

# 1 Taking advantage of pathogen 2 diversity and immune priming to 3 minimize disease prevalence in 4 host mixtures: a model

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12 **Abstract** Host mixtures are a promising method for agroecological plant disease  
13 control. Plant immunity is key to the success of host mixtures against polymorphic  
14 pathogen populations. This results from priming-induced cross-protection, whereby  
15 plants able to resist infection by specific pathogen genotypes become more  
16 resistant to other pathogen genotypes. Strikingly, this phenomenon was thus far  
17 absent from mathematical models aiming at designing host mixtures. We  
18 developed a model to specifically explore how priming affects the coexistence of  
19 two pathogen genotypes in host mixtures composed of two host genotypes, and  
20 how it impacts disease prevalence. The main effect of priming is to reduce the  
21 coexistence region in the parameter space (due to cross protection), and to  
22 generate a singular mixture of resistant/susceptible hosts corresponding to the  
23 maximal reduction disease prevalence (in absence of priming, a resistant pure  
24 stand is optimal). The epidemiological advantage of host mixtures over a resistant  
25 pure stand thus appears as a direct consequence of immune priming. We also  
26 showed that there is indirect cross-protection between host genotypes in a mixture.  
27 Moreover, the optimal mix prevents the emergence of a resistance-breaking  
28 pathogen genotype. Our results highlight the importance of considering immune  
29 priming to design optimal and sustainable host mixtures.

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31 **Keywords:** cultivar mixtures, gene-for-gene, virulence, avirulent, polymorphism, induced  
32 resistance, systemic acquired resistance, priming

## 33 **1 Introduction**

34 Growing awareness of the negative impacts of pesticides on biodiversity and hu-  
35 man health is increasingly driving the development of more sustainable methods to  
36 control plant diseases (Matthews, 2015). Until now, the main alternative to using  
37 pesticides against plant pathogens has been to breed genetically resistant plant va-  
38 rieties or cultivars and deploy them as pure stands (Wolfe and Ceccarelli, 2020). Un-  
39 der these conditions, pathogen populations often evolve and break down resistance  
40 genes after a few years, while a breeding program may require a least a decade  
41 (Brown, 2015; Zhan et al., 2015). More lasting control methods will require manag-  
42 ing genetic resistances in time (Bargués-Ribera and Gokhale, 2020; Nilusmas et al.,  
43 2020), and/or in space (Fabre et al., 2012, 2015; Djidjou-Demassee et al., 2017; Pa-  
44 païx et al., 2018; Rimbaud et al., 2018b,a; Rousseau et al., 2019; Watkinson-Powell  
45 et al., 2019; Burdon et al., 2020).

46 Host mixtures are one of the possible methods to achieve host diversification in  
47 space. They consist in growing several varieties of the same plant species in the  
48 same field and at the same time (Wolfe, 1985; Mundt, 2002). Host mixtures are or  
49 have been used against plant pathogens in various regions of the world, including  
50 Asia, Europe and North America (Finckh et al., 2000; Zhu et al., 2000; Mundt, 2002;  
51 Han et al., 2016; Reiss and Drinkwater, 2018). In the Yunnan province of China, a  
52 large-scale experiment on rice blast was carried out over two years with thousands  
53 of farmers (Zhu et al., 2000). Disease-susceptible rice varieties were planted in two-  
54 component mixtures with resistant varieties. The effectiveness was such that the  
55 fungicide treatments could be stopped in the following year. The overall prevalence  
56 (more specifically the percentage of rice stems that were showing symptoms) was  
57 reduced by 94% compared to pure stands. Although host mixtures have long been  
58 studied both theoretically (Kampmeijer and Zadoks, 1977; Jeger et al., 1981a; Oht-  
59 suki and Sasaki, 2006) and experimentally (Jeger et al., 1981b; Wolfe, 1985; Zhu  
60 et al., 2000; Ben M'Barek et al., 2020), their design remains to be optimized to be  
61 more widely and efficiently used (Mikaberidze et al., 2015).

62 Host mixtures are often composed of resistant and susceptible plants in which  
63 resistance is qualitative, meaning that infection either succeeds or fails (as opposed  
64 to quantitative resistance, which only partially decreases the success of infection).

65 The majority of studies of mixtures of quantitatively resistant host genotypes have  
66 shown relatively low levels of disease control (Mundt, 2002). By contrast, the Yunnan  
67 large-scale experiment mixed qualitatively resistant and susceptible varieties (Zhu  
68 et al., 2000). Qualitative resistance is often conferred by major resistance genes  
69 and driven by gene-for-gene interactions (Flor, 1971; Milgroom, 2015). Pathogen  
70 genotypes can then be classified into two types: the resistance-breaking (virulent)  
71 type, which can successfully infect both resistant and susceptible hosts, and the wild  
72 (avirulent) type, which can successfully infect susceptible hosts only. In biotrophic  
73 pathogens (those feeding on living host tissues), an interaction between a wild-type  
74 pathogen and a resistant genotype generally triggers a hypersensitive response: the  
75 plant blocks the infection process by killing its own cells around the point of infection.

76 Such a strong defense response may result in the plant being primed against fu-  
77 ture infections. Immune priming is defined as increased defense to pathogen infec-  
78 tions following previous exposure to a pathogen or an elicitor (Tidbury et al., 2012).  
79 In the plant disease epidemiology literature, and in particular in host mixtures with  
80 gene-for-gene interactions, priming corresponds to the elicitation of specific defense  
81 responses which can lead to “induced resistance” (Lannou et al., 1995; Tellier and  
82 Brown, 2008). These defense responses include in particular the Systemic Acquired  
83 Resistance (SAR) (Vallad and Goodman, 2004; Walters et al., 2005; Conrath, 2011;  
84 Pastor et al., 2013). SAR is systematically induced when the aerial tissues of resis-  
85 tant plants are tentatively infected by a wild-type biotrophic pathogen (Ross, 1961;  
86 Vlot et al., 2008). This defense mechanism involves the activation of signaling path-  
87 ways (usually the salicylic acid pathway in the case of biotrophic pathogen infec-  
88 tions; Pastor et al. (2013)), allowing SAR to be triggered and active in the entire  
89 plant (Cameron et al., 1999; Mishina and Zeier, 2007). SAR effects are long-lasting,  
90 and confer partial resistance against subsequent attacks by a broad spectrum of  
91 pathogens, including viruses, bacteria, and fungi (Verberne et al., 2000; Durrant and  
92 Dong, 2004; Mishina and Zeier, 2007). From now on, for the sake of generality and  
93 to avoid confusion with constitutive resistance mechanisms, we will use the term  
94 “priming” to denote “induced resistance”.

95 The epidemiological effectiveness of mixtures of resistant and susceptible plants  
96 can be explained by three main mechanisms (Wolfe, 1985; Mikaberidze et al., 2015):

97 (i) dilution of susceptible hosts in space, (ii) interception of pathogen transmission  
98 forms by resistant hosts (so-called “barrier effect”), and (iii) priming of resistant  
99 hosts by wild-type pathogen genotypes. For instance, in the Yunnan large-scale  
100 experiment, the prevalence was reduced from 20% to 1% on susceptible varieties in  
101 mixtures compared to pure stands. This suggests that resistant varieties indirectly  
102 protected susceptible varieties at the population scale, as expected from dilution and  
103 barrier effects. More surprisingly, the prevalence on resistant varieties significantly  
104 decreased from 2.3% to 1% in mixtures compared to pure stands. This means that  
105 susceptible varieties somehow protected resistant varieties, which may be due to a  
106 priming effect (Zhu et al., 2000). From a broader perspective, priming is considered  
107 as a key to the success of host mixtures. This is because the wild-type pathogen  
108 produces little or no symptoms on resistant hosts but triggers a long-lasting immune  
109 response protecting against subsequent infections from other pathogen genotypes  
110 (Lannou et al., 1995; Calonnec et al., 1996). However, priming was thus far mostly  
111 absent from mathematical models aiming at designing host mixtures.

112 This theoretical study aims at exploring the impact of priming on the efficiency of  
113 host mixtures against plant diseases. By means of mathematical analyses of a par-  
114 simonious model, we analyzed under which conditions the wild-type and resistance-  
115 breaking pathogen genotypes can coexist, and whether we can take advantage of  
116 pathogen diversity and priming to minimize disease prevalence. In particular, we  
117 explored whether susceptible hosts indirectly protect resistant hosts in a mixture,  
118 as experimentally observed (Chin and Wolfe, 1984; Zhu et al., 2000), and to what  
119 extent this effect is related to immune priming.

## 120 **2 Modelling**

121 We consider a mixture of susceptible and resistant plant hosts. Note that in plant  
122 pathology, the term “susceptible” means the opposite of resistant. We will stick  
123 to this terminology and we will refer to “uninfected” plants when it comes to epi-  
124 demiology. However, uninfected plants will be denoted as  $S$ , in accordance with the  
125 reference SIR model in epidemiology. We will consider a continuous-time model with  
126 continuous planting and replanting best adapted to perennial crops in tropical re-

127 gions (Madden et al., 2007). More specifically, we consider that the host is present  
128 yearlong and we ignore seasonality in climatic conditions for simplicity. This will al-  
129 low us to identify the general mechanisms promoting the success (or failure) of host  
130 mixtures, which are expected to hold in annual crops as well.

131 We define as  $0 \leq p \leq 1$  the proportion of resistant hosts in the mixture;  $1-p$  is the  
132 proportion of susceptible hosts. As we are interested in epidemiological dynamics in  
133 an agricultural context,  $p$  is assumed to be a constant. This parameter is a control  
134 variable in the hands of the grower.

135 We assume the resistance-breaking (RB) pathogen genotype incurs a cost which  
136 reduces its transmission rate by a factor  $0 \leq c \leq 1$  relative to the wild-type (WT).  
137 The idea of a cost as a counterpart to the ability of breaking a resistance gene  
138 originated as a theoretical hypothesis to explain the often observed maintenance  
139 of polymorphism in pathogen populations, in both agricultural and wild ecosystems  
140 (Vanderplank, 1968; Sasaki, 2000; Gandon et al., 2002; Tellier and Brown, 2007;  
141 Brown, 2015). Since then, such a cost has been demonstrated and measured in a  
142 number of parasites, including bacteria (Cruz et al., 2000; Wichmann and Bergelson,  
143 2004), fungi (Carson, 1998; Thrall and Burdon, 2003; Bahri et al., 2009; Huang et al.,  
144 2010; Caffier et al., 2010; Bruns et al., 2014; Bousset et al., 2018), viruses (Jenner  
145 et al., 2002; Janzac et al., 2010; Fraile et al., 2010; Poulicard et al., 2010; Ishibashi  
146 et al., 2012; Khatabi et al., 2013), nematodes (Castagnone-Sereno et al., 2007) and  
147 oomycetes (Montarry et al., 2010).

148 We assume that priming reduces the probability that a resistant host is infected  
149 by a RB genotype by a factor  $0 \leq \rho \leq 1$  (priming effect). Priming is effective relatively  
150 rapidly: a few days after pathogen inoculation in experiments (Ross, 1961; Maleck  
151 et al., 2000). Note that priming can be fully effective (Kuć, 1982). In such a case  
152 ( $\rho = 1$ ), the RB genotype cannot infect the primed resistant hosts as long as priming  
153 is active.

154 The rate at which priming loses its effectiveness is  $\gamma$ . It corresponds to the inverse  
155 of the mean time during which priming is effective. Several studies have shown  
156 that SAR can last for several weeks. The original one (Ross, 1961) estimates that  
157 it persists for 20 days, but more recent reports show that it can last for weeks to  
158 months (Kuć, 1982; Fu and Dong, 2013).

159 We assume that infected hosts remain infectious until harvest, as is the case for  
 160 most plant viruses and many other parasites. The rate at which a host is replaced  
 161 with an uninfected one (due to harvesting and replanting) is  $\alpha$ . It corresponds to the  
 162 inverse of the length of the growing period.

163 We assume that the total host density  $N$  is constant. Since the proportion of  
 164 resistant hosts is  $\rho$ , the total density of resistant host is  $N_r = \rho N$ , and the total  
 165 density of susceptible hosts is  $N_s = (1 - \rho)N$ . The density of uninfected susceptible  
 166 host is  $S_s$ . The density of uninfected resistant host is  $S_r$ . The density of resistant host  
 167 primed by the WT is  $S_r^*$ . Priming makes resistant hosts partially immune to the RB  
 168 genotype until its effect vanishes (Fig. 1). The density of susceptible hosts infected  
 169 by the WT is  $I_s$ . The densities of susceptible and resistant hosts infected by the RB  
 170 genotype are  $J_s$  and  $J_r$ , respectively. Although susceptible plants may be co-infected  
 171 by the WT and the RB genotype, we do not allow for coinfections for simplicity. We  
 172 have  $S_s = N_s - I_s - J_s$ , and  $S_r = N_r - S_r^* - J_r$ . The transmission rate of the WT is  $\beta$ . The  
 173 forces of infection of the WT and RB genotypes are therefore, respectively:  $F = \beta I_s$ ,  
 174 and  $G = (1 - c)\beta(J_s + J_r)$ . The model is formulated as a system of ordinary differential  
 175 equations, in which the dot denotes differentiation with respect to time  $t$ :

$$\begin{aligned}
 \dot{I}_s &= F S_s - \alpha I_s, \\
 \dot{S}_r^* &= F S_r - (1 - \rho) G S_r^* - (\gamma + \alpha) S_r^*, \\
 \dot{J}_s &= G S_s - \alpha J_s, \\
 \dot{J}_r &= G S_r + (1 - \rho) G S_r^* - \alpha J_r.
 \end{aligned} \tag{1}$$

176 We re-scale variables and parameters according to

$$x = \frac{I_s}{N}, \quad m = \frac{S_r^*}{N}, \quad y = \frac{J_s}{N}, \quad z = \frac{J_r}{N}, \quad t^* = \alpha t, \quad R = \frac{\beta N}{\alpha}, \quad \nu = \frac{\gamma + \alpha}{\alpha} \geq 1.$$

177 Biologically, the parameter  $R$  corresponds to a basic reproduction number (Mad-  
 178 den et al., 2007). This is the mean number of secondary infections produced by a  
 179 pathogen able to infect  $N$  hosts with transmission rate  $\beta$  during an average time  $1/\alpha$ .  
 180 From now on, we assume  $R > 1$ , otherwise the pathogen would go extinct.

181 We define the total prevalence of the disease as the proportion of infected hosts  
 182 in the plant population:  $P = (I_s + J_s + J_r)/N = x + y + z$ . The prevalences of the WT and

183 RB genotypes are defined as  $P_w = I_s/N = x$  and  $P_b = (J_s + J_r)/N = y + z$ , respectively.  
 184 In addition, we define the total prevalences in susceptible and resistant host sub-  
 185 populations as  $P_s = (I_s + J_s)/N_s = (x + y)/(1 - p)$ , and  $P_r = J_r/N_r = z/p$ , respectively.  
 186 Lastly, we define the Area Under Disease Progress Curve (AUDPC) as:

$$A_{UDPC}(t) = \int_0^t P(\tau) d\tau. \quad (2)$$

187 The AUDPC is a standard metric to summarize the epidemic size at time  $t$  as it  
 188 takes into account the speed at which the epidemic spread from time zero to time  $t$   
 189 (Madden et al., 2007).

190 Model (1) can be formulated in dimensionless form, where the prime denotes  
 191 differentiation with respect to  $t^*$ :

$$\begin{aligned} x' &= Rx[(1-p) - x - y] - x, \\ m' &= Rx(p - m - z) - (1-p)(1-c)R(y+z)m - \nu m, \\ y' &= (1-c)R(y+z)[(1-p) - x - y] - y, \\ z' &= (1-c)R(y+z)(p - m - z) + (1-p)(1-c)R(y+z)m - z. \end{aligned} \quad (3)$$

192 Model (3) has four biologically possible equilibria:

- 193 •  $(0, 0, 0, 0)$ : the disease (pathogen)-free equilibrium. The prevalence is  $P = 0$ .
- 194 •  $(\hat{x}, \hat{m}, 0, 0)$ : the WT-only equilibrium, which is biologically possible if and only if  
 195  $R(1-p) > 1$ . The associated prevalence is  $P_{WE} = (1-p) - 1/R$ .
- 196 •  $(0, 0, \hat{y}, \hat{z})$ : the RB-only equilibrium, which is biologically possible if and only if  
 197  $R(1-c) > 1$ . The associated prevalence is  $P_{RB} = 1 - 1/[R(1-c)]$ .
- 198 • The coexistence equilibrium  $(\bar{x}, \bar{m}, \bar{y}, \bar{z})$  is biologically possible if and only if

$$\left\{ c > p \text{ and } p(1-c)R - c > 0 \text{ and } \rho < \frac{[p(1-c)R - c][(1-p)R + \nu - 1]}{[R(1-p) - 1](1-c)R\rho} \right\}, \quad (4)$$

199 see Supplementary Information (Section S2).

200 Biologically,  $R(1-p)$  and  $R(1-c)$  are the basic reproduction numbers of the WT  
 201 and RB genotypes, respectively. The above set of conditions implies  $R(1-p) > 1$

202 and  $R(1-c) > 1$ , meaning that for the coexistence equilibrium to be biologically  
 203 possible, both the WT and the RB genotypes must be able to invade when alone.

204 The associated prevalence is

$$P_{CE} = \frac{[(1-p)R + \nu - 1][(1-c)R - 1] - \rho(1-c)R[R(1-p) - 1]}{(1-c)R[(1-\rho)(1-p)R + \nu - 1]}. \quad (5)$$

### 205 3 Results

206 **Conditions for polymorphism persistence in the pathogen population.** Fig. 2  
 207 shows the outcome of the competition for susceptible hosts between the WT and the  
 208 RB genotype in the parameter space  $(p, c)$ , for representative values of  $R$ ,  $\rho$  and  $\nu$   
 209 (see Fig. S1 for additional parameter sets). The polymorphism region is delimited  
 210 by the conditions (4) of biological feasibility of the coexistence equilibrium. In that  
 211 region, we proved (Supplementary Section S4) that the coexistence equilibrium is  
 212 globally asymptotically stable, meaning that the dynamics converge to this equi-  
 213 librium regardless the initial conditions. This implies that complex dynamics such  
 214 as cycles or chaos cannot occur in this model. Therefore, polymorphism is stable  
 215 in the pathogen population. Both the WT and the RB genotype can persist without  
 216 excluding each other, although they compete for susceptible hosts.

217 **Disease prevalence as a function of the proportion of resistant hosts**  
 218 **and priming.** In Figure 3B,  $p^*$  is a threshold value separating the WT-only region  
 219 from the coexistence (middle) region (i.e., the solution of  $P_{CE} = P_{WT}$ ). For  $p < p^*$ , the  
 220 WT competitively excludes the RB genotype (Fig. 2). In this region, the prevalence  
 221 ( $P_{WT} = 1 - p - 1/R$ ) decreases linearly with respect to  $p$ . For  $p > c$ , the RB genotype  
 222 competitively excludes the WT (Fig. 2). Since susceptible and resistant hosts are  
 223 equally susceptible to the RB genotype in the RB-only region, the disease prevalence  
 224 in the latter region is a constant ( $P_{RB} = 1 - 1/[R(1-c)]$ ) whenever  $c < p < 1$ .

225 In the absence of priming (specific case  $\rho = 0$ , dashed line), the prevalence in  
 226 the coexistence (middle) region is equal to the prevalence in the RB-only region (i.e.  
 227  $P_{CE} = P_{RB}$ ). If  $\rho = 0$ , we define  $\hat{p} = c/[R(1-c)]$  such that  $P_{WT} = P_{CE} = P_{RB}$ . The WT  
 228 and the RB genotypes actually coexist for all  $p \in (\hat{p}, c)$ . In the absence of priming,  
 229 susceptible and resistant hosts are equally susceptible from the RB genotype per-



230 spective (in the coexistence and RB-only regions). Consequently, the growth rate of  
231 the RB genotype only depends on available hosts ( $1 - P$ ), regardless of whether the  
232 WT persists or not. This is why the equilibrium prevalence ( $P$ ) is a constant in the  
233 regions where the RB genotype persists.

234 Taking priming into account ( $\rho > 0$ , solid line), the coexistence interval is reduced  
235 as the WT outcompetes the RB genotype for all  $p \in (\hat{p}, p^*)$ . In the WT-only region, the  
236 prevalence decreases down to  $p^*$ . In the adjacent coexistence region, the prevalence  
237 increases up to that in the RB-only region. The prevalence is then not a constant in  
238 the coexistence region, since uninfected and primed hosts are not equally suscep-  
239 tible from the RB genotype perspective and their equilibrium ratio depends on the  
240 proportion of resistant plants  $p$ .

241 As a result, priming (solid line) generates an optimal intermediate proportion of  
242 resistant host  $p^*$  that minimizes the disease prevalence  $P$ . In the absence of priming  
243 (dashed line), any  $p \in (\hat{p}, 1)$  minimizes the prevalence, meaning that host mixtures  
244 will not perform better than a pure stand of resistant hosts. The existence of an  
245 optimal host mixture is therefore a direct consequence of priming. Note that for a  
246  $p$  just below  $p^*$ , the RB genotype cannot invade. Decreasing  $R$  and/or increasing  $\rho$   
247 increases the optimal proportion  $p^*$ , which is a critical threshold to prevent the RB  
248 genotype emergence (supplementary Section S1).

249 **Transient dynamics and optimal mixtures in terms of both prevalence**  
250 **and AUDPC.** Figure 4 shows the prevalence  $P$  and the Area Under Disease Progress  
251 Curve ( $A_{UDPC}$ ) over time as a function of the proportion of resistant hosts  $p$ , with  
252 and without priming. Initially ( $0 \leq t \leq 3$  growing periods in Fig. 4 the prevalence  
253 and AUDPC are the same regardless whether priming occurs ( $\rho > 0$ ) or not ( $\rho =$   
254  $0$ ). In both cases, the optimal strategy (minimizing both  $P$  and  $A_{UDPC}$ ) is to use  
255 resistant hosts only ( $p = 1$ ). This is because in the initial phase of the epidemic, the  
256 probability that a RB genotype enters into contact with a primed host is very small.  
257 Mathematically, this translates into the largest eigenvalue of the linearized system  
258 evaluated at disease-free equilibrium being independent of parameters associated  
259 with priming ( $\rho$  and  $\nu$ ), see supplementary section S2.3.1. After this initial phase ( $t >$   
260  $3$  growing periods in Fig. 4), the prevalence of the disease becomes sufficiently large  
261 for priming to have a significant effect on the epidemiological dynamics. Therefore,

262 the optimal strategy is to mix resistant and susceptible hosts. The optimal mixture  
263 is approximately the same in terms of both prevalence and AUDPC. As time goes on,  
264 the optimal mix converges towards  $p^*$  (the optimal proportion of resistant plants at  
265 equilibrium). Overall, these numerical explorations show that our results hold well  
266 before reaching equilibrium, provided the epidemiological dynamics have passed an  
267 initial phase.

268 **Protection of resistant hosts in the mixture by priming.** Figure 5 shows the  
269 cumulated prevalences in susceptible and resistant hosts ( $P_s$  and  $P_r$ ) as a function  
270 of the proportion of resistant hosts  $p$ , with and without priming.

271 Let us start by considering the case with no priming ( $\rho = 0$ ). Starting from the  
272 RB-edge of the coexistence region and decreasing  $p$  decreases the prevalence of the  
273 RB genotype  $P_b$  (Fig. 5A). This is because the RB genotype actually competes with  
274 the WT for susceptible hosts but incurs a cost. As a result, the total prevalence in the  
275 resistant host ( $P_r$ ) decreases as well (Fig. 5A). Therefore, there is indirect protection  
276 of resistant hosts by susceptible hosts in the coexistence region. Since resistant  
277 hosts indirectly protect susceptible hosts by being unavailable for the WT, there is  
278 then indirect cross-protection between susceptible and resistant hosts.

279 Taking priming into account ( $\rho > 0$ ) does not change the prevalence in the sus-  
280 ceptible host  $P_s$  (Fig. 5B). By contrast, the slope of  $P_r$  is steeper and occurs on a  
281 narrower interval, corresponding to a smaller coexistence region. That happens be-  
282 cause presence of the WT leads to a certain proportion of the resistant population  
283 to be primed and hence less conducive to the RB genotype. By priming, the WT  
284 can decrease host availability of the RB genotype and outcompete it. Therefore,  
285 the WT outcompetes the RB genotype faster with the help of priming as  $p$  is de-  
286 creased, which creates a narrower coexistence region. Likewise, the prevalences of  
287 the WT ( $P_w$ ) and of the RB genotype ( $P_b$ ) are qualitatively the same as in the case  
288 with no priming, even though their slopes are steeper in the smaller coexistence  
289 region (Fig. 3B). Overall, priming has no qualitative effect on the prevalences in re-  
290 sistant and susceptible hosts. Host mixtures generally decrease the prevalences in  
291 susceptible and resistant hosts compared to pure stands ( $p = 0$  and  $p = 1$ , resp.),  
292 regardless of whether priming occurs or not. Quantitatively however, priming ex-  
293 acerbates the effect of mixtures regarding the prevalence in resistant hosts as the

294 decrease is sharper than in the absence of priming.

## 295 **4 Discussion**

296 Developing new or preexisting methods based on bio-diversification forms the basics  
297 of agroecology (Altieri, 2018); host mixtures are one of these. Indeed, mixtures  
298 involving at least one host with gene-for-gene resistance have shown a strong ability  
299 to decrease disease prevalence compared to pure stands (Garrett and Mundt, 1999)  
300 and are a promising alternative to the unstable dynamics commonly observed in  
301 gene for gene systems (the famous “boom and bust” cycles; Wolfe (1985)).

302 Our study not only confirmed the theoretical effectiveness of genetic host mix-  
303 tures against plant diseases, but allowed us to clearly disentangle the role of priming  
304 in this performance. In particular, we showed that the time during which priming  
305 is effective is a key parameter for mixture performance (Fig. S1F and Section S1).  
306 However, few references document its value. Our study encourages experiments  
307 designed to uncover priming duration in a variety of pathosystems. A key feature of  
308 our model is that the epidemiological dynamics necessarily converges to an equilib-  
309 rium state (Supplementary Section S4). As a corollary, complex dynamics such as  
310 cycles or chaos are impossible in our plant epidemic model with immune priming.  
311 This observation contrasts with a previous study reporting cycles in an animal epi-  
312 demic model with immune priming (Tidbury et al., 2012). From an epidemiological  
313 standpoint, immune priming in animals is comparable to immune priming in plants.  
314 Tidbury et al. (2012) considered a Susceptible-Primed-Infected model, and showed  
315 that cycles can occur if and only if infected hosts bear fecundity costs. Priming does  
316 not promote cycles unless host population dynamics are taken into account, which  
317 is consistent with our agricultural model, where we observed a globally stable equi-  
318 librium in a fixed host population. We showed that disease prevalence at equilibrium  
319 was minimized for an intermediate proportion of resistant hosts, which highlights  
320 the benefits that can be made by promoting host diversity over growing pure stands  
321 of either susceptible or resistant hosts. This proportion depends upon the cost of  
322 resistance-breaking, but also on the effectiveness of priming.

323 Moreover, the optimal proportion of resistant plants is also a critical threshold to

324 prevent the emergence of the resistance-breaking pathogen genotype, and hence  
325 resistance breakdown. Growing resistant varieties as pure stands increases the se-  
326 lection pressure on pathogen populations and thereby promotes the emergence of  
327 resistance-breaking pathogen genotypes. Once resistance is broken, the resistance-  
328 breaking pathogen genotype may invade and even outcompete the WT, (e.g. Flor,  
329 1971; Wolfe, 1985). To control the associated epidemics, breeders then select for  
330 new resistance genes and the cycle repeats until the genetic resource is depleted.  
331 This “boom and bust” cycle is thus often referred to as an “arms race” co-evolutionary  
332 pattern (Tellier and Brown, 2007). By decreasing the disease prevalence on the re-  
333 sistant component of the mixture, priming should actually protect resistant hosts  
334 during the epidemic, and increase the durability of the resistance gene. Unfortu-  
335 nately, there is at the moment little experimental evidence to confirm this theoreti-  
336 cal prediction, as few large scale experiments exist (Finckh et al., 2000), and fewer  
337 still with pathogen genotypic data. The stability of polymorphism is a central issue in  
338 host-parasite coevolution (Hamilton et al., 1990). It has been mainly addressed with  
339 population genetics models (Brown and Tellier, 2011), which focus on the frequen-  
340 cies of alleles in the host and parasite populations. Stable polymorphism requires  
341 negative direct frequency dependent selection (ndFDS), meaning that the frequency  
342 of an allele affects its own fitness (Tellier and Brown, 2007). A mechanism pro-  
343 moting ndFDS is intraspecific competition, namely negative density-dependence. In  
344 population genetics models, density-dependence is not considered explicitly. Mod-  
345 els combining epidemiology (i.e. demography) and population genetics checked the  
346 stability of polymorphism by numerical simulations (Gandon et al., 2002; Tellier and  
347 Brown, 2009; Zivković et al., 2019). Although our model addressed polymorphism in  
348 the pathogen population only, its stability was demonstrated mathematically. Con-  
349 sistent with a previous study (Tellier and Brown, 2008), priming indeed promotes  
350 the fixation of the wild-type and narrows the parameter range for coexistence.

351 We also showed that susceptible hosts indirectly protect resistant hosts, which  
352 was less expected than the opposite effect. In the Yunnan province large-scale ex-  
353 periment (Zhu et al., 2000), the disease prevalence in resistant varieties significantly  
354 and unexpectedly decreased in mixtures compared to pure stands. Disease reduc-  
355 tion on resistant hosts was interpreted as a possible effect of priming (Zhu et al.,

356 2000). Our study confirmed the potential effect of priming but also showed that  
357 priming is not necessary to explain this observation. The key point is that compe-  
358 tition between the wild-type and the resistance-breaking genotype for susceptible  
359 hosts generates apparent cross-protection between resistant and susceptible hosts.  
360 This is because increasing the density of susceptible hosts promotes the wild-type,  
361 which outcompetes the RB genotype on susceptible hosts and in that way protects  
362 resistant hosts. Therefore, although resistant hosts are protected by susceptible  
363 hosts even in the absence of priming, priming exacerbates indirect cross-protection.

364 The multiple effects of priming show that priming (provided it occurs) has the po-  
365 tential to significantly improve mixture performance. The fact that priming is more  
366 likely in gene-for-gene systems (implying a hyper-sensitive response) than in quan-  
367 titatively resistant cultivars may explain why most mixtures and multilines are de-  
368 signed with resistant components possessing major, race-specific resistance. How-  
369 ever, priming also occurs in cultivars with quantitative resistance, and may explain in  
370 part why mixtures involving this type of resistance also work (Andrivon et al., 2003).  
371 As a first step towards understanding the combined effects of genetic resistance  
372 and immune priming against plant diseases, we assumed a two-component mixture  
373 of a susceptible and a resistant host. Future research may consider a larger num-  
374 ber of components in the mixture (Mikaberidze et al., 2015). To begin with, a mix-  
375 ture of two distinct resistance genes with two single-resistance-breaking pathogen  
376 genotypes could be considered. This way, priming would occur in two directions  
377 (both host genotypes could be primed) and it is likely that the benefits in terms of  
378 prevalence would be even greater. Although the presence of an additional pathogen  
379 genotype capable of breaking both resistances (a “super-race”) might challenge this  
380 optimistic view (Groth, 1976; Lannou and Mundt, 1997; Carson, 2009), both sim-  
381 ulation and experimental evidence suggest that this risk might actually be limited  
382 (Barrett and Wolfe, 1978; Lannou et al., 2005; Xu, 2012) and strongly depends on  
383 resistance-breaking costs, i.e. relative fitness penalties on non-resistant hosts. Since  
384 priming actually reduces the fitness advantage of resistance breaking by decreasing  
385 the performance of these pathogen genotypes on the resistant host, it is expected  
386 to decrease the risk of emergence of such super races in complex mixtures. Explor-  
387 ing the stochastic emergence of resistant-breaking genotypes (Bourget et al., 2013;

388 Chabas et al., 2018) would offer additional insights into the sustainability of host  
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**Table 1. Acronyms, model variables and parameters**

Acronym	Definition
WT	Wild-type
RB	Resistance-breaking
AUDPC	Area Under Disease Progress Curve
Parameter	Definition
$p$	proportion of resistant hosts in the mixture: $p \in [0, 1]$
$c$	resistance-breaking cost: $c \in [0, 1]$
$\rho$	priming effect: $\rho \in [0, 1]$
$\gamma$	priming loss rate: $\gamma \geq 0$
$\alpha$	harvest and replanting rate: $\alpha > 0$
$\beta$	pathogen transmission rate: $\beta > 0$
$N$	total host population density: $N > 0$
$N_r$	resistant host population density: $N_r = pN$
$N_s$	susceptible host population density: $N_s = (1 - p)N$
$R$	basic reproduction number: $R = \beta N / \alpha > 1$
$\nu$	dimensionless parameter: $\nu = (\gamma + \alpha) / \alpha \geq 1$
Variable	Definition
$t$	time: $t \geq 0$
$I_s$	density of WT-infected susceptible hosts
$S_r^*$	density of primed resistant hosts
$J_s$	density of RB-infected susceptible hosts
$J_r$	density of RB-infected resistant hosts
$S_s$	density of uninfected susceptible hosts: $S_s = N_s - I_s - J_s$
$S_r$	density of uninfected resistant hosts: $S_r = N_r - S_r^* - J_r$
$F$	force of infection of the WT genotype: $F = \beta I_s$
$G$	force of infection of the RB genotype: $G = (1 - c)\beta(J_s + J_r)$
$x$	proportion of WT-infected susceptible hosts: $x = I_s / N$
$m$	proportion of primed resistant hosts: $m = S_r^* / N$
$y$	proportion of RB-infected susceptible hosts: $y = J_s / N$
$z$	proportion of RB-infected resistant hosts: $z = J_r / N$
$P$	total prevalence of infected hosts: $P = (I_s + J_s + J_r) / N = x + y + z$
$P_{WT}$	total prevalence at the WT-Only equilibrium: $P_{WT} = (1 - p) - 1/R$
$P_{RB}$	total prevalence at the RB-Only equilibrium: $P_{RB} = 1 - 1/[R(1 - c)]$
$P_{CE}$	total prevalence at the Coexistence equilibrium
$P_s$	total prevalence in susceptible hosts: $P_s = (I_s + J_s) / N_s = (x + y) / (1 - p)$
$P_r$	total prevalence in resistant hosts: $P_r = J_r / N_r = z / p$
$P_w$	prevalence of the WT genotype: $P_w = I_s / N = x$
$P_b$	prevalence of the RB genotype: $P_b = (J_s + J_r) / N = y + z$
$AUDPC$	Area Under Disease Progress Curve: $AUDPC(t) = \int_0^t P(\tau) d\tau$

Table 1

630 **Figure 1**

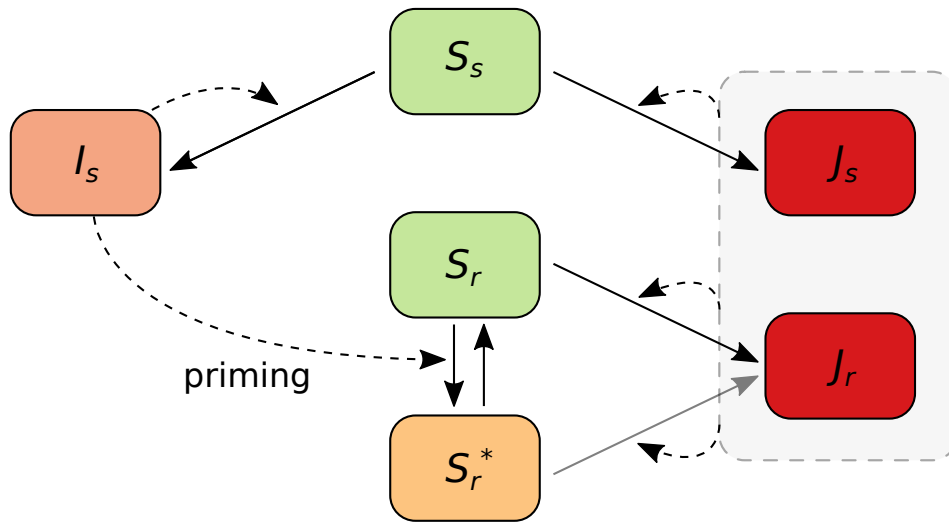


Figure 1: Simplified compartmental diagram for the epidemiological model described by equations (1). The model notations and their definitions are listed in Table 1.

631 **Figure 2**

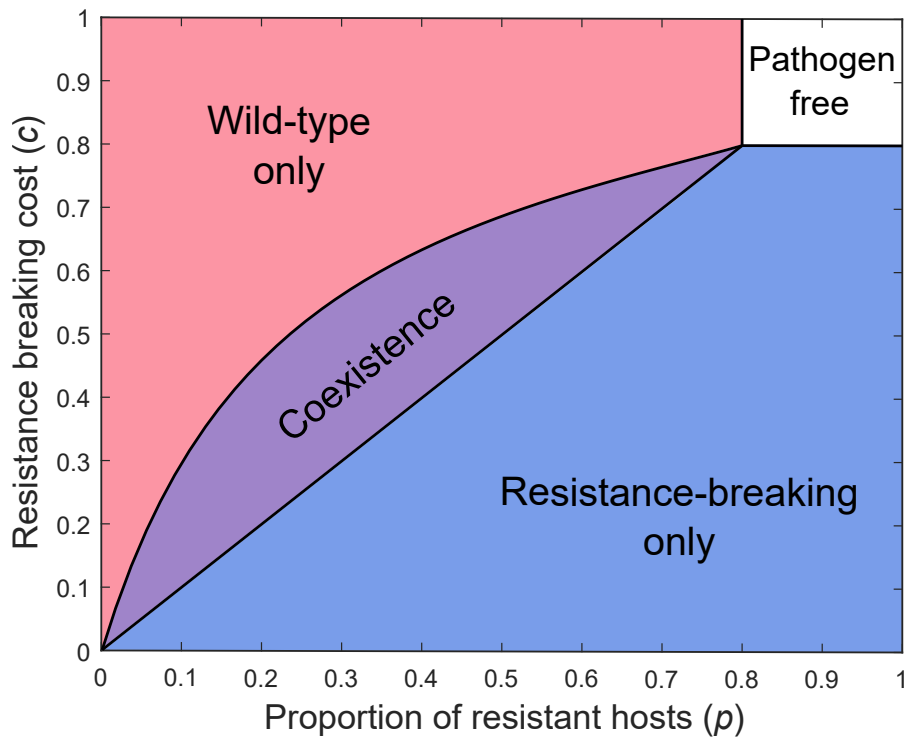


Figure 2: Epidemiological outcomes in the parameter space  $(p, c)$ . Other parameter values:  $R = 5$ ,  $\rho = 0.5$ , and  $\nu = 1$ . The model notations and their definitions are listed in Table 1.



632 **Figure 3**

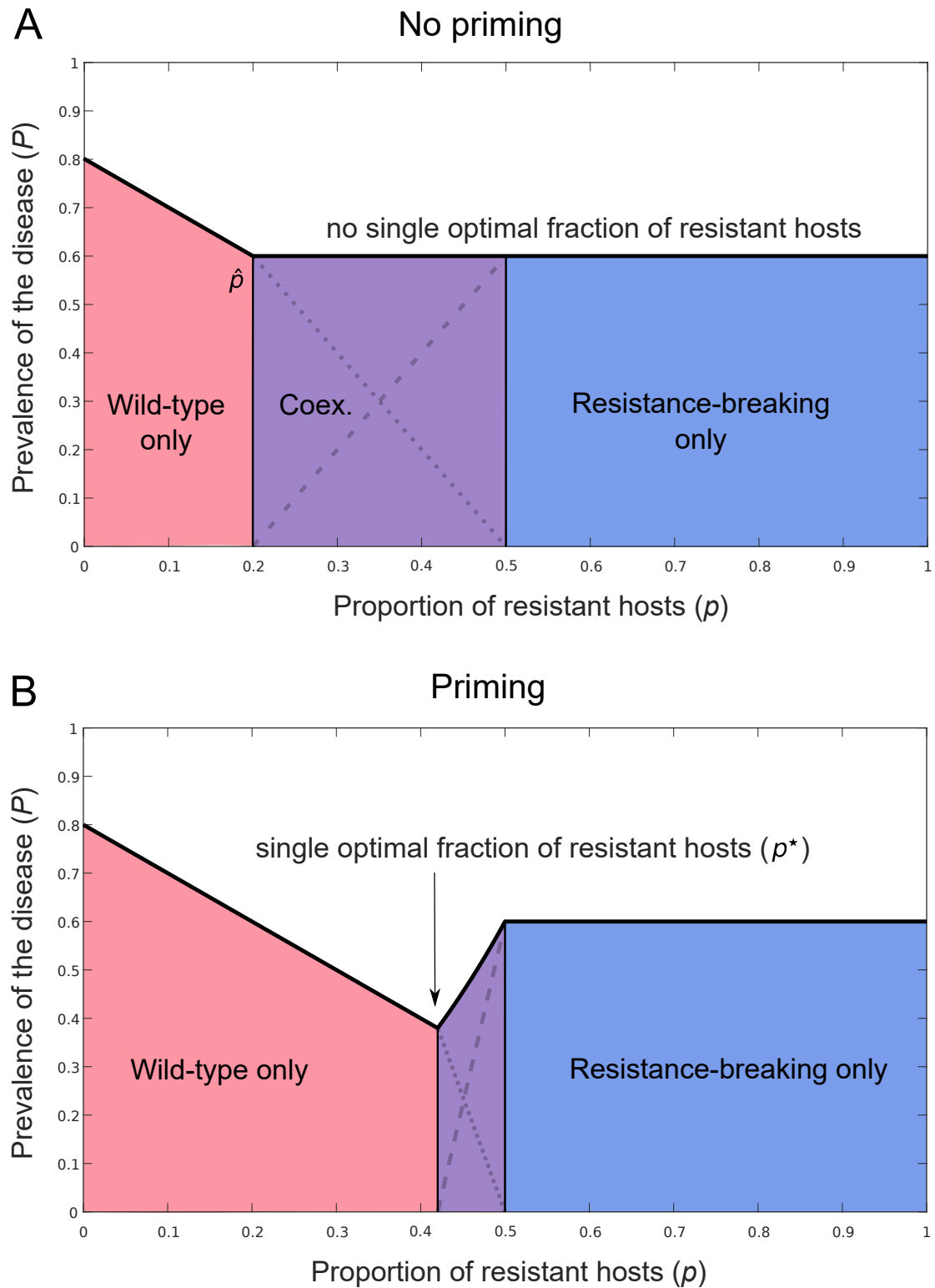


Figure 3: The total prevalence of the disease ( $P$ ) as a function of the proportion of resistant hosts  $p$ . Panel A shows the baseline without priming ( $\rho = 0$ ): all  $p$  such that  $\hat{p} \leq p \leq 1$  equally minimize the disease prevalence. Panel B shows the effect of priming ( $\rho = 0.8$ ): there is a single optimal fraction of resistant host  $p^*$ . Other parameter values:  $c = 0.5$ ,  $R = 5$ , and  $\nu = 1$ . The model notations and their definitions are listed in Table 1. The crossing lines in the coexistence region represent the prevalences of the WT ( $P_w$ : dotted line) and RB genotype ( $P_b$ : dashed line).

## Figure 4

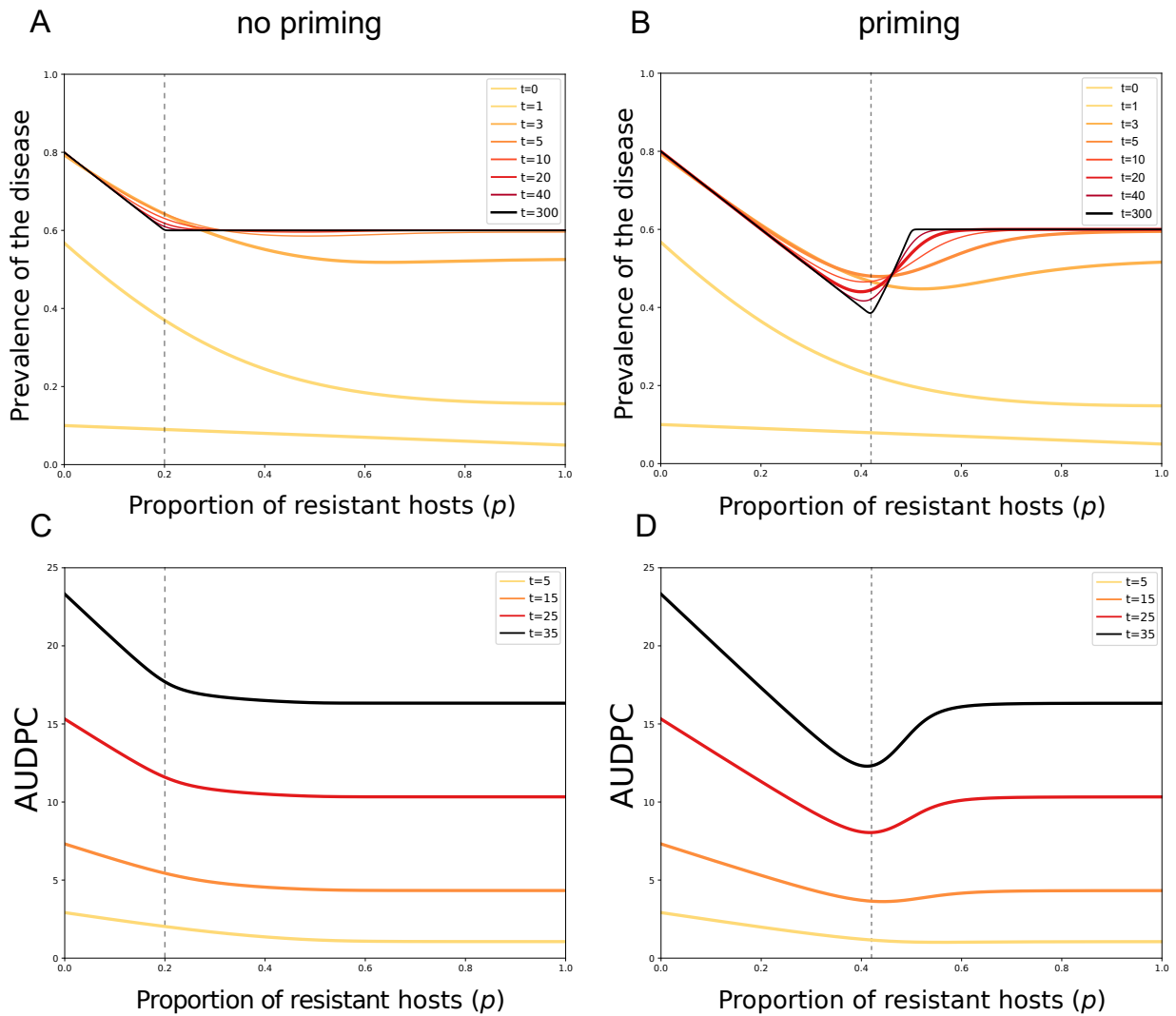


Figure 4: Prevalence of the disease ( $P$ ) and Area Under the Disease Progress Curve (AUDPC) over time and as a function of  $\rho$ , without priming (left column:  $\rho = 0$ ) and with priming (right column:  $\rho = 0.8$ ). Other parameter values:  $R = 5$ ,  $c = 0.5$  and  $\nu = 1$ . The initial conditions are  $I_s = 0.01(1 - \rho)/2$ ,  $S_r^* = 0.01\rho/2$ ,  $J_s = 0.01(1 - \rho)/2$  and  $J_r = 0.01\rho/2$ .

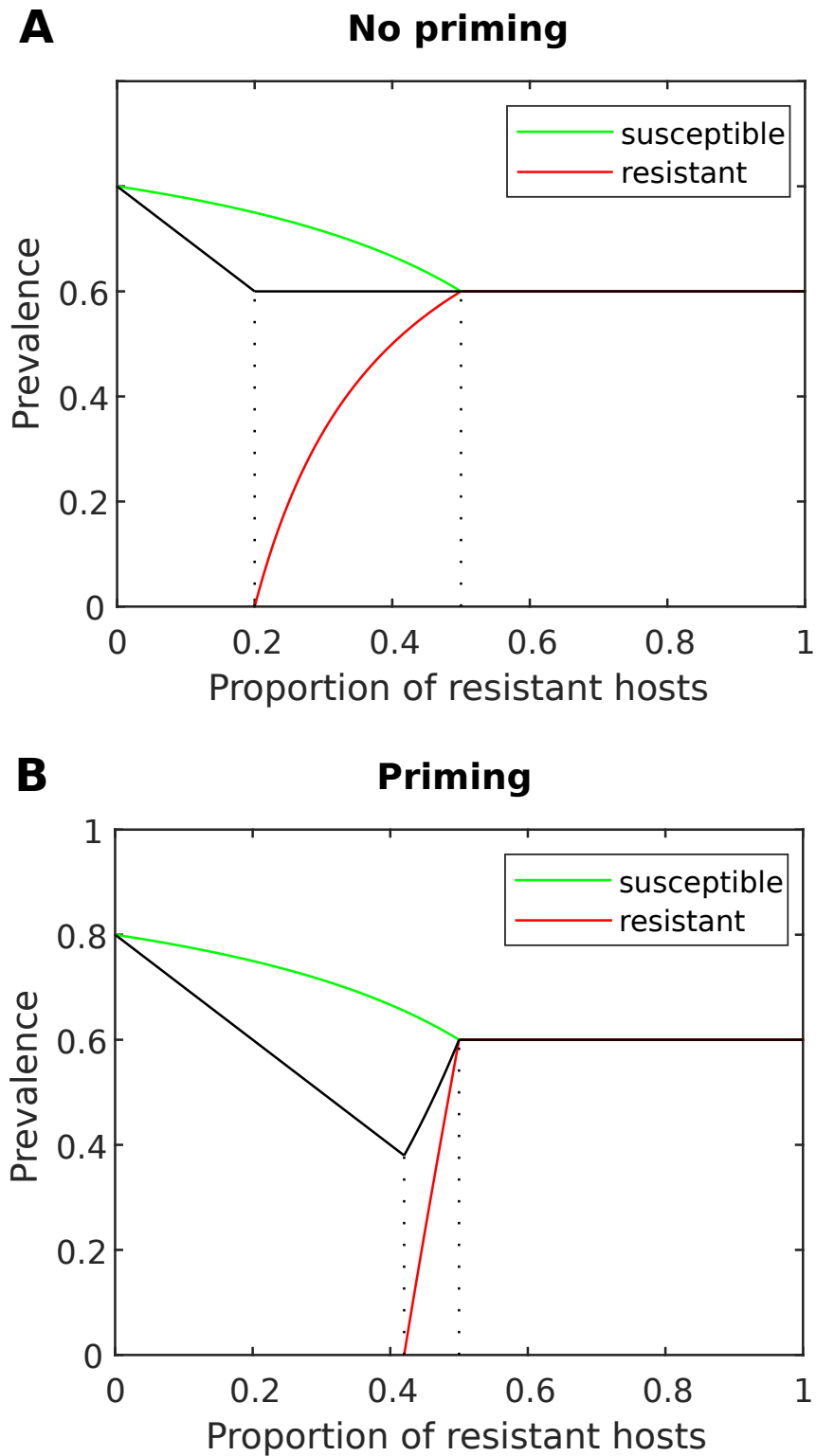
**Figure 5**

Figure 5: Prevalences in the host population as a function of the proportion of resistant hosts ( $p$ ). The black lines represent the total prevalence ( $P$ ). The green and red lines represent the prevalences in susceptible ( $P_s$ ) and resistant hosts ( $P_r$ ), respectively. The dotted vertical lines represent transitions from the WT-only, coexistence, and RB-only regions (Fig. 3). Panel A considers no priming ( $\rho = 0$ ), and Panel B takes priming into account ( $\rho = 0.8$ ). Other parameter values:  $c = 0.5$ ,  $R = 5$ , and  $\nu = 1$ . The model notations and their definitions are listed in Table 1.