Control strategies for heterogeneous plant pathogens: evolutionary and agricultural consequences

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ABSTRACT

Optimising the use of chemical pesticide is required in order to reduce the inevitable environmental and economic costs related to it. The consequences of chemical control are particularly tricky to foresee in the presence of pathogens, displaying heterogeneous traits involved in their life cycle, because its effect will likely differ across the population. In this work, we investigate the effects of trait-dependent pesticide on heterogeneous plant pathogens, by means of a minimal model connecting evolutionary and agricultural states of the system. We model a pathogen population displaying continuous levels of virulence and transmission. Control strategies are modelled by the quantity of pesticide released and its degree of correlation with the pathogen's heterogeneous traits. We show that the pathogen population can adapt towards opposite evolutionary states, that may be reversed by chemical control due to its heterogeneous selective pressure. This dual behaviour triggers saturating effects in yield production, with respect to pesticide use. As a consequence, we show that maximising yield production and minimising pesticide application are conflicting objectives. We identify Pareto-efficient solutions, where the optimal pesticide type depends on the applied quantity. Our results provide a theoretical framework to explore how to harness heterogeneity in pathogen populations to our advantage.

Crop pathogens and pests (P&Ps) are responsible for reduction in the yield and quality of agricultural production. They cause important economic losses and reduce food security at household, national and global level[1]. Nowadays, although

alternative practices to protect crops are gaining scientific support[2,3], the use of chemical pesticides is still the primary means to control P&Ps and faces an increasing food demand worldwide[4]. Although the use of pesticides, among other practices, has led to a greater than twofold increase in food production during the last century[5], worldwide surveys have documented the contamination and impact of pesticide residues in soils, terrestrial and aquatic ecosystems, and their toxic effects on humans and nonhuman biota[5,6]. A reduction in the use of pesticide is sought worldwide and demanded by the EU pesticide Regulation N 1107/2009. A report on pesticide residues in food is due every year by the European Food Security Agency (EFSA)[7]. Recent works suggest that pesticide use could be reduced, without impacting crop productivity and profitability, through the adoption of new production strategies and optimisation; this is particularly true in those cases with high pesticide use[2,5].

Mathematical modelling provides an excellent tool, in addition to field and lab experiments, to assess the efficacy of different control strategies[8–10]. Significant attention has been devoted to design and explore different strategies to overcome the problem of pesticide resistance[11]. Models are often framed in terms of sensitive *versus* resistant pathogen strains[12–14], and aim at understanding optimal spatial[15,16], and temporal[17,18] patterns of pesticide release. Foreseeing the consequences of a prolonged use of pesticide is particularly tricky when the pathogen displays a more general heterogeneity, *i.e.* when the composition of the pathogen population is more complex than simply resistant versus sensitive. In these populations, individuals characterised by genetically related variants, may differ from each other by phenotype traits possibly involved in the pathogen's virulence, transmission, viability etc. This phenomenon is ubiquitous in plant pathogens, including viruses[19], bacteria[20,21], fungi[22–24]. When such heterogeneity is maintained (rather than transient), the population is then trait-structured. In such populations, the overall effect of a control strategy will depend on the trait distribution of the heterogeneous pathogen, which in turn will be affected by the control's selective pressure[25,26]. Ultimately, the performance of any management scenario will result from the complex interplay between the epidemiological plant-pathogen interactions, and the pathogen's evolutionary dynamics. However, despite few exceptions (*e.g.* see Shaw et al.[27]), in the context of pest management, heterogeneous pathogen populations are modelled only rarely.

In this work, we move away from the sensitive/resistant duality, and investigate the role of continuous heterogeneity in pest control. In the framework of a classical type *SIS* model, we consider a trait-structured pathogen population and we investigate the evolutionary dynamics of its trait distribution[28]. The trait variable might determine the pathogen levels of virulence, transmission and the pesticide sensitivity. This framework will allow to account for the transmission-virulence trade-off, as well as to possible heterogeneous pesticide effects. The transmission-virulence trade-off hypothesis, introduced to explain the evolution of intermediate levels of virulence[29,30], assumes a positive correlation between the two traits, so that an increase in

the former comes at the expenses of an increase in the latter. In fact, pathogen spread is generally favoured by high levels of transmission and low levels of virulence[29]. Despite its validity still being the subject of lively debate[31], this hypothesis has found popularity in epidemiological models, and some evidence has been collected in the context of plant pathology[32,33].

On the other hand, the introduction of a trait-dependent sensitivity of the pesticide is, to the best of our knowledge, a novelty in agricultural disease management literature. The rationale is that, if a pesticide differentially affects pathogens with heterogeneous traits (*e.g.* virulence or transmission), complex population effects resulting from the balance of control and selection are expected[34]. Modelling pesticide treatment, a distinction is typically made between protectant and eradicant (or curative) effects[35]. The former is described by reducing the infection's transmission, while the latter by increasing hosts' recovery. Here, we shall consider the sole eradicant effect, and discuss future extensions accounting for protection as well. Particularly, we will allow pesticide-induced eradication to depend on the pathogen trait. That is, we model a spectrum of possible pesticide types with different degrees of specialisation – *e*.g. more effective on highly virulent (or transmitting) pathogens, or more effective on less virulent (or transmitting) ones, or generically effective – and investigate the performance, in terms of both economic and environmental objectives, of different control strategies characterised by the type (*i.e.* specialist or generalist) and the quantity (*i.e.* rate of application) of the pesticide used.

Our minimal model allows for mathematical tractability, analytical investigation of the pathogen's trait distribution and of the endemic crop yield at equilibrium, and is potentially extendable to different management and ecological scenarios. Particularly, it allows to disentangle the role of the different ecological interactions in the choice of pesticide. Finally, we show that the optimal pesticide and its degree of correlation with the heterogeneous trait will depend on the rate of its application, suggesting that both unnecessary pollution and economic loss can be avoided if a proper trait-dependent treatment is introduced in agricultural practice.

Results

The analysis is based on a standard epidemiological model of *SIS*-type, where hosts are divided into (S)usceptible and (I)infected. The heterogeneous formulation of the dynamics assumes the existence of a pathogen with a *continuum-of-strains*, described by a continuous trait variable $x \in \mathscr{T}$. In the heterogeneous formulation, the system is described by the ecological and the evolutionary state. The ecological state is given by the number of susceptible S and infected I hosts. The evolutionary state is given by the trait distribution $i(x)$, that is the density of hosts infected by the pathogen with trait value x. Both ecological and evolutionary states vary over time according to a set of coupled integro-differential equations, detailed in the Methods. The

parameters of the model and their description are summarised in Table 2.

Trait-dependent epidemiological rates

For sake of simplicity, we shall consider as trait space the unit segment $\mathscr{T} = [0,1]$. The generalisation to any positive interval $[x_{min}, x_{max}]$ is straightforward, and can be mapped to the $[0,1]$ interval upon rescaling of the parameters. The trait variable determines the pathogen's transmission and virulence rates, and the pesticide sensitivity, as specified in the following.

Virulence. We define virulence as the disease induced mortality rate experienced by an infected host[28]. We assume that the pathogen virulence ν may vary linearly with the trait x:

$$\nu(x) = \nu_0 + \nu_1 x, \tag{1}$$

with the parameters ν_0 being the baseline virulence, and ν_1 the trait-dependent contribution[28,36,37].

Transmission. Similarly, we assume that transmission rate β may be linearly affected by the trait variable x, that is:

$$\beta(x) = \beta_0 + \beta_1 x, \tag{2}$$

where β_0 is the baseline transmission rate, and β_1 the trait-dependent contribution. For values of both ν_1 and $\beta_1 > 0$, pathogens with higher transmission will also have higher virulence, consistent with the Transmission-Virulence trade-off hypothesis. Although nonlinear, concave-down functions are typically considered[25,36–38], a simpler linear choice has the following advantages: first, it is sufficient to capture the essential biological features we are interested in, that is the cost for the pathogen to increase transmission; second, it allows to fully exploit mathematical analysis; finally, it provides the baseline results against which one can in future compare nonlinear functions, so as to disentangle the role of nonlinearities from the role of the trade-off alone. Possible extensions to other functions will be discussed later.

Pesticide sensitivity. Finally, the pesticide sensitivity $\phi(x)$ is considered to depend on the heterogeneous trait, and is maximal for either the extreme values of the trait ($x = 0,1$). Consistently with previous works[37], we choose a linear functional dependence:

$$\phi(x) = C_{\phi_1} + \phi_1 x, \tag{3}$$

where the parameter ϕ_1 represents the pesticide's degree of correlation with the trait, and C_{ϕ_1} is a normalisation factor. A graphical summary of the pesticides spectrum is shown in Fig. 1 panel B (note that the bound $|\phi_1| < 2$ ensures a positive $\phi(x)$).

Equations 1-3 allow to account for all the possible trade-offs occurring between the considered epidemiological traits: if $\beta_1 = 0$, sensitivity of the eradication correlates only with virulence, and transmission is trait independent: this is the Virulence-Eradication (VE) case. If $\nu_1 = 0$, sensitivity correlates only with transmission, and virulence is trait independent: this is the Transmission-Eradication (TE) case. Finally, the case $\beta_1, \nu_1 \neq 0$ corresponds to the scenario with full complexity; we call this the Transmission-Virulence-Eradication (TVE) case. Note that $\phi_1 = 0$ describes the case when sensitivity of eradication is trait independent, *i.e.* the pesticide has a purely generalist effect over the trait space, and can be considered as a sub-case of TVE.

Pest management

We assume that the environmental and economic cost of pesticide use is proportional to its application rate c, regardless of their type. The degree of correlation ϕ_1 with the heterogeneous trait determines the type of pesticide: a positive ϕ_1 models a pesticide with maximal eradicant effect on pathogens that may also be the most virulent (and/or most transmitting), and minimal effect on the least virulent (and/or least transmitting) one; instead, a negative ϕ_1 models the opposite scenario.

The normalisation factor $C_{\phi_1} = 1 - \phi_1/2$ ensures that $\int_{\mathscr{T}} \phi(x)\mathrm{d}x$ is always normalised to 1, for any type ϕ_1. Besides removing one arbitrary degree of freedom, this condition also imposes a plausible constraint on the pesticide design, and allows the comparison between different choices. In fact, while the ideal pesticide has maximum effect on all pathogens, in practice a *specialist-generalist* trade-off is expected to hold. By virtue of this trade-off, a high maximal eradication effect on a particular trait value should come at the expenses of a general reduction of the effect on the others; concomitantly, generalist pesticides will affect more uniformly over the trait space, with a reduction of the maximal eradicant effect. The parameter ϕ_1 is then a control parameter modelling the pesticide choice, out of a spectrum of possible degrees of correlation with the heterogeneous trait.

Henceforth, with the term 'specialist' will refer to pesticides with large degree of correlation (large $|\phi_1|$), and the term 'generalist' will refer to pesticides with small degree of correlation (small $|\phi_1|$). Particularly, the choices $\phi_1 = \pm 2$ represent the most specialised types; the choice $\phi_1 = 0$ represents the most generalist type, with a homogeneous effect over the trait space.

A control strategy is specified by choosing both application rate c and pesticide type ϕ_1. The aim of the pest management is then to assess which type to employ, in order to maximise yield production.

Equilibrium trait distribution and evolutionary states

The behaviour of the equilibrium pathogen's trait distribution, with linear trait-dependent functions (Eqs. 1-3), is entirely determined by the following compound parameter Ω (details in the Supplementary Material):

$$\Omega = \beta_1 (\delta + \nu_0) - \beta_0 \nu_1 + c (\beta_1 - \beta_1 \phi_1 / 2 - \beta_0 \phi_1) . \tag{4}$$

Particularly, if $\Omega < 0$, the trait distribution is monotonically decreasing and is mostly distributed close to the trait $x = 0$. We will refer to this as the *low-virulence* and/or *low-transmission* state, because such trait display minimal value for $x = 0$. On the other hand, if $\Omega > 0$, the the trait distribution is mostly distributed close to the trait $x = 1$. We will refer to this as the *high-virulence* and/or *high-transmission* state, because such trait display maximal value for $x = 1$. In the following, we characterise the phase diagrams of all the possible trade-offs that our model can account for, both in the presence and absence pesticide treatment.

Virulence-Eradication VE case. In this case, the pesticide sensitivity $\phi(x)$ and virulence $\nu(x)$ both depend on the trait x. The transmission of infection is then homogeneous, that is $\beta_1 = 0$. The relevant compound parameter of Eq. 4 reduces to $\Omega_{\mathrm{VE}} = -\beta_0 (\nu_1 + c\phi_1)$. In absence of pesticide (*i.e.* $c = 0$, corresponding to the x-axis in panel A of Fig. 2), Ω_{VE} is always negative, meaning that the distribution is in the low-virulence state for any combination of the parameters. When pesticide is employed, if its application rate c exceeds the threshold $c_{\mathrm{th}} = -\frac{\nu_1}{\phi_1}$, the sign of Ω_{VE} reverses, and a distribution in the high-virulence state is obtained. We note that for this to occur, one needs to employ a pesticide type with negative ϕ_1, since for positive ϕ_1 the change would occur for negative c. The larger the degree of correlation ϕ_1, the lower the threshold c_{th} will be (panel B of Fig. 2). The adaptation towards the two possible states is shown in Fig. 3, where we plot the trajectories of the simulated agent-based dynamics (solid lines), differing for the pesticide type employed. The other parameters (specified in the figure's caption) and initial conditions are identical. For $\phi_1 = 1$, the system adapts towards the low virulence state, and towards the high virulence state for $\phi_1 = -1$. Consequently, the quantity of yield reached at equilibrium differs in the two cases.

Transmission-Eradication TE case. In this case, pesticide sensitivity $\phi(x)$ and transmission $\beta(x)$ both depend on the trait x. Virulence is then homogeneous, that is $\nu_1 = 0$. The relevant compound parameter of Eq. 4 reduces to $\Omega_{\mathrm{TE}} = \beta_1 (\delta + \nu_0) + c[\beta_1 (1 - \phi_1/2) - \beta_0 \phi_1]$. In absence of pesticide (*i.e.* $c = 0$, corresponding to the x-axis in panel C of Fig. 2), Ω_{TE} is always positive, meaning that distribution is in the high-transmission state for any combination of the parameters. Upon employment of a pesticide positively correlated with the trait ($\phi_1 > 0$, thus focusing the effect on the most transmitting pathogens), the system may adapt towards the low-transmission state: panel C of Fig. 2 shows that for this to occur, the

application rate c must exceed a threshold value that increases with the trait-dependent transmission β_1, and with $\delta + \nu_0$, (here we have fixed the pesticide type $\phi_1 = 2$), while it decreases with baseline transmission β_0. In general, for fixed values of β_1, ν_0, δ, such threshold value decreases as correlation ϕ_1 increases (panel D of Fig. 2)

Transmission-Virulence-Eradication TVE case. In the TVE case, the heterogeneous trait simultaneously determines all three epidemiological interactions. The relevant compound parameter is then given by the Ω of Eq. 4. Contrary to the cases previously shown, in absence of pesticide (*i.e.* $c = 0$), the pathogen population can already be found in both *high* or *low* states. With reference to panel A of Fig. 4, *low* states will be favoured for large baseline transmission β_0 and trait-dependent virulence contribution ν_1; instead, high transmission-high virulence states will be favoured for large trait-dependent transmission β_1, harvesting rate δ and baseline virulence ν_0. The presence of pesticide may lead to a change of state, depending on both the rate of application c and the degree of correlation ϕ_1 with the heterogeneous trait. In panel B of Fig. 4, we show how a system initially in the *high* state adapts after pesticide application, as a function of the management control parameters c and ϕ_1. For low use of pesticide (*i.e.* low c), the infected population remains in the *high* state, regardless of the type of pesticide employed. However, increasing pesticide application will eventually bring the system into the *low* state, if positive ϕ_1 or generalist types are employed. If the system is initially in the *low* state in absence of pesticide (panel C of Fig. 4, same parameters as panel A but ν_1 doubled), the complementary behaviour is observed.

Equilibrium yield and pesticide choice

In the following, we will refer to $\widehat{S}$ as the equilibrium yield, that is the amount of harvest with economic value. The host population equilibria are obtained by setting Eqs. 9-10 to zero, and they are equivalent to the classical formulation. If $R_0 < 1$, we have a trivial disease-free equilibrium:

$$\left(\widehat{S}_0 = \frac{\theta}{\delta}; \widehat{I}_0 = 0\right) \tag{5}$$

corresponding to the extinction of the pathogen. If $R_0 \geq 1$, we have the following stable endemic equilibrium:

$$\left(\widehat{S} = \frac{\delta + \overline{\nu} + c\overline{\phi}}{\overline{\beta}}; \widehat{I} = \frac{\overline{\beta}\theta - \delta\left(\delta + \overline{\nu} + c\overline{\phi}\right)}{\overline{\beta}\left(\delta + \overline{\nu}\right)}\right), \tag{6}$$

where the bar notation refers to average quantities over the trait distribution (see Eq. 12 of the Methods). In Fig. 5 we plot the equilibrium yield $\widehat{S}$ (rescaled with respect to the disease-free yield $\widehat{S}_0$), as a function of application rate c, and compare the

effect of five different types of pesticides: $\phi_1 = -2, -1, 0, 1$ and 2. The set of parameters correspond to the TVE case, with the system in the *low* state in absence of pesticide (white region in panel A of Fig. 4); the complementary case starting in the *high* state is not shown, but it preserves the same qualitative behaviour.

Employing a pesticide type inconsistent with the state of the trait distribution in absence of control (*e.g.* $\phi_1 = 2$ in this example), leads to a small increase of yield as the dose is increased (green curve). Instead, employing a pesticide extremely specialised on *low* trait values ($\phi_1 = -2$), leads to a more significant increase in yield, at least for low application rates (blue curve). However, as increasing application rate leads the system towards the opposite *high* state, this extremely specialist pesticide becomes less effective, and the gain in yield eventually saturates. At this point, switching to a more moderate ($\phi_1 = -1$) or to a generalist ($\phi_1 = 0$) type provides more gain in yield, rather than increasing further the rate of application c (red and yellow curves). Depending on the value of the replanting rate θ, the system may eventually reach the disease-free equilibrium (where $\widehat{S} \equiv \widehat{S}_0$), as the dose is further increased. Overall, we note that, regardless of the choice, increasing c always corresponds to an increase of the yield. Hence, it is evident that maximising yield and minimising pesticide application are contrasting objectives. Nonetheless, for a given application rate c, it is possible to optimise its use by choosing the right type ϕ_1.

Optimal pesticide choice

In general, for a given value of pesticide application rate c, there will exist an optimal pesticide type ϕ_1^{opt} maximising the yield $\widehat{S}$ at the endemic equilibrium. Under the linear assumptions considered here, the optimal pesticide can be computed analytically. In the Supplementary Material, we show that the optimal pesticide type ϕ_1^{opt} is given by:

$$\phi_1^{opt} = \frac{2}{2\beta_0 + \beta_1} \left[\frac{\beta_1 (\delta + \nu_0) - \beta_0 \nu_1}{c} - \beta_1 \right]. \tag{7}$$

With respect to Figs. 2 and 4, the above equation corresponds to the curves separating the two states in the (ϕ_1, c) phase diagrams, for which $\Omega = 0$. The effect of each parameter on ϕ_1^{opt} is summarised in Table 2. We note that the degree of specialisation is a decreasing function of application rate c, so that extremely specialised pesticide types will perform better for low c. Also, we note that the impact of the harvesting rate δ and of the baseline virulence ν_0 are mediated by the trait-dependent transmission β_1; hence, in absence of heterogeneity in transmission, such parameters will be irrelevant for pesticide choice. Overall, Eq. 7 provides a qualitative insight into the role played of each ecological interaction in shaping the optimal pesticide choice.

Discussion

Theoretical works treating trait-structured populations typically aim at deriving equations that characterise the evolutionary state of the system, namely the population's average virulence[26,28,39]. Instead, our approach highlights the environmental and economic implications of evolutionary adaptation by framing the problem in the context of pest management: that is, understanding how the pesticide's dependence on the heterogeneous trait relates to its application rate, with the aim of maximising the amount of yield at equilibrium for a given quantity of pesticide deployment.

We have considered a pathogen expressing continuous levels of disease-induced mortality and infection transmission (Eqs. 1-2), and a pesticide exerting an eradicant action that can be either positively or negatively correlated with such traits (Eq. 3 and Fig. 1), depending on the chosen type. We have shown that, in absence of pesticide treatment, the infected population may adapt towards either a high virulence-high transmission or a low virulence-low transmission state, depending on the ecological parameters, and on the trait-dependent contributions to the epidemiological traits. We have shown that, due to its heterogeneous selection pressure, the use of pesticides with trait-dependent sensitivity may induce a transition in the pathogen trait distribution, depending on pesticide type ϕ_1 and application rate c (panels B & D of Fig. 2, panels B & C of Fig. 4). Pesticide sensitivity has been treated as a potentially continuous control parameter; however, focusing on only few classes (as we do in Fig. 5) is enough to provide significant guidance, since in practice there will only be a limited number of choices on the market.

Despite increasing pesticide application rate always leading to an absolute gain in yield, such gain will eventually saturate as a consequence of this transition, if improper pesticide types are used (Fig. 5). Finally, we have shown that the optimal choice of pesticide has a nontrivial relation with the application rate (Eq. 7): as a general rule, our results suggest that very specialised pesticides, exhibiting a strong (positive or negative) degree of correlation, should be employed at low application rates; instead, generalist pesticides, with a more uniform action over the trait space, are likely to perform better at high application rates.

In terms of multi-criteria optimisation analysis[40], Fig. 5 shows that maximising yield ($\widehat{S}/\widehat{S}_0$) and minimising pesticide application (c) are conflicting objectives. As a consequence, we can identify the Pareto-efficient solutions to our control strategy, highlighted by the solid curves. Choosing a different combination of the control parameters (c, ϕ_1) will necessarily worsen the outcome (dashed curves), by either decreasing the amount of yield, or increasing the costs related to pesticide application.

Despite our analytical derivation of the optimal pesticide choice relying on many simplifying assumptions, it highlights the qualitative role of the various ecological interactions, and it provides a starting point for the introduction of further elements of

complexity. For example, the effects of nonlinearities in the Transmission-Virulence trade-off ([36,38]) can be straightforwardly analysed numerically. Our analysis has been carried out using and underpinning model with an *SIS*-type dynamics, although it can be straightforwardly extended to other epidemiological models, potentially including explicit vital dynamics of the pathogen[41,42]. For instance, in *SIR*-type models, one may want to calculate optimal curves based on different quantities (e.g. $S+R$). Particularly, we note that an *SI*-type model, typically used for those diseases that do not allow for recovery, would preserve the above results, as far as the crop health is concerned. However, as the functional form of host demography may have a significant impact on the population composition at equilibrium[43], the optimal pesticide curves may depend on the host growth function as well.

Modelling pesticide application, we have deliberately focused on the eradicant effect and neglected protectant contributions[14]. The latter might be introduced by relaxing the form of the TV trade-off (Fig. 1, panel B): a trait-dependent protectant effect may modify or break the monotonicity of the transmission function, thus opening the possibility of choices significantly different from the linear one. Different transmission functions may also emerge as a consequence of physiological alterations of hosts' level of activity, in the case of animal (and human) systems, and of intervention policies in the context of human disease modelling (quarantine, contact tracing, etc...). Our framework might also be relevant to study the optimisation of inevitably imperfect treatments[44], such as a potential eradication-protection trade-off: indeed, due to its inhibitory action on transmission events, an investment in the protectant contribution is expected to be efficient whenever the infected population is in a high-transmission state. However, if such investment is paid for by a reduced eradicant effect, it is not obvious how the pathogen would adapt to such intervention; hence, the importance of a tool able to predict the trait distribution. Performing a similar analysis, one might be able to compute the optimal balance between the two actions, and to relate this choice to the ecological interactions at play.

Validating our results will require the measurement of the trait-dependent epidemiological functions, for specific pathogen-pesticide systems. This achievement depends on the identification of heterogeneous phenotypic traits, and of their chemical interaction with the pesticide. Examples of potential candidate traits in fungi are the level of expression of the virulence-associated adhesin *Epa1*[45,46], or drug transporters responsible for fungicide resistance[47]. Furthermore, many other genes controlling virulence may reveal heterogeneous levels of expressions, such as *CPS1* in the corn fungus *Cochliobolus heterostrophus*[48] or necrotrophic effectors in the wheat fungus *Parastagonospora nodorum*[49], and hence become potential targets for heterogeneous pesticide action. Targeting virulence is considered a promising strategy for the development of antifungal drugs[50], and our work may help to identify the optimal type of pesticide according to the biological and environmental conditions of the

considered system.

Several plant bacteria are united by the use of phytotoxins as virulence factors[51]: for instance, *Candidatus* Liberibacter spp. (affecting different species of citrus), *Erwinia amylovora* (the Fire Blight infesting apple and pear orchards), *Xanthomonas* spp. (Black Rot disease affecting *Brassica* crops) are among the most destructive pathogens, in terms of agricultural loss[52]. Potential chemical strategies based on the inhibition of phytotoxin production[53], or acting on virulence-related gene regulators[54], may be implemented in pesticide design in order to develop a spectrum of trait-dependent chemical treatments.

Combining such experimental development with our theoretical methods of investigation, may allow us to harness heterogeneity in pathogen populations - which is almost always considered to be a key difficulty in management, by allowing evolution of resistance to chemical controls - to our advantage.

Methods

Classical *SIS* formulation. We consider a classical *SIS* model for a plant-pathogen system, where the host population is divided into (S)usceptible and (I)nfected individuals. As is commonly done for microparasites, we do not explicitly model within host pathogen abundance[55]. Our assumptions are summarised as follows: (*i*) susceptible hosts are replanted at a constant rate, and (*ii*) they become infected at a rate proportional to the amount of infected hosts; transmission events are modelled with a density-dependent term, since we assume the area of the crop to remain constant[56]; (*iii*) hosts share an equal harvesting rate that removes them from the system, regardless of their epidemiological class; (*iv*) Infected hosts experience additional mortality due to the virulent charge of the pathogen; (*v*) the host recovers from the infection proportionally to the rate of pesticide application, with the effect of reallocating the host in the susceptible class[57].

Under the above assumptions, the dynamics of S and I hosts is given by the following system of equations:

$$\begin{aligned} \frac{dS}{dt} &= \theta - \delta S - \beta SI + c\phi I \\ \frac{dI}{dt} &= \beta SI - [\delta + \nu + c\phi]\, I, \end{aligned} \tag{8}$$

where θ is the replanting rate; δ is the harvesting rate; β and ν are, respectively, the pathogen's rate of infection transmission and virulence. The term $c\phi$ is the rate of eradication, where parameter c is the application rate of the pesticide, and ϕ pesticide sensitivity to the pathogen. In order to emphasise the role of heterogeneity in the dynamics, we do not consider non-linear dose-response curves[13].

Heterogeneous *SISx* formulation. Following[28,36,39,58,59] we elaborate the formulation equivalent to the above model Eq. 8, in the case of a trait-structured pathogen. The following assumptions are introduced: (*i*) The pathogen has a *continuum-of-strains*, mathematically described by a continuous variable $x \in \mathscr{T}$, where $\mathscr{T}$ is the trait space. Heterogeneity is described by the trait distribution $i(x)$, that is the density of hosts infected with trait x. (*ii*) The trait determines the pathogen's levels of virulence, transmission, and pesticide sensitivity, which are now represented by the functions $\nu(x), \beta(x), \phi(x)$. (*iii*) Pathogens undergo rapid within-host mutations which induce small changes in their traits, and maintain heterogeneity among the infected population; mutation rates are unbiased and no preferential direction is assumed; mutations are modelled by allowing the trait distribution to diffuse over the trait space.

Given the above assumptions, the dynamics of the heterogeneous system is given by the following system of equations (details in the Supplementary Material):

$$\frac{dS}{dt} = \theta - \delta S - \overline{\beta(t)} SI + c\overline{\phi(t)} I \tag{9}$$

$$\frac{dI}{dt} = \overline{\beta(t)} SI - \left[\delta + \overline{\nu(t)} + c\overline{\phi(t)}\right] I \tag{10}$$

$$\frac{di(x)}{dt} = \mu \nabla^2 i(x) + i(x)\left[\beta(x)S - \nu(x) - c\phi(x) - \left(\overline{\beta(t)}S - \overline{\nu(t)} - c\overline{\phi(t)}\right)\right], \tag{11}$$

where ∇^2 is the diffusion operator over the trait space $\mathscr{T}$, μ being the diffusion coefficient related to mutations. The bar notation indicates the average over the trait distribution, thus $\overline{\beta(t)}$ is the average transmission rate of the infected population:

$$\overline{\beta(t)} = \int_{\mathscr{T}} \beta(x)\, i(x)\, dx. \tag{12}$$

In the above equation, the temporal dependence is kept in order to remark that such average quantities are not fixed, rather they change in time alongside the temporal variations of the trait distribution $i(x)$. Equivalent definitions hold for the average virulence $\overline{\nu(t)}$ and for the average pesticide sensitivity $\overline{\phi(t)}$. Eqs. 9-10 describe the epidemiological *SIS* dynamics at the demographic level. They are equivalent to the classical formulation Eqs. 8, upon replacing the single-strain parameters ν, β, ϕ with their population average counterparts $\overline{\nu(t)}, \overline{\beta(t)}, \overline{\phi(t)}$.

The last Eq. 11 describes the mutation-selection dynamics of the trait distribution. Phenotypic mutations are captured by diffusion over the trait space; this choice assumes that mutations induce small perturbations on the quantitative trait, *i.e.* when

pathogens mutate into 'phenotypically close' variants (possible biases in the direction of mutations may be accounted for, by introducing a gradient term in the last equation)[60–62]. Concomitantly, pathogens compete between each other for the infection of a limited number of hosts, according to the trait-dependent function $F(x) = \beta(x)S - \nu(x) - c\phi(x)$. The overall success of pathogens with trait x depends on the difference between its value of $F(x)$ and the population average, as in a replicator dynamics[63]. The function $F(x)$ driving such competition is not assumed, rather it behaves as a fitness landscape emerging from the ecological interactions[39]: the transmission term $\beta(x)S$ contributes to the increase of trait x density, whereas virulence $\nu(x)$ and sensitivity $\phi(x)$ contribute to its decrease (see Supplementary Material for details).

Agent-based numerical simulations. We compared the deterministic dynamics presented in our work with numerical simulations of the equivalent agent-based dynamics. The python code is available here. The agent-based dynamics simulates the events of *replanting*, *harvesting*, *disease induced death*, *infection transmission* and *eradication*, each occurring at a rate consistent with the deterministic Eqs. 9-11. The deterministic theory is expected to be consistent with our agent-based simulations as long as large populations are involved. Our purpose is to provide a numerical validation of the existence and stability of the endemic equilibrium solution predicted by the theory. The analysis of finite size effects on the system goes beyond the scope of the present manuscript, although it is straightforward to perform once the agent-based codes are set up[64]. Details of the numerical simulations can be found in the Supplementary Material.

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Table 1. **List of the variables and parameters used in the model.**

Name	Description
S	Number Susceptible hosts
I	Number Infected hosts
x	Trait variable
$i(x)$	Trait distribution
$\bar{x}$	average trait value
μ	Mutations diffusion coefficient
θ	Replanting rate of S hosts
δ	Harvesting rate
c	Pesticide application rate
$\nu(x)$	Trait-dependent virulence (additional mortality)
ν_0	Baseline virulence rate
ν_1	Trait-dependent virulence coefficient
$\beta(x)$	Trait-dependent transmission
β_0	Baseline transmission rate
β_1	Trait-dependent transmission coefficient
$\phi(x)$	Pesticide sensitivity to trait
ϕ_1	Type of pesticide

Table 2. Effect of the parameters on the optimal pesticide choice ϕ_1^{opt}. The symbol $\uparrow$ ($\downarrow$) indicates that an increase in the parameter in question leads to an increase (decrease) of ϕ_1^{opt}.

Parameter	**Effect on ϕ_1^{opt}**
β_0	$\uparrow$ if $(\delta + v_0 + v_1/2 - c) > 0$ and $\downarrow$ otherwise
β_1	$\uparrow$ if $(\delta + v_0 + v_1/2 - c) < 0$ and $\downarrow$ otherwise
c	$\uparrow$ if $(\beta_0 v_1 - \beta_1 \delta - \beta_1 v_0) > 0$ and $\downarrow$ otherwise
v_0	$\uparrow$ always
v_1	$\downarrow$ always
δ	$\downarrow$ always

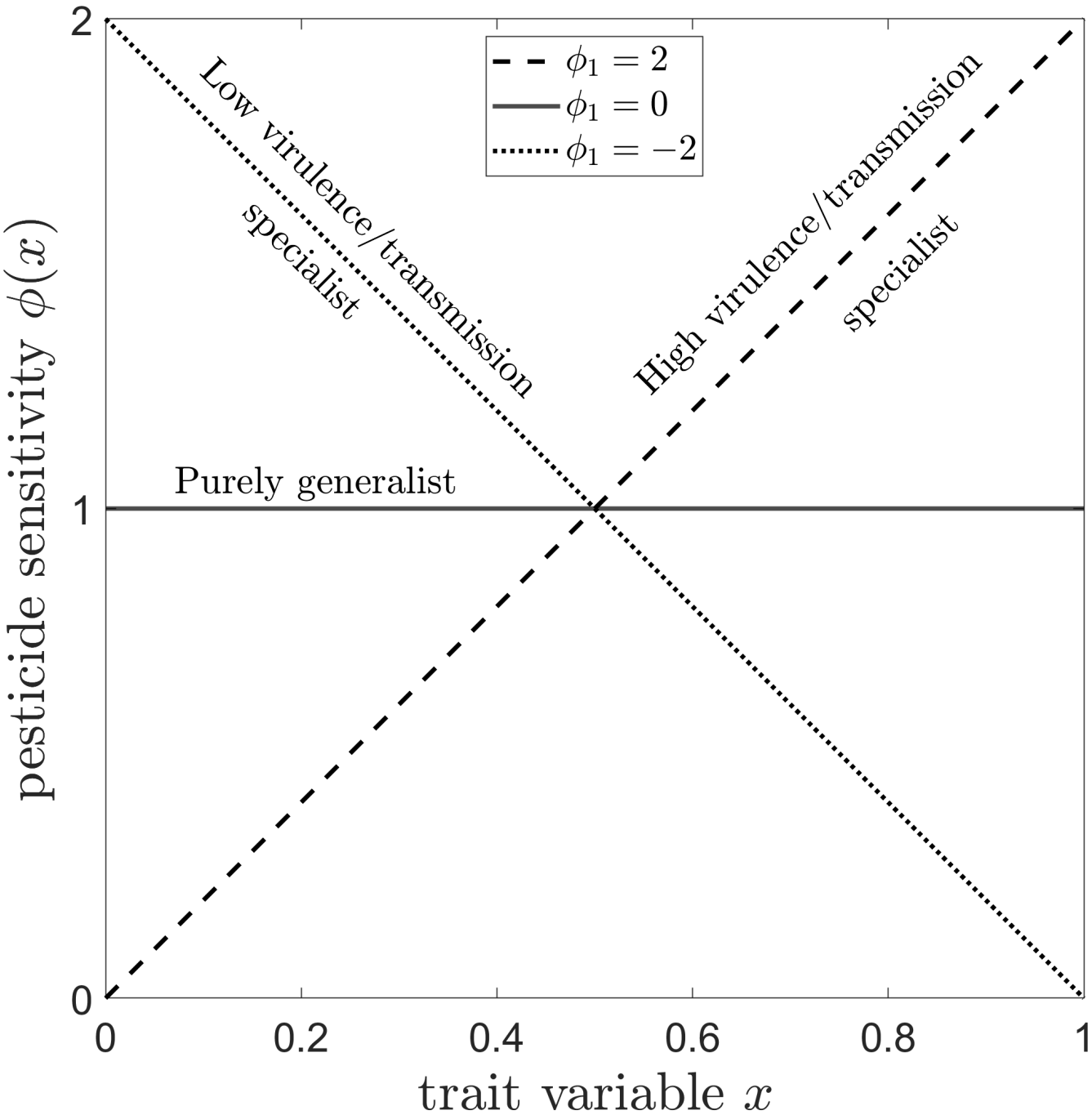

Figure 1. Spectrum of pesticides with trait-dependent sensitivities. The type of pesticide is determined by the sign and the magnitude of the parameter $\phi_1 \in [0,2]$: positive ϕ_1 models types with maximal effect on pathogens with higher virulence and/or transmission ($x = 1$); negative ϕ_1 models types with maximal effect on pathogens with lower virulence and/or transmission ($x = 0$). Large $|\phi_1|$ are specialised in targeting extreme values of the trait; small $|\phi_1|$ are generalist types with more uniform action.

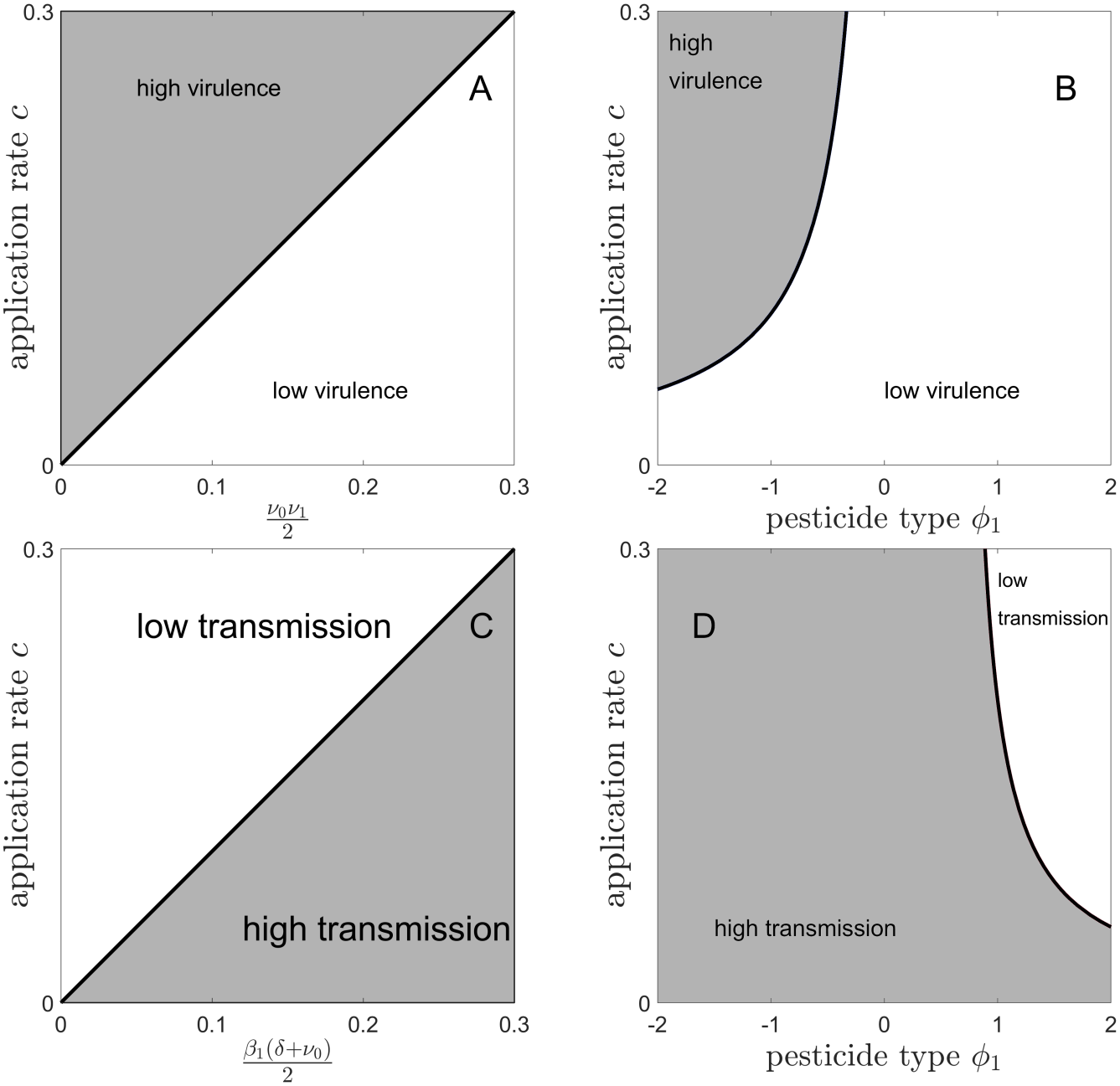

Figure 2. Trait distribution states - VE & TE cases. Color code: white (grey) region refers to *low* (*high*) states. Panel A: VE case for a fixed pesticide (*i.e.* $\phi_1 = -2$). In absence of pesticide ($c = 0$), the infected population is always in the *low* state, regardless of the trait-dependent virulence contribution ν_1. In the presence of pesticide ($c > 0$), the system can adapt towards the *high* state, for sufficiently high c. Panel B: state diagram for control strategy parameters c and ϕ_1 (with fixed $\nu_0 = 0.1, \nu_1 = 0.1$). Panel C: TE case for a fixed pesticide (*i.e.* $\phi_1 = 2$). In absence of pesticide ($c = 0$), the infected population is always in the *high* state. In the presence of pesticide ($c > 0$), the system can adapt towards the *low* state, for sufficiently high c. Panel D: state diagram for control strategy parameters (with fixed $\beta_1 = 0.0001, \delta + \nu_0 = 0.1$).

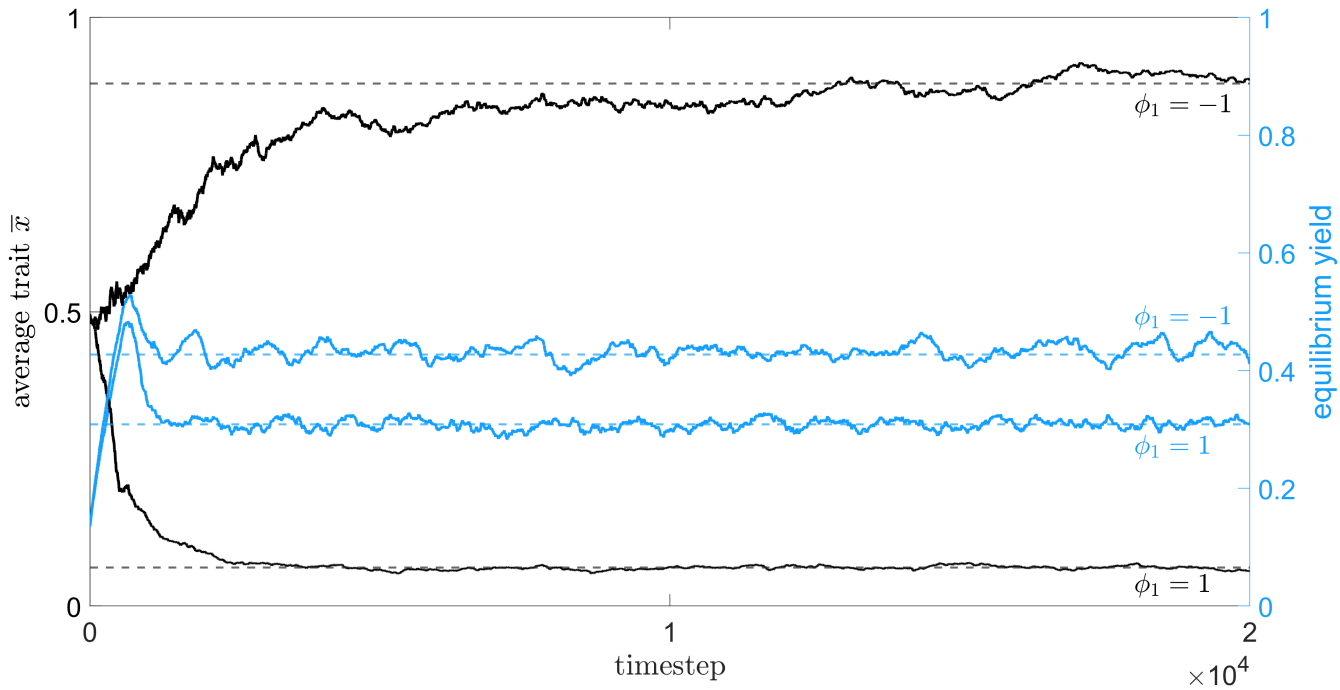

Figure 3. Simulated temporal trajectories. Solid lines: Temporal trajectories of the equilibrium yield ($\frac{\hat{S}}{\hat{S}_0}$) and of the average trait ($\overline{x}$), obtained from agent-based numerical simulations of the dynamics. Dashed lines: analytical equilibrium values. The system is initialised with identical initial conditions and same application rate ($c = 0.15$), but different pesticide type. For $\phi_1 = -1$ ($\phi_1 = 1$), the system adapts towards the high (low) state. Other parameters: $\theta = 300, d = 0.04, \beta_0 = 0.0001, \beta_1 = 0, \nu_1 = 0.1, \nu_1 = 0.1, \mu = 0.00007$.

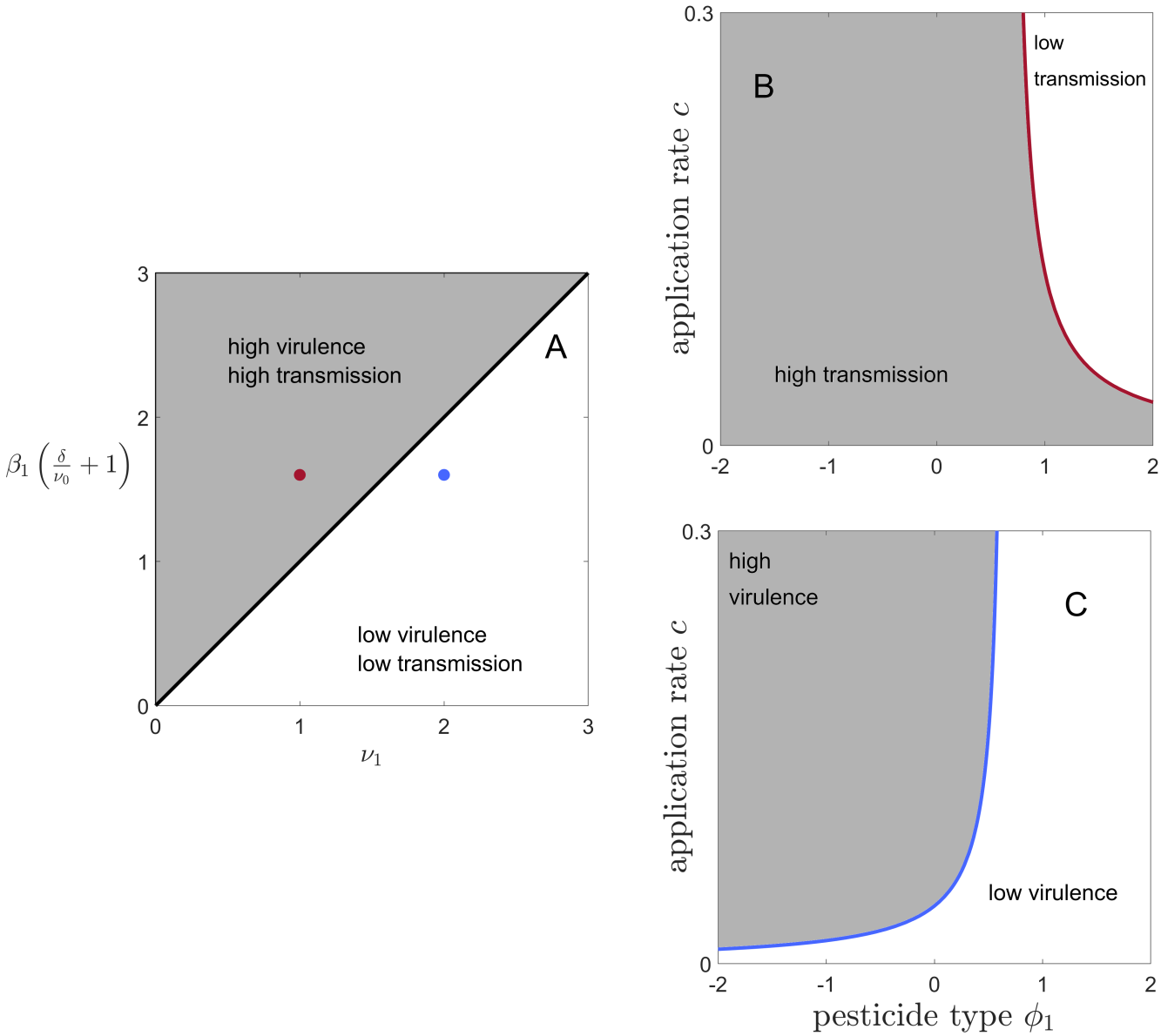

Figure 4. Trait distribution states - TVE case. Panel A: state diagram of the trait distribution in absence of pesticide. The infected population can adapt towards either the high virulence-high transmission state, or the low virulence-low transmission state. Large β_1, harvesting rate δ and baseline virulence ν_0 push the system towards the *high* state; instead, large baseline transmissionβ_0 and trait-dependent virulence contribution ν_1 push it towards the *low* state. Panel B: a system initially in the *high* state (red point panel A) can switch towards the *low* state under a range of control strategies. The red curve separates the two regions of the control parameters. Panel C: likewise, a system initially in the *low* state (blue point panel A) can switch towards the *high* state under a range of control strategies. The blue curve separates the two regions of the control parameters. Parameters: $\delta = 0.06, \nu_0 = 0.1, \beta_0 = \beta_1 = 0.0001$.

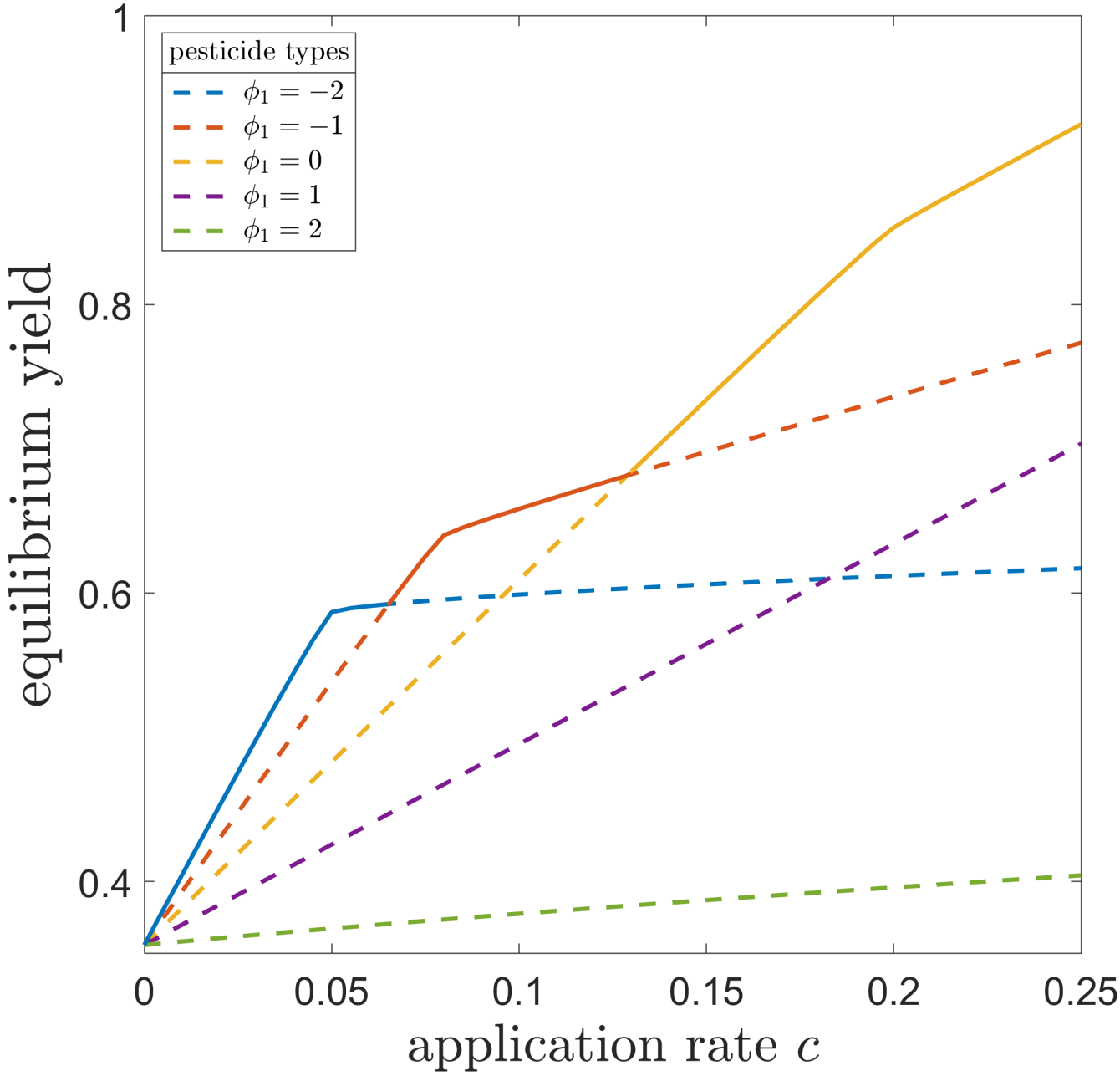

Figure 5. Equilibrium yield as function of pesticide application rate - TVE case. The yield at equilibrium $\widehat{S}$ obtained using five different pesticide types, as function of application rate c (the y-axis is normalised with respect to the disease free yield $\widehat{S}_0$). In absence of pesticide, the system is in the low-virulence state. Very specialised pesticides (*e*.g. $\phi_1 = -2$) are optimal for low c, but their correspondent gain in yield quickly saturates as application rate is increased. For higher values of c, switching to more generalist types grants a higher return. The Pareto-efficient solutions of the control strategy as function of application rate are highlighted with solid curves. Parameters:

$\mu = 0.00007, \theta = 150, \delta = 0.04, \beta_0 = \beta_1 = 1e-4, \nu_0 = 0.08, \nu_1 = 4\nu_1$.