

Developing smarter host mixtures to control plant disease

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How to develop smarter host mixtures to control plant disease?

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Running Head: Smarter host mixtures

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Abstract

1
2 Adaptation of plant pathogens to disease control measures (both chemical and genetic) is facilitated
3 by the genetic uniformity underlying modern agroecosystems. One path to sustainable disease
4 control lies through increasing genetic diversity at the field scale by using genetically diverse host
5 mixtures. We utilized a robust population dynamical approach to investigate how host mixtures
6 can improve disease control. We find that when pathogens exhibit host specialization, the overall
7 disease severity decreases with the number of components in the mixture. This finding makes it
8 possible to determine an optimal number of components to use in the host mixture. In a simple
9 case where two host varieties are exposed to two host-specialized pathogen species or strains we
10 identify quantitative criteria for optimal mixing ratios. Using these model outcomes, we propose
11 ways to optimize the use of host mixtures to decrease disease in agroecosystems.

12 Introduction

13 The two most widely used disease control measures are applications of chemicals (fungicides and
14 antibiotics) and breeding for disease resistant crop cultivars by incorporating resistance genes.
15 Both of these control measures are highly vulnerable to pathogen adaptation. Many pathogens
16 have repeatedly evolved to overcome resistance conferred by major resistance genes (reviewed in
17 (McDonald and Linde, 2002; Parlevliet, 2002; Singh et al., 2011)). Similarly, many fungicides
18 rapidly lose their efficacy because of the emergence and fixation of mutations encoding fungicide
19 resistance (e. g. (Torriani et al., 2009; Brunner et al., 2008). As a result of pathogen evolution,
20 the current commonly practiced disease control measures will likely be inadequate to enable a
21 sustainable intensification of food production.

22 Quantitative or partial resistance is thought to be more durable (Parlevliet, 2002; Papaïx et al.,
23 2011), but has not been as widely utilized as major gene resistance. Recent research has begun
24 to provide insights into the molecular mechanisms responsible for quantitative resistance (Poland
25 et al., 2009; Kou and Wang, 2010), but studies that include quantitative resistance in epidemiolog-
26 ical models are rare (Lo Iacono et al., 2012). Pathogens can still adapt to quantitative resistance
27 leading to an erosion of its effects (Stuthman et al., 2007; Mundt et al., 2002; McDonald and Linde,
28 2002; Lehman and Shaner, 1997), although at a much slower pace compared to major resistance
29 genes.

30 More effective and longer-lasting disease control methods are urgently needed to achieve a sus-
31 tainable intensification of crop production. One way to develop such methods is to focus on the
32 underlying properties of modern agricultural ecosystems (agroecosystems) that make them vul-
33 nerable to plant pathogens. Compared to natural ecosystems, agroecosystems are more environ-
34 mentally homogeneous, have a higher density of plants, and possess much less genetic and species

35 diversity. It is increasingly recognized that these underlying properties of agroecosystems, espe-
36 cially the lack of genetic diversity due to the dominance of monoculture crops grown as clones,
37 make them especially susceptible to disease epidemics (Mundt, 2002; Wolfe, 2000; Garrett and
38 Mundt, 1999).

39 For these reasons, many researchers propose to deliberately increase genetic diversity in agro-
40 cosystems (McDonald, 2014; Newton et al., 2009; Zhu et al., 2000) in order to decrease disease
41 in the short-term and enhance the durability of disease resistance in the long-term. This diversity
42 can be created within a single genetic background by developing multiline cultivars (Browning
43 and Frey, 1969) or involve many genetic backgrounds by using variety mixtures (Wolfe, 1985;
44 Smithson and Lenne, 1996; Mundt, 2002). In this study, we do not distinguish between multiline
45 cultivars and variety mixtures and we will refer to both options simply as host mixtures.

46 Many field experiments have been performed to determine whether host mixtures reduce the
47 amount of fungal disease on crop plants (e.g. (Huang et al., 2012; Ning et al., 2012; Newton and
48 Guy, 2011; Cowger and Mundt, 2002; Zhu et al., 2000; Newton et al., 1997; Mundt et al., 1994;
49 Chin and Wolfe, 1984), see also reviews (Walters et al., 2012; Mundt, 2002; Finckh et al., 2000;
50 Smithson and Lenne, 1996; Wolfe, 1985) and references therein). The findings of over 30 studies
51 (mostly in barley, wheat, rice and beans) were summarized in (Smithson and Lenne, 1996). The
52 vast majority of experiments showed less disease in mixtures as compared to the mean of the pure
53 stands for obligate pathogens such as rusts and mildews. However, there was a large variation in
54 the percentage of disease reduction: for example, between 9 % and 80 % for powdery mildew in
55 barley, and between 13 % and 97 % for stripe rust in wheat. A recent meta-analysis of stripe rust
56 on wheat considered 161 mixture cases reported in 11 publications (Huang et al., 2012). In 83 %
57 of these cases the average disease level was found to be lower in mixtures compared to the mean
58 of the pure stands. A reduction in disease of between 30 % and 50 % was found most frequently.

59 A large-scale study performed in China demonstrated that row mixtures of rice varieties could
60 strongly reduce rice blast (Zhu et al., 2000). Thus, host mixtures reduce the amount of disease
61 in most studied cases, but the outcomes exhibit a wide variation, even within a single study (for
62 example (Cowger and Mundt, 2002)).

63 This variation is one of the reasons why multilines and cultivar mixtures have so far gained little
64 acceptance among seed companies or growers. To achieve reliable disease control, we need to
65 identify the conditions under which mixtures work best and use this knowledge to design optimal
66 mixtures. This requires a better understanding of the underlying mechanisms of disease reduc-
67 tion in mixtures. Our study contributes to this understanding in three important ways by using a
68 population dynamics model of plant-pathogen interactions. First, we identified conditions where
69 mixtures are superior compared to pure stands. Second, we defined optimal ratios of components
70 to include in the mixture. Third, we determined optimal numbers of components to include in the
71 mixture.

72 This was done by exploring possible disease outcomes when two or more hosts are mixed in the
73 presence of two or more pathogen strains or species. Moreover, we obtained analytical solutions
74 that allowed us to investigate the disease reduction over the whole range of parameters that includes
75 both qualitative and quantitative host resistance (see Appendix A.5).

76 **Materials and methods**

77 We first consider a general case of a mixture with n hosts that is exposed to n pathogens. These
78 could be either different strains (races or pathotypes) of the same pathogen or different pathogen
79 species capable of infecting the same host tissue. The dynamics of the host-pathogen interactions
80 are described by the susceptible-infected model that consists of $2n$ equations:

$$81 \quad \frac{dH_i}{dt} = r_H(K_i - H_i) - \sum_{k=1}^n \beta_{ki} I_k H_i, \quad (1)$$

$$82 \quad \frac{dI_i}{dt} = \sum_{k=1}^n \beta_{ik} I_i H_k - \mu I_i, \quad i = 1, \dots, n \quad (2)$$

83

84 This model is an extension of the model described previously (Mikaberidze et al., 2014) for the case
85 of two pathogen strains infecting a single host variety. This model can be applied to a variety of
86 aerially and splash-dispersed, polycyclic pathogens of cereal crops, such as the fungi and bacteria
87 causing rusts, mildews, blasts, spots and blotches. There are $2n$ compartments in the model:
88 susceptible hosts H_i , hosts I_i infected by the pathogen i , where $i = 1, \dots, n$. The quantities H_i, I_i
89 represent the total amount of the corresponding host tissue within one field, which could be leaves,
90 stems or grain tissue, depending on the host-pathogen combination.

91 Susceptible hosts H_i grow with the same rate r_H . Their growth is limited by their “carrying
92 capacities” K_i , implying limitations in space or nutrients.

93 The matrix elements β_{ik} in Eqs. (1)-(2) constitute the transmission matrix \mathbf{B} , an $n \times n$ square
94 matrix [often called WAIFW (Who Acquires Infection From Whom) matrix]. The element β_{ik}
95 describes the transmission rate of the pathogen that originates from the infected host of type i and
96 infects the healthy host of variety k . We assume that the two host varieties differ only in their
97 susceptibility to the two pathogens, and the two pathogens differ only in their capability to infect

98 different hosts, which is reflected in the rate of spore production and the ability of resulting spores
 99 to infect additional host tissue. Both host susceptibility and pathogen virulence are described in the
 100 model by the transmission rates β_{ik} . The infected host tissue loses its infectivity (i. e. the ability to
 101 produce infectious spores) with the rate μ (μ^{-1} is the average infectious period), which is assumed
 102 to be the same for all I_i , $i = 1, \dots, n$.

103 We neglected spatial dependence of pathogen dispersal: every infected host is equally likely to
 104 infect every other infected host within the population (often called the “mass-action” approxima-
 105 tion). This approximation is valid for air-borne pathogens with long-range dispersal (for example,
 106 rusts and mildews), for sufficiently small plot sizes and for a uniform mixture of host varieties.
 107 There is evidence that when the overall disease severity is large enough, the disease may develop
 108 uniformly across the experimental plots [for example, observations in (Robert et al., 2004) for *Zy-*
 109 *moseptoria tritici* and *Puccinia striiformis* on wheat]. In other cases this assumption appears to
 110 be an idealization (i. e. (Lannou et al., 2008; Mundt, 2009)), especially when looking at the initial
 111 stages of an epidemic. In the current study, we are focusing more on the disease severity at the
 112 end of the growing season. Understanding of the basic model presented here is a necessary step
 113 and a point of reference for further inquiries that will consider autoinfection and spatial dimension
 114 explicitly.

115 We will vary the number of host varieties in the mixture n , while keeping the total carrying
 116 capacity constant: $K_{\text{tot}} = \sum_{i=1}^n K_i = nK$. We will consider the total amount of healthy and
 117 infected hosts at the infected equilibrium (denoted by an “*”-superscript) of the system of Eqs. (1)-
 118 (2)

$$119 \quad H_{\text{tot}}^* = \sum_{i=1}^n H_i^*, \quad I_{\text{tot}}^* = \sum_{i=1}^n I_i^*, \quad (3)$$

120 The equilibrium corresponds a fixed point of the system Eqs. (1)-(2) (as explained in the Appendix

121 A.1 and A.2) and can be achieved over long periods of time, depending on the stability properties of
 122 the system. The total disease severity is defined by

$$123 \quad y_{\text{tot}}^* = \frac{I_{\text{tot}}^*}{I_{\text{tot}}^* + H_{\text{tot}}^*}. \quad (4)$$

124 In order to obtain an analytical solution for the disease severity Eq. (4), we consider the trans-
 125 mission matrix of a simple form

$$126 \quad \mathbf{B} = \begin{pmatrix} \beta_d & \beta_{\text{nd}} & \cdots & \beta_{\text{nd}} \\ \beta_{\text{nd}} & \beta_d & \cdots & \beta_{\text{nd}} \\ \vdots & & \ddots & \\ \beta_{\text{nd}} & \cdots & & \beta_d \end{pmatrix} \quad (5)$$

127 Here, every diagonal element of the matrix \mathbf{B} is equal to β_d and every non-diagonal element is
 128 β_{nd} . We generally assume partial specialization, where $\beta_d \geq \beta_{\text{nd}}$. Furthermore, assuming that all
 129 healthy and infected hosts start with the same initial conditions, their dynamics will be the same.
 130 Hence, the amount of healthy and infected hosts is the same in each compartment i and equal to
 131 H_p and I_p , correspondingly. So, we substitute $H_i = H_p$, $I_i = I_p$ in Eqs. (1)-(2) and simplify these
 132 equations:

$$133 \quad \frac{dH_p}{dt} = r_H(K - H_p) - \beta_{\text{eff}}I_pH_p, \quad (6)$$

$$134 \quad \frac{dI_p}{dt} = \beta_{\text{eff}}I_pH_p - \mu I_p, \quad (7)$$

136 where $\beta_{\text{eff}} = \beta_d + (n - 1)\beta_{\text{nd}}$.

137 We also consider the simpler case when two host varieties H_1 and H_2 are exposed to two types

138 of pathogen: 1 and 2 (we also refer to them as P_1 and P_2), because mixtures of two host varieties
 139 are used most often. The model of susceptible-infected dynamics is described schematically in
 140 Fig. 1 and mathematically by the four equations:

$$141 \quad \frac{dH_1}{dt} = r_H(K_1 - H_1) - (\beta_{11}I_1 + \beta_{21}I_2)H_1, \quad (8)$$

$$142 \quad \frac{dH_2}{dt} = r_H(K_2 - H_2) - (\beta_{12}I_1 + \beta_{22}I_2)H_2, \quad (9)$$

$$143 \quad \frac{dI_1}{dt} = (\beta_{11}H_1 + \beta_{12}H_2)I_1 - \mu I_1, \quad (10)$$

$$144 \quad \frac{dI_2}{dt} = (\beta_{21}H_1 + \beta_{22}H_2)I_2 - \mu I_2. \quad (11)$$

146 There are four compartments in the model: susceptible hosts H_1 of variety 1, susceptible hosts H_2
 147 of variety 2, hosts I_1 infected by pathogen 1 and hosts I_2 infected by pathogen 2. One can vary
 148 the proportion of host plants of the two varieties by adjusting the ratio of the corresponding seeds
 149 to be planted. This is reflected in the change of the ratio $\phi_1 = K_1/(K_1 + K_2)$ in the model. We
 150 assume that the seeds of the two host varieties are well mixed before planting, such that the spatial
 151 distribution across the field is uniformly random for both types of plants.

152 Both host susceptibility and pathogen virulence are described in the model by the four transmis-
 153 sion rates β_{11} , β_{22} , β_{12} , and β_{21} . The corresponding transmission matrix has the form

$$154 \quad \mathbf{B} = \begin{vmatrix} \beta_{11} & \beta_{12} \\ \beta_{21} & \beta_{22} \end{vmatrix}. \quad (12)$$

155 As before, the first index of matrix elements represents the source of infection and the second index
 156 represents the recipient of infection (see Fig. 2). For example, β_{12} describes the transmission rate
 157 from I_1 to H_2 . Possible relationships between the elements of the transmission matrix (12) are
 158 discussed in Appendix A.5.

159 The model describes two distinct limiting cases. First case corresponds to the situation when
 160 I_1 includes the tissue of both hosts infected by pathogen 1. Similarly, I_2 includes host tissue of
 161 both hosts infected by the pathogen 2. This formulation assumes that the transmission rate does
 162 not depend on the host variety of the source of infection, but only depends on the host variety of
 163 the recipient of infection. In other words, under this assumption, the spore production rate and the
 164 quality of spores produced depend on the pathogen genotype, but not on the host genotype. But
 165 the infection efficiency (or infection success) of a spore depends on the host genotype on which
 166 it lands. Second case is realized when I_1 includes the tissue of host 1 that is infected by any one
 167 of the two pathogens. Similarly, I_2 includes the tissue of host 2 that is infected by any one of the
 168 two pathogens. This represents the other limiting case, when the spore production rate and the
 169 quality of spores produced depend on the host genotype, but not on the pathogen genotype. We In
 170 order to relax these assumptions, one needs to subdivide each of I_1 and I_2 into two compartments,
 171 according to the type of host tissue infected (first case), or according to the infecting pathogen
 172 (second case).

173 In this simplified case, the equilibrium disease severity Eq. (4) has the form

$$174 \quad y_{\text{tot}}^* = (I_1^* + I_2^*) / (I_1^* + I_2^* + H_1^* + H_2^*). \quad (13)$$

175 We use y_{tot}^* that corresponds to the disease severity close to the end of the growing season, to
 176 quantify the efficacy of host mixtures in terms of disease reduction. Previous modeling studies
 177 (Gumpert et al., 1987; Gumpert, 1989; Gumpert and Geiger, 1995) considered the other limiting
 178 case by assuming that the amount of disease is growing exponentially over time.

Results

First, we present the outcomes of the general model that describes many pathogen strains and host varieties and determine an optimal number of components in a host mixture. Next, we determine proportions of hosts in the mixture that will minimize the disease.

What is the optimal number of components to use in a host mixture?

In order to answer this question, we consider a mixture of n hosts exposed to n pathogens. and use the mathematical framework of Eqs. (6)-(7). In the case of partial specialization all elements of the transmission matrix \mathbf{B} are positive. All the diagonal elements are equal to β_d and the non-diagonal ones are equal to β_{nd} , with $\beta_d > \beta_{nd} > 0$ (see Eq. (5)). In this case, we determined (see Appendix A.3) the analytical expression for the total disease severity at the infected equilibrium, assume that every host variety is planted at the same proportion, i. e. $K_i = K$:

$$y_{\text{tot}}^*(n) = r_H \frac{(\beta_d + (n-1)\beta_{nd}) K_{\text{tot}} - \mu n}{n\mu(\mu - r) + rK_{\text{tot}}(\beta_d + (n-1)\beta_{nd})}. \quad (14)$$

Using this expression, we plotted in Fig. 3 the disease severity as a function of the number of components in the mixture n . Panel (a) illustrates the case of a pathogen with the high rate of transmission and panel (b) shows the case a pathogen with the intermediate rate of transmission. The grey solid curves represent the homogeneous case when $\beta_{nd} = \beta_d > 0$, i. e. no specialization, every pathogen strain or species is equally likely to infect every host. Evidently, in this case the disease severity is independent of the number of mixture components. In all other cases considered in Fig. 3, the disease severity decreases with n . The black solid curves in Fig. 3 illustrate the case of full specialization, when $\beta_{nd} = 0$, $\beta_d > 0$. In this case, the disease severity decreases steeply

199 with increasing n , eventually reaching zero. The dashed curves in Fig. 3 correspond to intermediate
 200 cases with different degrees of partial specialization. As the degree of host specialization increases,
 201 the decrease in disease severity becomes stronger.

202 Can one eradicate the disease by adding a large enough number of components to the host
 203 mixture? As we increase the number of components in the host mixture, each pathogen strain can
 204 infect less of its preferred host. At the limit of very large n , the amount of preferred host tissue
 205 available for each pathogen strain is so small that they are not able to survive only on it. Therefore,
 206 whether we can eradicate the disease depends on the ability of pathogen strains to survive on hosts
 207 that are not their favorite. This is determined by the parameter $R_{0\text{nd}} = \beta_{\text{nd}}K_{\text{tot}}/\mu$, which is the
 208 basic reproductive number of pathogen strains as a whole in the absence of their preferred hosts.
 209 If $R_{0\text{nd}} > 1$, then pathogen strains can survive in the absence of their preferred hosts. In this case,
 210 disease severity tends to a constant positive value at large n and never decreases to zero (dash-
 211 dotted curve in Fig. 3). In contrast, when $R_{0\text{nd}} < 1$, pathogen strains die out in the absence of their
 212 preferred hosts.

213 We take the the limit of very large n in Eq. (14) and find that the disease severity is proportional
 214 to $R_{0\text{nd}} - 1$ in this case:

$$215 \quad y_{\text{tot}}^*(n)_{n \rightarrow \infty} = r_H \frac{R_{0\text{nd}} - 1}{\mu + r_H(R_{0\text{nd}} - 1)}, \quad (15)$$

216 where $R_{0\text{nd}} = \beta_{\text{nd}}K_{\text{tot}}/\mu$ is the basic reproductive number of pathogen strains overall in the
 217 absence of their preferred hosts. It follows from Eq. (15) that if $R_{0\text{nd}} \leq 1$, then the disease severity
 218 will eventually reach (or approach) zero as we increase n . However when $R_{0\text{nd}} > 1$, the disease
 219 severity will approach a constant positive value given by Eq. (15). This means that, by increasing
 220 the number of components in the mixture, we decrease (eventually to zero) the impact of host-
 221 specialized infections characterized by rate β_{d} . However, the impact of non-specialized infections

222 characterized by β_{nd} remains unchanged with the corresponding severity given by Eq. (15).

223 From the expression for the disease severity in Eq. (14), one can determine the optimal number
 224 of components to use in the mixture. One way to do this is to define an economically acceptable
 225 disease severity, y_{acc} , (for example 5%), and then determine the number of components in the
 226 mixture that decrease the disease severity down to y_{acc} . This is done by solving Eq. (14) with
 227 respect to n . As a result, we obtain

$$228 \quad n_{opt1} = r_H K_{tot} \frac{(\beta_d - \beta_{nd})(1 - y_{acc})}{\mu(r_H + y_{acc}(\mu - r_H)) - r_H \beta_{nd} K_{tot}(1 - y_{acc})}. \quad (16)$$

229 Here, n_{opt1} is the number of mixture components at which the disease severity y_{acc} is reached. This
 230 is illustrated in Fig. 3, where the horizontal dashed line corresponds to $y_{acc} = 5\%$. The values of
 231 n at which this line intersects with disease severity curves correspond to optimum n_{opt1} given by
 232 Eq. (16). The optimum shifts to larger values with decreasing degrees of specialization [e. g. from
 233 $n_{opt1} = 9$ for the solid curve corresponding to full specialization to $n_{opt1} = 16$ for the dashed
 234 curve representing partial specialization in Fig. 3(a)]. Also, the optimum number of components is
 235 proportional to the total host population size K_{tot} .

236 Another way to determine an optimal number of mixture components uses the fact that $y^*(n)$ de-
 237 creases with n , but also considers that the rate of this decrease (i. e. the derivative $\frac{dy^*(n)}{dn}$) decreases
 238 with n . Hence, the benefit of adding one more component to a mixture that already has n compo-
 239 nents decreases with increasing n . Because of this, the dependence $y^*(n)$ eventually saturates to a
 240 constant value given by Eq. (15). Therefore, one can define a minimum decrease in disease severity
 241 due to adding one more host variety to the mixture Δy_{min} that is still economically plausible. The
 242 number of mixture components at this minimum is optimal, i. e. $n = n_{opt2}$. Mathematically, n_{opt2}
 243 can be found from the equation $y_{tot}^*(n_{opt2} - 1) - y_{tot}^*(n_{opt2}) = \Delta y_{min}$, where $y_{tot}^*(n)$ is given by

244 Eq. (14). The solution reads as

$$245 \quad n_{\text{opt}2} = \frac{\sqrt{\Delta y} [\mu^2 - r_H (K_{\text{tot}}(2\beta_d - 3\beta_{\text{nd}}) + \mu)] + \sqrt{4(\beta_d - b_{\text{nd}})r_H K_{\text{tot}}\mu^2 + \Delta y C}}{2\sqrt{\Delta S C^2}}, \quad (17)$$

246 where $C = \mu^2 + r_H(\beta_{\text{nd}}K_{\text{tot}} - \mu)$. This is also illustrated in Fig. 3, where the dotted vertical
 247 lines shows $n_{\text{opt}2} = 3$ [panel (a)] and $n_{\text{opt}2} = 2$ [panel (b)] that correspond to the severity curves
 248 for the case of strong partial specialization (dashed curves). When the degree of specialization is
 249 increased further up to full specialization (solid curve), $n_{\text{opt}2}$ shifts to the larger value of four.

250 We expect mixtures to be more effective against pathogens with intermediate and low trans-
 251 mission [cf. panels (a) and (b) in Fig. 3]. In Fig. 3(b) a mixture with three components not only
 252 decreased the disease below the acceptable level [optimum number of components, according to
 253 Eq. (16)], but even eradicated the pathogen. A two-component mixture provided an economical op-
 254 timum, according Eq. (17). In contrast, for pathogens with high transmission [Fig. 3(a)], mixtures
 255 with more components need to be used to reach the optimal effects.

256 The optimum number of components in the mixture, defined according to Eq. (16), can only
 257 be found if the acceptable severity y_{acc} can be reached by increasing n (that is when $R_{0\text{nd}} < 1$).
 258 This restriction is removed in the definition based on Eq. (17). But even in cases when y_{acc} can
 259 be reached by increasing n , the second definition seems to be more plausible, since it incorporates
 260 the economic costs of introducing an additional component into the mixture. However, it does not
 261 ensure that the disease will be reduced down to an acceptable value. Hence, additional disease
 262 control measures (e. g. applications of fungicides) may need to be implemented in order to further
 263 reduce the disease.

264 **Is there an optimal mixture of host varieties?**

265 Planting a mixture of host varieties provides an additional parameter that can be adjusted, namely
266 the proportions of the varieties in the mixture. Does planting a mixture of hosts reduce the total
267 amount of disease compared to the case of monoculture stands? Furthermore, is there an optimal
268 proportion of the host varieties at which the amount of disease is minimized? Answers to these
269 questions depend on the relationships between the elements of the transmission matrix **B**.

270 We calculate the disease severity at equilibrium y^* [Eq. (13)] as a function of the proportion of
271 the host variety 1 in the mixture $\phi_1 = K_1/K$ [see Fig. 4(a)]. The quantity ϕ_1 is varied from zero
272 to one, while keeping the total carrying capacity of hosts $K = K_1 + K_2$ constant.

273 When each pathogen can infect both hosts equally well (i. e. $\beta_{12} = \beta_{11}, \beta_{21} = \beta_{22}$, no special-
274 ization), disease severity does not depend on ϕ_1 [horizontal dashed curve in Fig. 4(a)]. The same
275 outcome is observed when the host-pathogen interaction follows the pure gene-for-gene scheme
276 (scenario (A) in Appendix A.5), i. e. $\beta_{11} = \beta_{21} = \beta_{22} > 0, \beta_{12} = 0$ [horizontal dashed curve in
277 Fig. 4(a)]. We used the values of the transmission rates, which satisfy $\beta_{22} > \beta_{11}$. Hence, pathogen
278 2 is fitter than pathogen 1 and dominates the population and at any value of ϕ_1 [the two horizontal
279 dashed curves overlap completely in Fig. 4(b)].

280 In the case of a single pathogen infecting a mixture of hosts with different degrees of suscep-
281 tibility ($\beta_{22} = \beta_{12} > \beta_{11} = \beta_{21}$), the disease severity decreases linearly with ϕ_1 . In this case,
282 simply using a monoculture with the more disease-resistant host variety ($\phi_1 = 1$) would reduce the
283 disease most strongly [green dashed-dotted curve in Fig. 4(a)]. This is in agreement with findings
284 of an experiment, in which a mixture of a susceptible and resistant barley variety was infected by
285 barley powdery mildew (caused by *Blumeria graminis* f. sp. *hordei*) reported in (Finckh et al.,
286 2000). In this study the disease reduction was found to decrease linearly with the proportion of the

287 susceptible variety in the mixture.

288 The picture changes if there is a degree of specialization of pathogen strains or species to host
289 varieties ($\beta_{22}, \beta_{11} > \beta_{12}, \beta_{21}$, scenario (D) in Appendix A.5). In this case the disease severity y^*
290 first decreases with ϕ_1 , then reaches a constant value, and after that increases again. Thus, the
291 disease is reduced over a range of intermediate values of ϕ_1 (solid and dotted curves in Fig. 4(a)).
292 The magnitude of this reduction increases with the degree of specialization and reaches a maximal
293 value at full specialization (solid red curve). Also, the range of ϕ_1 -values, over which the propor-
294 tion of disease remains minimal, increases with the degree of specialization [cf. solid and dotted
295 curves in Fig. 4(a)].

296 The ranges over which the frequency of pathogen 2 remains constant or changes as a function
297 of the cropping ratio ϕ_1 correspond to the ranges of stability of different fixed points of the model
298 system Eqs. (8)-(11). This can be seen from Fig. 4(b), where the frequency f_2 of pathogen 2 is
299 shown versus ϕ_1 . In the region where y^* decreases with ϕ_1 , pathogen 2 dominates the population
300 ($f_2 = 1$). In the region where y^* stays constant, the two pathogens co-exist, but the frequency of
301 pathogen 2 decreases with ϕ_1 until it reaches zero. This occurs at the border, where another fixed
302 point becomes stable, the one corresponding to pathogen 1 dominating the population ($f_2 = 1$).
303 Here, the disease severity increases with ϕ_1 .

304 Why does the disease severity decrease with ϕ_1 at small values of ϕ_1 ? In this parameter range,
305 pathogen 2 dominates the population in the long term. Since pathogen 2 specializes on host 2, it
306 develops best when only host 2 is planted, i. e. at $\phi_1 = 0$. By adding a small amount of host 1 to the
307 mixture, we create suboptimal conditions for pathogen 2: it is still able to outcompete pathogen 1,
308 but since there is less of its preferred host tissue, the resulting disease severity is smaller. A similar
309 explanation holds for the increase of disease severity with ϕ_1 at large values of ϕ_1 .

310 Why does the disease severity stay constant over a range of intermediate values of ϕ_1 ? This

311 range corresponds to co-existence of the two pathogens. Since there is a degree of specialization,
312 by increasing ϕ_1 we make pathogen 1 more fit while pathogen 2 becomes less fit. These two
313 changes compensate each other, so that the total disease severity, which includes both pathogen
314 strains, remains the same.

315 Thus, mixing host varieties reduces the overall disease severity if each of the pathogens performs
316 better on its preferred host. In this case, an optimal proportion of host varieties in the mixture lies
317 in the intermediate range, over which the two pathogens exhibit stable co-existence. This result is
318 in agreement with previous theoretical studies (Lively, 2010) and also explains some experimental
319 findings (Zhan and McDonald, 2013).

320 We also investigated the time dependence of the disease severity before the equilibrium is
321 reached (see Appendix 4, Figure A.1) by numerically solving the system of Eqs. (8)-(11). The
322 solutions indicate that the optimal suppression of disease at intermediate cropping ratios, ϕ_1 , ap-
323 pears much before the equilibrium is approached. Also, the optimal range of ϕ_1 -values at the
324 equilibrium that we determined analytically is indicative of the optimal range in the early phases
325 of the dynamics.

326 Further, our results indicate that the benefit of mixing two host varieties increases with decreas-
327 ing the pathogen's basic reproductive number. To illustrate this effect, we quantified this benefit
328 using the ratio between the mean disease severity in pure stands and the disease severity of the
329 50/50 host mixture. We considered this quantity as a function of the mean basic reproductive num-
330 ber of the two pathogens. This reveals, that mixing host varieties can be an effective measure to
331 control pathogens (with the reduction of disease severity by more than 20 %) with intermediate
332 values of R_0 (between 5 and 20, for example, *Zymoseptoria tritici* has R_0 of about 10), but will
333 bring only about 10 % reduction in disease severity when controlling diseases with high R_0 's, such
334 as stripe rust of wheat (where R_0 is about 50 (Segarra et al., 2001)).

335 In addition, within the range of maximal overall suppression of disease, the ratio of the two
336 pathogens can be controlled by varying the proportion of hosts in the mixture [Fig. 4(a) and (b)].
337 This can be useful, if one of the pathogens is much less desirable, for example, because of myco-
338 toxin production or the risk of fungicide resistance.

339 **Discussion**

340 We have shown that when a population of crop plants is exposed to two host-specialized pathogen
341 strains or species, the overall severity of both diseases is smaller in the mixture of two host varieties
342 than in either of the pure stands. We obtained analytical expressions for the disease reduction
343 which allowed us to quantify it across the whole range of parameters. These findings may help to
344 identify crop cultivars to be deployed in mixtures that will successfully control diseases prevalent
345 in a given region. The overall disease severity can be minimized over a range of mixing ratios. The
346 two pathogens coexist in this range and further adjusting the mixing ratio within this range makes
347 it possible to control the relative abundance of each pathogen. This can be useful when one of
348 the pathogens is less desirable, for example due to mycotoxin production or fungicide resistance,
349 while a certain amount of the other pathogen can be tolerated. Alternatively, the mixing ratio can
350 be adjusted within this optimal range to increase the economic output of the crop, if the two host
351 varieties differ in their quality or commercial value.

352 We also generalized the model to describe host mixtures with more than two components. We
353 find that when there is a degree of host specialization, the overall disease severity decreases with
354 the number of components in the mixture. The more specialized the host-pathogen pairs are, the
355 stronger is the decrease in the disease severity. Based on this understanding, we proposed ways
356 to determine economically optimal numbers of components in host mixtures. Furthermore, this

357 more general framework is capable of describing many hosts exposed to many pathogen strains
358 or species and can also be used to better understand plant-pathogen dynamics in natural ecosys-
359 tems, such as *Linum marginale*–*Melampsora lini* (Thrall et al., 2002), or *Plantago lanceolata*–
360 *Podosphaera plantaginis* (Laine, 2007). Local adaptation was observed in these natural inter-
361 actions (Thrall et al., 2002; Laine, 2007) and also modelled within a simplified metapopulation
362 framework (Papaix et al., 2014). Hence, the insight we gained in the case of partial specializa-
363 tion may advance our understanding of evolutionary forces operating in these wild plant-pathogen
364 systems.

365 It is desirable to study the benefit of mixing host varieties representing the whole range of val-
366 ues of the matrix elements of \mathbf{B} (see Appendix A.5 for the discussion of plausible relationships
367 between the matrix elements). We have done this here by obtaining analytical expressions for
368 the disease severity and frequencies of pathogens as functions of the matrix elements β_{ij} and
369 other model parameters (see Appendix A.3). This is an advantage of our study with compared to
370 previous theoretical investigations that assumed a “pure GFG” interaction, without fitness costs
371 associated with losing effectors (Ohtsuki and Sasaki, 2006; van den Bosch and Gilligan, 2003; Lo
372 Iacono et al., 2013), or that assumed full specialization (Lively, 2010), where each pathogen can
373 only infect its preferred host and is unable to infect any other hosts (also called the “matching al-
374 leles” model (King and Lively, 2012)). The latter scenario seems to represent only a hypothetical
375 limiting case, because it requires full resistance, which is unlikely given the simultaneous presence
376 of many pairs of R- and E-proteins. In contrast, partial specialization (scenario (D)), when the
377 diagonal elements β_{11} and β_{22} are larger than non-diagonal ones β_{12} and β_{21} , but the non-diagonal
378 ones are still significantly larger than zero, seems to be the most generic case. This is because it
379 arises from a ubiquitous GFG-type of interaction with many R-proteins present in the host, many
380 corresponding E-proteins present in the pathogen, as well as fitness costs for the pathogen due to

381 elimination or modification of E-proteins and fitness costs for the host due to having unnecessary
382 R-proteins.

383 Some modeling studies considered the effect of varying the proportion of mixture components
384 and partial specialization in host mixtures (Gumpert and Geiger, 1995), but they did not investigate
385 the dependence of the mixture efficacy on the degree of specialization. To the best of our knowl-
386 edge, the optimal number of components in a host mixture and the optimal ratios of two-component
387 mixtures as functions of the pathogen's reproductive ability and the degree of host specialization
388 have not yet been quantified in the existing modeling literature. Here, we obtained analytical ex-
389 pressions for these quantities that allow to investigate the mixture efficacy in the whole range of
390 parameters and also understand the underlying mechanisms of disease reduction in mixtures.

391 Mixtures and pure stands of several wheat cultivars were inoculated using a mixture of two
392 wheat stripe rust races in a series of field experiments (Finckh and Mundt, 1992*a,b*). The pathogen
393 population exhibited host specialization with respect to two of the host mixtures. The pattern of
394 disease severity corresponding to different proportions of host cultivars in mixtures corresponds
395 qualitatively to our model predictions (i. e. solid curve in Fig. 4(a) in the case of host specialization
396 and dash-dotted curve for mixtures of susceptible and resistant cultivars). Our model also predicts
397 coexistence of host-specialized pathogen races in the intermediate range of mixing ratios. This
398 could be tested in experiments similar to (Finckh and Mundt, 1992*a,b*) by measuring the frequen-
399 cies of the different pathogen races in the experimental plots. However, interactions between plant
400 genotypes had considerable effect on the disease severity in host mixtures (Finckh and Mundt,
401 1992*a,b*) and need to be included in the model in order to achieve quantitative agreement.

402 Four distinct mechanisms of disease reduction by host mixtures are described in the literature
403 (Chin and Wolfe, 1984; Wolfe, 1985; Finckh et al., 2000): (i) the effect of reduced density of
404 susceptibles; (ii) the "barrier effect"; (iii) induced resistance (Goleniewski, 1996); and (iv) com-

405 petition between pathogens. In scenario (i) the disease is reduced in the mixture simply because
406 it has less of the susceptible variety than the susceptible pure stand. This “reduced density” effect
407 can be observed most clearly by comparing the amount of disease in two pure stands of the suscep-
408 tible variety, which differ only in planting density (Chin and Wolfe, 1984). The introduction of the
409 resistant variety further reduces the disease in the mixture (scenario (ii)), because the transmission
410 between susceptible hosts is hindered (a resistant “barrier” is created between adjacent susceptible
411 plants). Induced resistance (scenario (iii)) takes place when spores of an avirulent pathogen acti-
412 vate a host resistance mechanism that is also effective against another pathogen (or another race
413 of the same pathogen), which is normally able to infect the host (Chin and Wolfe, 1984; Lannou
414 et al., 1995, 2005). Finally, in scenario (iv) mixing host cultivars is expected to make the pathogens
415 compete with each other for host tissue (Finckh et al., 2000; Ohtsuki and Sasaki, 2006).

416 The “reduced density” effect originally referred to the mixture of a susceptible and a resistant
417 variety (Chin and Wolfe, 1984). Hence, it cannot lead to a disease level lower than in the pure stand
418 of the resistant variety. Here we extended the notion of the “reduced density” effect to the case
419 of two or more host-specialized pathogen strains or species. For example, this may correspond to
420 host 1 being susceptible to pathogen 1, but resistant to pathogen 2 and host 2 being susceptible to
421 pathogen 2, but resistant to pathogen 1. We find that it is only in such cases that disease level in
422 the mixture is lower than in both pure stands.

423 Our model does not include the “barrier” effect, since it does not explicitly consider the spatial
424 dependence of pathogen dispersal (see Sec.). Also, induced resistance (Chin and Wolfe, 1984;
425 Lannou et al., 1995, 2005) was not considered. Therefore, we likely underestimate the effect of
426 host mixtures on disease reduction. Moreover, interesting effects of adjusting other landscape
427 variables than the cropping ratio ϕ_1 , such as the host patch size and the size of initial disease
428 foci, were observed in recent field experiments on wheat stripe rust (Mundt et al., 2011; Estep

429 et al., 2014). These developments stimulate the extension of the basic model for host mixtures
430 presented here using a spatially-explicit approach. In this way, a unified mathematical framework
431 for description of the effect of host mixtures on plant disease can be developed on the basis of the
432 model presented here. This would allow one to better understand the relative contributions of each
433 of these effects in disease reduction and design better host mixtures.

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561 **Figure captions**

562 Figure 1. Sheme of the model equations (8)-(11).

563 Figure 2. Scheme of the host-pathogen interaction. “+” refers to full susceptibility, “-” refers to
564 full resistance to disease, and these signs correspond to a “pure” gene-for-gene (GFG) interaction.
565 The transmission matrix β_{ij} , $i, j = 1, 2$ represents a more general description with “pure” GFG
566 ($\beta_{11} = \beta_{22} = \beta_{21} > 0$; $\beta_{12} = 0$) and full host specialization ($\beta_{11}, \beta_{22} > 0$; $\beta_{12} = \beta_{21} = 0$) as
567 limiting cases.

568 Figure 3. Disease severity at the infected equilibrium versus the number of components in
569 the host mixture plotted according to Eq. (14) in the case of no specialization (grey solid), full

570 specialization (solid), partial specialization with the specialization index $\sigma = \beta_{nd}/\beta_d = 0.5$ (dash-
571 dotted) and $\sigma = 0.05$ (dashed). Parameter values: (a) pathogen with high transmission $\beta_d = 2$;
572 (b) pathogen with low transmission $\beta_d = 0.5$. The rest of parameters are the same in (a) and (b):
573 $K_{tot} = 1$, $\mu = 0.2$, $r = 0.1$. Dotted horizontal curve shows an example of a maximum disease
574 severity, $S_{acc} = 5\%$, that is still economically acceptable. Dotted vertical lines show the optimal
575 number of components $n_{opt2} = 3$ [panel (a)] and $n_{opt2} = 2$ [panel (b)], according to Eq. (17) taking
576 $\Delta S = 10\%$, for the dashed curves.

577 Figure 4. Disease severity y^* (upper panel) and the frequency $f_2^* = I_2^*/(I_1^* + I_2^*)$ of pathogen 2
578 (lower panel) at equilibrium as functions of the proportion of host 1 in the mixture $\phi_1 = K_1/(K_1 +$
579 $K_2)$, according to Eqs. (A.16), (A.17). Parameter values: $\beta_{11} = 6$ (unless specified otherwise
580 below), $\beta_{22} = 8$, $K = K_1 + K_2 = 1$, $r = 0.2$, $\mu = 1$. The non-diagonal elements of the infection
581 matrix \mathbf{B} determine the degree of specialization: (a) full specialization $\beta_{12} = \beta_{21} = 0$ (red dotted);
582 (b) small degree of specialization $\beta_{12} = \beta_{21} = 0.9$ (blue, solid); (c) no specialization $\beta_{12} = \beta_{11} =$
583 6 , $\beta_{21} = \beta_{22} = 8$ (black, upper); (d) “pure” gene-for-gene interaction $\beta_{11} = \beta_{21} = \beta_{22} = 8$,
584 $\beta_{12} = 0$ (yellow, upper); (e) single pathogen $\beta_{11} = \beta_{21} = 6$, $\beta_{22} = \beta_{12} = 8$ (green, dash-dotted).
585 Cases (c) and (d) correspond to the upper horizontal lines and overlap completely.

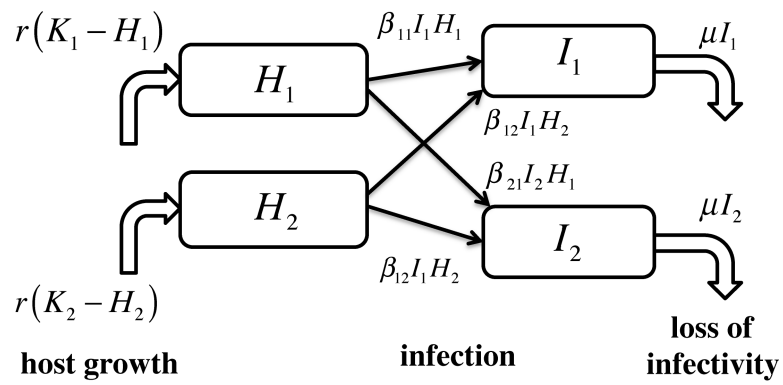


Figure 1

	H₁	H₂
P₁	$\beta_{11} +$	$\beta_{12} -$
P₂	$\beta_{21} +$	$\beta_{22} +$

Figure 2

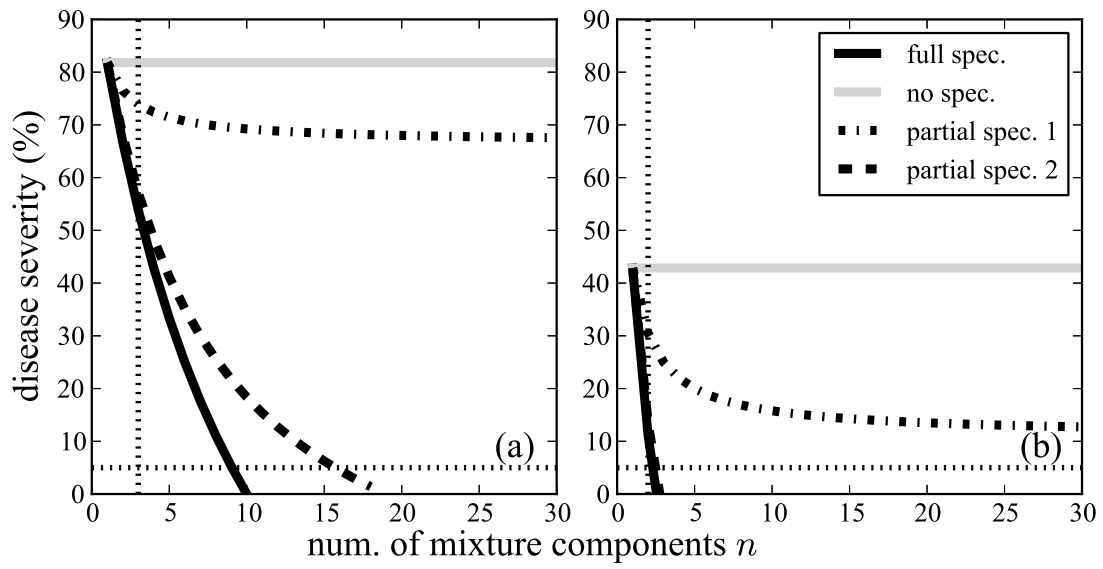


Figure 3

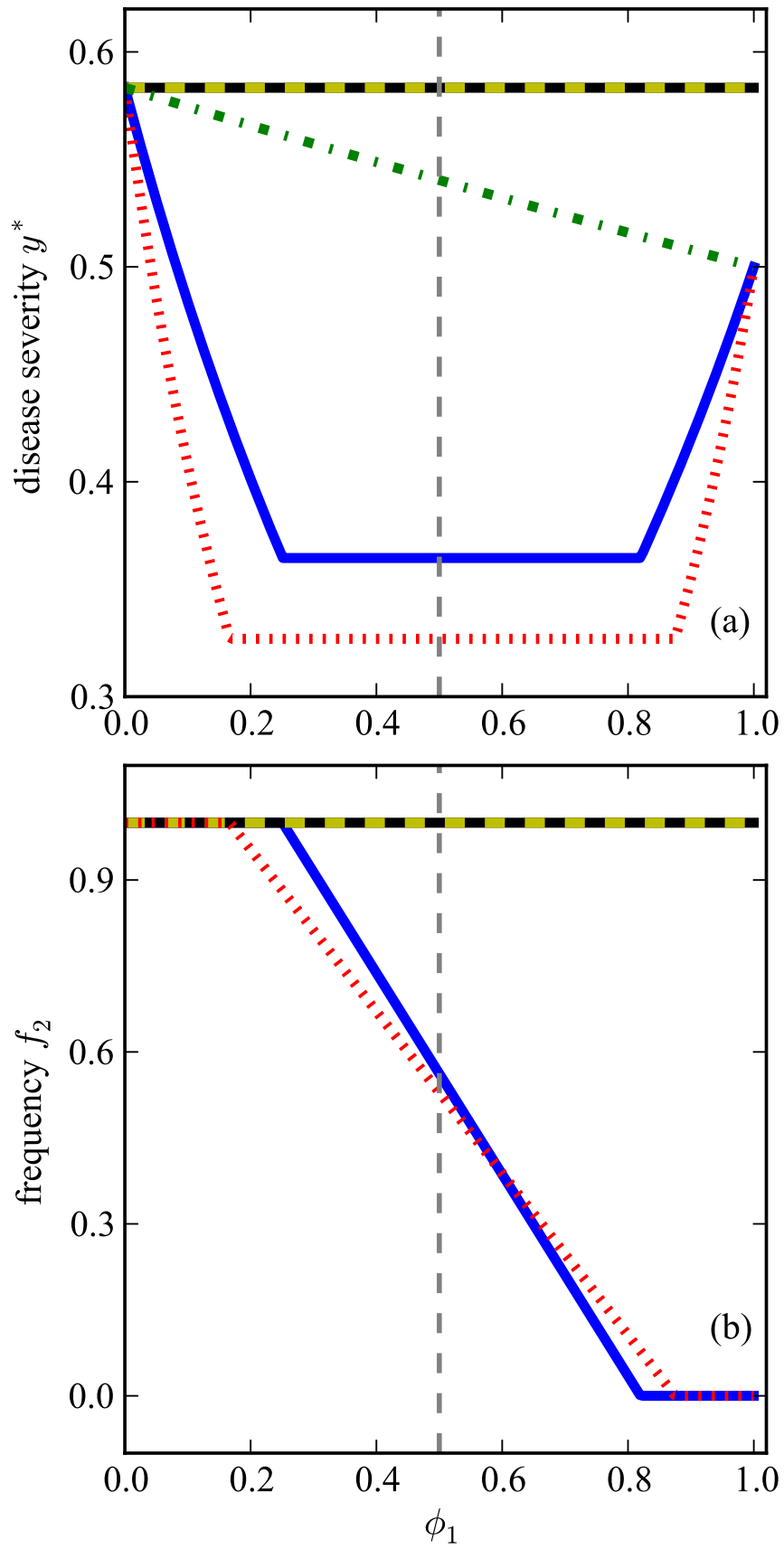


Figure 4