The cost of fungicide resistance evolution in multi-field plant epidemics

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The cost of fungicide resistance evolution in multi-field plant epidemics

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Abstract

Epidemics of plant diseases are estimated to cause significant economic losses in crop production. Fungicide applications are widely used to control crop diseases but incur substantial indirect costs. One essential class of indirect costs arises due to the evolution of fungicide resistance. This indirect cost must be estimated reliably to design economic policy for more sustainable use of fungicides. Such estimation is difficult because the cost depends on economic parameters and the evo-epidemiological properties of crop pathogens. Even a conceptual framework for such estimation is missing. To address this problem, we combined a spatially implicit mathematical model of crop epidemics with an economic analysis at the landscape scale. We investigated how the net economic return from a landscape depends on the proportion of fungicide-treated fields. We discovered a pattern of accelerating (or decelerating) returns, contrary to expected diminishing returns. Next, we calculated the economic cost of the evolution of fungicide resistance as the difference between the optimal net return of the landscape in the absence and presence of resistance. We found that this cost depends strongly on the fungicide price, the degree of resistance, the pathogen's basic reproduction number and the yield loss due to disease. Surprisingly, the cost declines with the fungicide price and exhibits a non-monotonic pattern as a function of the basic reproduction number. Hence, to calculate the cost, we must estimate these parameters robustly, incorporating variations in environmental conditions, crop varieties and the genetic composition of pathogen populations. Appropriate estimation of the cost of resistance evolution can inform economic policy and encourage more sustainable use of fungicides.

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Author summary

Fungicides protect crops from diseases and are essential for securing the global food supply, but they incur serious indirect costs to society and the environment. One such cost arises because of the evolution of fungicide resistance. Part of the pathogen population (fungicide-resistant) can gain protection from a fungicide via a genetic change. If fungicide applications continue, the fungicide-resistant subpopulation increases and dominates the population, leading to low efficacy. Resistance can lead to severe economic losses, but no conceptual framework exists for estimating them. We present a novel mathematical framework to estimate the economic costs of fungicide resistance at the landscape scale. We combined an epidemiological model describing disease spread with an economic cost-benefit analysis. Surprisingly, we found that the economic cost of resistance declines for more expensive fungicides. This cost also depends on the pathogen's capacity to spread (invasiveness): the cost is highest for pathogens with intermediate invasiveness. Thus, the cost of resistance depends on economic parameters and the biological characteristics of plant diseases. Our findings can inform economic policies for sustainable fungicide use, such as taxes or subsidies. Our paper also contributes to the broader discourse on agricultural sustainability while ensuring global food security.

Introduction

Epidemics of plant diseases are estimated to cause significant economic losses in crop production [1–4]. To reduce losses, farmers frequently apply fungicides. They can maximize the net economic return of fungicide applications, e.g., by optimizing the fungicide dose based on the balance between the yield benefit and the cost of fungicide application [5,6]. However, this approach is problematic for at least two reasons.

First, fungicide applications not only have direct economic costs, but they also incur considerable indirect costs, such as environmental costs, human health costs, and costs associated with the evolution of fungicide resistance [7–9]. One opportunity to manage crop diseases in a more sustainable manner is to incorporate indirect costs, at least partially, into fungicide prices. This opportunity can be realized using economic policy instruments, e.g., by introducing special pesticide taxes or subsidies, as has been done in several countries, including France, Denmark, Norway and Sweden [10,11]. However, it is not easy to design pesticide tax rates or subsidies to reflect indirect costs, as indirect costs are notoriously difficult to estimate [7–9].

Second, many crop pathogens of economic relevance can disperse over long distances, not only within individual fields but also between fields and across entire regions [12]. Therefore, decisions regarding disease management made at a particular farm can affect epidemic development in other farms across a region, and decisions that are optimal for an individual farm may turn out to be sub-optimal at the scale of a regional cultivated landscape. This is also the case when managing weeds: for instance, [13] used computational modeling to show that aggregating the best herbicide resistance management practices at the landscape scale can slow down the evolution of resistance.

An essential class of indirect costs of fungicide applications arises because pathogen populations can adapt to fungicides via the evolution of fungicide resistance, which reduces fungicide efficacy [14]. From an economic perspective, these costs represent an externality [15]: development of resistance is caused by fungicide applications on specific fields, but

resistance can spread between fields and across farms and entire regions. Hence, a much wider community of farmers will eventually suffer the economic costs of fungicide resistance evolution.

These costs are difficult to estimate because they depend on the economic parameters of the affected cropping system, the epidemiological, and the evolutionary properties of a particular pathosystem. A phone survey of 137 growers in Western Australia's Wheatbelt revealed that growers spent, on average, AU$42 per hectare on fungicide treatments of barley diseases in the 2019/2020 growing season. The growers were further willing to spend on average AU$18 per hectare to delay or mitigate fungicide resistance [16]. The latter estimate represents a perceived economic cost of fungicide resistance, and it remains to be investigated to what extent this perception corresponds to the actual cost. At a wider national scale in the USA, the economic impact of pesticide resistance was estimated at US$1.5 billion in 2005, which, when adjusted for inflation, amounts to U$2.5 billion today, excluding the rising costs associated with increased pesticide use [17]. A national-scale investigation of herbicide resistance in black-grass (*Alopecurus myosuroides*) across the UK indicated that herbicide resistance can double the economic costs of weed management [18]. Rough estimates of economic losses in crop production due to insecticide resistance were in the range 10-15 % [7,8]. These were based on economic data on cotton production in the USA, assuming that insecticide use increases due to resistance and that this increase is the only cost incurred by resistance. However, it is unclear to what extent this assumption is fulfilled; it is also difficult to extrapolate these estimates to other crops and regions and extrapolate from insecticide resistance to fungicide resistance. Only a few attempts have been made to estimate the economic costs of fungicide resistance in crop pathogens in the literature, and these have focused on individual fields [19,20]. Even a conceptual framework to enable the calculation of economic costs of fungicide resistance across wider spatial scales is lacking. To fill this knowledge gap, we addressed the following questions: (i) "How to calculate the economic cost of fungicide resistance?" and (ii) "How does the economic cost of fungicide resistance depend on the economic and epidemiological/evolutionary parameters of the crop-pathogen system?"

For this purpose, we combined a spatially implicit epidemiological model of crop epidemics with an economic analysis at the landscape scale (bioeconomic modeling). Using this approach, we calculated the economic cost of the evolution of fungicide resistance, C_R, as the difference between the optimal net return of the landscape in the absence and presence of resistance. This allowed us to explore how C_R depends on the key epidemiological/evolutionary and economic parameters of the system. Our results provide a conceptual basis for the estimation of C_R as a key component of indirect costs of fungicide applications, which can inform economic policy to achieve a more sustainable use of fungicides.

Materials and methods

Epidemiological model for multiple fields

We study the epidemiological dynamics of a generic fungal pathogen of crop plants at the scale of multiple fields (Fig 1). We consider a regional cultivated landscape composed of N fields growing the same annual crop (e.g., wheat or maize). The key variables and parameters are given in Table 1. First, we devise a model considering a wildtype (fungicide-sensitive) pathogen strain with a fungicide treatment. Then, we extend this model to incorporate a fungicide-resistant pathogen strain.

Model with fungicide treatment Each field can be either healthy (H) or infected (I) with a wildtype pathogen (subscript w), and each field can be treated (subscript t) or untreated (subscript u) with the fungicide. Hence, we have four possible field states: H_u, H_t, I_{uw}, and I_{tw}.

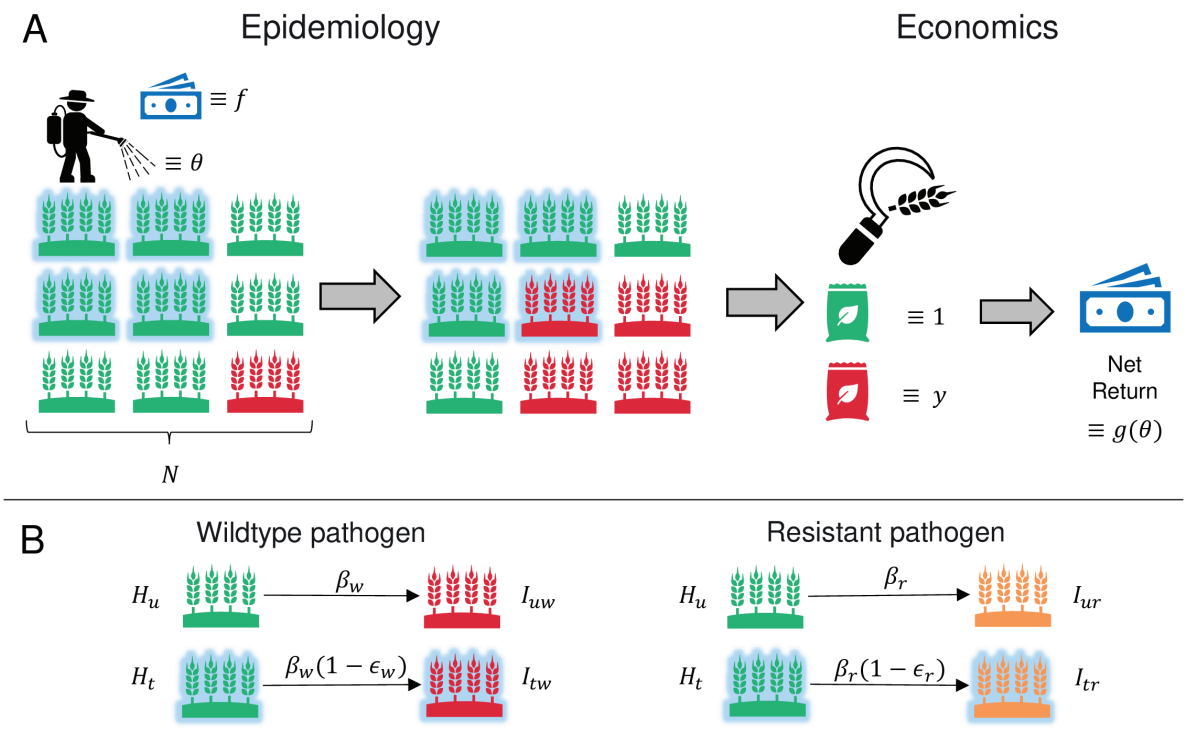

Fig 1. Overview of the multiple field model of plant disease incorporating both epidemiology and economics aspects in the presence of fungicide treatment. Healthy fields (H_u and H_t) are shown in green, fields infected with the wildtype pathogen strain (I_{uw} and I_{tw}) are shown in red, fields infected with the resistant pathogen strain (I_{ur} and I_{tr}) are shown in orange. Fungicide-treated fields have a light-blue glow around them. (A) Out of the total N fields, initially, only a small proportion of fields are infected, while the rest are healthy. A fraction θ of all fields are treated with a fungicide, which comes at a price f. The net return ($g(\theta)$) of the harvest is calculated as the monetary equivalent of the yield from all healthy and infected fields (1 and y, respectively) minus the total fungicide price. (B) The state variables of the epidemiological model and the transitions between them: healthy fields can become infected over time.

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Table 1. Key variables and parameters of the model.

Symbol	Description
Variables	
H_i	Number of healthy fields with treatment status i ($i = u$ for untreated, $i = t$ for treated)
I_{ij}	Number of fields infected by pathogen strain j ($j = w$ for wildtype, $j = r$ for resistant) with treatment status i ($i = u$ for untreated, $i = t$ for treated)
Parameters	
N	Total number of fields
θ	Fraction of fungicide-treated fields (or fungicide coverage); 0-1
ϵ_i	The efficacy of fungicide treatment in reducing the transmission rate of the pathogen strain i ($i = w$ for wildtype, $i = r$ for resistant); 0-1
β_i	Transmission rate of pathogen strain i ($i = w$ for wildtype, $i = r$ for resistant) from infected to the healthy field
μ	Recovery rate of infected fields to become healthy fields
c	The price of fungicide application
y_H	Yield from a healthy field per season
f	Relative fungicide price with respect to yield from a healthy field
y	Relative yield of a diseased field with respect to the yield from a healthy field
Y	Total yield of the landscape (expressed as a fraction of the monetary equivalent of the maximum yield)
$g(\theta)$	Net return relative to yield from a healthy field, y_H
θ^*	Optimal fraction of treated fields that maximizes $g(\theta)$

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H_u and I_{uw} represent the numbers of untreated healthy and infected fields, respectively, while H_t and I_{tw} represent the treated fields. The dynamics of the disease are captured by equations that are similar to the epidemiological susceptible-infected model:

$$\begin{aligned}
\dot{H}_u &= -\beta_w \left[I_{uw} H_u + I_{tw} H_u\right] + \mu I_{uw} \\
\dot{H}_t &= -\beta_w \left(1 - \epsilon_w\right) \left[I_{uw} H_t + I_{tw} H_t\right] + \mu I_{tw} \\
\dot{I}_{uw} &= \beta_w \left[I_{uw} H_u + I_{tw} H_u\right] - \mu I_{uw} \\
\dot{I}_{tw} &= \beta_w \left(1 - \epsilon_w\right) \left[I_{uw} H_t + I_{tw} H_t\right] - \mu I_{tw}
\end{aligned} \tag{1}$$

The wildtype pathogen strain spreads from infected fields to healthy fields at a rate β_w. In treated fields, this rate is reduced by a factor $1 - \epsilon_w$, where ϵ_w is the fungicide efficacy. Infected fields recover and convert back to healthy at a rate μ. The fraction $\theta = (H_t + I_{tw})/N$ of all fields is treated with fungicide. Hence, the number of untreated and treated fields can be calculated as,

$$\begin{aligned}
H_u + I_{uw} &= N\left(1 - \theta\right) \\
H_t + I_{tw} &= N\theta
\end{aligned} \tag{2}$$

First, consider the no-treatment scenario, $\theta = 0$, for the calculation of the basic reproduction number. It can be interpreted as the average number of secondarily infected fields produced by a single infected field introduced into a population of healthy fields. The basic reproduction number (R_0) for no-treatment scenario is,

$$R_0 = \frac{\beta N}{\mu}, \tag{3}$$

as derived in Subsect A.1 in S1 Appendix. A higher value of R_0 indicates a higher potential for the pathogen to spread.

When we include fungicide treatment ($\theta > 0$), we use the next-generation matrix method in Subsect A.2.3 in S1 Appendix [21,22] to derive the effective reproduction number as

$$\mathcal{R}_0 = R_0\left(1 - \epsilon_w \theta\right). \tag{4}$$

This expression quantifies how fungicide treatment affects the pathogen's capacity to invade and spread. The critical fungicide coverage, for which $\mathcal{R}_0 = 1$ can be calculated as:

$$\theta_{cw} = \frac{1}{\epsilon_w}\left(1 - \frac{1}{R_0}\right). \tag{5}$$

Treating the fields beyond the critical coverage level ($\theta > \theta_{cw}$) prevents an epidemic. This criterion depends on the fungicide efficacy, ϵ_w, and the pathogen's R_0 without treatment. Thus for a given R_0, when $\theta > \theta_{cw}$, fungicide treatment will suppress $\mathcal{R}_0$ to a value below one if ϵ_w is high enough, i.e. if $\epsilon_w > \epsilon_{cw} = 1 - 1/R_0$. However, at a low fungicide efficacy $\epsilon_w < \epsilon_{cw}$, even treating all fields ($\theta = 1$) will not prevent an epidemic as $\mathcal{R}_0$ will remain higher than one. Similarly, for a fungicide with a given efficacy ϵ_w, increasing θ to values above the critical, θ_{cw}, will drive the pathogen to extinction only for pathogens with $R_0 < R_{0cw}$, where

$$R_{0cw} = 1/\left(1 - \epsilon_w\right). \tag{6}$$

The expressions for the critical R_{0cw} and θ_{cw} will help us to better understand and perform bioeconomic analysis below in section Bioeconomic analysis of fungicide use. However, to conduct a bioeconomic analysis, we must consider the evolutionary aspect of the problem as repeated fungicide application can lead to the evolution of resistance in pathogen populations [14,23,24], which we explore next.

Model with fungicide treatment and resistance We extend the model in Eq (1) to incorporate a resistant pathogen strain that could be fully or partially protected from the fungicide. We assume that either a wildtype (w) or a resistant (r) pathogen strain dominates each infected field [25]. The epidemiological dynamics are given by:

$$\begin{aligned}
\dot{H}_u &= -\beta_w \left[I_{uw} + I_{tw}\right] H_u - \beta_r \left[I_{ur} + I_{tr}\right] H_u + \mu \left[I_{uw} + I_{ur}\right] \\
\dot{H}_t &= -\beta_w \left(1 - \epsilon_w\right) \left[I_{uw} + I_{tw}\right] H_t - \beta_r \left(1 - \epsilon_r\right) \left[I_{ur} + I_{tr}\right] H_t + \mu \left[I_{tw} + I_{tr}\right] \\
\dot{I}_{uw} &= \beta_w \left[I_{uw} + I_{tw}\right] H_u - \mu I_{uw} \\
\dot{I}_{tw} &= \beta_w \left(1 - \epsilon_w\right) \left[I_{uw} + I_{tw}\right] H_t - \mu I_{tw} \\
\dot{I}_{ur} &= \beta_r \left[I_{ur} + I_{tr}\right] H_u - \mu I_{ur} \\
\dot{I}_{tr} &= \beta_r \left(1 - \epsilon_r\right) \left[I_{ur} + I_{tr}\right] H_t - \mu I_{tr}.
\end{aligned} \tag{7}$$

Resistance reduces fungicide efficacy. Consequently, fungicide efficacy against the resistant strain is lower than its efficacy against the wildtype strain, $\epsilon_r < \epsilon_w$. Further, the transmission rate of the resistant strain, β_r, can be reduced because of possible fitness costs associated with resistance mutations. We neglect this effect here (i.e., set $\beta_r = \beta_w$) but consider it in Subsect B.2.2 in S1 Appendix. The fraction of treated fields is given by $\theta = (H_t + I_{tw} + I_{tr})/N$. The stability analysis for the Eq (7) is presented in Subsect A.3.1–A.3.3 in S1 Appendix.

Using the next-generation matrix approach, we derive the following expression for the effective reproduction number in the more general case of a partially effective fungicide and partial resistance (Subsect A.3.4 in S1 Appendix):

$$\mathcal{R}_0 = \max\left(\frac{N\beta_w}{\mu}\left(1 - \epsilon_w\theta\right), \frac{N\beta_r}{\mu}\left(1 - \epsilon_r\theta\right)\right). \tag{8}$$

We consider equal transmission rates for the wildtype and resistant strains ($\beta_w = \beta_r$) but unequal fungicide efficacies for the two strains ($\epsilon_w > \epsilon_r$). As a result, the second expression on the right-hand side of Eq (8) is larger than the first expression, and the effective reproduction number takes the form:

$$\mathcal{R}_0 = R_0\left(1 - \epsilon_r\theta\right). \tag{9}$$

The above expression is similar to Eq (4) but has ϵ_r instead of ϵ_w as a factor reducing the basic reproduction number. Based on Eq (9), we determine the critical fungicide coverage, above which the fungicide treatment leads to the extinction of resistance:

$$\theta_{cr} = \frac{1}{\epsilon_r}\left(1 - \frac{1}{R_0}\right). \tag{10}$$

If $\theta_{cr} > 1$, then the fungicide treatment cannot drive the pathogen population (consisting of the resistant strain) to extinction even when fungicide coverage is complete $\theta = 1$. This is

the case when the fungicide efficacy against the resistant strain is lower than the critical value, $\epsilon_r < \epsilon_{cr}$, where

$$\epsilon_{cr} = 1 - \frac{1}{R_0}. \tag{11}$$

For a fungicide with a given efficacy ϵ_r against the resistant strain, increasing the fraction of treated fields θ to values above the critical, θ_{cr}, can drive the pathogen to extinction for a sufficiently low basic reproduction number, $R_0 < R_{0cr}$, where

$$R_{0cr} = 1/\left(1 - \epsilon_r\right). \tag{12}$$

Methodological features and assumptions

Our model assumes density-dependent transmission or pseudo-mass-action dynamics (Eq (7)) [26]. Disease transmission increases with the density of fields, and there is no explicit spatial structure. The approximation works well when the primary mode of long-distance dispersal of plant pathogens is via networks of transportation/trade (e.g., via movement of infected plants or other materials). For plant pathogens that disperse via air-borne spores, a spatially explicit model would need to consider a distance-dependent transmission [27,28] that has been characterized empirically in a number of important crop diseases (e.g., by [29,30]). In this case, our model provides a valuable reference scenario, but is expected to overestimate the number of diseased fields at endemic equilibrium.

Although our model considers multiple growing seasons, we simplified it as in [25] by neglecting the cyclic nature of multi-seasonal dynamics due to, e.g. the periodic absence of host plants. Environmental stochasticity associated with such multi-seasonal dynamics may play a role in the emergence of novel, better-adapted pathogen genotypes [31].

The model belongs to the class of spatially implicit metapopulation models and is similar to the model developed previously [25]. Similarly to [25], we assume that environmental conditions and cropping practices are the same in different fields and that all fields have the same size. Hence, the model parameters do not vary between different fields. We set possible states for each field to be either healthy or infected (and infectious). Although in reality, the level of infection can be continuous, our assumption implies that each infected field produces a similar amount of inoculum that can be transmitted to other fields and the characteristic time scale of within-field epidemic development is much shorter than the time scale of regional-scale dynamics. This idealized scenario is likely to be closer to reality for foliar fungal diseases of field crops caused by pathogens with long-distance dispersal in regional cultivated landscapes with relatively uniform environments and where crop cultivars have a similar degree of susceptibility to the disease. Examples of such diseases and cropping systems include northern corn leaf blight disease of maize in the corn belt regions of the US; target spot in soybean in major soybean-producing areas of Brazil (e.g., Mato Grosso); and wheat rusts (e.g., stripe rust and leaf rust) in major wheat-producing areas of the US (e.g., Central Great Plains). It will be interesting to relax this assumption in future work, allowing for heterogeneous disease levels among different fields, and investigate how this heterogeneity affects the conclusions of this study.

The model assumes that recovered fields are susceptible to re-infection (i.e., no induced resistance) and neglects demographic stochasticity [24]. In contrast to [25], our model does not have an explicit spore compartment, assuming that dispersal occurs much faster than other relevant epidemiological processes. We also assume that a field can be infected by either a sensitive or a resistant pathogen strain, but not by both. We justify this assumption

similarly to [25]. When a resistant strain appears in a fungicide-treated field, it can invade and outcompete the sensitive strain if the selection is strong enough and the fitness cost of resistance is low enough [23]. This condition is often fulfilled, as the fitness costs are typically below 10% [32,33], and hence most resistant strains, even those carrying partial resistance, will have a substantial fitness advantage over the sensitive strains in fungicide-treated fields. Alternatively, the resistance strain can fail to invade and die out or remain at a low level according to mutation-selection or migration-selection balance. In the latter scenario, the resistant strain does not affect the fungicide efficacy and is unlikely to spread to other fields, and therefore, the assumption that the field is infected only by the sensitive strain is justified.

The above assumptions (along with their caveats) allowed us to formulate a simple landscape-scale model of a generic fungal disease of crop plants. We can then obtain analytical outcomes and capture essential features of disease dynamics across entire ranges of plausible parameter values. To describe specific crop-pathogen systems with a higher degree of biological realism, our model will need to relax some of the assumptions at the expense of increased model complexity.

Having incorporated fungicide resistance into the model, we now analyze the economic aspects of fungicide treatment. We aim to determine the optimal fungicide treatment coverage that maximizes the net economic return.

Economic analysis: Net return and optimal fungicide coverage

We define the net return as the total income resulting from the sales of the harvested yield minus the cost of fungicide treatment across all N fields in the landscape over the course of K growing seasons. Mathematically, the net return is:

$$G = y_H \left(\sum_{k=1}^{K} \left(H(t_k) + I(t_k) y \right) - \theta N f \right), \tag{13}$$

where y_H is the yield of a healthy field, t_k is the time point corresponding to the end of season k, $y = y_I/y_H$ is the relative yield of a diseased field (hence, the relative yield loss is $1-y$), $f = c/y_H$ is the relative fungicide price. Here, c, the cost of fungicide application per field, includes the cost of spraying material and application cost. The total yield of the landscape, Y, is given by the sum of the first and the second terms in Eq (13): $Y = y_H \sum_{k=1}^{K} \left(H(t_k) + I(t_k) y \right)$; and the total fungicide price over the landscape, F, is given by the third term in Eq (13): $F = y_H \theta N f$.

The net return does not change after the system reaches a stable equilibrium. Besides being analytically tractable, we consider this case as it corresponds to the limit of sustainable disease management. The outcomes will likely remain the same across a range of times, even before the equilibrium is strictly reached. However, they are expected to be different during the initial stages of dynamics as these are affected by initial conditions.

At equilibrium, we characterize the net return as follows. We compute it for a single season and divide it by the total number of fields N to obtain the average across fields. We also divide it by yield per season from a healthy field, y_H, to obtain the relative net return (which we will call "net return" for brevity) $g(\theta) = \left(H^* + I^* y \right) / N - \theta f$, where $H^* = H_u^* + H_t^*$ and $I^* = I_{uw}^* + I_{tw}^*$ represent the values of the state variables (numbers of healthy and diseased fields) at a stable fixed point. The yield from healthy and diseased fields boosts the net return (the first term), while the cost of fungicide treatment reduces the net return (the second term). Since the total

number of fields remains constant, $H^* = N - I^*$, we rewrite the expression for the net return in the form that supports further analyses:

$$g(\theta) = 1 - (1 - y)\left(\frac{I^*}{N} + \alpha\theta\right). \tag{14}$$

Here, the net return without disease and without treatment is equal to one (the first term in Eq (14)). The second term in Eq (14) quantifies the reduction of the net return due to disease, which is proportional to the fraction of diseased fields I^*/N. The third term in Eq (14) quantifies the reduction of the net return due to the cost of fungicide treatment. This term is proportional to θ with the coefficient α that we call the cost ratio parameter:

$$\alpha = \frac{f}{1 - y}, \tag{15}$$

where f is the relative fungicide price, and $1–y$ is the yield loss in a diseased field (expressed as its monetary equivalent). The proportion of diseased fields $I^*/N = (I^*_{uw} + I^*_{tw})/N$ in the second term also depends on θ albeit in a complex manner according to Eqs. (A4-A11) (Subsect A.2 in S1 Appendix) and the associated linear stability conditions.

We define the optimal fungicide coverage or simply optimal coverage, θ^*, as the proportion of treated fields that results in the highest net return. The optimal coverage θ^* can be determined by calculating the value of $g(\theta)$ across a fine grid of θ-values. The θ-value that maximizes $g(\theta)$ is the optimal coverage θ^*. In cases where multiple values of θ yield the same highest value of $g(\theta)$, we define the lowest among these as the optimal coverage θ^*.

Net return in an individual field

While the focus of this work is on cultivated landscapes with multiple fields, we provide the model for the net return in an individual field for comparison. When managing disease in an individual field, growers can adjust the fungicide dose to maximize the net return, g, given by

$$g(D) = Y_0 + Y_m\frac{D}{D + D_{50}} - qD, \tag{16}$$

where Y_0 is the yield without fungicide application, and D is the fungicide dose. The second term in Eq (16) is the yield benefit of the fungicide application, where the functional form used is a simplification of the Hill function, which describes a typical empirical dose-response relationship for fungal diseases in cereal crops [24]. Hence, the total yield of a field, Y, is given by the sum of the first and second terms in Eq (16): $Y = Y_0 + Y_m\frac{D}{D+D_{50}}$. (We also defined Y above as the total yield of a landscape; to avoid confusion, we specify the context every time we use Y). The parameter Y_m represents the maximum effect at large doses, and D_{50} corresponds to the dose for which half of the maximum effect is achieved. The third term in Eq (16) quantifies the total fungicide price, $F = qD$, where q is the price per unit fungicide. Net return, $g(D)$, in Eq (16) exhibits a maximum at the fungicide dose

$$D^* = -D_{50} + \sqrt{D_{50}Y_m/q}. \tag{17}$$

If the fungicide becomes sufficiently expensive ($q > Y_m/D_{50}$), the expression for the optimum dose in Eq (17) becomes negative, meaning that the net return is maximized when no fungicide is applied. For less expensive fungicides, the net return does exhibit a maximum

at positive doses. The optimum dose is higher for cheaper fungicides. We refer the reader to Subsect B.1 in S1 Appendix for more details on the individual field model.

Results

Bioeconomic analysis of fungicide use

To perform a bioeconomic analysis, we first set the context by comparing the optimal fungicide treatments between individual fields and cultivated landscapes. Next, we answer the central question: What fraction of fields should be treated with a fungicide to maximize the net return of a landscape?

Optimal fungicide treatments in individual fields versus cultivated landscapes When controlling disease in an individual field, the yield, Y (expressed as its monetary equivalent), typically exhibits a saturating increase as we increase the fungicide dose, D (second term in Eq (16); Fig 2A). The total fungicide price, F, increases linearly when increasing the fungicide dose with the slope given by the fungicide price per unit dose (third term in Eq (16); dark red lines in Fig 2A). The net return, $g(D)$, is then given by the difference between the yield, Y, and the total fungicide price, F (Eq (16), Fig 2A). $g(D)$ reaches a maximum for an intermediate (optimal) fungicide dose. For doses higher than optimal, the cost associated with increasing the dose is no longer compensated by an associated increase in yield. These relationships follow "the law of diminishing returns" that has achieved an almost universal status in the economics of crop production [34] and other areas of economics [35,36].

In contrast, when controlling disease in a cultivated landscape, the total yield of the landscape (Y, expressed as its monetary equivalent, Eq (B8) in S1 Appendix) exhibits an accelerating increase as we increase the fungicide coverage, θ (Fig 2C). The total price of the fungicide treatment increases linearly with θ (Fig 2C), as it did for an individual field above. The net return, $g(\theta)$, is again the difference between the monetary yield, Y, and the total fungicide price, F. However, here, the outcome is very different. The net return does not exhibit a maximum at any intermediate θ value. Thus, the net return can be maximized only at the extreme values of θ: $\theta = 0$ treating no fields or $\theta = 1$ treating all fields. When the fungicide is sufficiently cheap, $\theta = 1$ maximizes the net return (Fig 2C, 2D). However, when the fungicide is too expensive, then the no-treatment strategy ($\theta = 0$) maximizes the net return (Fig 2C, 2D).

Thus, the law of diminishing returns does not necessarily hold when controlling disease in cultivated landscapes. This finding has important implications for the economics of crop disease management, optimal decision making and associated policy-making, which is often done at scale and not for individual fields.

Optimal fungicide coverage without resistance Our analysis reveals that three parameters influence the optimal fungicide coverage, θ^*: (i) the fungicide price, f, (ii) the yield loss in a diseased field, $1-y$ and (iii) the critical fraction of treated fields, θ_{cw} (in Eq (5)). The first two parameters affect θ^* only through their ratio, the cost ratio parameter $\alpha = f/(1-y)$ (defined in Eq (15) above). Therefore, below, we study the effects of α and θ_{cw}.

When α is sufficiently low, treating all fields ($\theta^* = 1$, if $R_0 > R_{0cw}$; Fig 3A) or most fields ($\theta^* = \theta_{cw}$, if $R_0 < R_{0cw}$ Fig 3A) maximizes the net return (here, θ_{cw} is given by Eq (5)). When α is sufficiently high, not treating any fields maximizes the net return ($\theta^* = 0$; Fig 3A, 3B). Thus, the net return can only be maximized at extreme values of the fungicide coverage, either $\theta^* = 0$ or $\theta^* = 1$ (or $\theta^* = \theta_{cw}$ in case $\theta_{cw} < 1$, whereby θ_{cw} is still close to 1).

To gain a quantitative understanding of factors affecting the optimal coverage, θ^*, consider the regimes $\theta_{cw} > 1$ ($R_0 > R_{0cw}$) and $\theta_{cw} < 1$ ($R_0 < R_{0cw}$) in more detail. When $\theta_{cw} > 1$, it is impossible to wipe out the epidemic even if we treat all fields. This is the case for pathogens

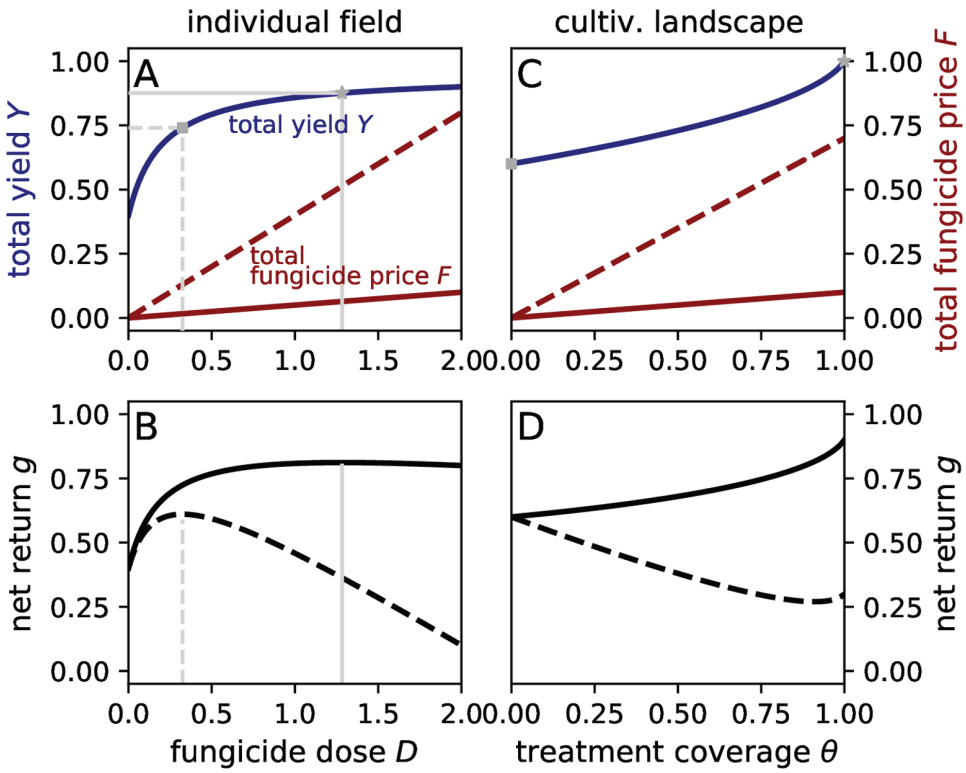

Fig 2. How does the net return depend on the intensity of treatment? (A) In an individual field, the yield Y exhibits a saturating increase as we increase the fungicide dose, D [solid blue; Eq (B2) in S1 Appendix]. Y is expressed as a fraction of the monetary equivalent of the maximum yield. The total fungicide price, F, is proportional to the dose, D, with the slope given by the price per unit: $q = 0.05$ (solid red); $q = 0.4$ (dashed red). (B) Black curves represent the net return computed as the blue curve in (A) minus one of the red lines in (A), with $q = 0.05$ (solid) and $q = 0.4$ (dashed). The net return exhibits a maximum for an intermediate dose [Eq (B4) in S1 Appendix]. Grey vertical lines in (A) and (B) show doses that maximize the net return. Other parameter values for (A) and (B): $y_m = 0.55$, $D_{50} = 0.2$, $y_0 = 0.4$. (C) In a cultivated landscape, the total yield of the landscape, Y, [Eq (B8) in S1 Appendix] exhibits an accelerating increase as we increase the fraction of treated fields, θ (blue). The total fungicide price, F, is proportional to θ, with the slope given by the relative fungicide price: $f = 0.1$ (solid red), $f = 0.7$ (dashed red). (D) As a result, the net return is maximum when treating either all fields ($\theta = 1$, solid, $f = 0.1$) or when not treating any fields ($\theta = 0$, dashed, $f = 0.7$); according to Eq (B7) in S1 Appendix. Other parameter values for (C) and (D): $\beta = 0.025$, $\mu = 5$, $N = 1000$ (hence, $R_0 = \beta N/\mu = 5$), $y = 0.5$.

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with a sufficiently high R_0, whereby, $R_0 > R_{0cw}$ (Fig 3A), where R_{0cw} is given by Eq (6). On the contrary, when $\theta_{cw} < 1$, one can wipe out the epidemic by treating a high enough proportion of fields, i.e., $\theta > \theta_{cw}$. This is the case for pathogens with a sufficiently low R_0, whereby, $R_0 < R_{0cw}$ (Fig 3B).

For $\theta_{cw} > 1$ ($R_0 > R_{0cw}$), not treating any fields ($\theta = 0$) maximizes the net return when the cost ratio parameter is sufficiently high ($\alpha > A$). In contrast, when $\alpha < A$ treating all fields ($\theta = 1$) maximizes the net return (Fig 3A), where

$$A = \frac{\epsilon_w}{R_0(1 - \epsilon_w)} \tag{18}$$

is a combination of epidemiological parameters.

For $\theta_{cw} < 1$ ($R_0 < R_{0cw}$), the optimal coverage, θ^*, depends on how the cost-ratio α relates to the fungicide efficacy ϵ_w. If $\alpha > \epsilon_w$, we can maximize the net return by not treating any

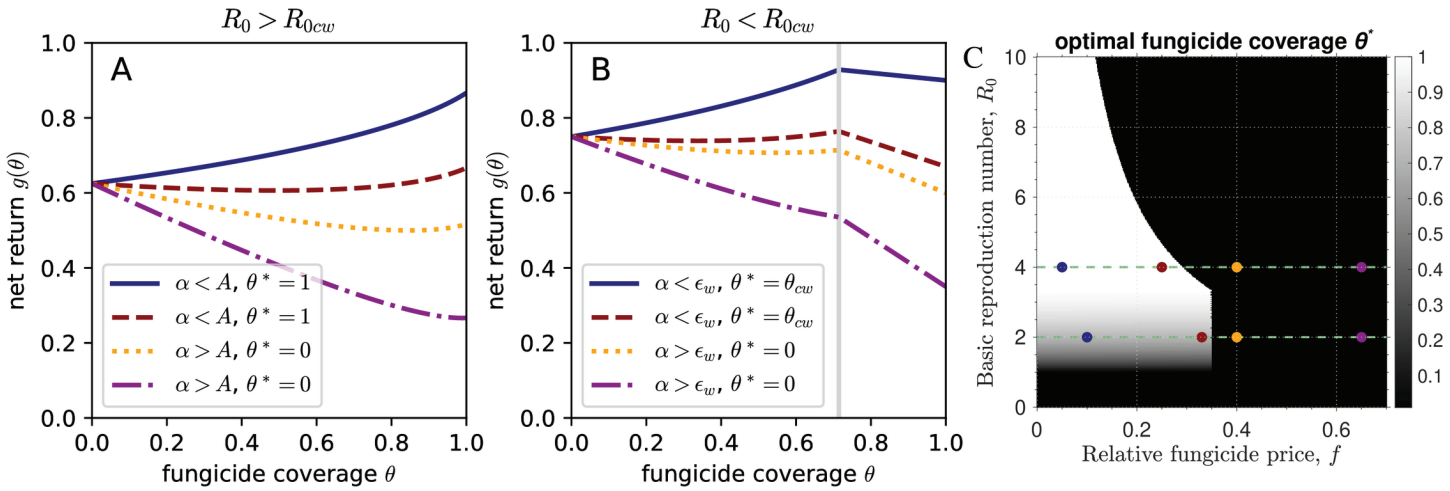

Fig 3. What is the optimal fungicide coverage in the landscape model without fungicide resistance? (A) The net return $g(\theta)$ is plotted against the fungicide coverage (fraction of treated fields θ) for $R_0 > R_{0cw}$ and $\theta_{cw} > 1$ (i.e., $\beta = 0.02$ and $R_0 = \beta N/\mu = 4$). The four curves represent different relative fungicide prices (f): 0.05 (solid blue), 0.25 (dashed red), 0.4 (dotted orange), and 0.65 (dash-dotted magenta). (B) The net return $g(\theta)$ is plotted against θ for $R_0 < R_{0cw}$ and $\theta_{cw} = 0.714 < 1$ (shown by a vertical grey line, i.e., $\beta = 0.01$ and $R_0 = \beta N/\mu = 2$). The four curves represent different values of f: 0.1 (solid blue), 0.33 (dashed red), 0.4 (dotted orange), and 0.65 (dash-dotted magenta). (C) The heatmap shows the optimal fungicide coverage θ^* for varying fungicide price f and basic reproduction number R_0. In the white region, treating all fields is optimal; in the black region, not treating any fields is optimal; in the grey region, treating only a fraction of fields is optimal. Each curve in (A) and (B) corresponds to a point on the green dashed lines in the heatmap (C). These points are highlighted by circles of the same color as lines in (A) and (B). Specifically, $R_0 = 4$ and $R_0 = 2$ correspond to (A) and (B) respectively. Other parameter values are constant for all panels: $N = 1000$, $\mu = 5$, $\epsilon_w = 0.7$, and $y = 0.5$.

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fields ($\theta = 0$). If, on the contrary, $\alpha < \epsilon_w$, then we can maximize the net return by treating a fraction of fields that corresponds to the critical value ($\theta = \theta_{cw}$, which constitutes a high fraction of fields; Fig 3B). We investigate $g(\theta)$ in more detail in Subsect B.2.1 in S1 Appendix, where we show that the net return can either increase/decrease monotonically or exhibit a minimum as a function of θ.

Fig 3C shows that the optimal coverage, θ^*, depends strongly on both the relative fungicide price, f, and the pathogen's basic reproduction number, R_0. This dependency exhibits three regimes for low, intermediate and high values of R_0. For low $R_0 < 1$, the optimal coverage does not depend on fungicide price because epidemics will not sustain even without treatment, and hence, not treating any field is optimal for any f. When $R_0 > 1$, the optimal coverage does depend on f, showing a threshold pattern. For low f-values below the threshold, it is optimal to treat at least some of the fields ($\theta^* > 0$). For high f-values above the threshold, not treating any fields yields a maximum net return ($\theta^* = 0$). For intermediate R_0-values, the threshold in f does not depend on R_0 (hence, the boundary between white/gray and black areas is a vertical line in Fig 3C). For high R_0 values, the threshold in f becomes lower when R_0 is increased. This threshold pattern, rather than a gradual increase in the optimal coverage with increasing f, occurs because, as we have shown above, the law of diminishing returns no longer holds when we increase the treatment coverage in multiple fields across a landscape. The identification of the threshold pattern can inform economic policy for achieving more sustainable fungicide use, as we elaborate in the Discussion.

Thus, the net return is maximized at extreme θ-values, and which of the extrema are optimal is determined by how the cost-ratio α relates to a combination of epidemiological parameters of the system.

Optimal fungicide coverage with resistance Now, we focus on the fraction of fields to be treated with fungicide to maximize the net return in a landscape model when resistance

exists. We consider a high-efficacy fungicide ($\epsilon_w = 1$), no fitness cost of resistance ($\beta_r = \beta_w$), and focus on partial resistance ($0 < \epsilon_r < 1$) (fitness cost of resistance is considered in Subsect B.2.2 in S1 Appendix). The fungicide can still suppress the partially resistant strain with efficacy ϵ_r, smaller than the efficacy against the wildtype strain, ϵ_w. As before, the optimal fungicide coverage depends on the cost-ratio α (in Eq (15)).

When $\theta_{cr} > 1$ ($\epsilon_r < \epsilon_{rc}$, where ϵ_{cr} is given by Eq (11)), fungicide treatment is ineffectual in clearing the resistance. In this case, the optimal coverage, θ^*, depends on how the cost-ratio α relates to the combination of epidemiological parameters,

$$B = \frac{\epsilon_r}{1 - \epsilon_r}/R_0. \tag{19}$$

The expressions for B is similar to A in Eq (18), but with ϵ_r instead of ϵ_w. When a fungicide is sufficiently cheap, $\alpha < B$, treating all fields maximizes the net return ($\theta^* = 1$; Fig 4A). When a fungicide is too expensive, $\alpha > B$, then not applying it is optimal ($\theta^* = 0$; Fig 4A).

When $\theta_{cr} < 1$ ($\epsilon_r > \epsilon_{cr}$), treating a sufficiently high fraction of fields ($\theta > \theta_{cr}$) will drive the dominant resistant strain to extinction. Here, the optimal θ depends on how the cost-ratio α relates to the efficacy of the fungicide against the resistant strain ϵ_r. If $\alpha < \epsilon_r$, then treating a significant fraction of fields maximizes the net return ($\theta^* = \theta_{cr}$; Fig 4B). If $\alpha > \epsilon_r$, then not treating any field maximizes the net return ($\theta = 0$; Fig 4B). Fig 4C provides a broader overview of the parameter space, considering how the optimal fungicide coverage θ^* depends on fungicide price, f, and fungicide efficacy against the resistant strain, ϵ_r.

Thus, when resistance is absolute, it is impossible to manage it apart from stopping or drastically reducing fungicide treatment (see Subsect B.2.2 in S1 Appendix). Nevertheless, when

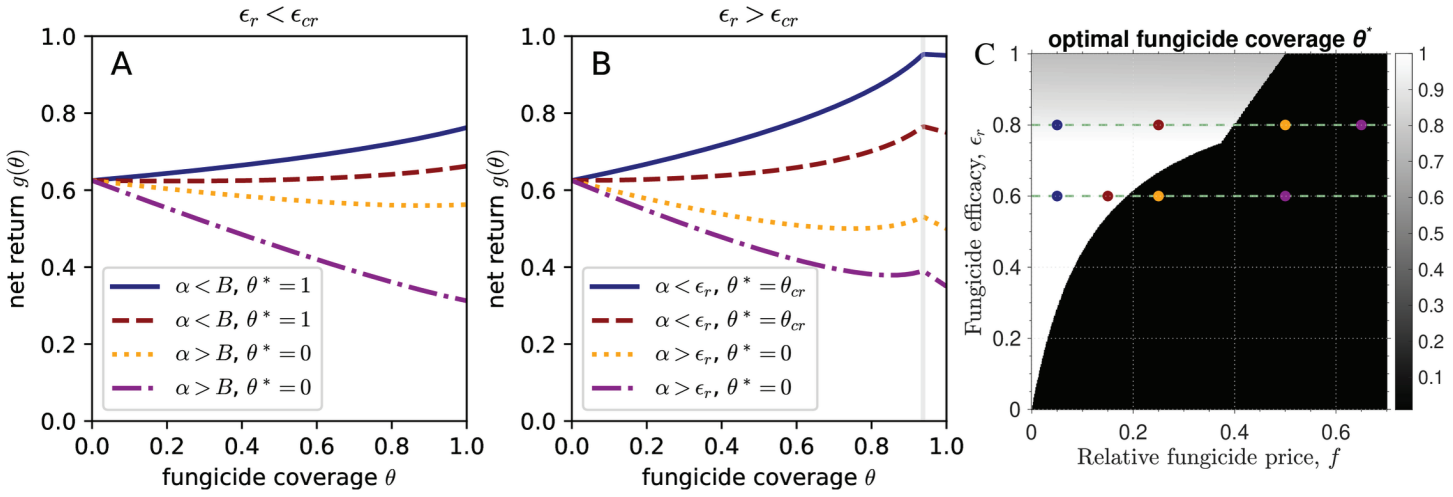

Fig 4. What is the optimal fungicide coverage in the landscape model with fungicide resistance? (A) The net return $g(\theta)$ is plotted against the fungicide coverage (fraction of treated fields θ) for a high degree of partial resistance ($\epsilon_r = 0.6 < \epsilon_{cr} = 0.75$). The four curves represent different relative fungicide prices (f): 0.05 (solid blue), 0.15 (dashed red), 0.25 (dotted orange), 0.5 (dash-dotted magenta). (B) The net return $g(\theta)$ is plotted against θ for a low degree of partial resistance ($\epsilon_r = 0.8 > \epsilon_{cr}$) which means that it is possible to drive the resistant strain to extinction by treating a high enough fraction of fields ($\theta = \theta_{cr}$, vertical grey line). The four curves represent different values of f: 0.05 (solid blue), 0.25 (dashed red), 0.5 (dotted orange), 0.65 (dash-dotted magenta). (C) Heatmap of the optimal fungicide coverage θ^* for varying fungicide price f and fungicide efficacy against resistant strain ϵ_r. In the white region, it is optimal to treat all fields with fungicide; in the black region, it is optimal to not treat any fields; in the grey region, it is optimal to treat only a fraction of the fields. Each curve in (A) and (B) corresponds to a point on the green dashed line in (C). These points are highlighted by circles of the same color as lines in (A) and (B). Specifically, points on green dashed lines for $\epsilon_r = 0.6$ corresponds to (A) and for $\epsilon_r = 0.8$ corresponds to (B). Other parameter values are constant for all panels: $\beta = 0.02$, $R_0 = \beta N/\mu = 4$; $N = 1000$, $\mu = 5$, $\epsilon_w = 1$, $y = 0.5$.

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resistance is partial, the net return can still be maximized by treating all fields or a significant fraction of fields (if the fungicide is sufficiently cheap) or by not treating any fields (if the fungicide is sufficiently expensive).

The economic cost of fungicide resistance

The maximum (or optimal) net return of a landscape becomes lower in the presence of resistance (compare Fig 3A and Fig 4A). Thus, the evolution of fungicide resistance can incur a substantial economic cost. Here, we propose a novel way to calculate the economic cost of fungicide resistance across a cultivated landscape using the expression for the net return in Eq (14). Firstly, we compute the net return in the absence of resistance and in the presence of resistance according to Eq (14). Secondly, we determine the optimal fraction of treated fields to maximize the net return in each of the cases. Finally, we calculate the economic cost of resistance, C_R, as the difference between the optimum net return in the absence and in the presence of resistance:

$$C_R = g_0(\theta_0^*) - g_1(\theta_1^*), \tag{20}$$

where $g_0(\theta_0^*)$ is the optimum net return and θ_0^* is the optimum coverage in the absence of resistance; $g_1(\theta_1^*)$ is the optimum net return and θ_1^* is the optimum coverage in the presence of resistance. In this calculation, we assume that, both with and without resistance, the optimum fraction of treated fields is known to farmers across the landscape and that they use these optimum values.

To illustrate this calculation, we plot the maximal net returns, $g_0(\theta_0^*)$ and $g_1(\theta_1^*)$, the optimal fractions of treated fields, θ_0^* and θ_1^*, and the economic cost of resistance, C_R, versus the relative fungicide price, f (Fig 5). Fig 5A compares the optimal net return in the absence and presence of resistance. The difference between these curves constitutes the economic cost of resistance evolution plotted in Fig 5C. Next, we elucidate the dependence of the cost of resistance on the fungicide price f, the degree of resistance $1 - \epsilon_r$, the basic reproduction number R_0 and the yield loss $1-y$.

Dependence on the fungicide price Fig 5C shows a typical dependence of C_R on f when the basic reproduction number of the pathogen exceeds its critical values ($R_0 > 1/(1-\epsilon_w)$ in Eq (6) and $R_0 > 1/(1-\epsilon_r)$ in Eq (12)). We explore three ranges of fungicide prices (f) – cheap, intermediate and expensive – corresponding to qualitatively different patterns in the C_R dependence. For cheap fungicides (low f-values), C_R remains constant and treating all fields maximizes the net return (Fig 5B). In this range, the optimal net return drops linearly with increasing f at the same rate with and without resistance. Hence, the difference between the optimal net return with and without resistance remains constant (the economic cost of resistance in this parameter range is given by Eq (C1) in S1 Appendix). For intermediate f-values, treating all fields remains optimal in the absence of resistance, but in the presence of resistance, the optimum switches to not treating any fields. The difference between the optimal net return without resistance and with resistance (that constitutes C_R) declines linearly with f (the economic cost of resistance in this range is given Eq (C2) in S1 Appendix). For expensive fungicides (high f-values), not treating any fields becomes optimal in the absence and in the presence of resistance. In this range, the cost of fungicide resistance remains at zero (Fig 5C). Here, the optimal net return is determined by the yield of untreated fields, independent of the fungicide price f and irrespective of resistance.

In a different scenario, when R_0 does not exceed the critical value for the wildtype strain [i.e., $R_0 < R_{0cw}$, Eq (6)], C_R increases, reaches a maximum and then decreases as a function

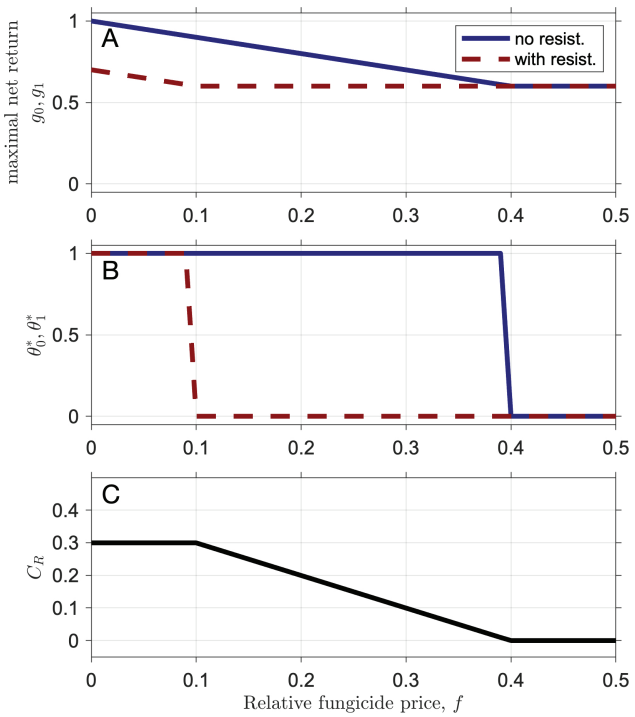

Fig 5. Calculation of the economic cost of fungicide resistance, C_R, versus relative fungicide price, f, according to Eq (20). (A) Optimal net return without resistance ($g_0(\theta_0^*)$, solid, blue curve) and with resistance ($g_1(\theta_1^*)$, dashed, red curve). (B) Optimal fraction of treated fields without resistance (θ_0^*, solid, blue curve) and with resistance (θ_1^*, dashed, red curve). (C) Economic cost of resistance, C_R, computed as the optimal net return without resistance minus the optimal net return with resistance. Parameter values: $\beta_r = \beta_w = 0.025$, $N = 1000$, $\mu = 5$ (hence, $R_0 = \beta N/\mu = 5$); $\epsilon_w = 0.8$, $\epsilon_r = 0.5$.

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of f, reaching zero (region of the plot corresponding to $1 < R_0 < 5$ in Fig 6B). This pattern arises due to a complex interplay between the optimal net return with and without resistance and the associated optimal fungicide coverage (we describe this in detail in Sect C in S1 Appendix).

Dependence on the degree of resistance The cost of resistance varies with the degree of resistance only for cheap fungicides (low f-values, Fig 6A). Herein, C_R remains zero at low degrees of resistance, $1-\epsilon_r$, and then increases linearly with increasing $1-\epsilon_r$. Thus, as expected, higher degrees of resistance correspond to higher economic costs of resistance (compare horizontal parts of contour lines in Fig 6A). This is because stronger resistance leads to higher numbers of fields becoming diseased despite treatment, which in turn results in lower overall yields of the landscape in the presence of resistance compared to the landscape in the absence of resistance.

For expensive fungicides (high f-values), the degree of resistance no longer affects the economic cost of resistance, which remains at zero in this range. In this scenario, the fungicide is so expensive that treatment is not economically justified, irrespective of resistance.

Dependence on the basic reproduction number The dependence of the economic cost of resistance, C_R, on the basic reproduction number, R_0, is counter-intuitive (Fig 6B). When the fungicide is expensive (the right-most region in Fig 6B), optimal fungicide coverage goes to zero both with and without resistance, and resistance incurs no economic cost. However,

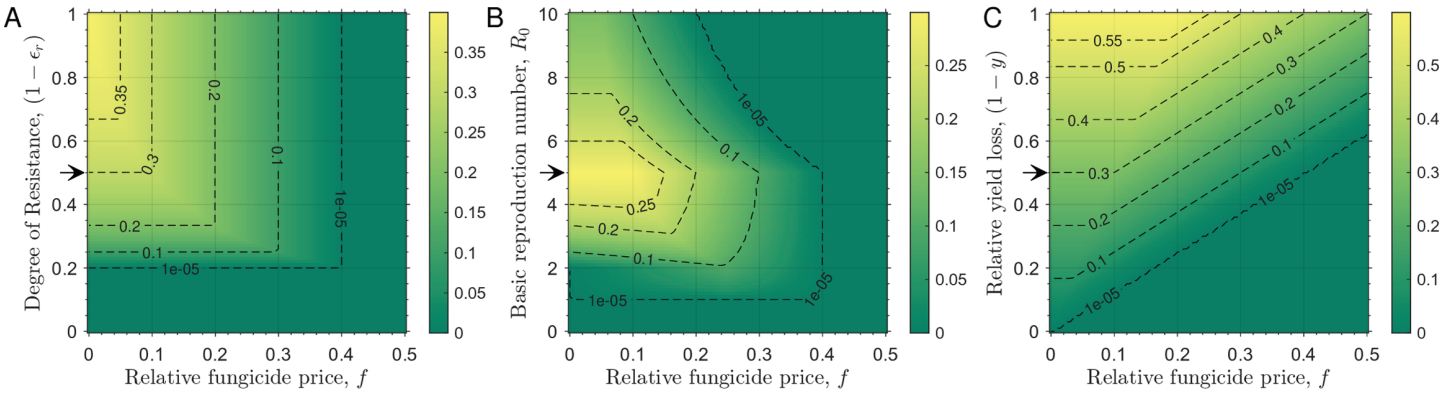

Fig 6. How does the economic cost of fungicide resistance, C_R, depend on fungicide price (f), degree of resistance ($1-\epsilon_r$), basic reproduction number (R_0), and yield loss due to disease ($1-y$)? Each panel illustrates how C_R depends on f along the x-axis and one of the other variables along the y-axis: (A) the effect of the degree of resistance, $(1-\epsilon_r)$, with $R_0 = 5$ and $y = 0.5$; (B) the effect of the basic reproduction number, R_0, with $\epsilon_r = 0.5$ and $y = 0.5$ ($R_{0cw} = 5$, $R_{0cr} = 2$); (C) the effect of the yield loss due to disease, $1-y$, with $\epsilon_r = 0.5$ and $R_0 = 5$. Values of ϵ_r, R_0 and y used to plot Fig 5 are highlighted with an arrow on the y-axis of panels (A), (B) and (C), respectively. Note that each panel uses a different grayscale mapping for C_R as shown in the grayscale bars. Parameter values that remain the same across all panels are: $N = 1000$, $\mu = 5$, and $\epsilon_w = 0.8$.

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in a more interesting regime of low- to intermediately-priced fungicide, C_R exhibits complex, non-monotonic patterns versus R_0 and f (Fig 6B).

For cheap fungicides (i.e., small f), as R_0 increases, C_R first remains at zero, then increases with R_0, reaches a maximum and then decreases (compare different contour lines in Fig 6B for small f-values). When $R_0 < 1$, no epidemic occurs, and hence, the relative net return is maximal $g_{\max} = 1$ both with and without resistance, resulting in $C_R = 0$. When $1 < R_0 < R_{0cr}$ (see Eq (12)), an epidemic can occur in both cases, but treating an optimal intermediate fraction of fields with a fungicide drives the pathogen to extinction: $\theta^* = \theta_{cw}$ without resistance and $\theta^* = \theta_{cr}$ with resistance. Hence, the optimal net return is given by $g_{\max} = 1 - f\theta_{cr}$ with resistance and $g_{\max} = 1 - f\theta_{cw}$ without resistance. Their difference $C_R = f(\theta_{cr} - \theta_{cw})$, increases with R_0 since $\theta_{cr} - \theta_{cw} \propto 1 - 1/R_0$ (see Eq (5) and Eq (10)). In other words, higher R_0 values require increased fungicide coverage to eliminate the pathogen in both scenarios. However, due to lowered efficacy against the resistant strain, this coverage, and thus C_R, increases faster in the presence of resistance.

For $R_{0cr} < R_0 < R_{0cw}$, applying fungicide to an optimal intermediate proportion of fields still drives the pathogen to extinction without resistance. While in the presence of resistance, treating all fields is optimal ($\theta^* = 1$), yet insufficient for elimination. In this regime, $g_{\max}$ without resistance continues to decline with R_0 due to increasing required coverage. With resistance, $g_{\max}$ declines more rapidly due to both lower fungicide efficacy and higher prevalence of disease. As a result, C_R continues to increase with R_0, reaching a maximum at $R_0 = R_{0cw}$.

Finally, and unexpectedly, when $R_0 > R_{0cw}$, C_R drops with increasing R_0. In this case, fungicide treatment cannot extinguish the pathogen population, irrespective of the presence of resistance. To clarify, consider a simplified scenario of a cheap fungicide ($f \to 0$). In this case, treating all fields ($\theta^* = 1$) becomes optimal both with and without resistance (Fig 5B). Both with and without resistance, the optimal net return declines with R_0 as the fraction of diseased fields increases with R_0. Without resistance, this fraction (at endemic equilibrium) is given by $i_w = 1 - 1/[R_0(1-\epsilon_w)]$. With resistance, this fraction (also at endemic equilibrium, but now with the resistant strain) is given by $i_r = 1 - 1/[R_0(1-\epsilon_r)]$. C_R is proportional to the difference $i_r - i_w$. Both i_r and i_w increase in a saturating manner with R_0 (eventually tending to

one at high R_0-values) but do so at different, nonlinear rates in such a way that the difference between the two diminishes at higher R_0-values, and so does the economic cost of resistance, C_R. In other words, resistance incurs a lower economic cost at higher R_0 values because even without resistance, it becomes challenging to suppress the disease due to the high invasiveness of the pathogen (as quantified by the basic reproduction number).

Dependence on yield loss The economic cost of fungicide resistance C_R is influenced by the yield loss in diseased fields, $1–y$ (relative to the yield of healthy fields; Fig 6C). As intuitively expected, C_R increases with higher yield losses. But, surprisingly, for higher fungicide prices, this increase starts at higher values of yield loss. Thus, an estimation of the economic cost of fungicide resistance requires detailed knowledge of key epidemiological and economic parameters.

Discussion

Farmers can maximize the net economic return of fungicide application by optimizing the amount of fungicide applied based on the balance between the yield benefit and the economic costs of fungicide application [5,6]. However, this analysis neglects the indirect costs of fungicide application incurred by the evolution of fungicide resistance, rendering decisions based solely on this analysis unsustainable. One way to address this issue is to design economic policy instruments that incorporate indirect costs into fungicide prices, such as pesticide taxes or subsidies encouraging a reduction in pesticide application [10,11]. However, this approach requires a robust estimation of the indirect costs, and a conceptual framework for such an estimation is absent from the existing literature. We build such a framework based on a simple but generic epidemiological model of crop epidemics across multiple fields combined with an economic analysis (Fig 1). Using this framework, we demonstrated how to estimate the economic cost of the evolution of fungicide resistance in crop pathogens with long-distance dispersal.

Derivation of the economic cost of fungicide resistance evolution (C_R) is a complex, multifaceted problem. However, with well-motivated assumptions, we derived analytical expressions for C_R. This derivation allows us to investigate how C_R depends on the system's critical epidemiological and economic parameters across entire ranges of plausible values. We found that C_R depends strongly on fungicide price, degree of resistance, pathogen's basic reproduction number, and yield loss due to disease. As intuitively expected, C_R increases with the degree of resistance and yield loss due to disease. Unexpectedly, it remains constant or decreases with the fungicide price. Also unexpectedly, C_R shows a non-monotonic pattern as a function of the basic reproduction number, R_0 (exhibiting a maximum at a critical value $R_0 = R_{0cw}$).

The three epidemiological parameters (degree of resistance, R_0, and yield loss due to disease) can vary significantly across different crop diseases [28,37–39]. Even for a single disease, the three epidemiological parameters can vary substantially depending on environmental conditions, crop varieties and genetic composition of pathogen populations. A strong dependence of C_R on these parameters highlights the need for a robust empirical estimation of these parameters. Even after the estimation of the three parameters, designing economic policy instruments that work across different regions and crops would be demanding. These instruments are more likely to succeed if they are adjusted for specific regions and crops. These instruments also need to be adapted over time according to changes in cropping systems and pathogen populations. Implementing economic and ecological interventions in a realistic system should feed back into the parameter values. Thus, like adaptive therapy in medicine,

the interventions are more likely to succeed if they are adapted to specific conditions and responsive in real-time.

One may consider the range of low R_0-values ($0 < R_0 < R_{0cw}$) to be unrealistic for most fungal pathogens of crop plants. Firstly, according to empirical knowledge accumulated in plant pathology, fungal crop pathogens are challenging to eradicate [40], suggesting that their R_0 values should be much higher than one. Secondly, existing estimates of the basic reproduction number, e.g., for the major fungal pathogens of wheat *Zymoseptoria tritici* and *Puccinia striiformis* tend to be relatively high: in the range 4–10 for *Z. tritici* [24] and 20–30 for *P. striiformis* [28]. The two arguments indicate that R_0-values for major fungal crop pathogens will likely exceed the eradication thresholds. Accordingly, it would make sense to focus more on the range of higher R_0-values, where it exceeds the eradication thresholds ($R_0 > R_{0cw}$, $R_0 > R_{0cr}$). At the same time, here we used R_0 as determined at the landscape scale, while most experimental estimates for fungal pathogens have been evaluated at the individual field scale. Due to lower transmission rates and greater spatial regularity in individual susceptible units, we expect lower R_0 estimates at the landscape scale than at the field scale, at least for certain landscape configurations [28,41]. In this case, the estimation of C_R across the entire range of R_0 values, as we did here, becomes of interest.

Along the way to calculating the economic cost of fungicide resistance, we also found that the law of diminishing returns does not hold for the economic return from fungicide applications over a cultivated landscape (Fig 2D). Optimal fungicide dosing for individual fields still exhibits the law of diminishing returns for the net economic return (Fig 2B). Hence, the economically optimum dose decreases gradually with increasing fungicide price. However, for multiple fields across the landscape, the optimal proportion of treated fields also decreases with the ratio of fungicide price and yield loss (α) but does so via a sudden jump (see Fig 5B). Thus, adjusting the magnitude of fungicide treatment to maximize the net return is more difficult at the landscape scale owing to coordinating fungicide applications across multiple farms and handling the discontinuous nature of how θ^* depends on α. At the same time, this presents an opportunity for economic policy to minimize pesticide use because a limited increase in α induced by a policy instrument may lead to a disproportionately high, sudden drop in the optimal fungicide coverage, θ^*. However, achieving this optimum requires cooperation between farmers across a regional landscape.

Our study considers a binary choice in fungicide application. In reality, farmers can adjust the fungicide dose [24,42], use mixtures or alternations of different fungicides [23,43]. Furthermore, the farmers can adopt disease-resistant crop varieties [44,45] and cultural control measures (such as crop rotations [46,47], cultivar mixtures [32,48,49] and restrictions on growing certain crops, e.g., soybean-free periods in Brazil [50]). These scenarios can be incorporated into our modelling framework to explore how different control measures can protect each other from pathogen adaptation [44,51,52] and mitigate the economic cost of pathogen adaptation.

We calculated the economic cost of fungicide resistance as a benchmark corresponding to an optimistic scenario where all farmers across the landscape coordinate their fungicide applications to reach the optimum proportion of treated fields that gives the maximum net return for the entire landscape. However, the choices made at individual farms do not always align with the landscape-wide optimum. Instead, they are influenced by access to information, risk perceptions, socio-demographics, structure of farm business, and other factors [53–56]. To address this, models should incorporate farmers' decision-making heuristics and dynamic choices [57]. This would allow us to adjust the fungicide coverage and explore how close to

the landscape-scale optimum one can get using different decision-making approaches. Including a socioeconomic point of view brings us closer to identifying policy interventions most likely to maximize crop protection's economic return at a regional scale.

The methodological novelty of our study lies in extending a spatially implicit metapopulation model of plant disease epidemics [25] to incorporate an economic analysis of fungicide use. Landscape perspective is recognized as crucial in plant disease epidemiology [58], and more recently, spatially explicit landscape-scale models addressed a range of epidemiological/evolutionary questions focusing mainly on pathogen adaptation to disease resistance in plants [59–63]. While some studies recognized the importance of the economic aspects of plant disease epidemics, they did not incorporate an explicit economic analysis. Qualitative conceptual frameworks integrating plant pathogen adaptation to control measures with socioeconomic aspects are only starting to appear [64] and remain a mathematical challenge [65].

Extending the marginal theory of pesticide use [5,6] from the scale of individual farms to a broader scale of cultivated landscapes, we incorporated economic analysis in our epidemiological study. More specifically, we extended the concept of economic yield [66,67] to the landscape scale. Earlier, [68] extended the marginal theory of pesticide use by incorporating the stochasticity of plant disease epidemics in calculating the optimal fungicide dose, maximizing the net return from a fungicide application programme at the scale of an individual farm. This approach has been subsequently developed to incorporate the evolution of fungicide resistance [19,20]. Nevertheless, focusing on individual farm management, they neglected the externalities of the evolution of resistance. Here, we addressed this issue by extending the marginal theory of pesticide use [5,6] from individual farms to cultivated landscapes in a mathematical approach that incorporates the epidemic development and the evolution of fungicide resistance and links these processes with an economic analysis. Given that our framework builds on fundamental equations of epidemiology and economic cost-benefit analysis, we envision applying our framework to modelling other biotic stresses of crops, such as insect pests and weeds [69].

Conclusion

We have developed a bioeconomic framework combining a plant disease epidemiological model with an economic analysis at the landscape scale. Using this approach, we found that the law of diminishing returns does not hold for economic returns from fungicide applications across cultivated landscapes. This is surprising given the almost universal status of this law. The breakdown of this law suggests that adjusting the amount of fungicide applied to maximize the net return is challenging at the landscape scale. The intervention needs to be coordinated across multiple farms, and the discontinuous nature of how the optimal coverage depends on fungicide price requires a drastic change in fungicide coverage.

Using the bioeconomic modeling framework, we calculated the economic cost of the evolution of fungicide resistance, C_R, which constitutes our study's primary novel outcome. We found that C_R depends strongly on the fungicide price, the basic reproduction number of the pathogen, its degree of fungicide resistance and the consequential yield loss. While intuitively, C_R increases with the degree of resistance and yield loss due to disease, surprisingly, it declines with the fungicide price and exhibits a complex non-monotonic pattern as a function of the basic reproduction number. Hence, to estimate C_R, robust estimations of these parameters are necessary, incorporating environmental variation, crop varieties and genetic composition of the pathogen population. Estimating the economic cost of resistance would then inform economic policy instruments to encourage more sustainable fungicide use.

Moving forward, our framework presents an opportunity for future empirical studies to validate the findings presented here across various agricultural landscapes and pathogen-crop systems. Future research focusing on extending our modeling framework to incorporate spatial heterogeneity, stochasticity, and multiple pathogen interactions will improve its applicability and help refine the estimation of the economic cost of fungicide resistance. Furthermore, incorporating farmers' decision-making heuristics and economic policy tools, such as taxes and/or subsidies, into our bioeconomic modelling framework may help in designing more effective policy interventions for sustainable disease management. Integrating our framework with real-time monitoring and predictive modeling of crop epidemics will have the potential to improve disease management. Ultimately, we envision this study to provide a conceptual and methodological basis for a fruitful integration of economics and eco-evolutionary dynamics necessary for achieving more sustainable agriculture.

Supporting information

S1 Appendix. Supplemental methods and analysis: Stability, optimization, and cost of resistance. (A) Linear stability analysis and computation of fixed points and basic reproduction number. (B) Maximizing economic return of fungicide treatments. (C) The economic cost of fungicide resistance.
(PDF)

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