that shown in Figure 2a, but the frequency of sprays was aggregated in half of the cultivation periods. Figure 2b also belongs to a repeated design for the Type 1 insecticide. Figure 2c corresponds to a uniform repeated design, where Type 1 insecticide is sprayed twice in all cultivation periods. The three panels, Figure 2d, Figure 2e and Figure 2f, correspond to rotational applications where two or more types of insecticides were used in the same cultivation period. Please note that the difference in the order of sprays within a cultivation period has no influence on the result.

In principle, the basic reproduction rate of resistance increases with increasing total number of sprays. Therefore, if we want to elucidate the mechanism for preventing the evolution of resistance, we should separate the influence of the spray pattern from the influence of the spray frequency. Thus, we should first examine the influence of aggregation when the total number of sprays is kept constant. If we keep the average number of sprays of Type 1 insecticide at one per cultivation period, Equation (3) is modified to

$$\log_e(R_0)=\frac{1}{k}\log_e\left[(r_1(x_1))^k\prod^{n-k}(s_i(x_i))+\theta\right]-\frac{1}{k}\log_e\left[(s_1(x_1))^k\prod^{n-k}(s_i(x_i))+\theta\right]-\log_e(C), \tag{4}$$

because the selection works only for $1/k$ of the cultivation periods.

The number of repeated applications of Type 1 insecticide, which is denoted by k, may be changed to several patterns. Let n_j and k_j be the jth pattern of n and k ($j=1,2,...,m$), respectively, and w_j be the proportion (weight) of the jth pattern. Let θ_j be the jth pattern of θ;

the quantity of θ may seasonally change depending on the seasonal change in the relative increase rate (ρ) of the on-farm population. Then, we obtain

$$\log_e(R_0) = \sum_{j=1}^{m} \left\{ w_j \log_e \left[(r_1(x_1))^{k_j} \prod^{n_j-k_j} (s_i(x_i)) + \theta_j \right] - w_j \log_e \left[(s_1(x_1))^{k_j} \prod^{n_j-k_j} (s_i(x_i)) + \theta_j \right] \right\} - \log_e(C). \quad (5)$$

Equation (3) corresponds to a special case of Equation (5) where $m = 1$, $w_j = 1$, while Equation (4) corresponds to a special case of Equation (5) where $m = 1$, $w_j = 1/k$.

2.4 | Dose-survival curves

We can calculate the basic reproduction rate using Equation (5) for any form of dose-survival curves, $r_i(x_i)$ and $s_i(x_i)$, but here, we use a logarithmic probit model, which is a typical form of a dose-survival curve, to demonstrate the calculation. The survival rate of a susceptible individual for the ith type of insecticide is given by a function of the logarithmic dose, x:

$$s_i(x_i) = \Phi(-a - bx_i), \quad (6)$$

where Φ indicates the cumulative distribution function of the standard normal distribution and a and b are constants. The biological foundation of Equation (6) is shown in Supporting Information S1. The latest version of all Supporting Information is placed at http://cse.naro.affrc.go.jp/yamamura/Optimal_rotation_of_insecticides.html. We use data from Willrich, Leonard, and Cook (2003). They examined the field mortalities of the adult brown stink bug, *Euschistus servus* (Say), at different doses of dicrotophos, an organophosphate insecticide, in the laboratory (on a cotton leaf) and fields (on the cotton boll of a living plant). They suggested that the number of live insects divided by the total number of observed insects at doses of $\exp(x_i) =$ 0.28, 0.45 and 0.45 (unit: kg ai/ha) were 27/40, 34/40 and 33/43, respectively. The probit regression of Equation (6) yields the following estimates: $\hat{a} = 1.56$ and $\hat{b} = 0.87$, where a hat ($\hat{}$) indicates the corresponding estimate.

We further consider a case in which the survival curve of resistant individuals is given by a parallel movement of that of susceptible individuals:

$$r_i(x_i) = \Phi(-a - b(x_i - \delta_i)), \quad (7)$$

where δ_i indicates the amount of resistance for the ith type of insecticide. Uchiyama and Ozawa (2017) examined dose-survival curves for diamide insecticides, chlorantraniliprole, in the smaller tea tortrix, *Adoxophyes honmai* Yasuda. The lethal concentration 50 values (LC_{50}) for the resistant and susceptible strains were 48.2 and 1.33 ppm, respectively. The ratio is $48.2/1.33 = 36.2$. Then, we use $\delta_i = \log_e(30)$ as an example.

Estimates of the dose-survival curves in the field are required for calculating the effect of insecticide rotation. However, it may be troublesome to estimate the curves for every combination of insecticides and crop types. If we know the general influence of spatial heterogeneity in the field on the dose-survival curves, we will be able to estimate the dose-survival curves in the field from the corresponding dose-survival curves examined in the laboratory. Such a calculation procedure is also indicated in Supporting Information S1.

2.5 | Fitness cost of resistance genes

We must specify the parameter C, which corresponds to the fitness cost for maintaining the resistance per cycle of the cultivation period, to calculate $\log_e(R_0)$. Let c be the ratio of the increase rate of susceptible individuals to resistant individuals per generation without insecticides. The off-farm population may reproduce also during the non-cultivation period. No insecticide is applied during the non-cultivation period, and hence only the resistance cost is working during the non-cultivation period. If one more generation emerges in the non-cultivation period, for example, one more $\log_e(c)$ is added to $\log_e(C)$. Let g_{on} and g_{off} be the number of generations in a cultivation period and a non-cultivation period, respectively. Then, we have the relation $\log_e(C) = (g_{on} + g_{off})\log_e(c)$. Fitness cost may be fairly large for several cases. The spinosad-resistant strain of *Spodoptera frugiperda* (J. E. Smith) represents a 49% reduction in the number of generated females as compared with susceptible strain (Okuma et al., 2017). It indicates $\log_e(c) = 0.7$ per generation. For simplicity, we use $\log_e(C) = 0.1$ in the following examples.

2.6 | Relative abundance of the off-farm population

Estimating the relative potential abundance of the off-farm population, denoted by θ, may be difficult in several cases. We must estimate the parameter θ for each set of on-farm and off-farm fields; the quantity of θ will change depending on the place. Let d_{on} and d_{off} be the density of individuals per unit area that are averaged over on-farm and off-farm, respectively, after the dispersal at the beginning of the cultivation period. Let A_{on} and A_{off} be the

area of on-farm and off-farm fields, respectively, which are defined in Figure 1a. Then, the proportion of individuals that remain in the off-farm fields at the beginning of the cultivation period, which is denoted by q, is calculated by

$$q = \frac{d_{\text{off}} A_{\text{off}}}{d_{\text{off}} A_{\text{off}} + d_{\text{on}} A_{\text{on}}}. \quad (8)$$

The quantities of d_{on}, d_{off}, A_{on} and A_{off} should be estimated via field observations after the completion of dispersal at the beginning of the cultivation period. If the apparent area of off-farm field is very large, however, insects may not be mixed well within the off-farm field. In such cases, we should identify the "effective area" of off-farm field within which insects are well mixed during the non-cultivation period. Then, such an effective area of off-farm field should be used as A_{off} in the calculation. On the other hand, the relative increase rate of individuals (ρ) of the on-farm population without insecticide should be estimated by observing the increase rates in the number of individuals in the off-farm and on-farm populations. Then, we will be able to estimate θ by $\hat{\theta} = \hat{q}/[(1-\hat{q})\hat{\rho}]$. Insect outbreaks are frequently seen in cultivation fields rather than natural fields (Elton, 1958). The dense monoculture in cultivation fields increases the survival rate of herbivores (Yamamura, 1989, 2002a; Yamamura & Yano, 1999). Hence, the quantity of ρ may be sometimes very large. We use the parameters $q = 0.5$ and $\rho = 4$ (i.e., $\theta = 0.25$) in the following calculations, for simplicity.

If we know the dispersal curve that describes the distribution of the dispersal distance of insects, then we may be able to estimate q without conducting the field observation on the density of individuals; we can estimate the quantity of q by summing the effective off-farm area weighted by the dispersal curve. A mark-recapture method is usually used for estimating the dispersal curves of insects, but it is sometimes difficult to mark small insects. Some internal marks may be useful in such cases. Yamamura (2020) used the virus, *PPV*, as an internal marker for estimating the dispersal curve of aphids and estimated that 50% of dispersing aphids land within 84 m, by using the gamma-model of Yamamura (2002b, 2004) and Yamamura et al. (2007) that describes the non-random movements of insects. Supporting Information S2 indicates how we can estimate q using the dispersal curve.

The resistance gene can also be used as an internal marker in estimating the quantity θ, if the resistance gene is already prevalent in the field; that is, a naturally marked population already exists without artificially releasing them. We cannot apply the calculation of R_0 to the resistance gene that is already prevalent, but we can calculate R_0 for the next insecticide that will replace the current insecticide if we could estimate the parameter θ from the current insecticide. Let η be the abundance of the effective off-farm population divided by that of the on-farm population at the end of a cultivation period. Let $\psi_{1,\text{on}}$ be the proportion of resistance in the on-farm field at the end of the cultivation period. Let $\psi_{2,\text{on}}$ be the proportion of resistance in the on-farm field at the beginning of the next cultivation period. If no additional generation occurs during the non-cultivation period, that is, if $g_{\text{off}} = 0$, we have an inequality about η:

$$\eta \geq \left(\frac{\psi_{1,\text{on}}}{\psi_{2,\text{on}}}\right) - 1. \quad (9)$$

Thus, $\hat{\eta} = \left(\hat{\psi}_{1,\text{on}}/\hat{\psi}_{2,\text{on}}\right) - 1$ is a conservative estimate of η in this case in a sense that we do not underestimate the possibility of evolution of resistance if we used this estimate of η. The quantity of η corresponds to θ/(average insecticidal survival rate of individual in a cultivation period). Hence, we can estimate θ in this situation. Further explanation is given in Supporting Information S2.

3 | EXAMPLES OF CALCULATIONS

3.1 | Single type of insecticide

We first examine the influence of multiple applications of a single type of insecticide on the basic reproduction rate before examining the influence of multiple applications of multiple types of insecticides. This corresponds to the cases of $n = k$ in Equation (3) or (4). Figure 3a indicates how the logarithm of the basic reproduction rate changes if we increased the number of sprays (n) in a cultivation period, keeping the average number of sprays to one. This design is a type of aggregated design. The comparison corresponds to the comparison between Figure 2a and Figure 2b. The quantity of $\log_e(R_0)$ was calculated by Equation (4) for $n = 1, 2, ..., 6$ using the parameters described above. In contrast, Figure 3b indicates how the logarithm of the basic reproduction rate changes if we increased the number of sprays of Type 1 in all cultivation periods. This design is a type of uniform design. The comparison corresponds to the comparison between Figure 2a and Figure 2c. The quantity of $\log_e(R_0)$ was calculated using Equation (3). The frequency of sprays of the Type 1 insecticide increases with increasing n in this design.

The bold curve in Figure 3a or Figure 3b indicates the single use of a single type of insecticide; it corresponds to Figure 2a. The quantity of $\log_e(R_0)$ increases with

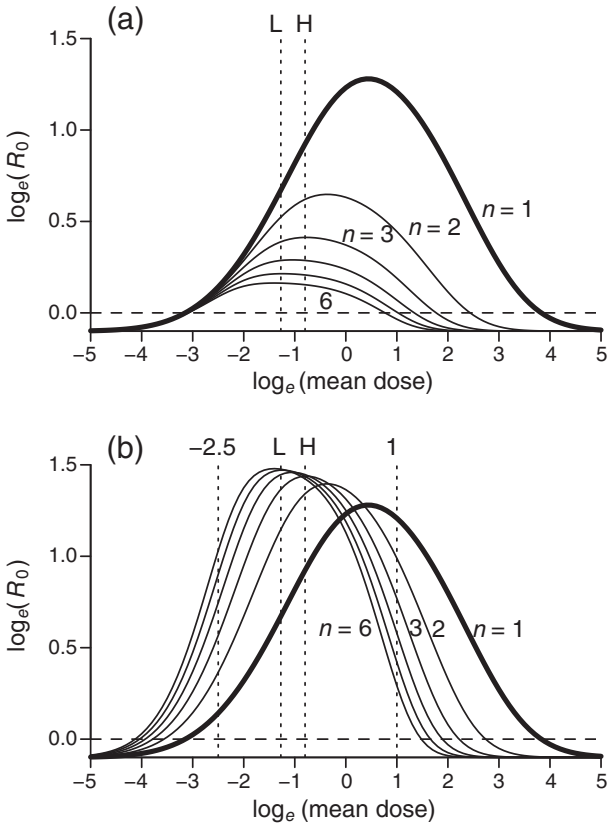

FIGURE 3 Influence of the number of sprays (n) on the basic reproduction rate of resistance when a single type of insecticide is used (i.e., when $n = k$). (a) Average number of sprays per cultivation period is fixed at 1. It corresponds to the comparison between Figure 2a and Figure 2b. (b) The same set of sprays is used for all cultivation periods. It corresponds to the comparison between Figure 2a and Figure 2c. L and H indicate two doses that were used by Willrich et al. (2003). L: Lower dose (0.28 kg ai/ha), H: Higher dose (0.45 kg ai/ha). The following parameters were used in Equations (3) and (4): $a = 1.56, b = 0.87, \delta_1 = \log_e(30), \theta = 0.25, \log_e(C) = 0.1$

increasing logarithmic dose if the dose is low, while it decreases with increasing logarithmic dose if the dose is high. In an unstructured environment where no off-farm population exists (i.e., if $\theta = 0$), $\log_e(R_0)$ increases monotonically with increasing logarithmic dose. The proof is given in Supporting Information S3. Thus, we cannot prevent the evolution of resistance in an unstructured environment, except for a mosaic application that we will discuss later. In contrast, in a structured environment, $\log_e(R_0)$ decreases with increasing logarithmic dose if the dose is high. The proof is given in Supporting Information S4. The influence of insecticide is multiplicative while the influence of off-farm individual is additive within the square brackets in Equation (3). Hence, if the mortality by insecticide is large, the influence of multiplicative part nearly vanishes; the additive part almost controls the results. In other words, nearly all on-farm individuals including resistant and susceptible individuals are killed by the high dose; the remaining on-farm population is zero or very small. Then, the off-farm population almost solely creates the on-farm population of the next cultivation period. That is, the fitness of resistant individuals (excluding the fitness cost) becomes identical to that of susceptible individuals if the dose is very high. In a structured environment, therefore, we can find the logarithmic dose over which the evolution of resistance is prevented if $\log_e(C) > 0$. In our example, the bold curve in Figure 3a or Figure 3b indicates that the evolution of resistance is prevented if we use a logarithmic dose higher than 4 for the design of single spraying ($n = 1$) because we have $\log_e(R_0) < 0$ for $x > 4$. However, we cannot use such a high dose of insecticide.

The comparison between the curves in Figure 3a indicates that we can decrease the quantity of $\log_e(R_0)$ by increasing the number of sprays (n) in a cultivation period, keeping the total number of sprays at a constant, except for a range of low doses. The proof is given in Supporting Information S5. However, the effect of the number of sprays is generally limited if we used only a single type of insecticide. Willrich et al. (2003) used two doses in the field; the doses are shown by vertical dotted lines accompanied by the letters L and H in Figure 3a. We can decrease the quantity of $\log_e(R_0)$ by increasing the number of sprays (n) in a cultivation period, but we cannot prevent the evolution of resistance even if we sprayed $n = 6$ times in a cultivation period for 1/6 of the cultivation periods if we adopted the dose used by Willrich et al. (2003), because the curve for $n = 6$ still lies in a positive area when the logarithmic dose is L or H in Figure 3a. The use of other types of insecticides is necessary in such doses to prevent the evolution of resistance.

The comparison of curves in Figure 3b indicates how the logarithm of the basic reproduction rate changes if we increase the number of sprays of Type 1 in all cultivation periods. Equations (3) and (4) indicate that, when we use a single type of insecticide (i.e., when $n = k$), we can calculate the quantity of $\log_e(R_0) + \log_e(C)$ of a uniform design by multiplying n to the corresponding quantity of an aggregated design. We already proved in Supporting Information S5 that the quantities of $\log_e(R_0)$ of different n values nearly coincide if the dose is low in an aggregated design. Therefore, for a uniform design, the curves of different n values cross each other at some logarithmic doses, as indicated by Figure 3b. Consequently, we can find that $\log_e(R_0)$ increases with increasing number of sprays (n) if the dose is low (e.g., $x = -2.5$ as indicated by the dotted vertical line) while $\log_e(R_0)$ decreases with increasing number of sprays (n) if the dose is high (e.g., $x = 1$ as indicated by the dotted vertical line). Thus, the increase in the number of sprays (n) in a cultivation

period effectively prevents the evolution of resistance if the dose is sufficiently high, but the increase in the number of sprays rather accelerates the evolution if the dose is low.

3.2 | Multiple types of insecticides with a fixed number of sprays

We next examine the spraying design using multiple types of insecticides, since Figure 3 indicated that the design using a single type of insecticide cannot easily prevent the evolution of resistance in our example, that is, we cannot easily keep $\log_e(R_0) \le 0$ for the design using a single type of insecticide. We assume that the dose-survival curves of resistant and susceptible individuals are the same for all types of insecticides, for simplicity; we use the same parameters described above for all dose-survival curves.

Figure 4a indicates the influence of the number (k) of repeated uses of the Type 1 insecticide for aggregated designs. We consider a design where the number of sprays in a cultivation period is fixed at $n = 4$ for convenience. This corresponds to the comparison between Figure 2d and Figure 2e. The curve for $k = 4$ in Figure 4a corresponds to a design where the Type 1 insecticide is repeatedly sprayed four times in some cultivation periods while Type 1 insecticide is used only 1/4 of the total cultivation periods. The curve for $k = 4$ is the same as the curve for $n = 4$ in Figure 3a. We can find from Figure 4a that we have $\log_e(R_0) < 0$ for $k \le 2$ if we adopted the dose H. This indicates that the repeated use of insecticides is permitted up to two times in each cultivation period if we used the dose H. The spray design of $k = 1$ can be expressed as $\{1,2,3,4\}\{1,2,3,4\}$, where the different numbers indicate different types of insecticides; the braces { } indicate one cultivation period cycle. The spray design of $k = 2$ is expressed as $\{1,1,2,2\}\{3,3,4,4\}\{1,1,2,2\}\{3,3,4,4\}$. The design of $k = 2$ will be optimal because only two types of insecticides are used for each cultivation period. The designs of $k = 3$, such as $\{1,1,1,4\}\{2,2,2,4\}\{3,3,3,4\}$ $\{1,1,1,4\}\{2,2,2,4\}\{3,3,3,4\}$, are not permitted; the evolution of resistance occurs if we used $k = 3$. On the other hand, if we adopted the lower dose L, we have $\log_e(R_0) < 0$ only for $k = 1$. Hence, the evolution of resistance is prevented only if we adopted the spray design of $\{1,2,3,4\}\{1,2,3,4\}$ when we adopted the lower dose L.

Figure 4b indicates the quantity of $\log_e(R_0)$ in uniform designs where the same set of sprays is used for all cultivation periods. This corresponds to the comparison between Figure 2d and Figure 2f. The curve for $k = 4$ is the same as the curve for $n = 4$ in Figure 3b. The total number of sprays of the Type 1 insecticide increases in proportion to k in these designs, and hence, the quantity of $\log_e(R_0)$ is larger than that in Figure 4a for $k > 1$.

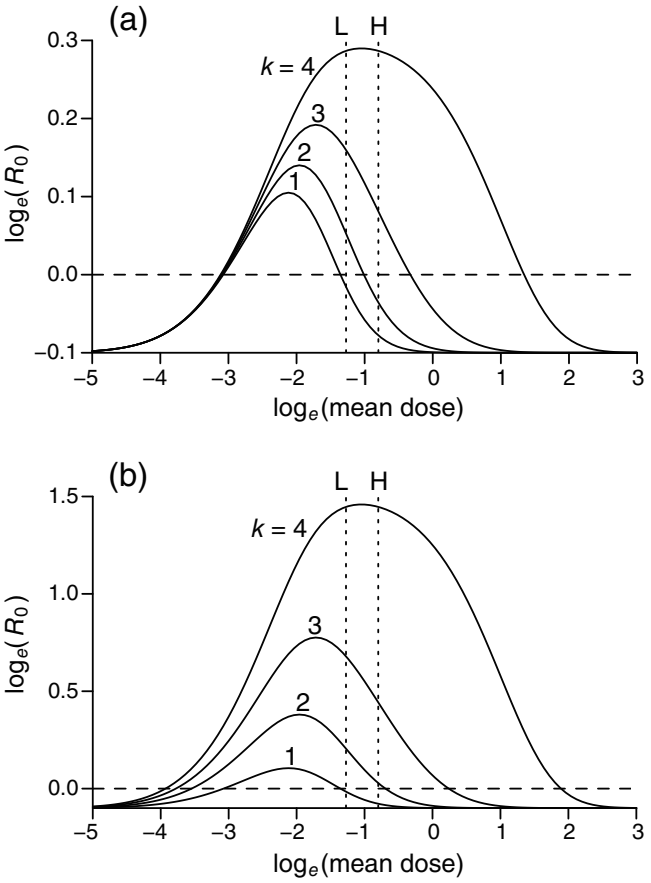

FIGURE 4 Influence of the number of repeated uses (k) of the same type of insecticide on the basic reproduction rate of resistance. Total number of sprays in a cultivation period was fixed at $n = 4$. (a) Average number of sprays of the Type 1 insecticide per cultivation period was fixed at 1. It corresponds to the comparison between Figure 2d and Figure 2e. (b) The same set of sprays was used for all cultivation periods. It corresponds to the comparison between Figure 2d and Figure 2f. The curve for $k = 4$ indicates the cases where the same type of insecticide was used for all four sprays in the same cultivation period. The curve of $k = 1$ indicates the cases where a different type of insecticide was used for each of the four sprays in the same cultivation period. The meanings of L and H are the same as those in Figure 3. The same parameters were used as in Figure 3

Please note that the vertical axis is different between Figure 4a and Figure 4b. We have $\log_e(R_0) < 0$ only for $k = 1$ in Figure 4b for both doses, L and H. In these uniform designs, therefore, we can prevent the evolution of resistance only if we adopted the design of $\{1,2,3,4\}\{1,2,3,4\}$, even if we used the higher dose H.

3.3 | Multiple types of insecticides with a fixed amount of total mortality

We compared $\log_e(R_0)$ for a fixed number of sprays (n) in the above section for the purpose of explanation, but the

number of sprays will be rather determined by the abundance of insects in the field. If the abundance is large, then the total mortality must be increased by increasing the number of sprays (n). Hence, we should calculate the optimal design of sprays for a given amount of mortality. Figure 5 indicates the logarithmic basic reproduction rate, $\log_e(R_0)$, calculated for uniform spray designs, for sets of the number of sprays per cultivation period (n) and the number of repeated applications (k). The number of sprays (n) was calculated to satisfy the required mortality expressed by $-\log_e(\text{survival rate})$. To enhance the interpretability of the graph, we plotted the quantity of $\log_e(R_0)$ calculated for $-\log_e(\text{survival rate})$ by a discrete step of 0.1.

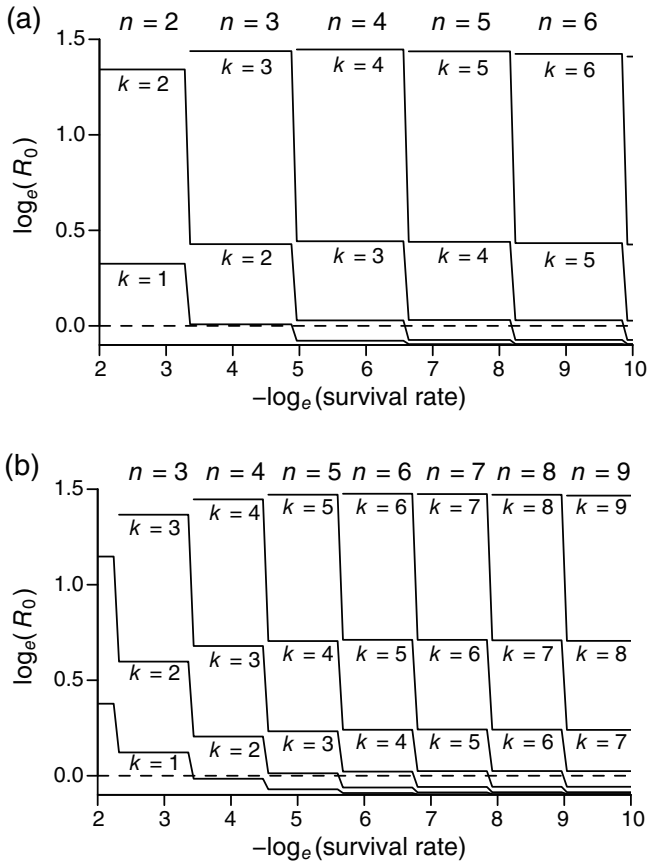

FIGURE 5 Influence of the required amount of mortality, $-\log_e(\text{survival rate})$, on the optimal uniform design of sprays. The logarithmic basic reproduction rate, $\log_e(R_0)$, was plotted for sets of the number of sprays per cultivation period (n) and the number of repeated applications (k) for the uniform spray designs. The required number of sprays (n) is shown in the upper side of graph; the quantity of the required n increases with increasing required amount of mortality. (a) Higher dose (0.45 kg ai/ha). (b) Lower dose (0.28 kg ai/ha). Other parameters are the same as those used in Figure 3. The combination of n and k that satisfies $\log_e(R_0) \le 0$ should be used for preventing the evolution of resistance, achieving the required amount of mortality

Figure 5a indicates the quantity of $\log_e(R_0)$ for the logarithmic dose $x = \mathrm{H} = \log_e(0.45)$, which is the higher dose used by Willrich et al. (2003). The upper bound of the quantity of $\log_e(R_0)$, which corresponds to $n = k$, was nearly constant in this case, even when we changed the mortality. This corresponds to the characteristics of the curves with the H dose in Figure 3b; the quantity of $\log_e(R_0)$ for the dose H was nearly constant even when we changed the number of sprays (n) in Figure 3b. If we want to realize a mortality of $-\log_e(\text{survival rate}) = 6$, for example, then the required number of sprays would be $n = 4$ per cultivation period. This case was already discussed in Figure 4b; we must use different types of insecticides for each of the four sprays to prevent the evolution of resistance in this case.

We must realize a larger amount of mortality by increasing the number of sprays (n) when the abundance of insects is large. If a mortality of $-\log_e(\text{survival rate}) = 9$ is required, for example, then the required number of sprays would be $n = 6$ if we used a logarithmic dose of $x = \mathrm{H} = \log_e(0.45)$, as indicated in Figure 5a. We have $\log_e(R_0) < 0$ for $k \le 3$ in this case, and hence, the repeated use of the same type of insecticide is permitted up to three times. Thus, we can use a design such as $\{1,1,1,2,2,2\}\{1,1,1,2,2,2\}$ using two types of insecticides. This will be the optimal design of spraying in this case to achieve the required mortality, preventing the evolution of resistance.

We should reduce the number of sprays when the abundance of insects is small, so that we can avoid the negative influence of sprays on natural enemies or other organisms living in the on-farm fields. This will be an important principle when we are promoting integrated pest management (IPM). If we want to realize a smaller mortality such as $-\log_e(\text{survival rate}) = 4$, then the required number of sprays should be $n = 3$, as indicated in Figure 5a. In this case, however, we cannot achieve $\log_e(R_0) \le 0$ even when we adopted $k = 1$; we cannot prevent the evolution of resistance even if we used a different type of insecticide for each of the three sprays. We should adopt a larger number of sprays, such as $n = 4$ if we want to prevent the evolution of resistance, which contradicts the principle of IPM. Thus, IRM sometimes contradicts IPM. In such cases, we can consider the use of different doses of insecticides. Figure 5b indicates the quantity of $\log_e(R_0)$ for a logarithmic dose of $x = \mathrm{L} = \log_e(0.28)$, which is the lower dose used by Willrich et al. (2003). If we want to realize a mortality of $-\log_e(\text{survival rate}) = 4$, then the required number of sprays should be $n = 4$. In this case, we have $\log_e(R_0) < 0$ when we adopted $k = 1$. Hence, we can prevent the evolution of resistance if we used a different type of insecticide for each of the four sprays.

4 | INFLUENCE OF GENETIC SYSTEMS

We assumed a situation where the phenotype of the resistance gene is always resistant to insecticides in the above argument, for simplicity. This theory is directly applicable to haploid insects that reproduce asexually or diploid insects in which the resistance gene is dominant. We can further show that the above argument is applicable to various genetic systems, in principle. We calculate the expectation of the basic reproduction rate of the proportion of resistance for various mating systems. Random binomial fluctuation will arise in the actual dynamics for the proportion of resistant phenotype as well as the proportion of resistance gene. We currently ignore such demographic fluctuations, for simplicity.

4.1 | Incomplete dominance gene

If the resistance gene is incompletely dominant in diploid insects, two types of resistance phenotypes will appear, which correspond to the homozygote and heterozygote of the resistance gene. In calculating the basic reproduction rate, we must consider a situation in which the proportion of the resistance gene is extremely small. Most resistance genes are included in heterozygotes in such situations. Hence, we can calculate the basic reproduction rate by using the dose–response curve (and the fitness cost) of heterozygote individuals in this case, in principle. Then, the evolution of resistance occurs if and only if $\log_e(R_0) > 0$ for the $\log_e(R_0)$ calculated by Equation (5) using the parameters of the heterozygote. However, if some kinds of assortative mating are performed locally, homozygote individuals emerge even if the proportion of resistance is extremely small. In such cases, we should use the parameters for homozygote individuals instead of heterozygote individuals to avoid the underestimation of the possibility of evolution.

4.2 | Recessive gene

The calculation of the basic reproduction rate becomes complicated if the resistance gene is recessive in a diploid insect because an individual having a resistance gene does not always indicate resistance. We first consider a special case in which only one generation arises in each cultivation period. Let us assume that the resistance phenotype appears at random for u cultivation periods among the U total cultivation periods. The component of $\log_e(R_0)$ equals 0 in a cultivation period where the resistance phenotype does not appear because the increasing rate of the resistance gene is the same as that of the susceptible gene in that cultivation period. Hence, the calculation of $\log_e(R_0)$ corresponds to a sampling problem in which we draw a sample of size u at random from the population of size U. The expectation of the sum of a random sample of size u is larger than 0 if and only if the sum of all U items of a population is larger than 0 (see, e.g., Cochran, 1977). Therefore, the evolution of resistance occurs if and only if $\log_e(R_0) > 0$ for the $\log_e(R_0)$ calculated by Equation (5). However, if the insect repeats two or more generations in each cultivation period, then the resistance phenotype will only appear at a part of generations in a cultivation period, and hence, the resistance gene will not experience k times sprays of the Type 1 insecticide during the cultivation period. Consequently, the actual quantity of $\log_e(R_0)$ becomes smaller. Hence, we can say that the evolution of resistance does not occur if we know $\log_e(R_0) \le 0$ for the $\log_e(R_0)$ calculated by Equation (5), but we cannot say that the evolution of resistance occurs even if we know $\log_e(R_0) > 0$ for the $\log_e(R_0)$ calculated by Equation (5) unless further conditions (such as those we see later) are specified.

If the number of applications of the Type 1 insecticide in one generation is fixed at a constant, we can calculate the basic reproduction rate by replacing the number of applications of the Type 1 insecticide in one cultivation period in Equation (5) by the number of applications of the Type 1 insecticide in one generation; this is because the resistance phenotype will arise at most once in a cultivation period when the frequency of the resistance gene is extremely small. Let h_j be the number of applications of the Type 1 insecticide that is applied in one generation in the jth pattern of sprays. Equation (5) should be modified to

$$\log_e(R_0) = \sum_{j=1}^{m} g_{\mathrm{on},j} \left\{ w_j \log_e \left[(r_1(x_1))^{h_j} (s_1(x_1))^{k_j - h_j} \prod^{n_j - k_j} (s_i(x_i)) + \theta_j \right] - w_j \log_e \left[(s_1(x_1))^{k_j} \prod^{n_j - k_j} (s_i(x_i)) + \theta_j \right] \right\} - \log_e(C), \tag{10}$$

where $g_{\mathrm{on},j}$ indicates the number of generations in a cultivation period, which may change depending on the conditions such as the temperature. The evolution of resistance occurs if and only if $\log_e(R_0) > 0$ for the $\log_e(R_0)$ calculated by Equation (10) in this case.

If some kinds of assortative mating are performed locally, the resistance phenotype may arise twice or more in a cultivation period even if the frequency of the resistance gene is extremely small. In such cases, we cannot use Equation (10) even if the number of applications of the Type 1 insecticide in one generation is fixed at a constant. Then, we should use Equation (5) as a conservative

approximation to avoid the underestimation of the possibility of evolution.

5 | DISCUSSION

We proposed a procedure to calculate the optimal spraying design to prevent the evolution of resistance, that is, the ESS for farmers. We can prevent the evolution of resistance only if $\log_e(C)$ is larger than 0, that is, only if some fitness cost exists for maintaining the resistance. However, such a cost has not been well studied for many problems of resistance. We cannot calculate the condition for preventing the evolution of resistance in such cases, but we can use a pre-determined quantity of $\log_e(C)$ as an index to indicate the strength of IRM. If we want to strongly delay the evolution of resistance, that is, if we want to strongly extend the "useful life" of a new insecticide, then we should calculate the spraying design by using a small quantity of $\log_e(C)$ that is close to 0. Such a spraying design will be characterized by (a) a higher dose, (b) a larger number of sprays (i.e., a larger n), (c) a smaller number of repeated uses of the same type of insecticide (i.e., a smaller k) and (d) a smaller quantity of on-farm fields (i.e., a larger θ). We can conversely calculate the threshold quantity of $\log_e(C)$ above which we can prevent the evolution by the spray design we are currently using. If such a threshold cost proves to be too large, we should consider revising our current spraying design.

The actual speed of evolution greatly varies depending on the genetic systems and the frequency of resistance genes, as is illustrated in Supporting Information S6 (Beverton & Holt, 1957). Simulation experiments will be required if we want to calculate the evolutionary speed, and hence, we cannot easily control the speed of evolution explicitly in most cases. In contrast, we can explicitly control the possibility of evolution by using the condition of $\log_e(R_0) \leq 0$, as discussed above. Therefore, the basic reproduction rate will be practically more useful than the speed of evolution as a measure for judging the effects of different strategies against the evolution of resistance. The quantities of the relative increase rate of the on-farm population per cultivation period (ρ) and the cost for resistance per cultivation period (C) will change if the number of generations in a cultivation period changes due to the change in temperature depending on the season and year. We should judge the possibility of evolution by calculating the temporal mean of $\log_e(R_0)$ over various ρ and C in such situations.

Several modifications may be required when applying the model to actual fields. For example, we assumed that the insects on off-farm and on-farm fields are mutually mixed only at the end of the cultivation period for simplicity. The lack of exchange between off-farm and on-farm populations during the cultivation period is a critical assumption. Such an assumption may be approximately appropriate for several insects, such as the small brown planthopper *L. striatellus* in Kanto district, Japan. The planthoppers of the overwintering generation live in the ridge of paddy fields in winter. They enter wheat or barley fields in May, and first-generation adults in June enter paddy fields in which they live three or four generations. Several other insect species may disperse before the end of the cultivation period. Our model is still applicable to such insects, but we must change the interpretation of the model. If the insects in on-farm fields disperse to mix with the insects in off-farm fields at the end of each generation, for example, then one cycle of the cultivation period in the model should be interpreted as one generation. Such a generation model was intensively discussed by Sudo, Takahashi, Andow, Suzuki, and Yamanaka (2017). Our model will not be applicable, however, if insects are continuously dispersing across on-farm and off-farm fields within each generation. The resistance gene will not experience sprays for specified times in such cases, and hence we may not be able to prevent the evolution of resistance.

The interpretation of the model should also be modified if we adopt a "mosaic" application of insecticides, where different types of insecticides are applied in the different spatial areas of on-farm fields. The mosaic application will be especially useful when no off-farm fields exist. Let us consider a case where we provide two types of mosaic patches, one of which does not include Type 1 insecticide, in a situation where no off-farm fields exist. As an example, we assume a uniform mosaic application where the half of the mosaic patches have a uniform design of $\{1,1\}\{1,1\}\cdots$ while the remaining half patches have a uniform design of $\{2,2\}\{2,2\}\cdots$. We can alternatively assume an out-of-phase aggregated mosaic application where the half of the mosaic patches have an aggregated design of $\{1,1\}\{2,2\}\{1,1\}\{2,2\}\cdots$ while the remaining half patches have an aggregated design of $\{2,2\}\{1,1\}\{2,2\}\{1,1\}\cdots$. Let us assume that two types of mosaic patches are separated by barriers during the cultivation period, but that the populations are mixed well at the end of the cultivation period by removing the barriers. Then, we can calculate the logarithmic basic reproduction rate from Equation (5) assuming the spray design of $\{1,1\}\{2,2\}\{1,1\}\{2,2\}\cdots$, by substituting $\theta = 0.5$ which was calculated from $q = 0.5$ and $\rho = 1$. An out-of-phase aggregated mosaic application will be more robust than a uniform mosaic application in certifying $\theta = 0.5$, because the bias caused by the spatial heterogeneity in ρ will be reduced in an out-of-phase aggregated mosaic application.

IRAC recommends "block rotation," where a block (or a window) is defined as a pest generation or a crop growth stage (Sparks & Nauen, 2015). In this strategy, one or more applications of the same insecticide are permitted within a block. However, a compound from the same MoA group as the prior block is not permitted to be treated in the next block. If the insects are mixed well at the end of each block, then a block corresponds to a cultivation period in our model. In this case, a block rotation of IRAC corresponds to an aggregated repeated application as for a specified type of insecticide in our definition (e.g., Figure 2b). The comparison between the curves in Figure 4a indicates that the quantity of $\log_e(R_0)$ increases with increasing number of repeated uses (k) of the same sprays in a cultivation period, except for a range of low doses. The proof is given in Supporting Information S7. Thus, the basic reproduction rate of an aggregated repeated spray such as $\{1,1\}\{2,2\}\cdots\{1,1\}\{2,2\}\cdots$ is larger than that of the uniform rotational spray such as $\{1,2\}\{1,2\}\cdots\{1,2\}\{1,2\}\cdots$. That is, the block rotation accelerates the evolution of resistance instead of preventing the evolution of resistance in this case. Thus, a block rotation should not be recommended. It should be noted that a block rotation might cause an erroneous impression because, for example, the basic reproduction rate of the Type 1 insecticide for a design of $\{1,1\}\{2,2\}\cdots\{1,1\}\{2,2\}\cdots$ is much smaller than that of $\{1,1\}\{1,1\}\cdots\{1,1\}\{1,1\}\cdots$, as indicated by the comparison of the $n=2$ curves in Figure 3a and Figure 3b. However, such a comparison is not meaningful; the total number of sprays should be the same for all types of insecticides, in principle, because we are preventing the evolution of resistance for all types of insecticides. Hence, the basic reproduction rate of the block rotational design of $\{1,1\}\{2,2\}\cdots\{1,1\}\{2,2\}\cdots$ should be compared with that of the sequential repeated use of the same sprays $\{1,1\}\{1,1\}\cdots\{2,2\}\{2,2\}\cdots$. Then, the basic reproduction rates are obviously the same; a block rotation has no effect in this case. In addition, please be careful about the difference in terminology. An aggregated repeated application such as $\{1,1\}\{2,2\}\cdots\{1,1\}\{2,2\}\cdots$ is called a rotational application by IRAC, while the effect of a uniform rotational application such as $\{1,2\}\{1,2\}\cdots\{1,2\}\{1,2\}\cdots$ is theoretically the same as that of the mixture application if no interaction exists between insecticides. If we use the terminology of IRAC, therefore, we can say that a mixture application is theoretically superior to a rotational application; a rotational application cannot be an effective measure in IRM in this terminology. We should therefore define the term "rotation" as the sequential exchange of insecticides that is performed within an interval between the consecutive two dispersal events of insects.

We will be able to objectively calculate the optimal design of spraying using Equation (5). However, to apply the method appropriately, we should also intuitively understand the mechanism for suppressing the evolution of resistance. In the structured environment shown in Figure 1, the dose of the insecticide is spatially heterogeneous in the sense that the dose is zero in off-farm fields, while it is non-zero in on-farm fields. On the other hand, the spatial heterogeneity in the dose of insecticides increases the basic reproduction rate of resistance, as illustrated in Figure S1. Thus, the spatial heterogeneity in a structured environment is quite different from the spatial heterogeneity we usually refer to for the dose of insecticides. The dose of insecticides in a structured environment is bifurcated; that is, insects in a structured environment scarcely encounter the intermediate dose, which yields many individuals with resistance. We cannot easily modify the environmental structure in most cases, but we should further consider conditions that enhance such bifurcation characteristics in the environment.

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CONFLICT OF INTEREST

The author declares no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Optimal rotation of insecticides to prevent the evolution of resistance in a structured environment

by Kohji Yamamura (March 7, 2021; A small misprint was corrected on Nov 19, 2022)

Supporting Information S1:
Dose-survival curves in the laboratory and field

Dose-survival curve in the laboratory

In this Supporting Information, we derive the logarithmic probit model (Equation (6)) by considering the potential mechanisms for inducing mortality. It is reasonable to assume that some types of lethal substances increase within an insect body after exposure to insecticide. We assume that the insect dies if the amount of lethal substance is larger than a threshold. We denote the amount of such substance by μ. We empirically assume that the expected amount of lethal substance $\mathrm{E}(\mu)$ increases linearly with increasing logarithmic dose of insecticide, $\log_e(y)$:

$$\mathrm{E}(\mu) = a_\mathrm{W} + b_\mathrm{W}\log_e(y), \tag{11}$$

where a_W and b_W are constants. The actual quantity of μ will fluctuate stochastically, depending on the condition within the insect body. If μ is given by the sum of many random factors that act independently, then the central limit theorem enables us to use a homoscedastic normal distribution, irrespective of the original form of distribution of each random variable. Thus, μ is given by

$$\mu = a_\mathrm{W} + b_\mathrm{W}\log_e(y) + e_\mathrm{W}, \qquad e_\mathrm{W} \sim N(0, \sigma_\mathrm{W}^2), \tag{12}$$

where e_W is a random variable that follows a normal distribution, $N(0, \sigma_\mathrm{W}^2)$, having a zero mean and a variance σ_W^2.

Let t_W be the threshold quantity of μ, above which the insect dies. The probability of death at a dose y, denoted by $p_\mathrm{W}(y)$, corresponds to the probability that satisfies a condition: $e_\mathrm{W} \le (a_\mathrm{W} + b_\mathrm{W}\log_e(y) - t_\mathrm{W})$. Hence, $p_\mathrm{W}(y)$ is given by

$$p_\mathrm{W}(y) = \Phi\left(\frac{a_\mathrm{W} + b_\mathrm{W}\log_e(y) - t_\mathrm{W}}{\sigma_\mathrm{W}}\right), \tag{13}$$

where Φ is the cumulative probability function of the standard normal distribution. We define new parameters, $a_\mathrm{B} = (a_\mathrm{W} - t_\mathrm{W})/\sigma_\mathrm{W}$ and $b_\mathrm{B} = b_\mathrm{W}/\sigma_\mathrm{W}$ for simplicity. Then, Equation (13) is given by a simpler form:

$$p_\mathrm{W}(y) = \Phi\big(a_\mathrm{B} + b_\mathrm{B}\log_e(y)\big). \tag{14}$$

In this case, therefore, we can utilize the following form of probit regression in estimating the parameters, although the classical probit regression has no such biological foundations.

$$\mathrm{Probit}(y) = a_\mathrm{B} + b_\mathrm{B}\log_e(y). \tag{15}$$

Dose-survival curve in the field

Various fluctuations will arise in the dose of insecticides in the field. We cannot apply the insecticides uniformly over the field. For example, the dose will be higher on the upper side of plant leaves than on the lower side of plant leaves. Thus, the dose-survival curve measured in the laboratory is not directly applicable to the field. We must estimate the shift that occurs in the mean and variance of the dose in the field. Various factors can act multiplicatively in the field. Therefore, the fluctuation of the logarithmic dose of insecticide will follow a normal distribution due to the central limit theorem, irrespective of the original probability distribution of each factor. Thus, the logarithmic dose $\log_e(y)$ in the field can be expressed by

$$\log_e(y) = \overline{\log_e(y)} + e_\mathrm{B}, \qquad e_\mathrm{B} \sim N(0, \sigma_\mathrm{B}^2), \tag{16}$$

where $\overline{\log_e(y)}$ is the mean quantity of the logarithmic dose, $\log_e(y)$, and e_B is the error that follows a normal distribution having a variance σ_B^2. Substitution of Equation (16) for Equation (12) yields

$$\mu = a_{\mathrm{W}} + b_{\mathrm{W}}\overline{\log_e(y)} + b_{\mathrm{W}}e_{\mathrm{B}} + e_{\mathrm{W}}, \quad e_{\mathrm{B}} \sim N(0, \sigma_{\mathrm{B}}^2), e_{\mathrm{w}} \sim N(0, \sigma_{\mathrm{W}}^2), \tag{17}$$

where the error term $b_{\mathrm{W}}e_{\mathrm{B}} + e_{\mathrm{W}}$ follows a normal distribution with a variance $b_{\mathrm{W}}^2\sigma_{\mathrm{B}}^2 + \sigma_{\mathrm{W}}^2$. The probability of death caused by the insecticide is expressed as follows by using a similar manner as that used for Equations (13) and (14):

$$\begin{aligned} p_{\mathrm{B}}\left(\overline{\log_e(y)}\right) &= \Phi\left(\frac{a_{\mathrm{W}} + b_{\mathrm{W}}\,\overline{\log_e(y)} - t_{\mathrm{W}}}{\sqrt{\sigma_{\mathrm{W}}^2 + b_{\mathrm{W}}^2\sigma_{\mathrm{B}}^2}}\right) \\ &= \Phi\left(\frac{a_{\mathrm{B}} + b_{\mathrm{B}}\,\overline{\log_e(y)}}{\sqrt{1 + b_{\mathrm{B}}^2\sigma_{\mathrm{B}}^2}}\right). \end{aligned} \tag{18}$$

The comparison between Equation (14) and Equation (18) indicates how the spatial heterogeneity of the logarithmic dose influences the mortality of insects if $\overline{\log_e(y)}$ is kept at a constant. Let $\log_e(y_{50})$ be the logarithmic dose that yields a mortality of 0.5 in the laboratory. The dose-survival curve of Equation (18) is given by stretching the curve of Equation (14) horizontally by $\sqrt{1 + b_{\mathrm{B}}^2\sigma_{\mathrm{B}}^2}$ around $\log_e(y_{50})$. If $\overline{\log_e(y)}$ is higher than $\log_e(y_{50})$, a smaller number of insects die if the spatial heterogeneity exists. Conversely, if $\overline{\log_e(y)}$ is smaller than $\log_e(y_{50})$, a larger number of insects die if spatial heterogeneity exists. Consequently, the dose-survival curve is smoothed around its convection point. Spatial heterogeneity generally has a smoothing effect, which leads to the stability of single-species systems (Yamamura, 1989), the stability of epidemiological systems (Yamamura, 1998) and the stability of multi-species communities (Yamamura, 2002a).

Let x be the logarithm of the mean dose that is sprayed in the field. Then, the mean of the logarithmic dose is given by $\overline{\log_e(y)} = x - 0.5\sigma_{\mathrm{B}}^2$ owing to the characteristics of the lognormal distribution. The effective quantity of insecticide will be smaller than the quantity applied in the field, owing to the outflow and degradation. Furthermore, the unit used to describe the dose of insecticides is sometimes different between the laboratory and field (e.g., Willrich et al. 2003). We consider such changes by assuming the mean of dose changes by a coefficient $\exp(\gamma)$ after it is applied in the field. Then, the mean of the logarithmic dose is given by

$$\overline{\log_e(y)} = x - 0.5\sigma_{\mathrm{B}}^2 - \gamma. \tag{19}$$

We use the following definition for simplicity of expression:

$$a = \frac{a_{\mathrm{B}} - b_{\mathrm{B}}(0.5\sigma_{\mathrm{B}}^2 + \gamma)}{\sqrt{1 + b_{\mathrm{B}}^2\sigma_{\mathrm{B}}^2}}, \quad b = \frac{b_{\mathrm{B}}}{\sqrt{1 + b_{\mathrm{B}}^2\sigma_{\mathrm{B}}^2}}. \tag{20}$$

Then, Equation (18) is expressed by a function of the logarithm of the mean dose sprayed in the field:

$$p(x) = \Phi(a + bx). \tag{21}$$

The survival rate of an insect that experienced the insecticide application of a logarithm of mean dose x, which is denoted by $s(x)$, is defined by subtracting $p(x)$ from 1.0. The cumulative distribution function of a normal distribution has point symmetry around the point of probability 0.5, and hence, $s(x)$ can be expressed by using Equation (21) as follows:

$$s(x) = 1 - \Phi(a + bx) = \Phi(-a - bx). \tag{22}$$

This is Equation (6), which we used throughout in the example calculation in our study.

Prediction of the dose-survival curve in the field

We can transform the dose-survival curve in the laboratory to the dose-survival curve in the field if we know two parameters: σ_{B}^2 and γ. Hence, the estimation of σ_{B}^2 and γ is important for this purpose. We first obtain the estimates $\hat{a}_{\mathrm{B}}$ and $\hat{b}_{\mathrm{B}}$ from Equation (14) using the usual probit regression based on the laboratory data. Next, we obtain the estimates, $\hat{a}$ and $\hat{b}$, of Equation (21) using the usual probit regression based on the field data. Then, we can estimate the parameters, σ_{B}^2 and γ, by calculating

$$\hat{\sigma}_{\mathrm{B}}^2 = \frac{1}{\hat{b}^2} - \frac{1}{\hat{b}_{\mathrm{B}}^2}, \quad \hat{\gamma} = \frac{\hat{a}_{\mathrm{B}}}{\hat{b}_{\mathrm{B}}} - \frac{\hat{a}}{\hat{b}} - 0.5\hat{\sigma}_{\mathrm{B}}^2. \tag{23}$$

Willrich et al.(2003) examined the field mortalities of the adult brown stink bug, *Euschistus servus* (Say), at different doses of dicrotophos, an organophosphate insecticide, in the laboratory (on a cotton leaf) and fields (on a cotton boll of a living plant). They reported the parameters of probit regression for the laboratory experiment as intercept $= -1.817$ and slope $= 1.58$ in an arithmetic scale where the measurement unit was wt/vial. For convenience, we transformed the slope of the natural logarithmic scale by using a linear approximation for the slope around LD_{50}. Then, we obtained the estimates $\hat{a}_{\mathrm{B}} = -0.254$ and $\hat{b}_{\mathrm{B}} = 1.817$. Willrich et al. (2003) also reported the results of a field experiment using doses of $\exp(x) = 0.28$, 0.45, and 0.45, where the measurement unit was kg ai/ha. They suggested that the number of live insects divided by the total number of observed insects at doses of $\exp(x) = 0.28$, 0.45, and 0.45 were 27/40, 34/40, and 33/44, respectively. The probit regression of Equation (21) yields the estimates $\hat{a} = 1.564$ and $\hat{b} = 0.873$. Then, Equation (23) yields the following estimates: $\hat{\sigma}_{\mathrm{B}}^2 = 1.011$ and $\hat{\gamma} = -2.438$.

Figure S1 illustrates how the spatial heterogeneity of doses in the field influences the logarithmic basic reproduction rate. The comparison between the bold curve (with heterogeneity) and thin curve (without heterogeneity) indicates that the spatial heterogeneity increases $\log_e(R_0)$ in a higher range of doses where the mortality due to insecticides is large. Thus, the spatial heterogeneity of doses accelerates the evolution of resistance in this range of doses.

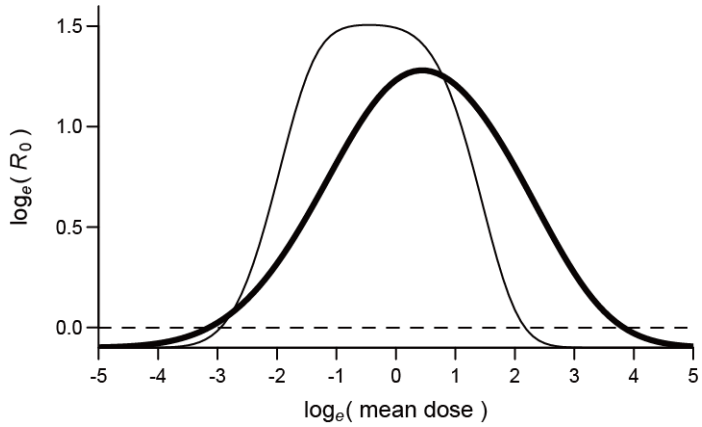

FIGURE S1 Influence of the spatial heterogeneity of doses in the field on the logarithmic basic reproduction rate. The bold curve indicates $\log_e(R_0)$ for a uniform single application of insecticide (i.e., $n = k = 1$), which is identical to the bold curves in Figure 3a and Figure 3b. The thin curve indicates $\log_e(R_0)$ for an imaginal situation where no variability exists in the field (i.e., $\sigma_{\mathrm{B}}^2 = 0$), keeping the applied dose of insecticide at the same quantity. The other parameters are the same as those used in Figure 3: $a = 1.56, b = 0.87, \delta_1 = \log_e(30), \theta = 0.25, \log_e(C) = 0.1$.

Optimal rotation of insecticides to prevent the evolution of resistance in a structured environment

by Kohji Yamamura (April 26, 2021; A small misprint was corrected on June 26, 2021)

Supporting Information S2:
Estimation of the relative abundance of off-farm population (θ)

Estimation from the dispersal curve using the gamma model

The gamma model was proposed for describing the non-random dispersal of organisms including insects and pollen (Yamamura, 2002b; Yamamura, 2004; Yamamura et al., 2007). The dispersal time weighted by the diffusion coefficient is described by a gamma distribution in this model. Let κ and λ be the shape parameter and scale parameter of the gamma distribution, respectively. The mean and variance are given by κ/λ and κ/λ^2, respectively. Then, the density of individuals at a spatial point of Euclidean dispersal distance r in the v-dimensional gamma model is given by the following form if we ignore the convection movement:

$$g(r|\kappa,\lambda,v)=\frac{2^{1-\kappa}}{\Gamma(\kappa)}\left(\frac{\lambda}{2\pi}\right)^{\frac{v}{2}}\left(r\sqrt{\lambda}\right)^{\kappa-\frac{v}{2}}K_{\frac{v}{2}-\kappa}\left(r\sqrt{\lambda}\right), \tag{24}$$

where $\Gamma(\cdot)$ indicates a gamma function. $K_{(v/2)-\kappa}(\cdot)$ indicates a modified Bessel function of the second kind of order $(v/2)-\kappa$. The mean dispersal distance and mean squared dispersal distance are given by

$$\mathrm{E}(r)=\frac{2\Gamma\left(\frac{v}{2}+\frac{1}{2}\right)\Gamma\left(\kappa+\frac{1}{2}\right)}{\sqrt{\lambda}\Gamma\left(\frac{v}{2}\right)\Gamma(\kappa)},$$
$$\mathrm{E}(r^2)=\frac{2v\kappa}{\lambda}. \tag{25}$$

The v-dimensional random dispersal, in which the stopping occurs at random, corresponds to the special case of $\kappa=1$. The gamma model arises in various situations either exactly or approximately. If the step length of random walk fluctuates following a generalized gamma distribution, for example, the gamma model arises approximately (Yamamura, 2004).

Let us consider the following situation which may be the most simplified approximation. A long straight line separates the on-farm and off-farm fields. Let ω be the width of the off-farm field belt. The insects in the off-farm field disperse at the beginning of cultivation period by following the gamma model given by Equation (24). The insects that dispersed into the on-farm side of the straight line create the new on-farm population of the on-farm field. We assume that the opposite edge of off-farm field behaves as a reflecting barrier in this dispersal process. After completing this dispersal, no interchange occurs between the on-farm and off-farm populations during the cultivation period. At the end of cultivation period, all individuals in the on-farm field enter the off-farm field due to the removal of crops. After completing this dispersal, the individuals are well mixed within the off-farm field during the non-cultivation period.

If the line separating the on-farm and off-farm fields is sufficiently long, we can use the one-dimensional gamma model ($v=1$), that is, the marginal distribution of the two-dimensional distribution, because the movement of individuals along the direction of straight line is mutually cancelled (Yamamura, 2004). Then, assuming the uniform density of individuals in off-farm field before dispersal, the proportion of individuals that remain in the off-farm field, which corresponds to q, is given by

$$q=1-\frac{1}{\omega}\int_0^{\omega}\left[\int_y^{\infty}g(r|\kappa,\lambda,1)\mathrm{d}r+\int_{2\omega-y}^{\infty}g(r|\kappa,\lambda,1)\mathrm{d}r\right]\mathrm{d}y. \tag{26}$$

The integral inside the square brackets is given by an analytical form, but the integral from 0 to ω requires a numerical integration. We have the estimates of parameters, $\hat{\kappa}=0.303$ and $\hat{\lambda}=2.16\times10^{-5}$, for the dispersal curve of aphids transmitting *Plum pox virus* (Yamamura, 2020). If we assume $\omega=50$ m, for example, Equation (26) yields $\hat{q}=0.50$ for these aphids.

Estimation from the change in the proportion of resistance during the non-cultivation period

Let η be the abundance of the off-farm population divided by that of the on-farm population at the end of a cultivation period. Let $\psi_{1,\mathrm{on}}$ and $\psi_{1,\mathrm{off}}$ be the proportion of resistance in on-farm and off-farm fields, respectively, at the end of the cultivation period. Let $\psi_{2,\mathrm{on}}$ be the proportion of resistance in the on-farm field at the beginning of the next cultivation period. Then, the odds of $\psi_{2,\mathrm{on}}$ are given by

$$\frac{\psi_{2,\mathrm{on}}}{1-\psi_{2,\mathrm{on}}} = \frac{\left(\eta\psi_{1,\mathrm{off}} + \psi_{1,\mathrm{on}}\right)c^{-g_{\mathrm{off}}}}{\eta\left(1-\psi_{1,\mathrm{off}}\right) + \left(1-\psi_{1,\mathrm{on}}\right)}, \tag{27}$$

where g_{off} is the number of generations in a non-cultivation period. The rearrangement yields the following equation for estimating η.

$$\hat{\eta} = \frac{\hat{\psi}_{1,\mathrm{on}} - \hat{\psi}_{2,\mathrm{on}}\left(\hat{\psi}_{1,\mathrm{on}} + c^{g_{\mathrm{off}}}\left(1-\hat{\psi}_{1,\mathrm{on}}\right)\right)}{-\hat{\psi}_{1,\mathrm{off}} + \hat{\psi}_{2,\mathrm{on}}\left(\hat{\psi}_{1,\mathrm{off}} + c^{g_{\mathrm{off}}}\left(1-\hat{\psi}_{1,\mathrm{off}}\right)\right)}. \tag{28}$$

This quantity corresponds to θ/(Average insecticidal survival rate of individual in a cultivation period). Hence, we can estimate θ by

$$\hat{\theta} = \frac{\hat{\eta}}{\dfrac{\hat{\psi}_{1,\mathrm{on}}}{\left(r_1(x_1)\right)^k \prod s_i(x_i)} + \dfrac{1-\hat{\psi}_{1,\mathrm{on}}}{\left(s_1(x_1)\right)^k \prod s_i(x_i)}}. \tag{29}$$

If no additional generation occurs during the non-cultivation period, that is, if $g_{\mathrm{off}} = 0$, we obtain the following inequality from Equation (28).

$$\hat{\eta} = \frac{\hat{\psi}_{1,\mathrm{on}} - \hat{\psi}_{2,\mathrm{on}}}{\hat{\psi}_{2,\mathrm{on}} - \hat{\psi}_{1,\mathrm{off}}} \geq \left(\frac{\hat{\psi}_{1,\mathrm{on}}}{\hat{\psi}_{2,\mathrm{on}}}\right) - 1. \tag{30}$$

The equality holds for $\hat{\psi}_{1,\mathrm{off}} = 0$. Thus, $\hat{\eta} = \left(\hat{\psi}_{1,\mathrm{on}}/\hat{\psi}_{2,\mathrm{on}}\right) - 1$ is a conservative estimate of η in this case in a sense that we do not underestimate the possibility of evolution of resistance if we used this estimate of η.

Optimal rotation of insecticides to prevent the evolution of resistance in a structured environment

by Kohji Yamamura (March 7, 2021)

Supporting Information S3:
Basic reproduction rate under an unstructured environment

In this Supporting Information, we show that the basic reproduction rate increases with increasing concentration of insecticide if no off-farm field exists. We first consider logarithmic probit models. Let $\phi(x)$ and $\Phi(x)$ be the probability density function and cumulative distribution function of the standard normal distribution, respectively. We assume $n = k = 1$ and $\log_e(C) = 0$ in Equation (3). Let us denote a $+ bx$ by z and $b\delta$ by Δ for simplicity. Then, Equations (3), (6), and (7) yield the following relation:

$$\log_e(R_0) = \log_e\big(\Phi(\Delta - z)\big) - \log_e\big(\Phi(-z)\big). \tag{31}$$

Now, we want to show $\frac{\mathrm{d}}{\mathrm{d}z}\log(R_0) > 0$ for any positive quantity of Δ, where

$$\frac{\mathrm{d}}{\mathrm{d}z}\log_e(R_0) = \frac{\mathrm{d}}{\mathrm{d}z}\Big(\log_e\big(\Phi(\Delta - z)\big)\Big) - \frac{\mathrm{d}}{\mathrm{d}z}\Big(\log_e\big(\Phi(-z)\big)\Big). \tag{32}$$

Notice that we have the following general relation for a function $f(x)$.

$$\frac{\mathrm{d}}{\mathrm{d}y}f(-y)\Big|_{y=x} = -\frac{\mathrm{d}}{\mathrm{d}y}f(y)\Big|_{y=-x}. \tag{33}$$

The right-hand side of Equation (32) indicates the difference in the first derivatives at a distance Δ. It is expressed by the integrated quantity of the second derivatives over Δ. Hence, Equation (32) is expressed by

$$\frac{\mathrm{d}}{\mathrm{d}z}\log_e(R_0) = \int_{-z}^{\Delta - z}\left[-\frac{\mathrm{d}^2}{\mathrm{d}\tau^2}\Big(\log_e\big(\Phi(\tau)\big)\Big)\right]\mathrm{d}\tau, \tag{34}$$

where we used a general relation of Equation (33). The elemental calculus indicates that the second derivative of a logarithm of function $f(\tau)$ is generally given by

$$\Big(\log_e\big(f(\tau)\big)\Big)'' = \frac{-[f'(\tau)]^2 + f(\tau)f''(\tau)}{[f(\tau)]^2}. \tag{35}$$

By substituting the derivatives about the standard normal distribution, $f(\tau) = \Phi$, $f'(\tau) = \phi$, and $f''(\tau) = -\tau\phi$ in Equation (35), we obtain

$$-\frac{\mathrm{d}^2}{\mathrm{d}\tau^2}\log_e(\Phi) = \frac{\phi(\phi + \tau\Phi)}{\Phi^2}. \tag{36}$$

The quantity of $\phi + \tau\Phi$ monotonically increases with increasing τ, since $\partial(\phi + \tau\Phi)/\partial\tau = \Phi > 0$. Furthermore, we have $\lim_{\tau\to-\infty}(\phi + \tau\Phi) = 0$. Therefore, $\phi + \tau\Phi$ is positive. Consequently, we obtain $-\frac{\mathrm{d}^2}{\mathrm{d}\tau^2}\Big(\log\big(\Phi(\tau)\big)\Big) > 0$ from Equation (36). Then, Equation (34) indicates that $\frac{\mathrm{d}}{\mathrm{d}z}\log(R_0) > 0$ for any positive quantity of Δ.

A similar argument is applicable to general survival curves. The quantity of $\log_e(R_0) + \log_e(C)$ for $\theta = 0$ is described by the following equation if $n = k = 1$:

$$\log_e(R_0) = \log_e\big(r_1(x_1)\big) - \log_e\big(s_1(x_1)\big). \tag{37}$$

The logarithmic survival curves, $\log_e\big(r_i(x_i)\big)$ and $\log_e\big(s_i(x_i)\big)$, have an upper bound 0 when the survival rate approaches 1. The derivatives, $\mathrm{d}\log_e\big(r_i(x_i)\big)/\mathrm{d}x_i$ and $\mathrm{d}\log_e\big(s_i(x_i)\big)/\mathrm{d}x_i$, are 0 near the upper bound, but the derivatives become negative quantities as the dose x_i increases. The absolute quantity of the derivative becomes

larger as the distance of the survival rate from the upper bound becomes larger, in principle. By definition, we have $\log_e\left(r_i(x_i)\right) > \log_e\left(s_i(x_i)\right)$. Therefore, we have $\mathrm{d}\log_e\left(r_i(x_i)\right)/\mathrm{d}x_i > \mathrm{d}\log_e\left(s_i(x_i)\right)/\mathrm{d}x_i$, which yields $\frac{\mathrm{d}}{\mathrm{d}x}\log_e(R_0) > 0$. Thus, $\log_e(R_0)$ increases monotonically with increasing dose, in principle, for general survival curves if no off-farm field exists.

Optimal rotation of insecticides to prevent the evolution of resistance in a structured environment

by Kohji Yamamura (March 7, 2021)

Supporting Information S4:
Basic reproduction rate under a structured environment

In this Supporting Information, we show that the basic reproduction rate becomes smaller in either low or high doses of insecticides if an off-farm field exists. We first consider logarithmic probit models. We use the same notation as in Supporting Information S3. Then, we have the following form in a structured environment:

$$\log_e(R_0) = \log_e(\Phi(\Delta - z) + \theta) - \log_e(\Phi(-z) + \theta). \tag{38}$$

Equation (34) changes to

$$\frac{\mathrm{d}}{\mathrm{d}z}\log_e(R_0) = \int_{-z}^{\Delta - z}\left[-\frac{\mathrm{d}^2}{\mathrm{d}\tau^2}\left(\log_e(\Phi(\tau) + \theta)\right)\right]\mathrm{d}\tau. \tag{39}$$

The term inside the bracket in Equation (39) is expressed by

$$-\frac{\mathrm{d}^2}{\mathrm{d}\tau^2}\log_e(\Phi + \theta) = \frac{\phi\left(\phi + \tau(\Phi + \theta)\right)}{(\Phi + \theta)^2}, \tag{40}$$

where ϕ and Φ are the abbreviations of $\phi(\tau)$ and $\Phi(\tau)$, respectively. The quantity of $\phi + \tau(\Phi + \theta)$ monotonically increases with increasing τ, since $\partial\left(\phi + \tau(\Phi + \theta)\right)/\partial\tau = \Phi + \theta > 0$. Furthermore, we have $\lim_{\tau \to -\infty}\left(\phi + \tau(\Phi + \theta)\right) = -\infty$ and $\lim_{\tau \to +\infty}\left(\phi + \tau(\Phi + \theta)\right) = +\infty$. Consequently, $\phi + \tau(\Phi + \theta) = 0$ has a single solution at $\tau = \tau^*$; the quantity of $\phi + \tau(\Phi + \theta)$ changes from a negative to a positive quantity at $\tau = \tau^*$ with increasing τ. Equation (40) indicates that $-\frac{\mathrm{d}^2}{\mathrm{d}\tau^2}\log_e(\Phi + \theta)$ changes from a negative to a positive quantity at τ^*. Then, Equation (39) indicates that $\frac{\mathrm{d}}{\mathrm{d}z}\log_e(R_0)$ is positive if the lower limit of the integral $(-z)$ is larger than τ^*, while it is negative if the upper limit of the integral $(\Delta - z)$ is smaller than τ^*. Therefore, the quantity of $\frac{\mathrm{d}}{\mathrm{d}z}\log_e(R_0)$ is positive for $z < -\tau^*$ and negative for $z > -\tau^* + \Delta$. That is, the curve of $\log_e(R_0)$ plotted against x has its maximum quantity for x within $\frac{(-\tau^* - a)}{b} < x < \frac{(-\tau^* - a)}{b} + \delta$.

A similar argument is applicable to general survival curves. The quantity of $\log_e(R_0) + \log_e(C)$ is described by the following equation if $n = k = 1$:

$$\log_e(R_0) = \log_e(r_1(x_1) + \theta) - \log_e(s_1(x_1) + \theta). \tag{41}$$

The quantities $\log_e(r_i(x_i) + \theta)$ and $\log_e(s_i(x_i) + \theta)$ have a lower bound, $\log_e(\theta)$, when the survival rate approaches 0 in a higher range of x_i. The derivatives, $\mathrm{d}\log_e(r_i(x_i) + \theta)/\mathrm{d}x_i$ and $\mathrm{d}\log_e(s_i(x_i) + \theta)/\mathrm{d}x_i$, are 0 near the lower bound, but the derivatives become negative quantities as the dose x_i decreases. The absolute quantity of the derivative becomes larger as the distance of the survival rate from the lower bound becomes larger, in principle. By definition, we have $\log_e\left(r_i(x_i)\right) > \log_e\left(s_i(x_i)\right)$. Therefore, we have $\mathrm{d}\log_e(r_i(x_i) + \theta)/\mathrm{d}x_i < \mathrm{d}\log_e(s_i(x_i) + \theta)/\mathrm{d}x_i$, which yields $\frac{\mathrm{d}}{\mathrm{d}x}\log_e(R_0) < 0$ in a higher range of x_i. On the other hand, the quantities, $\log_e(r_i(x_i) + \theta)$ and $\log_e(s_i(x_i) + \theta)$, have an upper bound $\log_e(1 + \theta)$ when the survival rate approaches 1 in a lower range of x_i. The derivatives, $\mathrm{d}\log_e\left(r_i(x_i)\right)/\mathrm{d}x_i$ and $\mathrm{d}\log_e\left(s_i(x_i)\right)/\mathrm{d}x_i$, are 0 near the upper bound, but the derivatives become negative quantities as the dose x_i increases. The absolute quantity of the derivative becomes larger as the distance of the survival rate from the upper bound becomes larger, in principle. By definition, we have $\log_e\left(r_i(x_i)\right) > \log_e\left(s_i(x_i)\right)$. Therefore, we have $\mathrm{d}\log_e\left(r_i(x_i)\right)/\mathrm{d}x_i > \mathrm{d}\log_e\left(s_i(x_i)\right)/\mathrm{d}x_i$, which yields $\frac{\mathrm{d}}{\mathrm{d}x}\log_e(R_0) > 0$ in a lower range of x_i. Consequently, $\log_e(R_0)$ becomes smaller for either too low or too high a dose, in principle, for general survival curves.

Optimal rotation of insecticides to prevent the evolution of resistance in a structured environment

by Kohji Yamamura (March 7, 2021)

Supporting Information S5:
Characteristics of an aggregated application of a single insecticide

In this Supporting Information, we show that the basic reproduction rate for the resistance of insecticide decreases with increasing repeated use of sprays per cultivation period (n), in the aggregated application of a single type of insecticide in which the total number of sprays is kept at a constant. We further show that the basic reproduction rate becomes nearly the same irrespective of the number of sprays (n) if the dose is low.

We consider the case of $n = k$ and $\log_e(C) = 0$ in Equation (4). Then, Equations (4) yields the following relation:

$$\log_e(R_0) = \frac{1}{n}\{\log_e\{[r_1(x_1)]^n + \theta\} - \log_e\{[s_1(x_1)]^n + \theta\}\}. \tag{42}$$

Differentiation about n yields

$$\frac{\mathrm{d}\log_e(R_0)}{\mathrm{d}n} = \zeta\big(r_1(x_1)\big) - \zeta\big(s_1(x_1)\big), \tag{43}$$

where

$$\zeta(y) = \frac{y^n \log_e(y)}{n(y^n + \theta)} - \frac{\log_e(y^n + \theta)}{n^2}. \tag{44}$$

We have $\mathrm{d}\zeta(y)/\mathrm{d}y < 0$ if $\theta > 0$. Hence, the quantity of Equation (43) is negative, since $r_1(x_1) > s_1(x_1)$. Thus, $\log_e(R_0)$ decreases with increasing n.

If the logarithmic mean dose, x_1, is sufficiently low, then both survival rates, $r_1(x_1)$ and $s_1(x_1)$, are close to 1; that is, $1 - r_1(x_1)$ and $1 - s_1(x_1)$ are close to 0. Hence, Equation (42) is approximately expressed by

$$\begin{aligned}
\log(R_0) &\approx \frac{1}{n}\Big\{\log_e\big\{\big[1 - n\big(1 - r_1(x_1)\big)\big] + \theta\big\} - \log_e\big\{\big[1 - n\big(1 - s_1(x_1)\big)\big] + \theta\big\}\Big\} \\
&= \frac{1}{n}\left\{\log_e\left\{1 - n\left(\frac{1}{1+\theta}\right)\big(1 - r_1(x_1)\big)\right\} - \log_e\left\{1 - n\left(\frac{1}{1+\theta}\right)\big(1 - s_1(x_1)\big)\right\}\right\} \\
&\approx \frac{1}{n}\left\{-n\left(\frac{1}{1+\theta}\right)\big(1 - r_1(x_1)\big) + n\left(\frac{1}{1+\theta}\right)\big(1 - s_1(x_1)\big)\right\} \\
&= \frac{r_1(x_1) - s_1(x_1)}{1 + \theta}.
\end{aligned} \tag{45}$$

Thus, the parameter n vanishes, indicating that the basic reproduction rate for different numbers of sprays (n) is nearly the same if the dose is low.

Optimal rotation of insecticides to prevent the evolution of resistance in a structured environment

by Kohji Yamamura (March 7, 2021)

Supporting Information S6:
Evolutional speed of resistance genes

Haploid organism with asexual reproduction

We can numerically calculate the speed of the evolution of resistance by using the basic reproduction rate if we specify the genetic systems, although we cannot always describe the speed using equations analytically. We consider the following special case in this Supporting Information for simplicity: the insects live one generation during each period of cultivation without reproducing during the non-cultivation period. We first consider haploid insects that reproduce asexually. Let p_i be the frequency of the resistant individuals in the ith generation. We assume $0 < p_1 < 0.5$ as an initial condition. Let F_i be the number of offspring of a susceptible individual, and N_i be the total number of individuals in the ith generation. Then, the number of resistant individuals at the tth generation is given by $N_1 p_1 \prod_{i=1}^{t-1}(R_0 F_i)$ while the number of susceptible individuals at the tth generation is given by $N_1(1-p_1)\prod_{i=1}^{t-1} F_i$. Consequently, the number of resistant individuals at the tth generation is given by

$$p_t = \frac{p_1 {R_0}^{t-1}}{p_1 {R_0}^{t-1} + 1 - p_1}. \tag{46}$$

Let us assume that the proportion of resistant individuals becomes 0.5 at time $t_{0.5}$. We have a relation of $p_1 {R_0}^{t_{0.5}-1} = 1 - p_1$, and hence, the quantity of $t_{0.5}$ is given by

$$t_{0.5} = \frac{\log(1-p_1) - \log(p_1)}{\log(R_0)} + 1. \tag{47}$$

The number of resistant individuals and the number of susceptible individuals at the $(t+1)$th generation are given by $N_t p_t R_0 F_t$ and $N_t(1-p_t)F_t$, respectively. Therefore, the curve that indicates the relation between p_{t+1} and p_t, which is called the "reproduction curve", is given by the following difference equation:

$$p_{t+1} = \frac{R_0 p_t}{1 + (R_0 - 1)p_t}. \tag{48}$$

The reproduction curve given by Equation (48) is identical to a discrete expression of the continuous logistic model (Beverton and Holt, 1957). Figure S2 shows the reproduction curve for $R_0 = 5$. As for haploid insects that reproduce asexually, the speed of the evolution of resistance genes per cultivation period coincides with R_0 during an early phase of evolution in which the frequency of resistance genes is small, but the speed decreases as the frequency of resistance gene increases, as indicated by the solid curve in Figure S2.

Diploid insects with random mating

We next consider a diploid insect that reproduces sexually with discrete generations. The number of individuals is assumed to be sufficiently large. Random mating is further assumed. If the resistance gene is dominant, then the reproduction curve of the number of alleles having the resistance gene is given by

$$p_{t+1} = \frac{R_0 p_t}{1 + (R_0 - 1)p_t(2 - p_t)}. \tag{49}$$

On the other hand, if the resistance gene is recessive, the reproduction curve is given by

$$p_{t+1} = \frac{p_t[1 + (R_0 - 1)p_t]}{1 + (R_0 - 1){p_t}^2}. \tag{50}$$

We can easily calculate the time series of the proportion of resistance numerically if we know the basic reproduction rate of resistance (R_0).

If the resistance gene is dominant in diploid insects, then the speed of evolution during the early phase of

evolution is nearly the same as that of haploid insects, but the speed becomes very small as the frequency approaches 1; the frequency of the resistance gene at time $t+1$, that is, p_{t+1}, is nearly equal to that at time t in this phase, as illustrated by the dashed curve in Figure S2. Conversely, if the resistance gene is recessive in diploid insects, then the speed of evolution during the early phase of evolution is very small, but the speed becomes larger as the frequency approaches 1; the speed becomes nearly equal to that of haploid insects, as illustrated by the dotted curve in Figure S2. The reproduction curves for the dominant gene and recessive gene intersect at $p_t = 1/\left(\sqrt{R_0}+1\right)$.

The reproduction curves become complicated in the case of incomplete dominance, but the characteristics of the reproduction curves will be intermediate between those of the dominant gene (Equation (49)) and recessive gene (Equation (50)). Thus, the reproduction curve for the incomplete dominant gene lies between the dashed and dotted curves in Figure S2, for example.

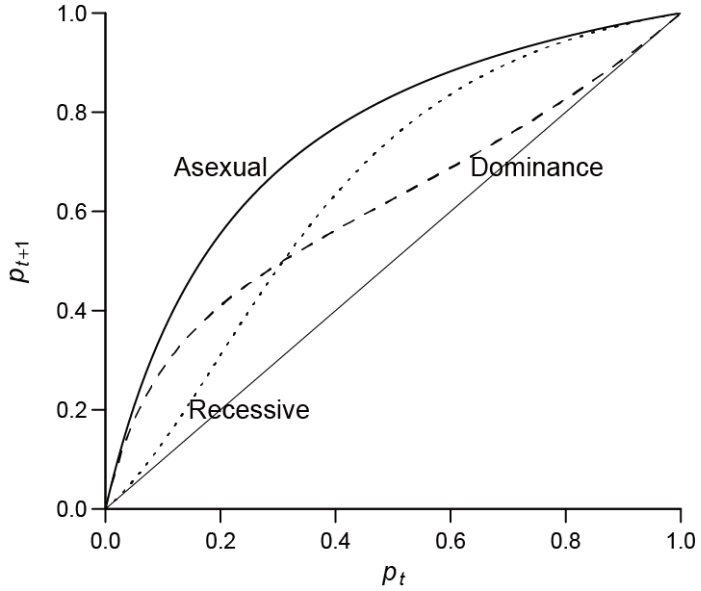

FIGURE S2 Influence of mating systems on the speed of evolution. Reproduction curves for $R_0 = 5$ are shown. Solid curve indicates the reproduction curve of the frequency of resistance genes for asexual reproduction (Equation (48)). Dashed curve indicates that for diploid insects where the resistance gene is dominant (Equation (49)). Dotted curve indicates that for diploid insects where the resistance gene is recessive (Equation (50)). Solid thin line indicates the line for $p_{t+1} = p_t$.

Optimal rotation of insecticides to prevent the evolution of resistance in a structured environment

by Kohji Yamamura (March 7, 2021)

Supporting Information S7:
Characteristics of a rotational application of insecticides

In this Supporting Information, we show that the basic reproduction rate for the resistance of type 1 insecticide increases with increasing repeated use of type 1 insecticide per cultivation period (k), in the application of multiple types of insecticides in which the total number of type 1 insecticide is kept at a constant. We further show that the basic reproduction rate becomes nearly the same irrespective of the number of repeated use of sprays (k) if the dose is low.

Let G be the geometric mean of $s_i(x_i)$ for $i \neq 1$ in Equation (4), that is, $G^{n-k} = \prod s_i(x_i)$. We consider a case of $\log_e(C) = 0$, for simplicity. Then, Equation (4) yields the following relation:

$$\log_e(R_0) = \frac{1}{k}\log_e\left[\left(r_1(x_1)\right)^k G^{n-k} + \theta\right] - \frac{1}{k}\log_e\left[\left(s_1(x_1)\right)^k G^{n-k} + \theta\right]. \tag{51}$$

Differentiation about k yields:

$$\frac{\mathrm{d}\log_e(R_0)}{\mathrm{d}k} = \xi\left(r_1(x_1)\right) - \xi\left(s_1(x_1)\right), \tag{52}$$

where

$$\xi(y) = \frac{y^k G^{n-k}(\log_e(y) - \log_e(G))}{k(y^k G^{n-k} + \theta)} - \frac{\log_e(y^k G^{n-k} + \theta)}{k^2}. \tag{53}$$

We have $\mathrm{d}\xi(y)/\mathrm{d}y > 0$ for the range of $y > G$ if $\theta > 0$. Hence, the quantity of Equation (52) is generally positive, since $r_1(x_1) > s_1(x_1)$. Thus, $\log_e(R_0)$ increases with increasing k.

If the logarithmic mean dose is sufficiently low, then G, $r_1(x_1)/G$, and $s_1(x_1)/G$ are close to 1; that is, $1 - G$, $1 - (r_1(x_1)/G)$, and $1 - (s_1(x_1)/G)$ are close to 0. Hence, Equation (51) is approximately expressed by

$$\begin{aligned}
\log(R_0) &\approx \frac{1}{k}\left\{\log_e\left\{\left[1 - k\left(1 - \frac{r_1(x_1)}{G}\right) - n(1-G)\right] + \theta\right\} - \log_e\left\{\left[1 - k\left(1 - \frac{s_1(x_1)}{G}\right) - n(1-G)\right] + \theta\right\}\right\} \\
&= \frac{1}{k}\left\{\log_e\left\{1 - \left(\frac{1}{1+\theta}\right)\left(k\left(1 - \frac{r_1(x_1)}{G}\right) + n(1-G)\right)\right\}\right. \\
&\qquad \left. - \log_e\left\{1 - \left(\frac{1}{1+\theta}\right)\left(k\left(1 - \frac{s_1(x_1)}{G}\right) + n(1-G)\right)\right\}\right\} \\
&\approx \frac{1}{k}\left\{-\left(\frac{1}{1+\theta}\right)\left(k\left(1 - \frac{r_1(x_1)}{G}\right) + n(1-G)\right) + \left(\frac{1}{1+\theta}\right)\left(k\left(1 - \frac{s_1(x_1)}{G}\right) + n(1-G)\right)\right\} \\
&= \left(\frac{1}{1+\theta}\right)\left(\frac{r_1(x_1) - s_1(x_1)}{G}\right) \\
&\approx \frac{r_1(x_1) - s_1(x_1)}{1+\theta}.
\end{aligned} \tag{54}$$

Thus, the parameter k vanishes, indicating that the basic reproduction rate for different numbers of repeated use of sprays (k) is nearly the same if the dose is low.