# Durable resistance or efficient disease control?
# Adult Plant Resistance (APR) at the heart of the dilemma

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## Abstract

Adult plant resistance (APR) is an incomplete and delayed protection of plants against pathogens. At first glance, such resistance should be less efficient than classical major-effect resistance genes, which confer complete resistance from seedling stage, to reduce epidemics. However, by allowing some 'leaky' levels of disease, APR genes are predicted to be more durable than major genes because they exert a softer selection pressure on pathogens towards adaptation to resistance. However, the impact of partial efficiency and delayed mode of action of APR on the evolutionary and epidemiological outcomes of resistance deployment has never been tested.

Using the demogenetic, spatially explicit, temporal, stochastic model *landsepi*, this study is a first attempt to investigate how resistance efficiency, time to resistance expression and target pathogenicity trait jointly impact resistance durability and disease control at the landscape scale. Our numerical experiments explore the deployment of APR in a simulated agricultural landscape, alone or together with a major resistance gene. As a case study, the mathematical model has been parameterised for rust fungi (genus *Puccinia*) of cereal crops, for which extensive data are available.

Our simulations confirm that weak efficiency and delayed expression of APR genes reduce the selection pressure applied on pathogens and their propensity to overcome resistance, but do not confer effective protection. On the other hand, stronger APR genes (which increase selection pressure on the pathogen) may be quickly overcome but have the potential to provide some disease protection in the short-term. This is attributed to strong competition between different pathogen genotypes and the presence of fitness costs of adaptation, especially when APR genes are deployed together with major resistance gene via crop mixtures or rotations.

***Keywords***: adaptation, adult plant resistance, disease control, immunity, mature plant resistance, ontogenic, puccinia, resistance, resistance durability, rust, simulation modelling.

## Introduction

In plant pathology, durable resistance and efficient disease control are two important considerations in the use of genetically controlled plant resistance to manage crop diseases (Burdon JJ et al., 2016). Indeed, strategies to deploy plant resistance should first be as efficient as possible to mitigate epidemics and preserve crop health. However, the high evolutionary potential of many plant pathogens means that they can adapt and overcome such resistance, sometimes quickly after deployment in the field (Johnson R, 1983; Parlevliet JE, 2002; García-Arenal F & BA McDonald, 2003). Resistance breakdown results in potentially destructive epidemics and economic losses, leading to increased reliance on pesticides and acceleration of associated environmental issues. In addition, resistance breakdown also means the loss of precious and non-renewable genetic resources, and the need to develop new resistant cultivars, a long and costly process (Zhan J et al., 2015). Therefore, in addition to the provision of efficient crop protection in the short-term, resistance must also be durable, even if these two goals are not necessarily compatible (van den Bosch F & CA Gilligan, 2003; Papaïx J et al., 2018; Rimbaud L et al., 2018a). In this context, simulation models provide powerful tools to explore and evaluate different crop deployment strategies with respect to their epidemiological and evolutionary outcomes, while circumventing the logistical challenges associated with field experiments at large spatio-temporal scales (Rimbaud L et al., 2021).

Plant breeding has typically focused on resistance conferred by major-effect genes, which often confer complete resistance, such that pathogens are unable to infect cultivars carrying those genes. Most major genes encode for an immune receptor of the nucleotide-binding leucine-rich repeat (NLR) protein family, which triggers the immune response (often involving a hypersensitive reaction) after recognition of a pathogen effector (de Ronde D et al., 2014; Gallois J-L et al., 2018). Nevertheless, pathogens may escape this recognition after mutation or suppression of this effector, leading to the restoration of infectivity and resistance breakdown. In these cases, the plant-pathogen genetic interaction is best described by the 'gene-for-gene' (GFG) model, according to which the occurrence of disease depends on whether or not the plant carries a resistance gene, and whether or not the pathogen possesses the matching effector (Flor HH, 1955). The scientific literature describes numerous examples of major resistance genes being rapidly overcome by fungi (Johnson R, 1983, 1984; McDonald BA & C Linde, 2002; Parlevliet JE, 2002; Stuthman DD et al., 2007; Park RF, 2008; Burdon JJ & PH Thrall, 2014), bacteria (McDonald BA & C Linde, 2002; Parlevliet JE, 2002), viruses (García-Arenal F & BA McDonald, 2003; Lecoq H et al., 2004; Moury B et al., 2010), and nematodes (McDonald BA & C Linde, 2002), although some of them have maintained effectiveness for many years. Such resistance breakdown results from the high selection pressure experienced by pathogen populations in the presence of such resistance, since only adapted individuals can infect resistant hosts. 'Resistance-breaking' mutants may be initially present in the population at low frequency, derive from other pathogen genotypes by mutation or recombination, or be introduced from distant areas through migration. In such cases, the frequency of the mutant genotype increases as it will be strongly favoured by selection and the whole host population may end up infected (Johnson R, 1983, 1984; Lecoq H et al., 2004; Moury B et al., 2010).

Resistance is, however, not always complete or continuous in time. Whether they may be insufficiently expressed, dependent on environmental conditions or simply weak, resistance genes sometimes confer only partial protection to pathogens. In this context, 'resistance efficiency' is a key component of partial resistance, and describes how well the infectious cycle of the pathogen is

mitigated, i.e., the extent of reduction of one or several pathogenicity traits, such as infection rate, latent or infectious period durations, and reproduction rate (Parlevliet JE, 1979; Lannou C, 2012). Resistance may also be specific to certain host developmental phases (Barrett LG & M Heil, 2012), such as is the case for adult plant resistance (APR, also called 'mature plant resistance'; Develey-Rivière M-P & E Galiana, 2007). APR genes are often described as being only expressed in adult plants (Burdon JJ et al., 2014; Niks RE et al., 2015), with an efficiency varying from 0% to 100% and depending on plant age and environment (Krattinger SG & B Keller, 2016). However, moderate levels of expression of APR genes can sometimes be detected in young plants (Park RF & RG Rees, 1989; Cromey MG, 1992; Broers LHM, 1997; Sandoval-Islas JS et al., 2007; Qamar M et al., 2012). This expression tends to increase progressively and the date after which APR genes are fully active (referred to as 'time to resistance expression' hereafter) depends on the resistance gene and may occur as late as the anthesis stage (Ma H & RP Singh, 1996). Many APR genes against rust fungi have been documented in cereal crops (Burdon JJ, 1987 p56; McIntosh RA et al., 1995; Boyd LA, 2005). They can impact all pathogenicity traits associated with the pathogen infectious cycle: infection rate (e.g. Lr34-Yr18; Qamar M et al., 2012), latent period (Lr16-Lr18, Lr34-Yr18; Tomerlin JR et al., 1983; Elahinia SA & JP Tewari, 2005; Qamar M et al., 2012), sporulation rate (Lr16-Lr18; Tomerlin JR et al., 1983), sporulation duration (Lr16-Lr18; Tomerlin JR et al., 1983). Nonetheless, a wide panoply of molecular mechanisms may underpin APR resistance and these are poorly known (Develey-Rivière M-P & E Galiana, 2007; Krattinger SG & B Keller, 2016). Exceptions include three resistance genes against leaf, stem and yellow rusts of wheat: Lr67 encoding a hexose transporter (Moore JW et al., 2015); Lr34 encoding an ATP-binding cassette (ABC) transporter (Krattinger SG et al., 2009); and Yr36 encoding a chloroplast-localised kinase protein involved in detoxification of reactive oxygen species (Fu D et al., 2009, see also Develey-Rivière M-P & E Galiana, 2007 for resistances against other pathogens).

To the best of our knowledge, the role of delayed expression of plant resistance in disease management and pathogen evolution has never been investigated in simulation models (Rimbaud L et al., 2021), despite its supposed potential to promote resistance durability. Complete resistance is often assumed in modelling studies, and always considered active from the seedling stage. Yet, hosts are thought to generate different selective pressures on pathogens if they express complete, partial or delayed resistance (Stuthman DD et al., 2007; Pilet-Nayel M-L et al., 2017). While complete resistance exerts hard selection on the pathogen to restore infectivity, the pressure imposed by partial and delayed resistances (such as the one conferred by APR genes) is likely lower since they allow some 'leaky' levels of disease. Partial and delayed resistances can thus be seen as soft selection mechanisms that slow down the speed of pathogen evolution compared to typical major resistance genes. This slower pathogen evolution comes nonetheless at the price of weaker protection against disease, hence the potential of such resistance for disease management is still intriguing, particularly when deployed in conjunction with major gene resistance.

The aim of the present study is to investigate how resistance efficiency, time to resistance expression and target pathogenicity trait of a resistance gene jointly impact resistance durability and epidemiological disease control. Additionally, because deploying different types of resistance is likely a promising approach to benefit from their respective advantages, we also investigate the best strategies to combine a major resistance gene with an APR gene. To study these questions, we use a general simulation framework implemented in the R package *landsepi* (Rimbaud L et al., 2018b). The model is flexible enough to vary parameters related to the deployed resistance genes, and to

encompass various pathogen epidemiological traits. Thus, although this work is motivated by rust diseases of cereal crops (for which there is considerable empirical data), our broad conclusions may, to some extent, apply to numerous pathosystems.

# Methods

## Model overview

We used a demogenetic, spatially explicit, temporal and stochastic model developed to explore different plant resistance deployment strategies in agricultural landscapes and evaluate their epidemiological and evolutionary outcomes. A description of the mathematical model is detailed in a previous article (Rimbaud L et al., 2018c). Briefly, the model simulates the spread (by wind) and evolution (via mutation) of a spore-borne fungal pathogen in a cropping landscape where susceptible and resistant cultivars are cultivated with controlled proportions and controlled level of spatial aggregation. While the model has the capacity to simulate sexual reproduction for the pathogen, here we assume clonality. In the simulated landscape, resistance genes may be deployed in a single host cultivar as a pyramid, or in different cultivars that can be segregated in a mosaic of fields, combined within the same field as mixtures, or alternated within crop rotations. Resistance genes may target one or several pathogenicity traits (reduction of infection rate, sporulation rate or sporulation duration, lengthening of latent period duration) with complete or partial efficiency. The pathogen has the potential to adapt to each of the deployed resistance genes independently, via single or multiple mutations (leading to the emergence of new pathogen strains), possibly associated with a fitness cost on the susceptible cultivar. The pathogen is disseminated across the landscape using a power-law dispersal kernel: $g(\|z'-z\|) = \frac{(b-2)(b-1)}{2.\pi.a^2}.\left(1+\frac{\|z'-z\|}{a}\right)^{-b}$ with $\|z'-z\|$ the Euclidian distance between locations $z$ and $z'$ in fields $i$ and $i'$, respectively, a the scale parameter and b a parameter linked to the width of the tail. The plant infection and immune status is modelled using a traditional SEIR ('susceptible-exposed-infectious-removed') framework. Plant harvests occur at the end of each cropping season, imposing potential bottlenecks (and thus genetic drift) on the pathogen population.

In this study, the *landsepi* model was extended to include resistance genes with a delayed expression (i.e., APR genes). Cultivars that carry an APR gene are susceptible at the beginning of the cropping season and become resistant once the gene activates. The time to resistance expression is drawn from a gamma distribution every year and for every field planted with a cultivar carrying an APR gene. For convenience, this distribution is parameterised with the expectation and variance of the time to expression. Both parameters, as well as the target pathogenicity trait and efficiency of resistance, are assumed to be genetically determined and thus characteristic of a given APR gene.

For the simulation experiments, we parameterised the model using available data from the empirical literature to represent wheat rust infection caused by a range of fungal pathogens in the genus *Puccinia* (**Table 1**, details on model calibration in Rimbaud L et al., 2018c), supporting information). The model is available in the R package *landsepi* version 1.1.1 (Rimbaud L et al., 2018b).

## Numerical experiments

Three successive numerical experiments were carried out to explore APR. Experiment 1 is a baseline scenario destined to evaluate how the deployment of a single APR gene mitigates epidemics

159 in absence of pathogen evolution (i.e., here epidemics are caused by a single pathogen strain, not
160 adapted to the APR gene). Experiment 2 reproduces the same scenario but includes pathogen
161 evolution, to measure the durability of the APR gene and the epidemiological impact of the possible
162 presence of adapted pathogen genotypes. Finally, Experiment 3 investigates whether APR genes and
163 major resistance genes are competing alternatives or can be complementary to each other via
164 appropriate spatio-temporal deployment strategies. **Table 1** summarises model parameters of
165 interest.

166 In the first two experiments, the landscape (representing approximately 150 fields, total area:
167 2x2 $km^2$, see Fig S1 in Rimbaud L et al., 2018c) was composed of a mosaic of a susceptible (1/3 of total
168 surface) and a resistant cultivar (2/3 of total surface) across the simulated landscape. Cultivars were
169 randomly allocated to fields within the landscape either at low or at high degree of spatial aggregation
170 (**Fig. 2**, left-hand column). The resistant cultivar carried a resistance targeting either infection rate,
171 latent period duration, sporulation rate, or sporulation duration of the pathogen. Analysis of field and
172 greenhouse trials on rust diseases of cereal crops revealed that resistance against these pathogenicity
173 traits measured in different host genotypes can vary from 0% to 100% compared to the most
174 susceptible cultivars (**Table S1**). Thus, in our simulations, resistance efficiency was varied from 0 to
175 100% with increments of 10%. The expected time to resistance expression varied from 0 to 90 days
176 with increments of 10 days; a time to expression of 90 days (the whole epidemic season being 120
177 days) represents the case where the gene activates at anthesis stage. For example, if the resistance
178 gene targets the latent period duration with an efficiency of 75% and a time to expression of 30 days,
179 a non-adapted (i.e., 'wild type', wt) pathogen infecting a resistant cultivar will have an expected latent
180 period of 10 days (see **Table 1**) until resistance activates, after which latent period is increased by 75%
181 (i.e., 17.5 days) until the end of the cropping season. In the first experiment, the pathogen was not
182 allowed to evolve, whereas in the second, it could adapt to the APR gene through mutation. In this
183 case, the impact of fitness cost of adaptation (where fitness cost was defined in terms of loss of
184 pathogenicity on the susceptible cultivar) was studied using three (0.00, 0.25, 0.50) different cost
185 values. Model stochasticity includes field shape and boundaries, cultivar allocation to the different
186 fields within the simulated landscape, time to APR gene expression, pathogen dispersal, mutation, off-
187 season survival, and SEIR transitions. To account for this stochasticity, simulations were run on five
188 different landscape structures and replicated 10 times, resulting in 50 replicates for every parameter
189 combination. Thus, the complete factorial design of the first two experiments resulted in a total of
190 44,000 and 132,000 simulations, respectively.

191 In the third numerical experiment, a major resistance gene and an APR gene were jointly
192 deployed according to one of four strategies: pyramiding, mixture, rotation or mosaic. The major
193 resistance gene was assumed to target pathogen infection rate with complete efficiency and to be fully
194 expressed from the beginning of the cropping season. Target pathogenicity trait, resistance efficiency
195 and time to expression of the APR gene were varied exactly as in the first two experiments. However,
196 for this experiment, spatial aggregation was fixed at a low value (representing a fragmented
197 landscape), and the fitness cost of pathogen adaptation to 0.50. Indeed, results obtained in the second
198 experiment showed that this parameterisation maximises the interaction between cultivars (in terms
199 of pathogen dispersal and competition between pathogen genotypes) within a spatial deployment
200 strategy. For all deployment strategies, 1/3 of the landscape was composed of the susceptible cultivar.
201 The remaining 2/3 were occupied either by a single cultivar carrying the two genes (pyramid strategy),
202 a mixture (in every field) of two resistant cultivars in balanced proportions (each cultivar carrying one

203 of the two genes; mixture strategy), a rotation of these two resistant cultivars (every year; rotation
204 strategy), or a mosaic of the two resistant cultivars in balanced proportions (every cultivar representing
205 1/3 of the landscape area; mosaic strategy) (**Fig. S6**). With 50 stochastic replicates, the complete
206 factorial design resulted in a total of 88,000 simulations.

207 Simulations were run for 120 time-steps per cropping season over a 30-year time period.
208 Initially, only the wild-type pathogen (i.e., not adapted to any resistance), 'wt', was present in
209 susceptible hosts, with a probability of any host being initially infected of $5.10^{-4}$. The wt strain is unable
210 to infect resistant hosts carrying an APR gene only if resistance is both complete and active. In all other
211 situations, the wt strain is able to infect the hosts carrying an APR gene. In any case, a single mutation
212 (with probability $10^{-4}$, except in the first experiment where evolution did not occur) is required to
213 overcome a resistance gene (should it be a major gene or an APR gene) and restore complete
214 pathogenicity, in conformity with a gene-for-gene interaction.

215 **Model outputs**

216 In this work, epidemiological control is defined as the ability of a given deployment strategy to
217 reduce disease impact on the resistant cultivar(s). Here, it is measured by the relative green leaf area
218 (GLA), i.e., the proportion of healthy hosts relative to the total number of hosts, averaged for every
219 cultivar across the whole simulation run. The higher the value of the GLA, the better the
220 epidemiological control.

221 Evolutionary control is quantified here using resistance durability (for experiments 2 and 3),
222 which measures the ability of a given deployment strategy to limit pathogen evolution and delay
223 resistance breakdown (i.e., emergence of the resistance-breaking, 'rb', pathogen). Durability is
224 evaluated using the time when the number of resistant hosts infected by the rb strain exceeds a
225 threshold above which extinction of this strain is unlikely (fixed at 50,000, see Rimbaud L et al., 2018c),
226 supporting Text S2 for details). To understand the contribution of the different pathogen genotypes to
227 an epidemic, we also calculate, across the whole simulation run and for every cultivar, the proportion
228 of infections due to each pathogen genotype relative to all infections.

229 **Table 1. Model parameter and simulation experiments**. See Text S1 in (Rimbaud L et al., 2018c) for calibration details. Parameters of interest (blue cells) were varied
230 according to a complete factorial design. Every simulation was replicated 10 times x 5 landscape structures to account for stochasticity, resulting in a total of 44,000,
231 132,000 and 88,000 simulations for the three numerical experiments, respectively.

| **Parameter** | **Experiment 1** (single APR gene, no evolution) | **Experiment 2** (single APR gene) | **Experiment 3** (major gene + APR gene) |
|---|---|---|---|
| **Pathogen parameters** | | | |
| Dispersal scale parameter (a) [a] | 40 | | |
| Width of the dispersal kernel tail (b) [a] | 7 | | |
| Maximal expected infection rate | 0.40 $spore^{-1}$ | | |
| Minimal expected latent period duration | 10 days | | |
| Variance of the latent period duration | 9 days | | |
| Maximal expected sporulation duration | 24 days | | |
| Variance of the sporulation duration | 105 days | | |
| Maximal expected sporulation rate | 3.125 $spores.day^{-1}$ | | |
| Initial probability of infection of susceptible hosts | $5.10^{-4}$ | | |
| Off-season survival probability | $10^{-4}$ | | |
| **Landscape organisation [b]** | | | |
| Number of fields in the landscape [c] | 155; 154; 152; 153; 156 | | |
| Deployment strategy | Mosaic | Mosaic | Mosaic, mixture, rotation, pyramid |
| Proportion of landscape area covered by the susceptible cultivar | 1/3 | | |
| Level of spatial aggregation | low; high | low; high | low |
| **Major gene resistance** | | | |
| Target pathogenicity trait | - | - | Infection rate |
| Resistance efficiency (ρ) | - | - | 1.00 |
| Expected time to resistance expression | - | - | 0 day |
| Variance of the time to resistance expression | Equal to the expected time | | |
| **Adult plant resistance** | | | |
| Target pathogenicity trait | Infection rate; latent period duration; sporulation rate; sporulation duration | | |

| | | | |
|---|---|---|---|
| Resistance efficiency [d] | 0.00; 0.10; 0.20; 0.30; 0.40; 0.50; 0.60; 0.70; 0.80; 0.90; 1.00 | | |
| Expected time to resistance expression [e] | 0; 10; 20; 30; 40; 50; 60; 70; 80; 90 days | | |
| Variance of the time to resistance expression [f] | Equal to the expected time | | |
| **Pathogen evolutionary ability [g]** | | | |
| Mutation probability [h] | 0 | $10^{-4}$ | $10^{-4}$ |
| Fitness cost of adaptation (θ) [i] | - | 0.00, 0.25; 0.50 | 0.50 |

[a] The mean dispersal distance is given by: $\frac{2a}{(b-3)} = 20\ m$, but long-distance dispersal may also occur due to the heavy-tail shape of the power law.

[b] crop cultivars are allocated using an algorithm based on latent Gaussian fields to control proportion and level of spatial aggregation of each cultivar; see Fig. S1 of (Rimbaud L et al., 2018a) for illustrations and (Rimbaud L et al., 2018c) for details on the algorithm.

[c] see Fig S1 in (Rimbaud L et al., 2018c) for illustrations of landscape structures generated using a T-tesselation algorithm, and see (Papaïx J et al., 2014a) for details on the algorithm.

[d] an efficiency of 0.00 is equivalent to the absence of a resistance gene.

[e] a time of 90 days represents gene activation at anthesis stage.

[f] when expectation and variance are 0 day, there is no variation in the time to expression.

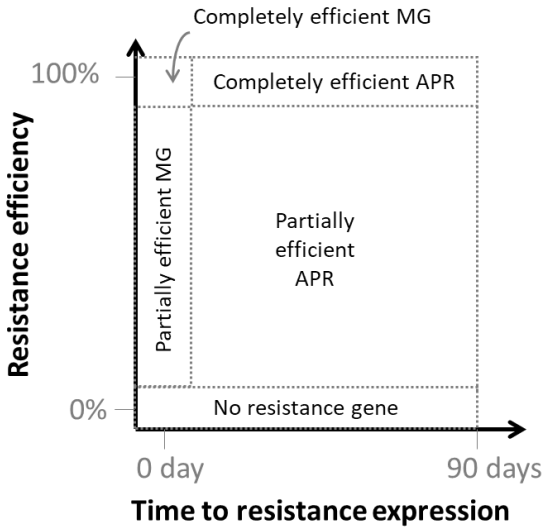
[g] same value for major gene and adult plant resistance.

[h] probability of a spore changing its phenotype on a resistant cultivar carrying a resistance gene.

[i] paid by adapted pathogens on hosts that do not carry an active resistance – it consists of a reduction in the same pathogenicity trait as the one targeted by the resistance.

249 # Results

250 Three separate numerical experiments were carried out to investigate the epidemiological and
251 evolutionary outcomes of deployment strategies based on APR: the first two experiments were
252 performed with an APR gene alone, and the third with a combination of an APR gene and a major
253 resistance gene. In all these experiments, three parameters were systematically allowed to vary:
254 resistance efficiency, time to resistance expression and target pathogenicity trait. Using this approach,
255 we were able to explore a wide range of situations, from the absence of resistance (if resistance
256 efficiency is 0%, **Fig. 1**) to a completely efficient major gene (if efficiency is 100% and there is no delay
257 in resistance expression) with all possible intermediate situations (partially-efficient major gene,
258 completely-efficient APR gene, partially-efficient APR gene).




259
260 **Figure 1.** Conceptual exploration of parameters associated with resistance genes: efficiency and time
261 to expression. This formal framework encompasses a wide range of situations. MG: major gene ; APR:
262 adult plant resistance.

263 **Experiment 1: Deployment of a single APR gene in a susceptible landscape with no pathogen**
264 **evolution**

265 Disease control, measured by the Green Leaf Area averaged for every cultivar across the whole
266 simulation run, was first evaluated when a single APR is deployed in the landscape and the pathogen
267 does not have the possibility to overcome the resistant cultivar.

268 As expected, for the resistant cultivar, disease control increases with higher efficiency and
269 shorter time to resistance expression (**Fig. 2**). Globally, the target pathogenicity trait offering the best
270 level of disease control is the infection rate when resistance is expressed early in the cropping season,
271 whereas it is the sporulation duration when resistance is expressed late (**Figs. 2 & S1**). On the
272 susceptible cultivar, disease control is globally poor except when the level of spatial aggregation
273 between cultivars is low and the APR carried by the resistant cultivar is almost completely efficient,
274 expresses very early (i.e., it is roughly similar to a major gene), and targets the pathogen infection rate,
275 sporulation rate or sporulation duration (**Fig. 2B**). This comes at the price of a slightly decreased level
276 of control for the resistant cultivar compared to an aggregated landscape.

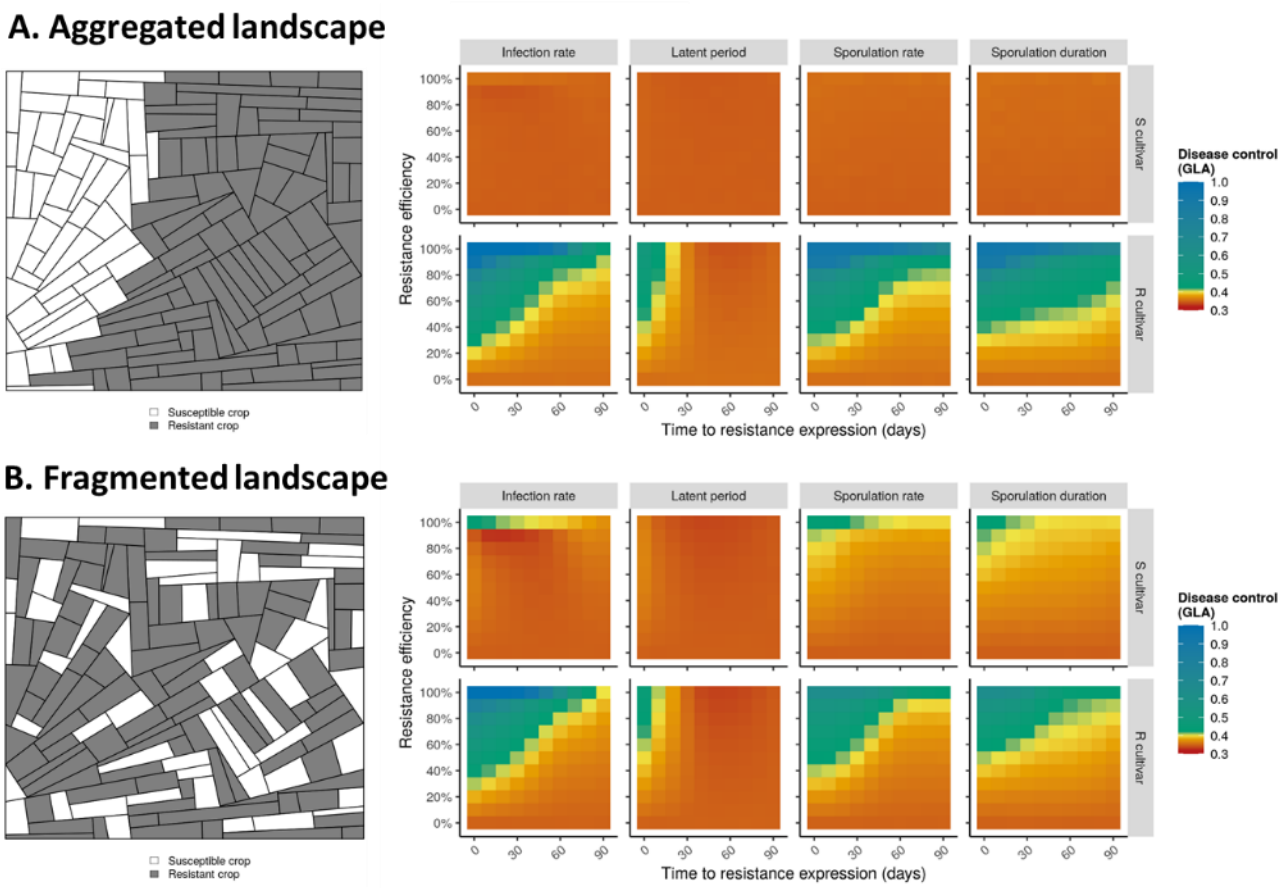



**Figure 2.** Simulated landscapes (examples on the left) and heatmaps (on the right) of the level of epidemiological control (i.e., disease limitation, measured by the Green Leaf Area, 'GLA') in the absence of pathogen evolution for different levels of resistance efficiency (vertical axis), time to resistance expression (horizontal axis) and target pathogenicity traits (columns), for strong (A) or weak (B) levels of spatial aggregation.

**Experiment 2: Deployment of a single APR gene in a susceptible landscape with pathogen evolution**

In this experiment, there were two possible pathogen genotypes: the rb and wt strains, respectively adapted and not adapted to the APR, whose performances on the different cultivars are summarised in **Table 2**.

**Table 2.** Plant-pathogen interaction matrix with a single resistance gene. The table shows the coefficients by which the value of the target pathogenicity trait (see **Table 1**) is multiplied (except for latent period duration: 1-ρ is replaced by 1+ρ and 1-θ is replaced by 1+θ). The coefficients reflect the relative performance of the different pathogen genotypes on the different cultivars. ρ is the efficiency of the resistance gene and θ is the fitness cost of adaptation.

| | **Susceptible cultivar** | **Resistant cultivar (APR)** | |
|---|---|---|---|
| | | Non-active | Active |
| **wild type pathogen (wt)** | 1 | 1 | 1-ρ |
| **resistance-breaking pathogen (rb)** | 1-θ | 1-θ | 1 |

*Impact of resistance efficiency and time to expression.*

Regardless of the target pathogenicity trait, fitness cost and level of spatial aggregation, the results indicate that weak resistance (whether it is inefficient or delayed in expression; bottom right corner of graphics in **Figs. 3, S2, S3, S4**) is always durable (**panels A and B**), meaning that rb pathogen genotypes never emerged in the 30-year simulations (**panels E and F**). However, in this situation, resistance does not confer good epidemiological protection against the wt pathogen, as shown by the second output variable ('Disease control', **panels C and D**). In contrast, strong resistance (highly efficient and activated early in the growing season; top left corner of graphics in **Figs. 3, S2, S3, S4**) shows poor durability (**panels A and B**), indicating that the rb pathogen genotype quickly emerged and invaded the resistant host population (**panels E and F**). This again results in poor epidemiological control for the resistant cultivar (**panels C and D**). However, when fitness costs are large ($\theta$=0.50), there is a critical zone where disease control by the resistant cultivar reaches a higher level, particularly when infection rate is targeted by the APR gene. This zone corresponds to resistance efficiencies higher than 60% and time to expression between roughly 30 and 80 days (**Fig. 3CD**). **Fig. S5** illustrates examples of simulations carried out in the three contrasted scenarios described just above (weak resistance, strong resistance, critical zone).

*Impact of fitness cost of adaptation.*

Decreasing the loss of pathogenicity of the rb pathogen on the susceptible cultivar (effect of columns in **Figs. 3, S2, S3, S4**) tends to decrease both durability and disease control (at intermediate resistance efficiency and with delayed expression, rb genotypes emerge more often and cause more damage). In particular, when there are no fitness costs of adaptation, the critical zone previously described disappears completely.

*Impact of the level of field spatial aggregation.*

The strongest impact of spatial aggregation is on the genetic composition of the pathogen population and the associated epidemic damage (**Figs. 3, S2, S3, S4, panels E and F**). The susceptible cultivar is mostly infected by the wt pathogen in aggregated landscapes, leading to severe epidemics. In contrast, for strong resistance (highly efficient or activated early in the growing season) and in presence of fitness costs of adaptation, the susceptible cultivar is mostly infected by the rb pathogen in fragmented landscapes, resulting in moderate to good epidemiological control (due to the fitness penalty). Conversely, epidemiological control for the resistant cultivar seems slightly better in aggregated landscapes (especially when resistance is strong but considerably delayed in the cropping season, top right corner of heatmaps, **Fig. 3CD**). In the absence of fitness costs of adaptation or for weak resistance (inefficient or activated late in the growing season), the genetic composition of the pathogen is similar on the two cultivars, and the associated damage is high.

*Impact of the target pathogenicity trait.*

All the previous results hold qualitatively with the different pathogenicity traits targeted by resistance. When resistance targets sporulation rate or the duration of the sporulation period, the genetic composition of the pathogen population and the level of evolutionary control (resistance durability) are similar to what was observed for the infection rate (**Figs. S3, S4**). There are, however, quantitative changes in the epidemiological outcome, as size and location of the critical zone are slightly different depending on the target pathogenicity trait. For infection rate, as mentioned before, the critical zone of good disease control corresponds to resistance efficiencies higher than 60% and expression between 30 and 80 days. For sporulation rate (or sporulation duration), the critical zone corresponds to efficiencies higher than 80% (respectively 90%) and expression after 50 days

(respectively 80 days). Resistances increasing the duration of the latent period and havinga high efficiency and a delayed expression (more than 30 days, **Fig. S2**, top right corner of graphics) are more durable than those targeting the other traits. This is a consequence of the absence of emergence of the rb pathogen. However, the level of epidemiological control is poor in comparison to the other target traits, and the size of the critical zone is considerably reduced (restricted to resistance efficiencies between 80 and 100% and times to expression of less than 20 days).

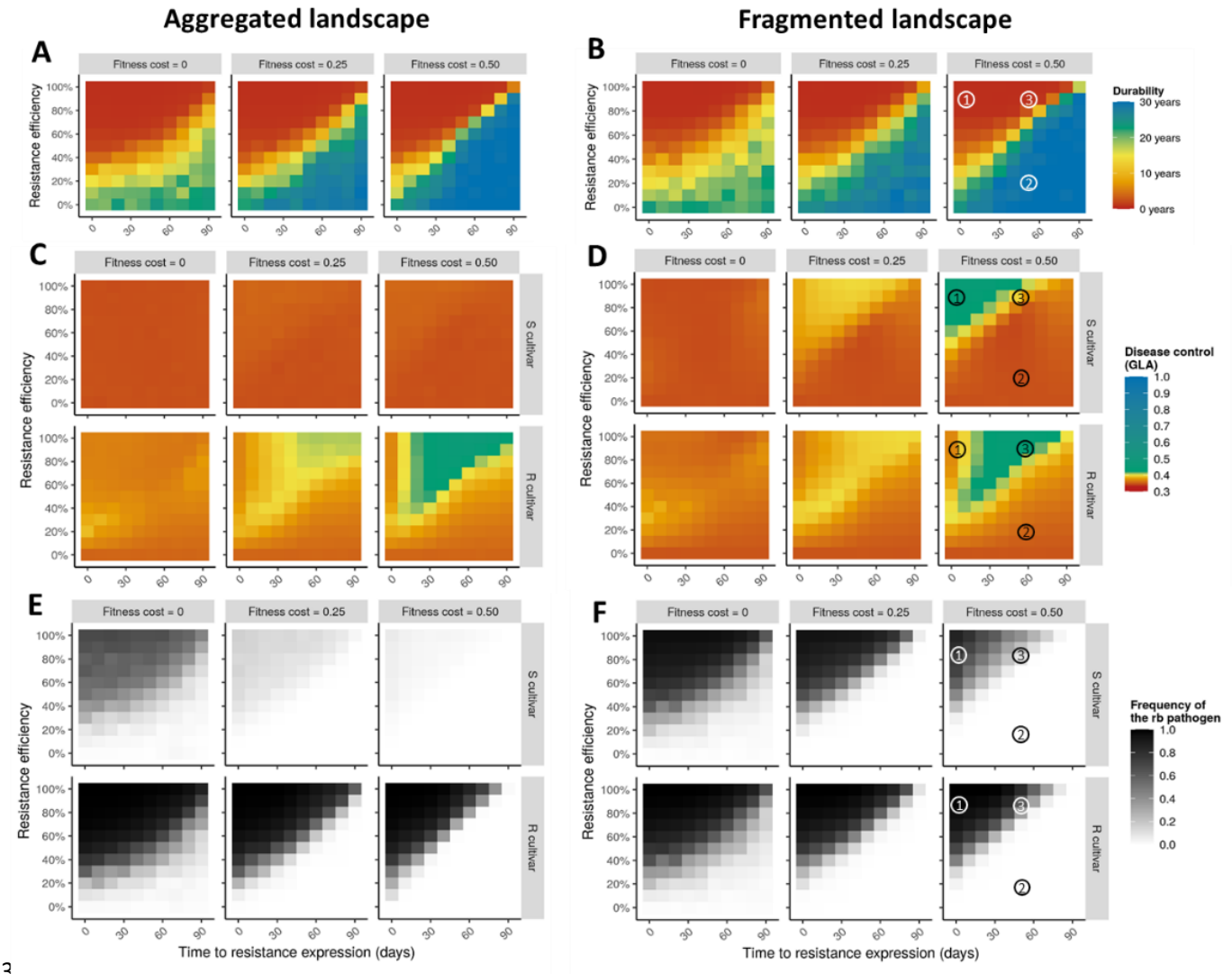



**Figure 3.** Heatmaps of the levels of evolutionary control (resistance durability as measured by the number of years before the emergence of the resistance-breaking ('rb') pathogen genotype; panels A and B), epidemiological control (i.e., disease limitation, measured by the Green Leaf Area ('GLA') on the susceptible ('S') and the resistant ('R') cultivars; panels C and D) and average frequency of the rb pathogen (panels E and F) for different levels of resistance efficiency (vertical axis), time to resistance expression (horizontal axis) and fitness cost of pathogen adaptation (columns), for strong (panels A, C, E) or weak (B, D, F) levels of spatial aggregation. The target pathogenicity trait is the infection rate. Circled numbers refer to example simulations in **Fig. S5**.

352 **Experiment 3: Simultaneous deployment of a major resistance gene and an APR gene in a**
353 **susceptible landscape**

354 In a third numerical experiment, resistance durability and disease control were evaluated when
355 a major resistance gene and an APR gene were simultaneously deployed across a landscape, either
356 within the same cultivar ($R_{12}$, pyramiding strategy) or in two distinct cultivars ($R_1$ and $R_2$, respectively)
357 which could be cultivated in different fields (mosaic strategy), within the same field as mixtures, or
358 alternated in time through crop rotations (see **Fig. S6** for examples of simulated landscapes). In this
359 experiment, there are four possible pathogen genotypes, whose performances on the different
360 cultivars are summarised in **Table 3**. Here, the level of spatial aggregation is fixed at a low value
361 (fragmented landscape), and the fitness cost is 0.50.

362 **Table 3.** Plant-pathogen interaction matrix with two resistance genes, giving the coefficients by which
363 the value of the target pathogenicity trait (see **Table 1**) is multiplied (except for latent period duration:
364 1-ρ is replaced by 1+ρ and 1-θ is replaced by 1+θ). It reflects the relative performance of the wild-type
365 (wt) and the resistance-breaking ($rb_1$, $rb_2$, $rb_{12}$) pathogen genotypes on the susceptible (S) and resistant
366 cultivars carrying a major resistance gene (MG; cultivar $R_1$), an APR gene ($R_2$) or both ($R_{12}$). $\rho_1$ and $\rho_2$
367 are the efficiencies of the resistance genes, and $\theta_1$ and $\theta_2$ are the fitness costs of adaptation.

| | **S** | **$R_1$ (MG)** | **$R_2$ (APR)** | | **$R_{12}$ (MG+APR)** | |
|---|---|---|---|---|---|---|
| | | | Non-active | Active | Non-active | Active |
| **wt** | 1 | 0 | 1 | $1-\rho_2$ | 0 | 0 |
| **$rb_1$** | $1-\theta_1$ | 1 | $1-\theta_1$ | $1-\rho_2$ | 1 | $1-\rho_2$ |
| **$rb_2$** | $1-\theta_2$ | 0 | $1-\theta_2$ | 1 | 0 | 0 |
| **$rb_{12}$** | $(1-\theta_1)(1-\theta_2)$ | $1-\theta_2$ | $(1-\theta_1)(1-\theta_2)$ | $1-\theta_1$ | $1-\theta_2$ | 1 |

368

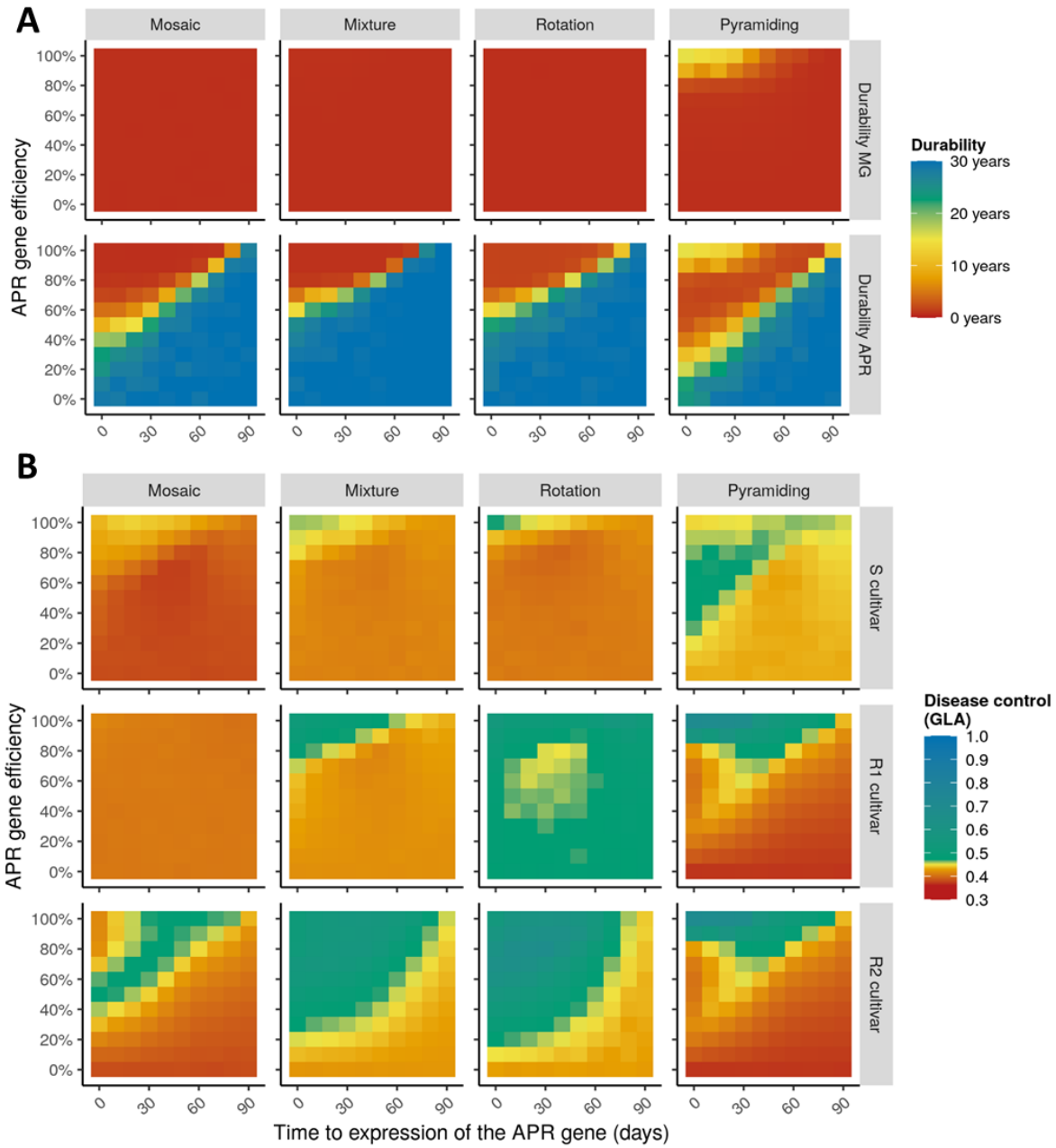



**Figure 4.** Heatmaps showing the levels of A) evolutionary control (resistance durability, measured by the number of years before the emergence of resistance-breaking genotypes) and B) epidemiological control (i.e., disease limitation, measured by the Green Leaf Area, 'GLA') on a susceptible cultivar 'S', a resistant cultivar 'R1' carrying a completely efficient major gene ('MG') and a resistant cultivar 'R2' carrying an APR gene, for different levels of APR efficiency (vertical axis), time to APR expression (horizontal axis) and deployment strategies (columns; note that for pyramiding, R1 and R2 refer to the same cultivar). The target pathogenicity trait of the APR gene is the infection rate, the level of spatial aggregation is low, and the fitness cost is 0.50.

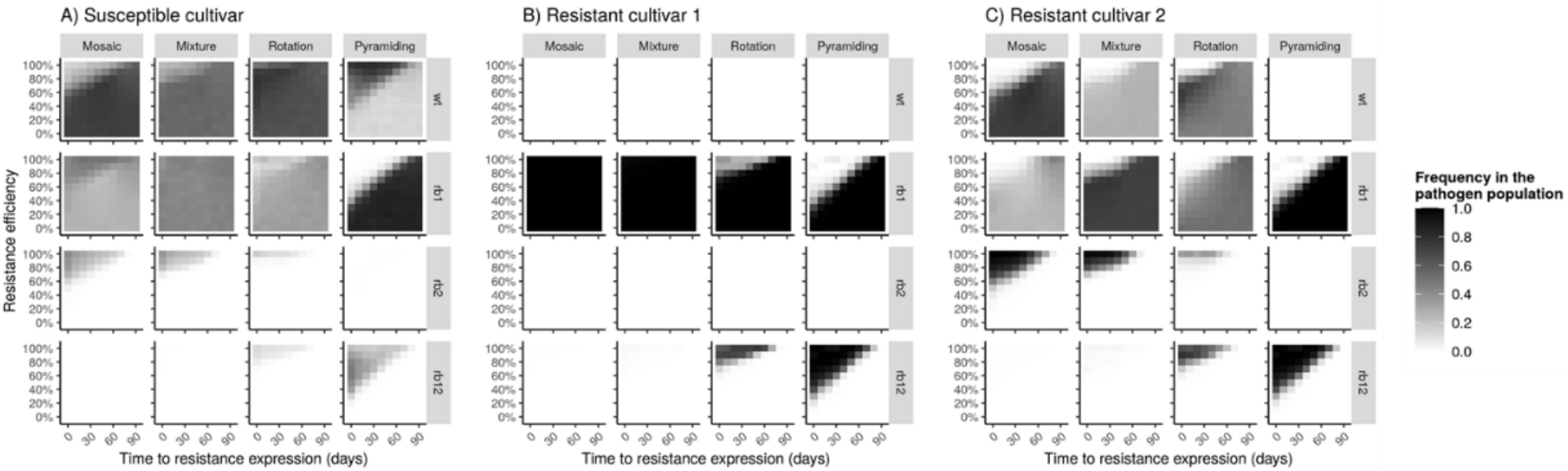



**Figure 5**. Average frequency of the different pathogen genotypes (see **Table 3** for notations) on a susceptible cultivar 'S', a resistant cultivar 'R1' carrying a completely efficient major gene and a resistant cultivar 'R2' carrying an APR gene, for different levels of APR efficiency (vertical axis), time to APR expression (horizontal axis) and deployment strategies (columns; note that for pyramiding, R1 and R2 refer to the same cultivar). The target pathogenicity trait of the APR gene is the infection rate, the level of spatial aggregation is low, and fitness cost is 0.50.

*Impact of resistance efficiency, time to expression and deployment strategy.*

Regardless of the characteristics of the APR gene (efficiency, time to expression, target pathogenicity trait), the major gene is always overcome quickly after deployment (**Figs. 4, S7, S8, S9**), except when it is pyramided with a very efficient APR gene that is activated early in the growing season (which is essentially the same as a pyramid of two major resistance genes). This rapid breakdown is mostly attributed to the emergence of the single mutant 'rb1' (except when the major gene is pyramided with a strong APR, in which case the breakdown is due to the double mutant 'rb12', **Fig. 5**). With respect to the durability of the APR gene and the level of protection it confers on the associated cultivar (R2), weak resistance (i.e., inefficient or delayed in expression) is durable (neither the 'rb2' nor the 'rb12' genotypes emerged) but offers poor protection against the 'wt' and 'rb1' genotypes (**Fig. 4 & 5**), similar to the results for Experiment 2. When resistance is strong (very efficient and activated early), it is quickly overcome (**Fig. 4**), either by 'rb2' in mosaics and mixtures, or by 'rb12' in rotations and pyramids (**Fig. 5**). In mosaics, this leads to the same critical zone previously described for Experiment 2. In contrast, in mixtures and rotations, the level of control stays high for a large range of resistance efficiencies and times to expression. In pyramids, there is a good level of control only for highly efficient resistances (**Fig. 4**). For the resistant cultivar carrying the major gene (R1), disease control shows contrasting results depending on the deployment strategy. It is globally poor in mosaics and globally good in rotations. In mixtures, it is good only when the second resistant cultivar (R2) carries a strong APR gene that is expressed early. In pyramids, it is good as long as the APR has a strong efficiency. For the susceptible cultivar, a good level of disease control can be obtained if the APR (deployed in cultivar R2) has a strong efficiency and early expression, especially if pyramided with a major gene. In this situation the susceptible cultivar is invaded by both the 'wt' and the 'rb12' pathogen genotypes (**Fig. 5**).

*Impact of targeted pathogenicity trait.*

The results are qualitatively the same when sporulation rate and sporulation duration are targeted by the APR gene instead of the infection rate (**Figs. S8 & S9**). When resistance conferred by the APR gene increases the length of the latent period (**Fig. S7**), it is durable for a larger range of parameter values (i.e., resistance efficiency and time to expression) compared with the other target traits. However, in this situation the level of epidemiological control for the different cultivars is poor in comparison to the other target traits.

## Discussion

To the best of our knowledge, adult plant resistance (APR) has never been explored in mathematical models dealing with plant resistance deployment (Rimbaud L et al., 2021), despite its presence in numerous resistant cultivars of cereals and other crops (Burdon JJ, 1987 p56; McIntosh RA et al., 1995; Boyd LA, 2005; Chen XM, 2005; Develey-Rivière M-P & E Galiana, 2007; Chen W et al., 2014). Therefore, and because APR may affect different pathogenicity traits, in a delayed and potentially incomplete manner, we used the mathematical model implemented in the R package *landsepi* (Rimbaud L et al., 2018c) to explore three parameters associated with this type of resistance: target pathogenicity trait, efficiency and time to expression. The main objective was to evaluate the impact of these parameters on resistance durability (evolutionary pathogen control) and disease limitation (epidemiological control). We designed numerical experiments to explore three scenarios: the deployment of a single APR gene in a susceptible landscape, firstly without and secondly with pathogen evolution. The third experiment assessed the deployment of an APR gene together with a

426 major resistance gene according to different spatiotemporal deployment strategies (**Table 1**). Although
427 this work was motivated by rust fungi of cereal crops, the generality of the model makes our results
428 likely applicable to other pathosystems. Adult plant resistance has also been described in viruses
429 (whilst rather called "mature plant resistance"). For instance, a cultivar of *Nicotiana edwardsonii*,
430 expresses a delayed monogenic resistance against *Tobacco mosaic virus*, *Tobacco necrosis virus* and
431 *Tobacco bushy stunt virus* (Cole AB et al., 2004). Mature plant resistance has also been demonstrated
432 in the greenhouse against *Cucumber mosaic virus* with a complete restriction of viral movement and
433 systemic colonisation in mature bell pepper plants (Garcia-Ruiz H & JF Murphy, 2001) and against
434 *Potato virus Y* with a restriction of tuber infection in potato (Kumar P et al., 2022).

435 **Favouring competition offers good epidemiological control in spite of pathogen adaptation**

436 Globally, our results show that an APR gene is never overcome when it is inefficient with respect
437 to reducing the target pathogenicity trait or is expressed late in the cropping season (**Figs. 3AB, 4A**).
438 This is due to the small selection pressure applied to the pathogen population, given that the wt
439 genotype can thrive on cultivars carrying such resistance genes almost as if they were susceptible. This
440 is in accordance with results obtained via different simulation models (Carolan K et al., 2017; Crété R
441 et al., 2020) and confirms one of the mechanisms according to which partially efficient resistance is
442 generally predicted to be more durable than complete resistance (Lecoq H et al., 2004; Stuthman DD
443 et al., 2007; Zhan J et al., 2015). Such phenomena have also been described for pest adaptation to
444 chemicals, where small application doses were shown to slow down the emergence of adapted
445 genotypes (Hobbelen PHF et al., 2014). Partial resistance with low efficiency or delayed expression,
446 however, results in severe epidemics and a weak level of epidemiological control (**Figs**. **2**, **3CD**, **4B**). In
447 contrast, when resistance strongly reduces the target pathogenicity trait of the wt pathogen,
448 particularly when this happens early in the cropping season, it has a high potential to protect the
449 resistant cultivar (Experiment 1, **Fig. 2**), as expected in absence of pathogen evolution and already
450 shown in demographic models (e.g., Papaïx J et al., 2014b). However, if pathogen evolution is possible,
451 the high selection pressure leads to the rapid emergence of a rb pathogen which invades the resistant
452 host population, resulting in both low durability and disease control (Experiment 2, **Fig. 3**). This is
453 similar to a scenario where a single major gene (i.e., complete resistance) is deployed in the landscape
454 and quickly overcome (Rimbaud L et al., 2018c).

455 There is, however, an intermediate region of the parameter space where the APR gene is broken
456 down but still confers a good level of epidemiological protection. This occurs in presence of pathogen
457 evolution only (i.e., in Experiment 2 but not in Experiment 1), and when resistance is delayed in the
458 cropping season but has sufficiently high efficiency once activated. The delay in resistance expression
459 allows the wt genotype to infect resistant hosts early in the season, more efficiently than potential rb
460 genotypes which suffer a fitness cost while resistance is inactive. As soon as it activates, resistance is
461 strong enough to select for rb genotypes, but many hosts are, at this time, already infected by the wt
462 genotype. The ensuing strong competition between the wt and rb genotypes (Experiment 2, **Fig. 3 &**
463 **S5**) explains the limitation on epidemic development (Keesing F et al., 2006). In this context, a resistant
464 crop carrying an APR may conceptually be seen as a within-season rotation between a susceptible and
465 a resistant cultivar. The size of the critical zone (i.e., the range of parameter values leading to optimal
466 epidemiological control for the resistant cultivar) is amplified whenever such competition between
467 pathogen genotypes is stimulated. In our results, this is the case for high fitness costs of pathogen
468 adaptation, which increases the penalty for rb genotypes on both susceptible hosts and hosts with still
469 inactive APR gene and reduces the performance of these genotypes relative to the wt genotype. This
470 corroborates other modelling studies showing that high fitness costs decrease epidemic severity

471 (Pietravalle S et al., 2006; Djidjou-Demasse R et al., 2017; Rimbaud L et al., 2018a; Watkinson-Powell
472 B et al., 2020). In the absence of pathogen adaptation (i.e., when there is only one pathogen genotype,
473 Experiment 1, **Fig. 2**) or fitness cost (Experiment 2, **Fig. 3**) this effect completely disappears.

474 **The level of spatial aggregation of the landscape impacts interactions between cultivars**

475 A high level of spatial aggregation between cultivars in the landscape (e.g. **Fig. 2A**) isolates
476 cultivars and the respective pathogen genotypes that infect them. In terms of epidemiological control
477 of a susceptible cultivar, it results in severe epidemics caused by the wt pathogen genotype (**Figs. 2A,**
478 **3C**). Conversely, in a fragmented landscape (weak level of aggregation, e.g. **Fig. 2B**), the increased
479 connectivity between different cultivars favours pathogen migration from one cultivar to another
480 (Taylor PD et al., 1993). This reduces epidemics on the susceptible cultivar as a result of two different
481 mechanisms which our two first experiments help disentangle. First, there is a dilution effect (Mundt
482 CC, 2002; Rimbaud L et al., submitted), especially in the presence of a cultivar carrying a very strong
483 resistance expressed early in the cropping season. Indeed, in this situation, spread of the wt genotype
484 across susceptible fields is mitigated by the intervening presence of resistant hosts (Experiment 1, **Fig.**
485 **2B**). This is similar to non-host plants that act as propagule sinks and thus decrease epidemic spread
486 on susceptible plants (Suzuki SU & A Sasaki, 2011; Papaïx J et al., 2014b). Second, competition occurs
487 between different pathogen genotypes when the resistant cultivar has an intermediate to strong
488 efficiency and a delayed expression (as described previously). In this case, rb genotypes emerging in
489 resistant fields disperse to susceptible fields (Experiment 2, **Fig. 3D**). This leads to a reduction in the
490 damage caused to the susceptible cultivar (provided that rb genotypes suffer a fitness cost compared
491 to the wt genotype) (Watkinson-Powell B et al., 2020). The side-effect of such a protective effect of
492 the susceptible cultivar by the resistant cultivar is a slightly reduced level of disease control on the
493 resistant cultivar when resistance is expressed late in the cropping season because it is more exposed
494 to wt pathogen genotypes emerging from susceptible fields. Indeed, wt genotypes are fitter than rb
495 genotypes on the resistant cultivar as long as resistance is inactive, due to the presence of fitness costs.
496 Spatial aggregation has been previously demonstrated to have an ambivalent effect on disease
497 management. In fact, earlier modelling work showed that fragmented landscapes better mitigate
498 epidemics on susceptible crops but are more prone to resistance breakdown, compared to aggregated
499 landscapes (Papaïx J et al., 2018; Rimbaud L et al., 2018a).

500 **Optimal efficiency and time to expression of APR genes depend on the target pathogenicity trait**

501 A recent opinion published by Saubin M et al. (2022) states that life history traits targeted by
502 resistance influences its durability. In fact, in the present work, the size and location of the critical zone
503 in parameter space depends on the pathogenicity trait targeted by the APR gene. When sporulation
504 rate or duration of the sporulation period are targeted, the critical zone is shifted towards higher
505 resistance efficiencies and longer times to resistance expression compared to the situation where
506 infection rate is targeted (top right of **Figs. 3CD, S3CD, S4CD**). This shift occurs probably because
507 sporulation takes place later than infection in the pathogen infectious cycle. Therefore, more time is
508 required for the wt pathogen genotype to generate sporulating lesions in the resistant host population
509 before resistance expression (which will favour rb genotypes). APR genes targeting the latent period
510 duration seem very durable, but offer poor disease control in comparison to APR genes targeting other
511 traits (**Fig. S2**). This is because even when resistance is fully efficient (i.e., latent period is multiplied by
512 2), pathogen spread is still possible, which imposes soft selection pressure in favour of rb genotype but
513 provides weak protection against the wt pathogen. This conclusion contrasts with published literature
514 suggesting that latent period duration should be the most influent component of pathogen

515 aggressiveness because it determines the number of possible infection cycles on a crop (Parlevliet JE,
516 1979; Leonard KJ & CC Mundt, 1984; Sandoval-Islas JS et al., 2007). Nevertheless, sensitivity analyses
517 of models simulating epidemics of wheat leaf rust (Kulkarni RN et al., 1982) and potato late blight (Van
518 Oijen M, 1992) have shown that latent period duration was equally or even less influential on disease
519 spread and severity than other pathogenicity traits. These contrasted results highlight the crucial
520 importance of the width of parameter variation ranges in numerical experiments. In our work, the
521 range of variation for resistance efficiency was based on available data for rust fungi. Analysis of the
522 minimal and maximal possible values of the pathogenicity traits measured on different cultivars of
523 cereal crops (**Table S1**) showed that these traits may vary from about 0% to -100% (0% to +100% for
524 latent period duration) relative to the most susceptible cultivar (except sporulation duration, for which
525 there is little data). We thus allowed resistance efficiency to vary from 0 to 100% for all pathogenicity
526 traits.

527 **Major resistance genes and APR genes can be combined at landscape scale**

528 The deployment of a single major resistance gene in a landscape results in rapid breakdown by
529 the corresponding rb1 pathogen and severe epidemics on both susceptible and resistant cultivars (the
530 bottom line of heatmaps in **Fig. 4** shows the situation where the APR is absent, its efficiency being 0%).
531 Combining a major gene with an APR gene in the landscape generally does not prevent the major gene
532 from being overcome, however it may have interesting synergies in terms of epidemiological control
533 depending on the deployment strategy (**Fig. 4**). As discussed earlier, one of the greatest benefits of
534 APR genes is the limitation of epidemics due to competition between pathogen genotypes. Therefore,
535 the presence of different sources of resistance in the landscape, should they be overcome, increases
536 the number of pathogen genotypes present and thus the number of competitors. Globally, this
537 decreases epidemic damage on all cultivars (Mikaberidze A et al., 2015).

538 More specifically, when a cultivar carrying a major gene is planted in mixtures (i.e., in the same
539 field) with a cultivar carrying an APR gene, the first cultivar benefits from a dilution effect (since only
540 rb1 genotypes can infect it) conferred by the presence of the second one, which itself benefits from
541 strong competition between the wt, rb1 and rb2 genotypes. While to some extent this should also
542 occur in mosaics (i.e., different cultivars segregated in different fields), our results do not show such
543 synergies for the mosaic strategy. This is probably because of the model assumption that the pathogen
544 was initially present in all susceptible fields of the landscape, added to the fact that pathogen dispersal
545 is mostly at the intra-field scale in our parameterisation (**Table 1**). The impact of landscape
546 heterogeneity on epidemic spread via competition and dilution effects might be stronger for
547 pathogens with different life histories (Mundt CC, 2002). Here, the best epidemiological control is
548 obtained when crop cultivars are mixed at the finest spatial grain. Indeed, optimal disease control
549 requires that the spatial scale of disease management matches the scale of pathogen dispersal (Gilligan
550 CA, 2008). When the two resistant cultivars are rotated over time (rotation strategy), pathogen
551 genotypes are confronted by an alternation of hard selection towards the rb1 genotype (when the
552 cultivar carrying the major gene is cultivated) and hard or soft selection towards the rb2 genotype
553 (when the cultivar carrying the APR gene is cultivated). If the APR is not too strong or has a delayed
554 expression, selection towards rb2 is soft, which allows competition between wt, rb1 and rb2 genotypes
555 and reduces epidemics. Otherwise, selection is strong and the genotype that performs best in the
556 system is the double mutant rb12 (generalist genotype able to infect all cultivars). However, this
557 genotype is penalised by severe fitness costs (**Table 3**), which reduces epidemic damage as well. This
558 is in line with a previous modelling study comparing mosaics, mixtures, rotation and pyramids of major
559 resistance genes: rotation had the best epidemiological outcome once all resistances had been

560 overcome (i.e., in the presence of rb genotypes) (Rimbaud L et al., 2018a). Finally, if the major gene
561 and the APR gene are pyramided in the same cultivar and the efficiency of the APR gene is strong
562 enough, the delayed action of the APR gene triggers competition between the single mutant rb1,
563 selected for as long as the APR is inactive, and the double mutant rb12, selected for as soon as the APR
564 expresses. This competition reduces epidemic damage on the pyramid cultivar. However, the presence
565 of the APR gene does not prevent the major gene from being overcome, unless it is expressed very
566 early in the cropping season. This is in agreement with previous modelling results: durability of a major
567 gene was greater when pyramided with a quantitative resistance (expressed from the beginning of the
568 cropping season), but only if the latter exhibited strong efficiency (Rimbaud L et al., 2018c).

569 **General conclusions, limits and perspectives**

570 There are several nonexclusive arguments for why APR genes are thought to be more durable
571 than traditional major genes. Firstly, it could be inherent to the molecular mechanism of APR genes,
572 that may be more difficult for the pathogen to overcome than classical NLR proteins frequently
573 encoded by major genes (Oliva R & IL Quibod, 2017; Mundt CC, 2018). As described in the Introduction,
574 the mechanisms of a few APR genes have been elucidated, such as Lr67, Lr34 and Yr36, which encode
575 for a sugar transporter (Moore JW et al., 2015), an ATP-binding cassette transporter (Krattinger SG et
576 al., 2009), and a detoxification protein (Fu D et al., 2009), respectively. Secondly, it could result from
577 the fact that APR genes are rarely alone in a susceptible host genetic background but may be shielded
578 by major genes. Finally, it could be due to the smaller selection pressure applied by APR genes on
579 pathogens (since they allow some infection by wt pathogens by being only partially efficient and
580 delayed in the season) (Mundt CC, 2018).

581 In the absence of relevant quantitative data concerning the first hypothesis, our
582 parameterisation of the model gives the same mutation probability to overcome major genes and APR
583 genes. Hence, the present study explores the latter two hypotheses. The possibility for APR genes to
584 be shielded by major genes has been tested in Experiment 3 while the effect of selection pressure is
585 highlighted by the difference between Experiments 1 and 2. The mutation probability to overcome the
586 resistances was set at a high value, which could explain why, in our simulations, the combination of an
587 APR gene with a major gene in a pyramided cultivar did not affect the durability of the APR gene in
588 comparison to a cultivar that carried the APR gene only. Future work could investigate the potential of
589 such pyramids with a lower mutation probability. On the other hand, our work emphasizes how shifts
590 in selection pressure influence resistance durability. Indeed, APR genes were found to be very durable
591 when they have a small efficiency and late expression. It may explain why some APR genes like Yr18,
592 which has a small to moderate efficiency against stripe rust (Elahinia SA & JP Tewari, 2005; Qamar M
593 et al., 2012) have shown high durability in the field (Krattinger SG et al., 2009). The efficiency of other
594 APR genes like Lr12, Lr13, Lr22, Lr34, Lr35 and Lr37 have been measured between 80% and 90% against
595 leaf rust (Burdon JJ, 1987 p56; McIntosh RA et al., 1995; Smale M et al., 1998). With such high
596 efficiency, our simulations predicts that these genes could be quickly overcome. Nevertheless,
597 depending on the time to resistance expression and the target pathogenicity trait, even if these genes
598 were broken down, the resulting harsh competition between the different pathogen genotypes has
599 the potential to provide some disease limitation, especially when deployed together with major
600 resistance genes in mixture or rotation strategies. However, this conclusion strongly depends on the
601 presence of fitness costs of pathogen adaptation to resistance. Furthermore, our results must be
602 nuanced by the fact that we assumed that rb pathogens were penalised by a fitness cost on inactive
603 APR genes, exactly as if the associated cultivars were susceptible. Experiments could be carried out in
604 controlled conditions to test this hypothesis. We also assumed that APR genes switch suddenly from

being inactive to active, whereas some rare available data rather indicate a gradual expression of APR genes (Ma H & RP Singh, 1996). Finally, while in our simulations, APR genes could target only one pathogenicity trait at a time, in the real world pathogenicity traits often vary in association (Parlevliet JE, 1979; Sache I & C de Vallavieille-Pope, 1995; Leclerc M et al., 2019). For example, Lr16-Lr18 targets latent period duration as well as sporulation rate and duration (Tomerlin JR et al., 1983) and Lr34-Yr18 affects both infection rate and latent period (Qamar M et al., 2012). Regardless, our study represents a first attempt to numerically explore evolutionary and epidemiological outcomes of the deployment of adult plant resistance for the management of plant diseases.


## Acknowledgements

The authors thank Marta Zaffaroni and Jean-Loup Gaussen for their contribution to improve the R package *landsepi*, Loïc Houde for computing assistance and Jeremy Burdon for stimulating discussions.

## Fundings

This work benefited from GRDC grant CSP00192, ANR project “ArchiV” (2019–2023, grant n°ANR-18-CE32-0004-01), AFB Ecophyto II-Leviers Territoriaux Project “Médée” (2020–2022), and the CSIRO/INRAE linkage program.


## Conflict of interest disclosure

The authors declare they have no conflict of interest relating to the content of this article. Benoît Moury is recommender for PCI Evol. Biol.

## Data, script and code availability

The model is available in the open-access R package *landsepi* (Rimbaud L et al., 2018b; webpage: https://csiro-inra.pages.biosp.inrae.fr/landsepi/). Simulations were performed on the BioSP computational cluster from INRAE (https://biosp-cluster.mathnum.inrae.fr/). Simulation results are available in supplementary information.

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862 # Supplementary information

863 **Figure S1.** Heatmaps of the optimal pathogenicity trait targeted by an APR gene.

864 **Figure S2.** Heatmaps of the levels of evolutionary and epidemiological control, and average genotype
865 frequencies in Experiment 2 when the target pathogenicity trait is the latent period duration.

866 **Figure S3.** Heatmaps of the levels of evolutionary and epidemiological control, and average genotype
867 frequencies in Experiment 2 when the target pathogenicity trait is the sporulation rate.

868 **Figure S4.** Heatmaps of the levels of evolutionary and epidemiological control, and average genotype
869 frequencies in Experiment 2 when the target pathogenicity trait is the sporulation duration.

870 **Figure S5.** Epidemiological outcome and dynamics of pathogen genotype frequencies in three
871 examples of simulations.

872 **Figure S6**. Example of simulated fragmented landscapes used in Experiment 3.

873 **Figure S7**. Heatmaps of the levels of evolutionary and epidemiological control in Experiment 3 when
874 the target pathogenicity trait is the latent period duration.

875 **Figure S8**. Heatmaps of the levels of evolutionary and epidemiological control in Experiment 3 when
876 the target pathogenicity trait is the sporulation rate.

877 **Figure S9**. Heatmaps of the levels of evolutionary and epidemiological control in Experiment 3 when
878 the target pathogenicity trait is the sporulation duration.

879 **Table S1.** Observed ranges of infection rate, latent period duration, sporulation rate and sporulation
880 duration for rust fungi.

881 **Raw data**. Dataset of simulation results used in this study.

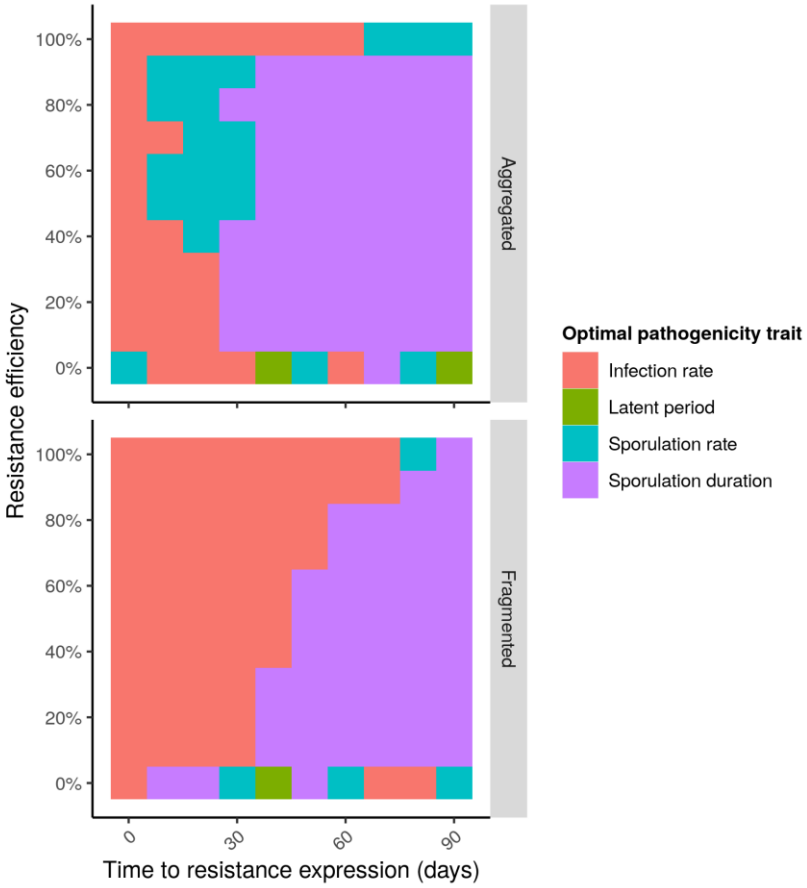


**Figure S1.** Heatmaps indicating the optimal pathogenicity trait targeted by an APR gene with respect to the level of epidemiological control (i.e., disease limitation, measured by the Green Leaf Area, 'GLA') on the resistant cultivar in the absence of pathogen evolution for different levels of resistance efficiency (vertical axis) and time to resistance expression (horizontal axis), for strong (top) or weak (bottom) levels of spatial aggregation.

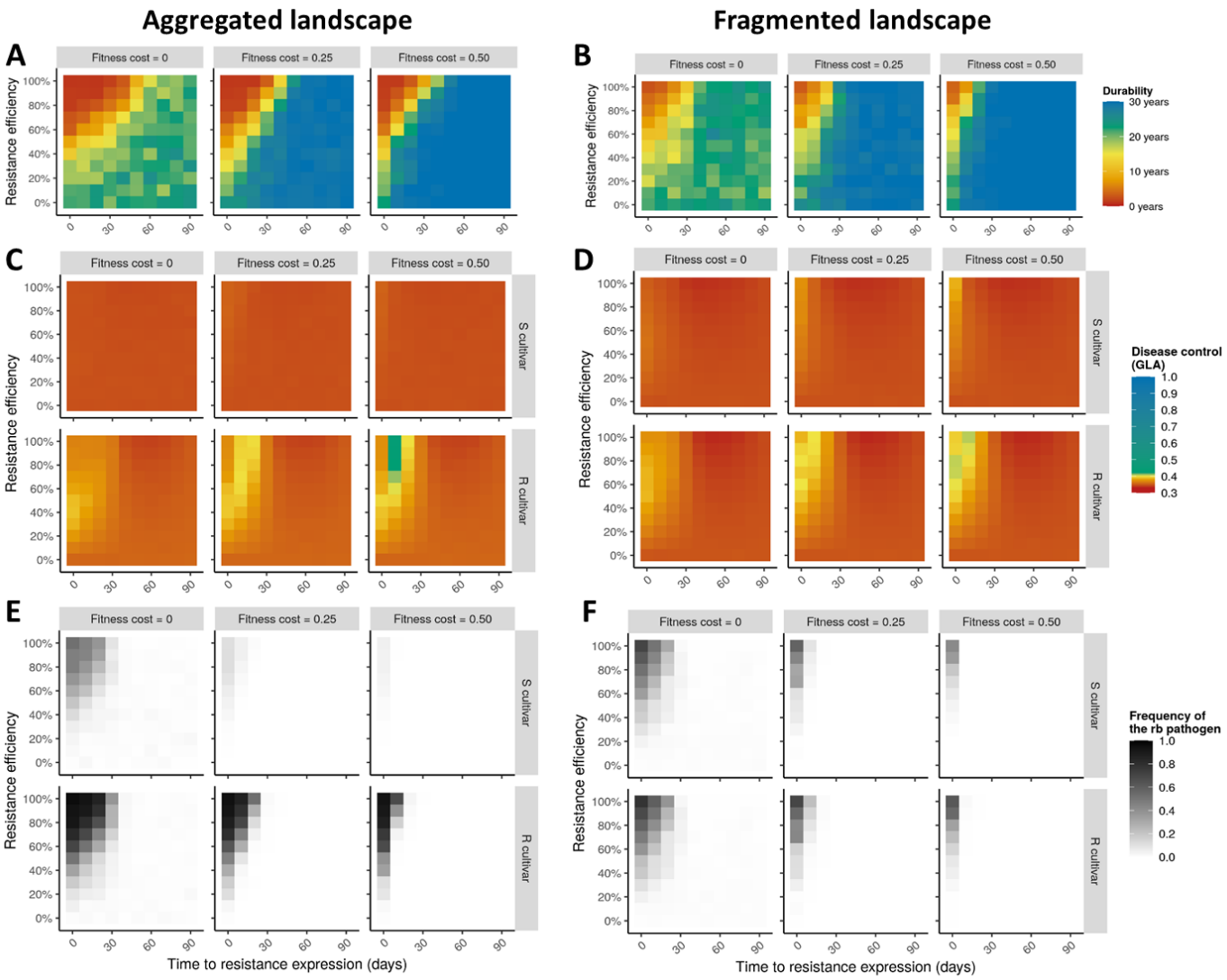


**Figure S2.** Heatmaps of the levels of evolutionary control (resistance durability as measured by the number of years before the emergence of the resistance-breaking ('rb') pathogen genotype, panels A and B), epidemiological control (i.e. disease limitation, measured by the Green Leaf Area ('GLA') on the susceptible ('S') and the resistant ('R') cultivars, panels C and D) and average frequency of the rb pathogen (panels E and F) for different levels of resistance efficiency (vertical axis), time to resistance expression (horizontal axis) and fitness cost of pathogen adaptation (columns), for strong (panels A, C, E) or weak (B, D, F) levels of spatial aggregation. The target pathogenicity trait is the latent period duration.

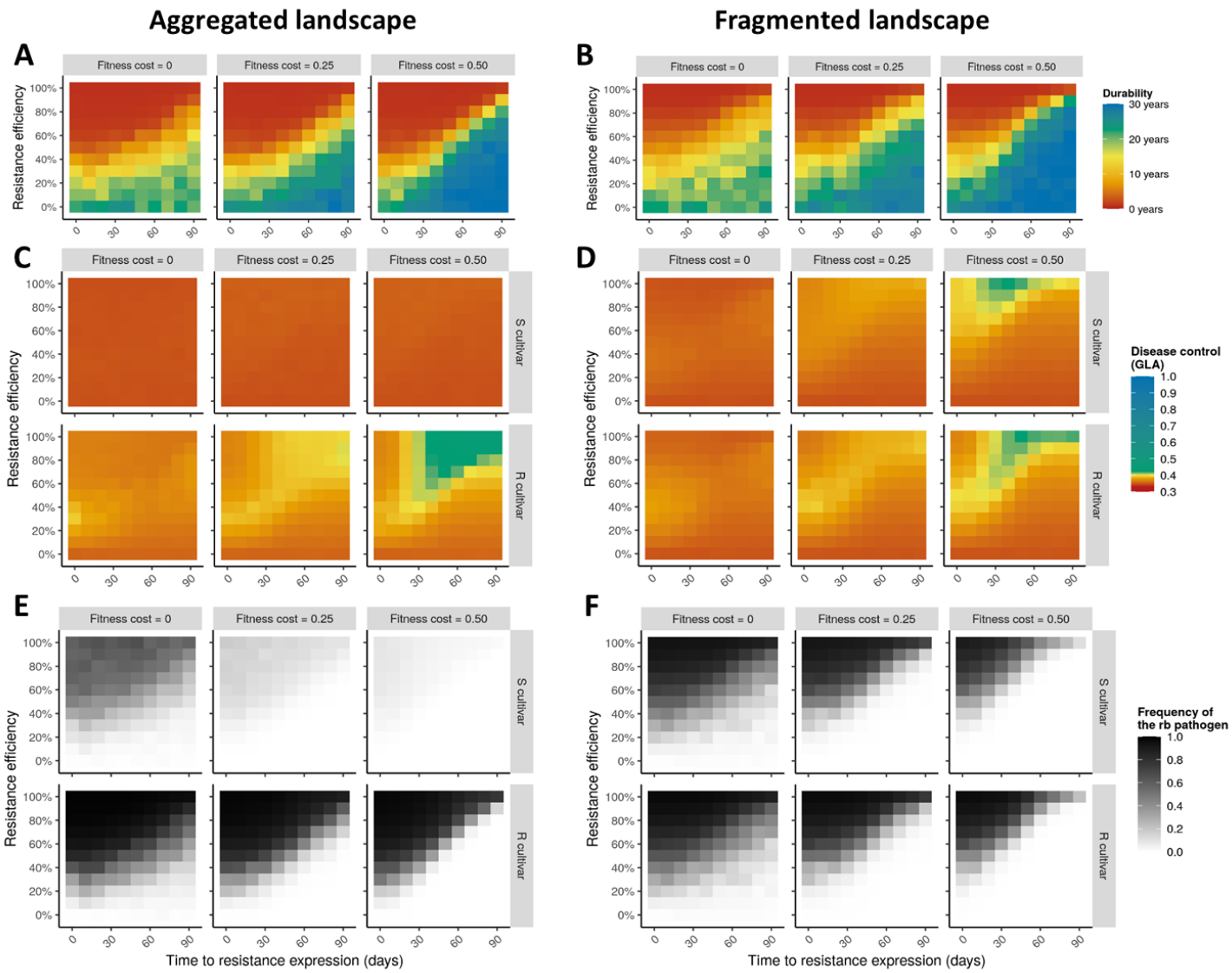


**Figure S3.** Heatmaps of the levels of evolutionary control (resistance durability as measured by the number of years before the emergence of the resistance-breaking ('rb') pathogen genotype, panels A and B), epidemiological control (i.e. disease limitation, measured by the Green Leaf Area ('GLA') on the susceptible ('S') and the resistant ('R') cultivars, panels C and D) and average frequency of the rb pathogen (panels E and F) for different levels of resistance efficiency (vertical axis), time to resistance expression (horizontal axis) and fitness cost of pathogen adaptation (columns), for strong (panels A, C, E) or weak (B, D, F) levels of spatial aggregation. The target pathogenicity trait is the sporulation rate.

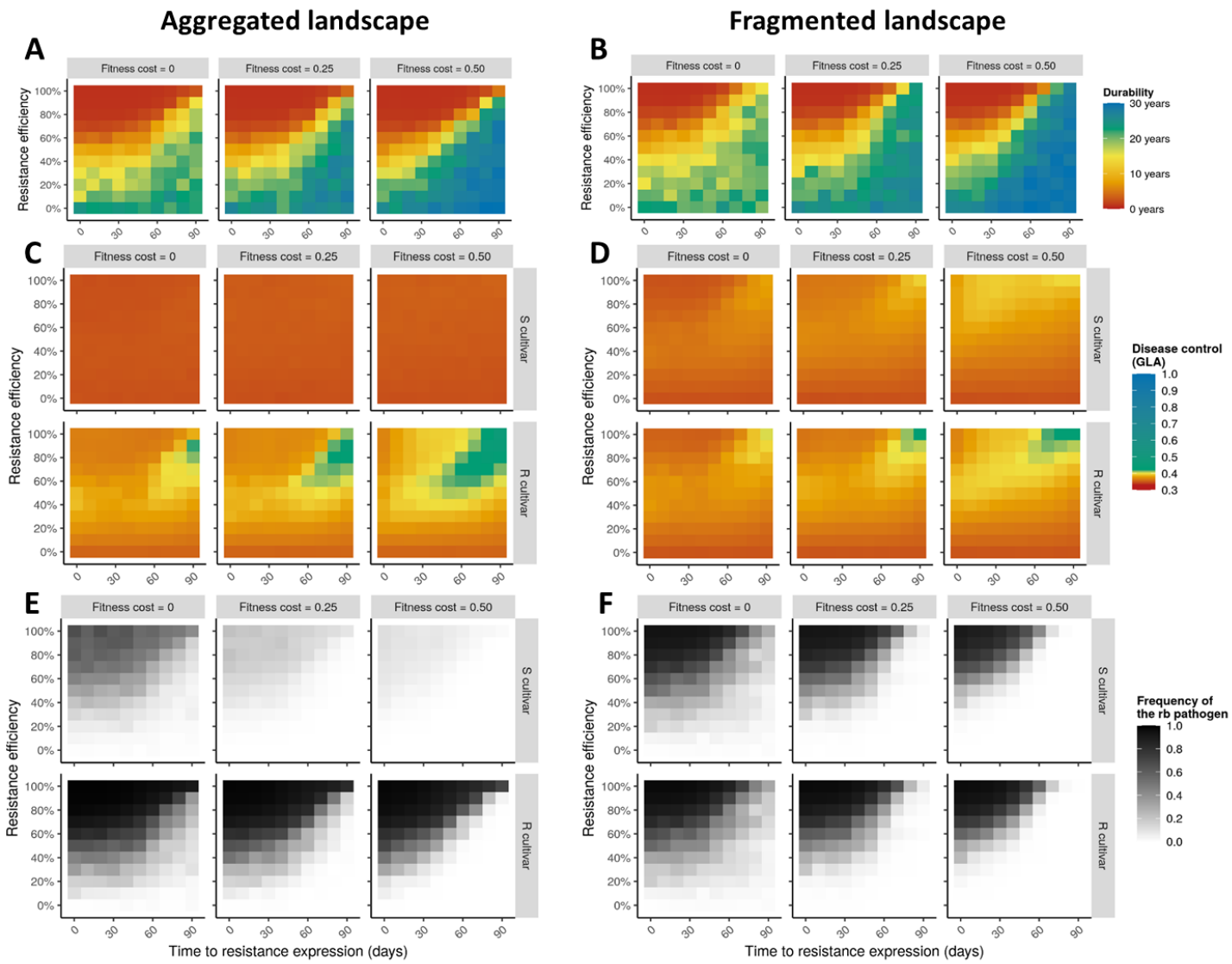


**Figure S4.** Heatmaps of the levels of evolutionary control (resistance durability as measured by the number of years before the emergence of the resistance-breaking ('rb') pathogen genotype, panels A and B), epidemiological control (i.e. disease limitation, measured by the Green Leaf Area ('GLA') on the susceptible ('S') and the resistant ('R') cultivars, panels C and D) and average frequency of the rb pathogen (panels E and F) for different levels of resistance efficiency (vertical axis), time to resistance expression (horizontal axis) and fitness cost of pathogen adaptation (columns), for strong (panels A, C, E) or weak (B, D, F) levels of spatial aggregation. The target pathogenicity trait is the sporulation duration.

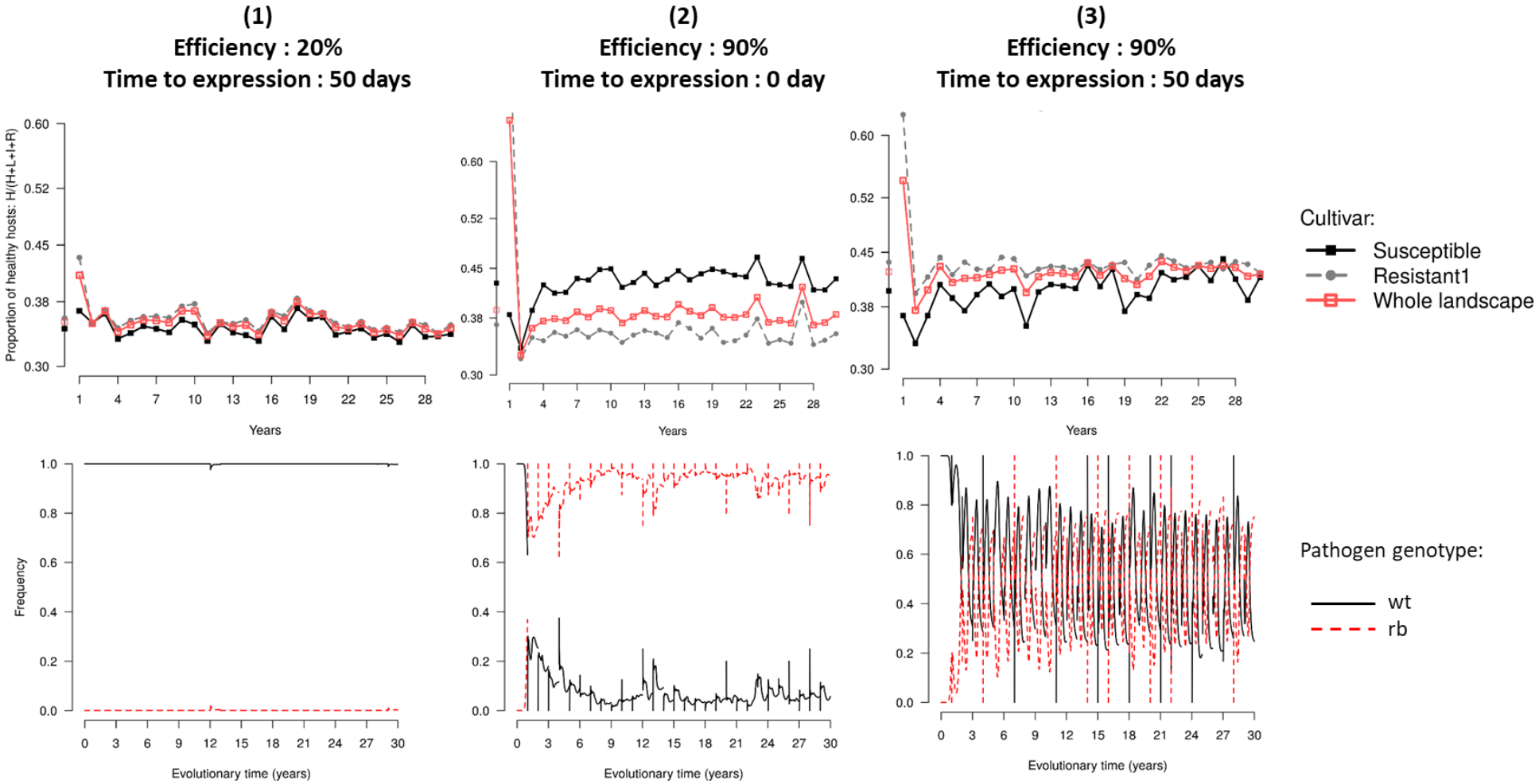


**Figure S5.** Epidemiological outcome (represented by the relative Green Leaf Area, top line) and dynamics of pathogen genotype frequencies (bottom line, 'wt' refers to the wild-type and 'rb' to the resistance-breaking pathogen genotype) in three examples of simulations where a single APR is deployed in a susceptible landscape with low level of spatial aggregation. Situations 1, 2 and 3 are pointed in Figure 3. The pathogenicity trait targeted by resistance is the infection rate and the fitness cost of adaptation is θ=0.50.

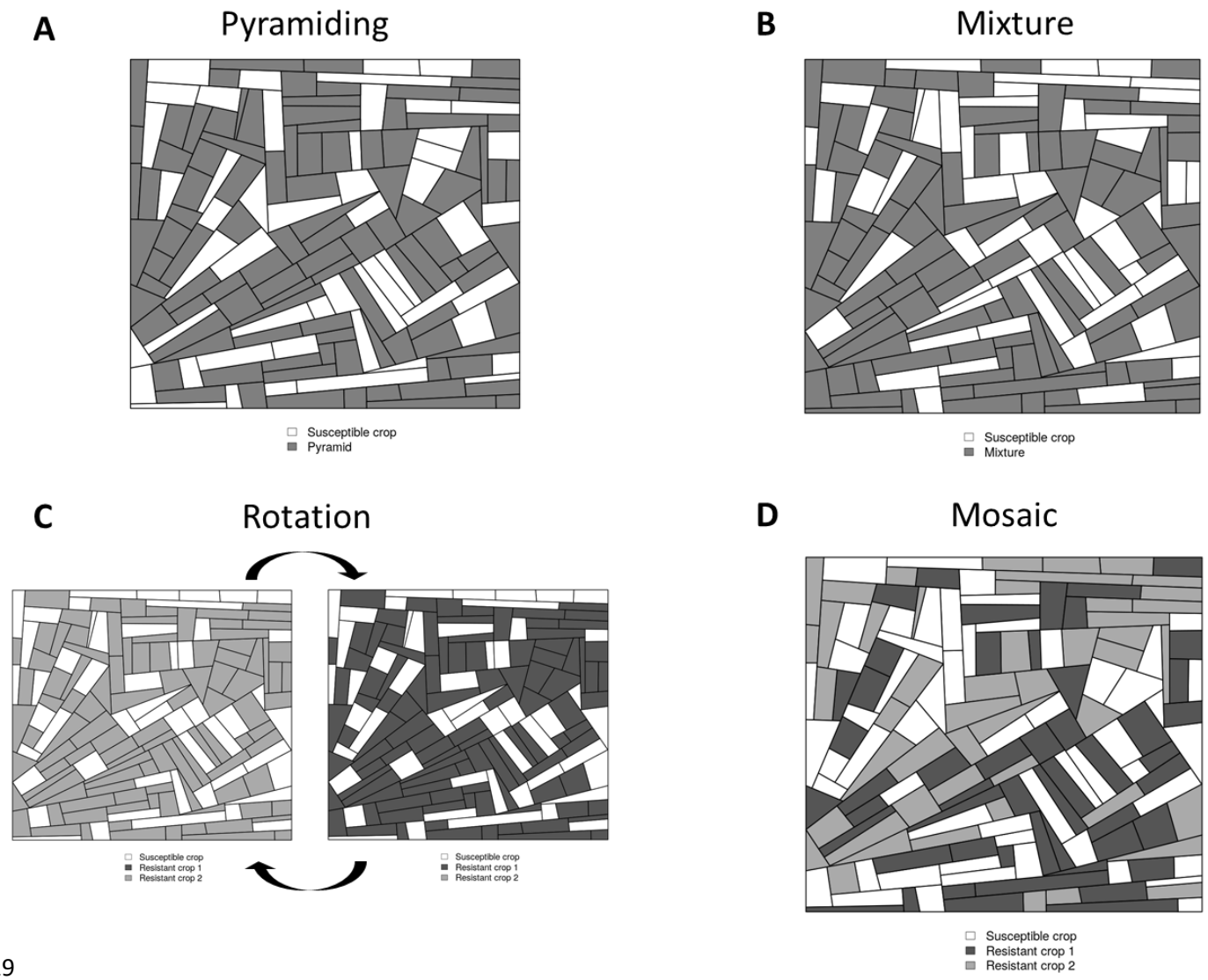


**Figure S6**. Example of simulated fragmented landscapes used in Experiment 3 (APR + MG). For all deployment strategies, 1/3 of the landscape was composed of the susceptible cultivar. The remaining 2/3 were occupied either by: A) a single cultivar carrying the two genes (pyramid strategy); B) a mixture (in every field) of two resistant cultivars in balanced proportions (each cultivar carrying one of the two genes); C) a rotation of these two resistant cultivars (every year); or D) a mosaic of the two resistant cultivars in balanced proportions (every cultivar representing 1/3 of the landscape area).

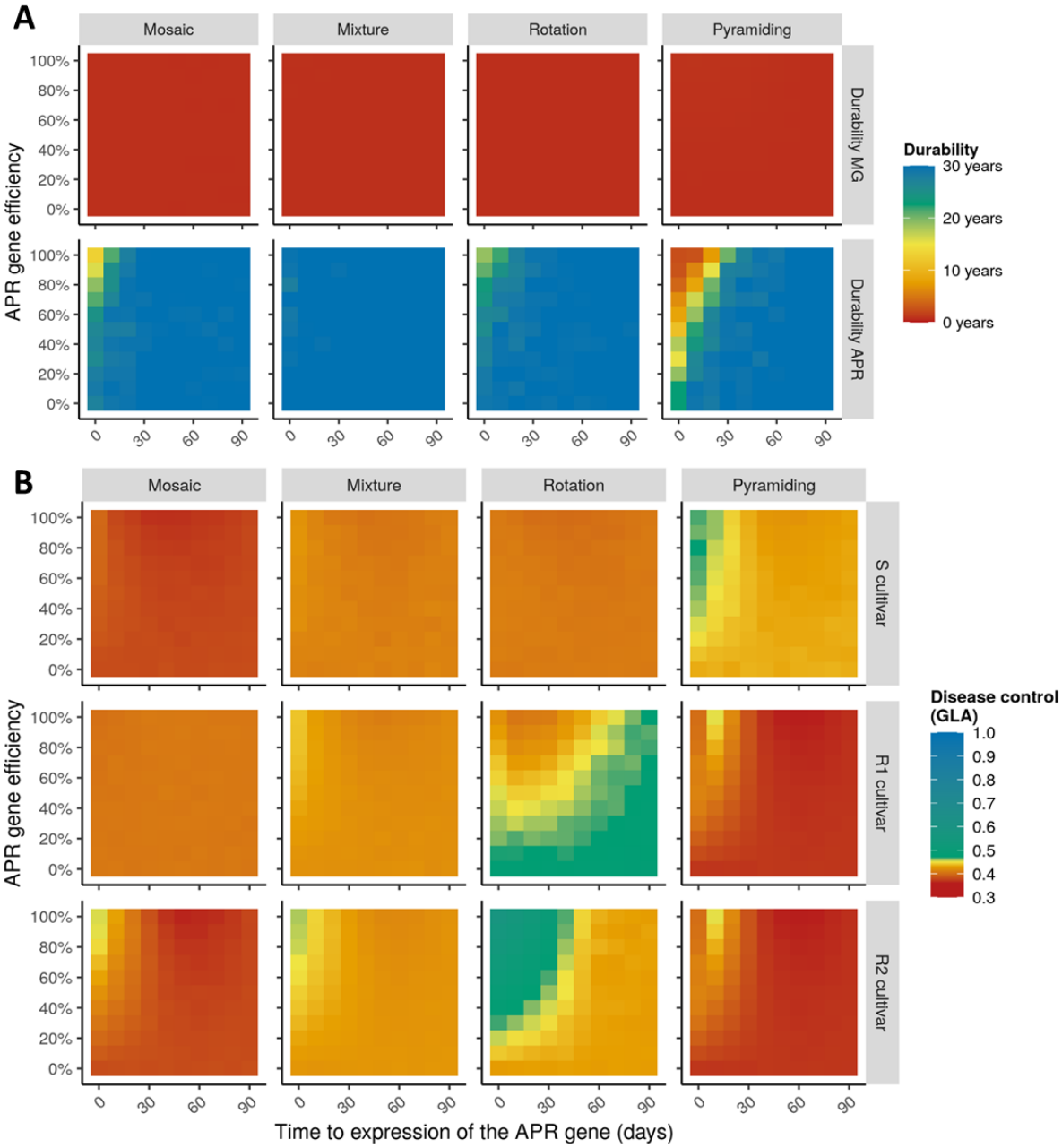


**Figure S7**. Heatmaps showing the levels of A) evolutionary control (resistance durability, measured by the number of years before the emergence of resistance-breaking genotypes) and B) epidemiological control (i.e., disease limitation, measured by the Green Leaf Area, 'GLA') on a susceptible cultivar 'S', a resistant cultivar 'R1' carrying a completely efficient major gene ('MG') and a resistant cultivar 'R2' carrying an APR gene, for different levels of APR efficiency (vertical axis), time to APR expression (horizontal axis) and deployment strategies (columns; note that for pyramiding, R1 and R2 refer to the same cultivar). The target pathogenicity trait of the APR gene is the latent period duration, the level of spatial aggregation is low, and the fitness cost is 0.50.

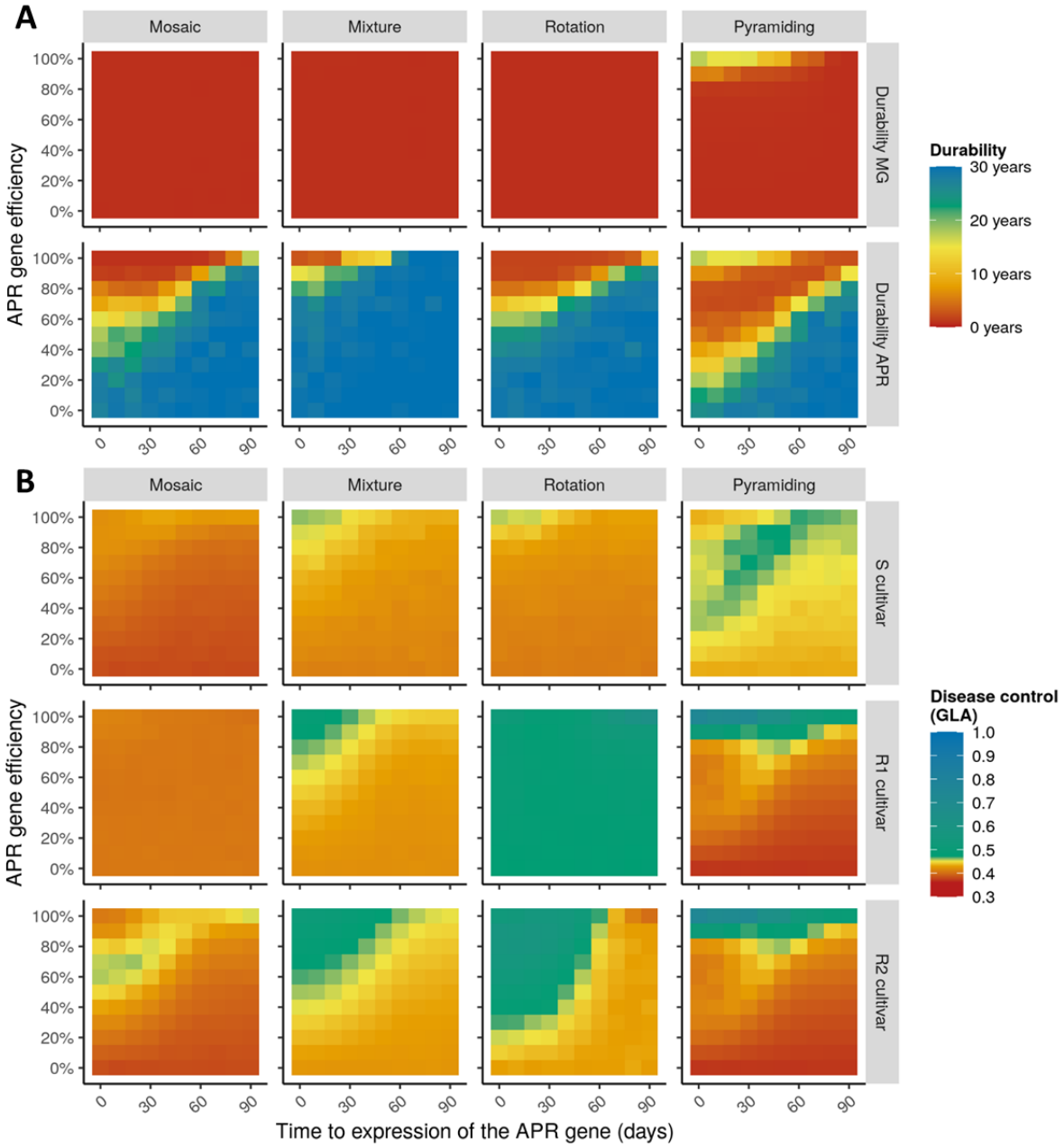


**Figure S8**. Heatmaps showing the levels of A) evolutionary control (resistance durability, measured by the number of years before the emergence of resistance-breaking genotypes) and B) epidemiological control (i.e., disease limitation, measured by the Green Leaf Area, 'GLA') on a susceptible cultivar 'S', a resistant cultivar 'R1' carrying a completely efficient major gene ('MG') and a resistant cultivar 'R2' carrying an APR gene, for different levels of APR efficiency (vertical axis), time to APR expression (horizontal axis) and deployment strategies (columns; note that for pyramiding, R1 and R2 refer to the same cultivar). The target pathogenicity trait of the APR gene is the sporulation rate, the level of spatial aggregation is low, and the fitness cost is 0.50.

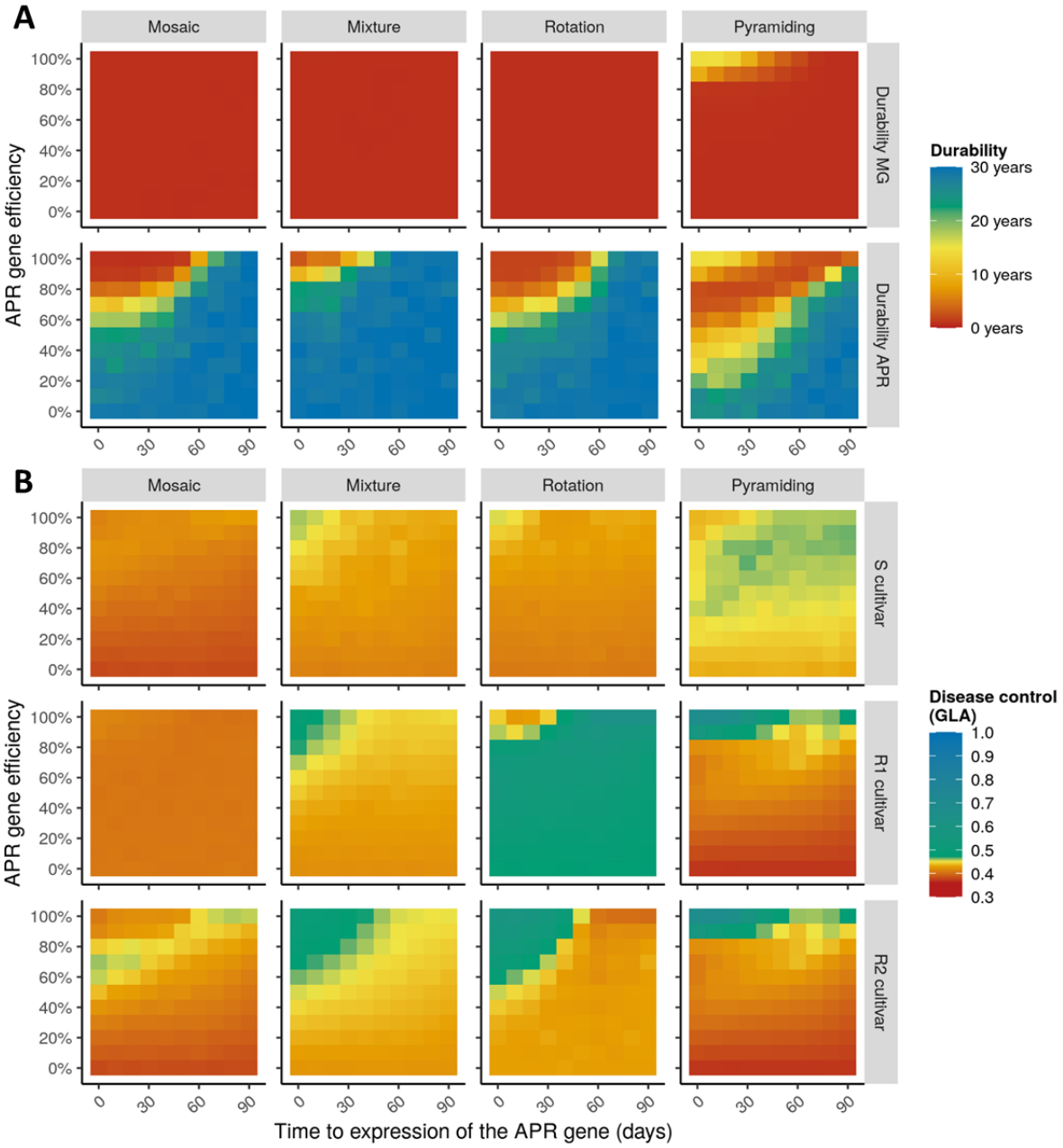


**Figure S9**. Heatmaps showing the levels of A) evolutionary control (resistance durability, measured by the number of years before the emergence of resistance-breaking genotypes) and B) epidemiological control (i.e., disease limitation, measured by the Green Leaf Area, 'GLA') on a susceptible cultivar 'S', a resistant cultivar 'R1' carrying a completely efficient major gene ('MG') and a resistant cultivar 'R2' carrying an APR gene, for different levels of APR efficiency (vertical axis), time to APR expression (horizontal axis) and deployment strategies (columns; note that for pyramiding, R1 and R2 refer to the same cultivar). The target pathogenicity trait of the APR gene is the sporulation duration, the level of spatial aggregation is low, and the fitness cost is 0.50.

**Table S1.** Observed ranges of infection rate, latent period duration, sporulation rate and sporulation duration for rust fungi (genus *Puccinia*) measured in different cultivars of wheat and barley. For a given study, different lines refer to different trials carried out in different conditions (time, temperature, pathogen genotype, leaf stage). Footnotes indicate when the measured variable is not exactly the same as the one used in the *landsepi* model (and of which a definition is given in the first line of the table).

| ***Pathogen*** | **Host** | **Nb of host genotypes** | **Nb of pathogen genotypes** | **Infection rate** (Prop. of inoculated spores resulting in a lesion) | | | **Latent period** (Nb days from inoculation to onset of 50% of sporulating lesions) | | | **Sporulation rate** (Nb spores/lesion/day) | | | **Sporulation duration** (Nb days from end of latent period to end of sporulation) | | | **Reference** [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Max* | *Min* | *Effect size* | *Min* | *Max* | *Effect size* | *Max* | *Min* | *Effect size* | *Max* | *Min* | *Effect size* | |
| *P. hordei* | Barley | 6 | 1 | | | **-60%** [b] | | | **95%** | | | **-50%** | | | **-30%** | Parlevliet JE, 1979, table 4 |
| *P. striiformis* | Wheat | 10 | 1 | 5,85 [b] | 0,33 [b] | **-94%** | | | | | | | | | | Broers LHM et al., 1996, Table 6 |
| | | | | 8,63 [b] | 0,67 [b] | **-92%** | | | | | | | | | | |
| *P. striiformis* | Wheat | 22 | 1 | 13,20 [b] | 3,30 [b] | **-75%** | 10,3 | 21,0 | **104%** | | | | | | | Qamar M et al., 2012, Tables 1 & 2 |
| | | | | 13,60 [b] | 4,70 [b] | **-65%** | 8,5 | 14,4 | **69%** | | | | | | | |
| | | | | 17,00 [b] | 11,90 [b] | **-30%** | 8,2 | 11,9 | **45%** | | | | | | | |
| *P. triticina* | Wheat | 22 | 1 | 36,70 [b] | 8,20 [b] | **-78%** | 9,3 | 18,7 | **101%** | | | | | | | Qamar M et al., 2012, Tables 3 & 4 |
| | | | | 45,00 [b] | 11,30 [b] | **-75%** | 8,9 | 12,7 | **43%** | | | | | | | |
| | | | | 46,70 [b] | 26,30 [b] | **-44%** | 8,2 | 10,0 | **22%** | | | | | | | |
| *P. triticina* | Wheat | 16 | 2 | 0,1303 | 0,0002 | **-100%** | 198,2 [d] | 296,1 [d] | **49%** | | | | | | | Denissen CJM, 1993, Table 4 |
| *P. striiformis* | Barley | 11 | 1 | 17,50 [b] | 1,20 [b] | **-93%** | 12,1 | 14,9 | **23%** | 0,79 [h] | 0,29 [h] | **-63%** | | | | Richardson KL et al., 2006, Fig 3 |
| *P. triticina* | Wheat | 8 | 1 | 0,849 | 0,143 | **-83%** | 156,4 [e] | 214,0 [e] | **37%** | 15,83 [i] | 5,12 [i] | **-68%** | | | | Azzimonti G et al., 2013, Table 3 |
| | | | 1 | 0,696 | 0,101 | **-85%** | 153,9 [e] | 210,9 [e] | **37%** | 17,73 [i] | 5,13 [i] | **-71%** | | | | |
| | | | 1 | 0,830 | 0,281 | **-66%** | 157,0 [e] | 193,2 [e] | **23%** | 20,85 [i] | 7,72 [i] | **-63%** | | | | |
| *P. striiformis* | Wheat | 5 | 1 | 4,10 [b] | 2,10 [b] | **-49%** | 12,6 [f] | 13,9 [f] | **10%** | | | | | | | Cromey MG, 1992, Table 1 & 2 |
| | | 7 | 1 | 3,50 [b] | 0,60 [b] | **-83%** | 12,2 [f] | 16,5 [f] | **35%** | 0,51 [h] | 0,25 [h] | **-51%** | | | | |
| *P. striiformis* | Wheat | 3 | 1 | 0,684 [c] | 0,631 [c] | **-8%** | 12,03 [f] | 13,20 [f] | **10%** | | | | | | | Elahinia SA & JP Tewari, 2005, Tables 1 & 2 |
| | | | | 0,597 [c] | 0,565 [c] | **-5%** | 14,11 [f] | 17,18 [f] | **22%** | | | | | | | |
| | | | 1 | 0,673 [c] | 0,623 [c] | **-7%** | 12,40 [f] | 13,51 [f] | **9%** | | | | | | | |
| | | | | 0,593 [c] | 0,558 [c] | **-6%** | 14,27 [f] | 17,40 [f] | **22%** | | | | | | | |
| *P. triticina* | Wheat | 1 | 3 | 18 [b] | 13 [b] | **-28%** | 147,7 [e] | 156,5 [e] | **6%** | 305 [i] | 198 [i] | **-35%** | | | | Pariaud B et al., 2009, Table 5 |
| | | | | 18 [b] | 15 [b] | **-17%** | | | | 93 [i] | 47 [i] | **-49%** | | | | |
| | | | | 80 [b] | 33 [b] | **-59%** | | | | | | | | | | |
| *P. graminis* | Wheat | 7 | 3 | 5,80 [b] | 3,60 [b] | **-38%** | | | | 0,44 [i] | 0,17 [i] | **-61%** | | | | Mortensen K & GJ Green, 1978, Tables 3, 4, 5, 6, 7 |
| | | | | 5,70 [b] | 1,60 [b] | **-72%** | | | | 0,82 [i] | 0,38 [i] | **-54%** | | | | |
| | | | | 5,20 [b] | 0,40 [b] | **-92%** | | | | 0,91 [i] | 0,20 [i] | **-78%** | | | | |
| | | | | 1,36 [b] | 0,18 [b] | **-87%** | | | | 1,70 [i] | 0,75 [i] | **-56%** | | | | |
| | | | | 1,57 [b] | 0,07 [b] | **-96%** | | | | 1,87 [i] | 0,16 [i] | **-91%** | | | | |
| | | | | 1,18 [b] | 0,01 [b] | **-99%** | | | | 2,62 [i] | 0,08 [i] | **-97%** | | | | |
| | | | | 3,18 [b] | 0,13 [b] | **-96%** | | | | | | | | | | |
| | | | | 2,65 [b] | 0,06 [b] | **-98%** | | | | | | | | | | |
| | | | | 2,12 [b] | 0,01 [b] | **-100%** | | | | | | | | | | |
| *P. striiformis* | Barley | 16 | 1 | 23,10 [b] | 0,01 [b] | **-100%** | 8,6 | 9,5 | **10%** | | | | | | | Sandoval-Islas JS et al., 2007, Tables 6, 7, 8 |
| | | | | 14,00 [b] | 0,00 [b] | **-100%** | 15,7 | 24,4 | **55%** | | | | | | | |
| | | | | | | | 16,4 | 26,0 | **59%** | | | | | | | |
| *P. striiformis* | Wheat | 10 | 1 | 23,00 [b] | 0,00 [b] | **-100%** | 10,7 | 13,5 | **26%** | 60 [h] | 15 [h] | **-75%** | | | | Broers LHM, 1997, Tables 1, 3, 4 |
| | | | | 14,60 [b] | 0,10 [b] | **-99%** | 13,7 | 16,8 | **23%** | 93 [h] | 26 [h] | **-72%** | | | | |
| | | | | | | | 13,5 | 19,1 | **41%** | 97 [h] | 13 [h] | **-87%** | | | | |
| | | | | | | | 12,6 | 19,6 | **56%** | 138 [h] | 18 [h] | **-87%** | | | | |
| *P. striiformis* | Wheat | 12 | 1 | | | | 11,4 [f] | 13,8 [f] | **21%** | | | | | | | Park RF & RG Rees, 1989, Table 5 |
| | | | | | | | 11,2 [f] | 14,5 [f] | **29%** | | | | | | | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 11,8 [f] | 14,5 [f] | **23%** | | | | | | | |
| *P. striiformis* | Wheat | 3 | 1 | | | | 12,5 [f] | 18,2 [f] | **46%** | | | | | | | Quan W et al., 2013, Table 3 |
| | | | | | | | 12,5 [f] | 17,8 [f] | **42%** | | | | | | | |
| | | | | | | | 13,2 [f] | 19,2 [f] | **45%** | | | | | | | |
| | | 5 | 1 | | | | 12,5 [f] | 18,8 [f] | **50%** | | | | | | | |
| *P. striiformis* | Wheat | 11 | 1 | | | | 319,2 [g] | 460,8 [g] | **44%** | 64,86 [h] | 19,45 [h] | **-70%** | | | | Sørensen CK et al., 2014, Fig 2 |
| | | | 1 | | | | 319,2 [g] | 465,6 [g] | **46%** | 71,35 [h] | 10,81 [h] | **-85%** | | | | |
| *P. striiformis* | Wheat | 11 | 1 | | | | 12,5 [f] | 20,1 [f] | **61%** | | | | | | | Ma H & RP Singh, 1996, Table 3 |
| | | | | | | | 12,6 [f] | 17,5 [f] | **39%** | | | | | | | |
| *P. recondita* | Wheat | 3 | 1 | | | | 8,3 | 8,8 | **6%** | 600,22 [j] | 214,51 [j] | **-64%** | 17,8 | 14,2 | **-20%** | Tomerlin JR et al., 1983, Table 1 & 2 |
| | | | | | | | 10,1 | 11,6 | **15%** | 83,69 [j] | 19,91 [j] | **-76%** | 37,3 | 33,9 | **-9%** | |
| | | | | | | | 8,3 | 9,1 | **10%** | 160,78 [j] | 48,85 [j] | **-70%** | 21,4 | 18,3 | **-14%** | |
| *P. triticina* | Wheat | 4 | 1 | | | | 149 [d] | 177 [d] | **19%** | | | | | | | Rimé D et al., 2005, Fig 1 |
| *P. triticina* | Wheat | 5 | 7 | | | | 7,75 | 12,60 | **63%** | | | | | | | Lehman JS & G Shaner, 1998, Fig 1 |

[a] in black a review of the literature, in green and blue experiments carried out in field and greenhouse conditions, respectively.

[b] lesion density (nb lesions/surf. unit).

[c] germination rate (prop. germinated spores).

[d] latent period measured in hours.

[e] latent period measured in degree-days.

[f] latent period measured with the nb. of days until first sporulating lesions.

[g] latent period measured with the nb. of hours until first sporulating lesions.

[h] lesion size (surface or distance unit).

[i] total sporulation per lesion (mass unit of spores/lesion).

[j] computed from total sporulation per lesion / sporulation duration (nb spores/lesion/day).