

# *A tradeoff between tolerance and resistance to a major fungal pathogen in elite wheat cultivars*

Article

Accepted Version

Mikaberidze, A. and McDonald, B. A. (2020) A tradeoff between tolerance and resistance to a major fungal pathogen in elite wheat cultivars. *New Phytologist*, 226 (3). pp. 879-890. ISSN 1469-8137 doi: 10.1111/nph.16418 Available at <https://centaur.reading.ac.uk/88100/>

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To link to this article DOI: <http://dx.doi.org/10.1111/nph.16418>

Publisher: Wiley-Blackwell

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1 **A tradeoff between tolerance and resistance to a major fungal pathogen**  
2 **in elite wheat cultivars**

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## 18 Summary

- 19 • Tolerance and resistance represent two strategies that hosts evolved to protect themselves  
20 from pathogens. Tolerance alleviates the reduction in host fitness due to infection without  
21 reducing a pathogen's growth, while resistance reduces pathogen growth. We investigated  
22 tolerance of wheat to the major fungal pathogen *Zymoseptoria tritici* in 335 elite wheat  
23 cultivars.
- 24 • We used a novel digital phenotyping approach that included 11,152 infected leaves and  
25 counted 2,069,048 pathogen fruiting bodies.
- 26 • We discovered a new component of tolerance that is based on the relationship between the  
27 green area remaining on a leaf and the number of pathogen fruiting bodies. We found a  
28 negative correlation between tolerance and resistance among intolerant cultivars, presenting  
29 the first compelling evidence for a tradeoff between tolerance and resistance to plant  
30 pathogens. Surprisingly, the tradeoff arises due to limits in the host resources available to the  
31 pathogen and not due to metabolic constraints, contrary to what ecological theory suggests.
- 32 • The mechanism underlying this tradeoff may be relevant for many plant diseases in which the  
33 amount of host resources available to the pathogen can limit the pathogen population. Our  
34 analysis indicates that European wheat breeders may have selected for tolerance instead of  
35 resistance to an important pathogen.

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38 keywords: *Triticum aestivum*, host-pathogen interaction, host defenses, plant disease, *Zymoseptoria*  
39 *tritici*, digital phenotyping

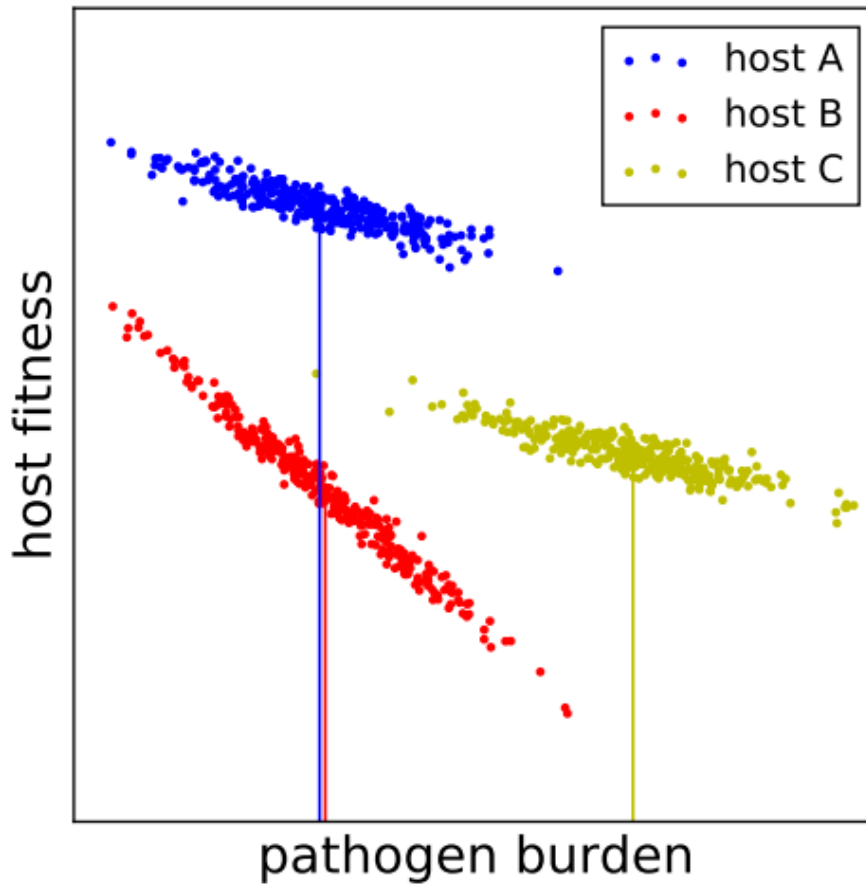
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## 47 **Introduction**

48

49 Tolerance and resistance represent two important mechanisms that plants and animals evolved to  
50 protect themselves from pathogens (Roy et al., 2000; Baucom & De Roode, 2011). Tolerance to a  
51 pathogen is usually defined as the host's ability to alleviate the reduction in its fitness due to infection  
52 without reducing the growth of the pathogen (Baucom & De Roode, 2011; Ney et al., 2013). A more  
53 tolerant host genotype will suffer a smaller loss in fitness per unit increase of pathogen population  
54 present within the host (called the pathogen burden) than a less tolerant host genotype. Hence,  
55 tolerance of a host genotype can be quantified as the reduction in host fitness per unit increase in  
56 pathogen burden. In contrast, resistance is usually measured as the host's ability to suppress the  
57 infection itself and reduce the resulting pathogen burden upon infection. The difference between  
58 tolerance and resistance is illustrated in Fig. 1.

59         Since the concept of tolerance was first coined more than a century ago (Cobb, 1894),  
60 numerous studies [reviewed by Pagan & Garcia-Arenal (2018)] investigated tolerance to pathogens in  
61 crop plants (Caldwell *et al.* 1958; Schafer, 1971; Newton *et al.*, 1998; Bingham *et al.*, 2009; Ney *et*  
62 *al.*, 2013; Newton, 2016), model plants (Kover & Schaal, 2002; Pagan et al., 2008, Shuckla et al.,  
63 2017) and wild plants (Roy et al., 2000; Inglese & Paul, 2006; Carr et al., 2006). Råberg et al. (2007)  
64 were the first to demonstrate tolerance to an infectious disease in animals. The therapeutic potential of  
65 tolerance in human medicine inspired a surge of further investigations (Medzhitov et al., 2012; Ayres  
66 & Schneider, 2012; Råberg, 2014; Soares et al., 2017). Several studies uncovered molecular  
67 mechanisms of tolerance in model animal species (Ayres & Schneider, 2008; Shinzawa et al., 2009;  
68 Richardson et al., 2010; Maze-Guilmo et al., 2014), while Blanchet et al. (2010); Jackson et al.  
69 (2014); Hayward et al. (2014); Maze-Guilmo et al. (2014) characterized tolerance to parasites in wild  
70 animal populations. Zeller & Koella (2017) used an experimental evolution approach to determine  
71 how tolerance/resistance evolves in mosquito populations exposed to microsporidian parasites.



72 **Figure 1** Differentiation and quantification of tolerance and resistance. The figure illustrates the  
 73 relationships between host fitness and pathogen load for three hypothetical host genotypes: A (blue),  
 74 B (red) and C (yellow). For each host genotype, tolerance is quantified as the rate at which the host  
 75 loses its fitness with an increase in pathogen burden. The difference in resistance between hosts can  
 76 be measured on the X-axis as the difference in the mean pathogen burden (vertical lines). The  
 77 position of each genotype on the Y-axis is determined by its fitness in the absence of the pathogen  
 78 and is not related to tolerance or resistance. Host genotypes A and B have the same resistance because  
 79 the average pathogen burden that they carry is the same. However, genotype A is more tolerant than  
 80 genotype B because the fitness of genotype B decreases at a higher rate with increasing pathogen  
 81 burden. This is reflected in the steeper slope in genotype B compared to genotype A. In contrast, host  
 82 genotypes A and C have the same tolerance, but genotype A is more resistant than genotype C.  
 83 Finally, the comparison of host genotype B and host genotype C represents a mixed case: genotype B  
 84 is more resistant, but less tolerant than genotype C.

85

86

87           It is generally thought that since both tolerance and resistance are defense strategies that  
88 require reallocation of host resources, they should confer fitness costs to the host (Roy & Kirchner,  
89 2000; Simms & Triplett, 1994; Brown, 2002). For this reason, a metabolic tradeoff between tolerance  
90 and resistance is expected due to a limitation in host resources. A large body of ecological theory has  
91 been developed based on this premise (van der Meijden et al., 1988; Herms & Mattson, 1992; Roy &  
92 Kirchner, 2000; Fornoni et al., 2004; Restif & Koella, 2004; Miller et al., 2005; Best et al., 2008).  
93 However, empirical evidence for a tradeoff between tolerance and resistance remains sparse. A few  
94 studies reported a negative relationship between tolerance and resistance to herbivory (Fineblum &  
95 Rausher, 1995; Stowe, 1998; Baucom & Mauricio, 2008) and Råberg et al. (2007) presented a similar  
96 finding in mice infected with malaria. Other studies reported no correlation between tolerance and  
97 resistance in plants subjected to herbivores (Mauricio et al., 1997), in humans infected with HIV  
98 (Regoes et al., 2014) or in wild sheep infected with a parasite (Maze-Guilmo et al., 2014).  
99 Interestingly, in *Drosophila melanogaster* populations exposed to a bacterial infection, tolerance and  
100 resistance exhibited a positive correlation (Howick & Lazzaro, 2014). Likewise, populations of the  
101 mosquito *Aedes aegypti* that were infected by the microsporidian parasite *Vavraia culicis* and evolved  
102 for 10 generations exhibited a positive relationship between tolerance and resistance (Zeller & Koella,  
103 2017). No evidence for a tradeoff between host tolerance and resistance was so far reported in the  
104 plant pathology literature.

105           In this study, we investigated tolerance to the fungal pathogen *Zymoseptoria tritici* (formerly  
106 *Mycosphaerella graminicola*) in 335 elite European wheat cultivars. *Z. tritici* causes septoria tritici  
107 blotch (STB), a disease that is a major constraint on wheat production globally and the most  
108 destructive disease of wheat in Europe (Fones & Gurr, 2015). *Z. tritici* spores germinate on wheat  
109 leaves and penetrate the leaves through stomata (Kema et al., 1996). After penetration, the fungus  
110 grows for several days within leaves without producing visible symptoms. During this asymptomatic  
111 period, the pathogen invades the host mesophyll around the position of the initial penetration. After  
112 10 to 20 days of asymptomatic growth, the fungus becomes necrotrophic and kills the invaded plant  
113 tissue, forming necrotic lesions. Asexual fruiting bodies called pycnidia begin to form in the necrotic  
114 lesions soon thereafter. Spores that form in the pycnidia provide inoculum to start the next cycle of  
115 pathogen reproduction. The formation of necrotic lesions corresponds to host damage caused by the  
116 pathogen that can be quantified as the proportion of leaf area covered by lesions (PLACL). The

117 number of pycnidia provides a measure of pathogen reproduction that can be quantified by counting  
118 the number of pycnidia present on an infected leaf,  $N_p$  (Stewart et al., 2016a; Karisto et al., 2018).

119 Control of STB relies mainly on applications of fungicides and deployment of STB-resistant  
120 wheat varieties. However, populations of *Z. tritici* are extremely diverse due to a high degree of  
121 sexual reproduction and large effective population sizes. As a result, the pathogen has the capacity to  
122 rapidly adapt to both fungicides (Fraaije et al., 2005; Zhan et al., 2006) and host resistances (Cowger  
123 et al., 2000; McDonald and Mundt, 2016) as a result of strong directional selection favoring particular  
124 pathogen genotypes. In contrast, host tolerance does not impair pathogen reproduction and is not  
125 expected to impose strong directional selection. For this reason, tolerance presents a promising  
126 alternative to protect wheat yield that is not prone to pathogen adaptation.

127 Several previous studies investigated tolerance of wheat to STB empirically (Eyal & Ziv,  
128 1974; Zuckerman et al., 1997; Parker et al., 2004; Foulkes et al., 2006; Collin et al., 2018). Van den  
129 Berg et al (2017) used mathematical modeling to reveal functional traits in wheat that contribute to  
130 tolerance. These studies used wheat yield (measured as tons of grain per hectare or as the thousand  
131 kernel weight) to quantify the plant fitness (the Y-axis in Fig. 1) and the PLACL or healthy area  
132 duration (HAD, Waggoner & Berger (1987)) to quantify the pathogen burden (the X-axis in Fig. 1).  
133 Accordingly, tolerance was quantified as the yield loss associated with each unit increase in PLACL  
134 or unit loss in HAD.

135 PLACL and HAD quantify the damage that the pathogen causes on an infected host plant.  
136 However, these quantities do not necessarily accurately reflect the size of the pathogen population  
137 present within the infected host plant (Stewart et al., 2016a; Karisto et al., 2018). For this reason,  
138 tolerance measured in these traditional ways is considered to be tolerance to the disease, which may  
139 not coincide with tolerance to the pathogen (Gaunt, 1981). The goal in this study was to characterize  
140 wheat tolerance to its pathogen, *Z. tritici*. With this in mind, we used (i) green leaf area to quantify a  
141 component of plant fitness and (ii) the number of pycnidia per leaf to quantify the pathogen burden.  
142 Grain yield is usually seen as a more comprehensive measure of fitness in crop plants than green leaf  
143 area. However, a number of field experiments have demonstrated that the reduction in the green area  
144 of the three upper-most leaf layers in wheat is a major driver of yield loss induced by STB (Eyal &  
145 Ziv, 1974; King et al., 1983; Forrer & Zadoks, 1983; Shaw & Royle 1989b, Thomas et al., 1989),  
146 thereby justifying our choice (i) (see Discussion for a more detailed justification). The choice (ii) is  
147 justified because the number of pycnidia per leaf was shown to be the main factor influencing the



148 number of pathogen spores produced on an infected leaf (Stewart et al., 2016a). Moreover, the  
149 proportion of the leaf area covered by STB lesions was demonstrated to be largely independent from  
150 the number of pycnidia produced on a leaf (Karisto et al., 2018). For these reasons, the number of  
151 pycnidia per leaf is a better indicator of the pathogen population inhabiting a leaf than the PLACL.

152 By conducting these measurements on 11,152 individual wheat leaves belonging to 335  
153 different cultivars (counting in total 2,069,048 individual pycnidia), we were able to identify and  
154 measure a novel component of wheat tolerance to *Z. tritici* that operates on the scale of individual  
155 leaves. We call this “leaf tolerance” as opposed to the “whole-plant tolerance” that was characterized  
156 previously. In this study, we focused on leaf tolerance and did not consider whole-plant tolerance. A  
157 way to estimate tolerance over a range of pathogen burdens as we describe here is to estimate range  
158 tolerance (Baucom & De Roode, 2011). The component of tolerance that we measured represents  
159 fecundity tolerance rather than mortality tolerance, because this disease does not kill its host but  
160 instead reduces its fecundity.

161 We used a combination of mathematical modeling and field experimentation to formulate and  
162 test several hypotheses connected to leaf tolerance of wheat to *Z. tritici*. First, based on our current  
163 understanding of the infection biology of *Z. tritici*, we formulated and tested empirically two  
164 alternative hypotheses regarding the relationship between the green leaf area and the number of  
165 pycnidia per leaf. Second, we tested the hypothesis that wheat cultivars differ in terms of their leaf  
166 tolerance. Finally, we tested the expectation of a tradeoff between leaf tolerance and resistance and  
167 found a significant negative relationship between tolerance and resistance. Surprisingly, our analysis  
168 indicates that this negative association arises due to the limitation in the leaf area of wheat plants and  
169 not as a result of metabolic costs associated with tolerance/resistance as predicted by ecological  
170 theory.

171

## 172 **Materials and Methods**

173 Here we analyzed a subset of the raw data reported in (Karisto et al., 2018). Below, we describe the  
174 main features of the experimental design that are relevant for this analysis. A comprehensive  
175 description of the experimental design can be found in (Karisto et al., 2018).

176

### 177 **Plant materials and experimental design**

178 In total, 335 elite European winter wheat (*Triticum aestivum*) varieties from the GABI-wheat

179 panel (Kollers et al., 2013a,b) were evaluated in this experiment. Two biological replicates of the  
180 wheat panel were grown during the 2015-16 growing season in two complete blocks separated by  
181 approximately 100 m at the Field Phenotyping Platform site of the Eschikon Field Station of the ETH  
182 Zurich, Switzerland (coordinates 47.449°N, 8.682°E) (Kirchgessner et al., 2017). The complete  
183 blocks were composed of 18 rows and 20 columns consisting of 1.2 x 1.7 m plots, with the genotypes  
184 arranged randomly within each block. Best practices recommended for conventional, high-input  
185 wheat production were used, including applications of fertilizers and pesticides. Complete details are  
186 given in (Karisto et al., 2018).

187

### 188 **Septoria tritici blotch inoculum, sampling of infected leaves**

189 All STB infection was natural, with the majority of primary inoculum likely originating from  
190 airborne ascospores coming from nearby wheat fields that surround the Eschikon field site. As a  
191 result, the infections analyzed in this experiment were caused by thousands of different pathogen  
192 strains. For this study we used leaves exhibiting obvious STB lesions that were collected on 4 July  
193 2016 (approximate range of GS 75 [milk development] to GS 85 [dough development]). Up to 16  
194 infected leaves were collected at random for each plot from the leaf layer below the flag leaf (i.e.,  
195 flag-1 or second leaf). The sampled leaves were placed into paper envelopes, kept on ice in the field,  
196 and stored at 4°C for 2 days before mounting onto A4 paper with printed reference marks and sample  
197 names, as described by Stewart et al. (2016b). Absorbent paper was placed between each sheet of  
198 eight mounted leaves and sheets were pressed with approximately 5 kg at 4°C for 2 to 3 days prior to  
199 scanning at 1,200 dpi with a Canon CanoScan LiDE 220 flatbed scanner.

200

### 201 **Determination of the green leaf area and the number of pycnidia per leaf**

202 Scanned images were analyzed with the software ImageJ (Schindelin et al., 2015) using the  
203 macro described by Karisto et al. (2018). The maximum length of the scanned area for each leaf was  
204 17 cm. When leaves were longer than 17 cm, bases of the leaves were placed within the scanned area,  
205 while the leaf tips extended outside the scanned area. For each leaf, the following quantities were  
206 automatically recorded from the scanned image: total leaf area ( $A_{\text{tot}}$ ), necrotic and chlorotic leaf area  
207 ( $A_{\text{necr}}$ ) and the number of pycnidia ( $N_p$ ). Necrotic and chlorotic leaf areas were detected based on  
208 discoloration of the leaf surface and were not based on the presence of pycnidia. We then calculated  
209 the green (healthy) leaf area as  $H = A_{\text{tot}} - A_{\text{necr}}$ .

210

## 211 **Statistical analysis**

212 Statistical analysis was conducted in the Python programming language (version 3.6.2, [https://](https://www.python.org)  
213 [www.python.org](https://www.python.org)) using the open-source packages scipy (version 0.19.1), numpy (version 1.11.1) and  
214 matplotlib (version 1.5.3; Jones et al., 2001). The Python package rpy2 (version 2.8.6,  
215 <https://rpy2.bitbucket.io/>) was used to access statistical routines of R (R Core Team, 2016).

216 To control for the effect of total leaf area on the number of pycnidia per leaf, we performed  
217 the adjustment  $N_{p,i} \rightarrow (A_{tot} / A_{tot,i}) N_{p,i}$  prior to the analysis, where  $N_{p,i}$  and  $A_{tot,i}$  is the number of pycnidia  
218 and the total area of an individual leaf  $i$  and  $A_{tot}$  is the mean total leaf area averaged over the whole  
219 dataset. First, we pooled together the data from leaves belonging to different cultivars and fitted the  
220 relationship between  $N_p$  and  $H$  using a linear function  $H = H_0(1 - \kappa N_p)$  and an exponential function  
221  $H = H_0 \exp(-\kappa N_p)$ , where  $H$  is the green leaf area and  $H_0$  is the green leaf area in the absence of  
222 disease. For both functions, the slope  $\kappa$  can be used to quantify tolerance: small  $\kappa$ -values correspond  
223 to high leaf tolerance and large  $\kappa$ -values correspond to low leaf tolerance. This overall fit gave us the  
224 baseline to which we then compared the tolerance of individual wheat cultivars. Second, we estimated  
225  $\kappa$  in each of the 335 wheat cultivars by fitting both the linear and the exponential functions to  
226 individual leaf data belonging to each of the cultivars. Next, we used multiple one-sided bootstrap t-  
227 tests with resampling cases (Davison and Hinkley, 2001) to compare  $\kappa$ -estimates in each cultivar to  
228 the baseline  $\kappa$ -estimate, where we used the false discovery rate correction for multiple comparisons.  
229 Fits were performed using the nonlinear ordinary least-squares optimization with the Nelder-Mead  
230 method in the lmfit package (version 0.9.7) for Python (Newville et al., 2014). We also determined  
231 the significance of the effects of the spatial block and the cultivar on tolerance: we used likelihood  
232 ratio tests to compare more complex models in which data from each cultivar/spatial block was fitted  
233 using separate  $\kappa$  or  $H_0$ -values to simpler models where only single  $\kappa$  or  $H_0$  parameters were fitted to  
234 the whole dataset.

235 To determine whether there is a relationship between tolerance and resistance of wheat to *Z.*  
236 *tritici*, we used the correlation test based on the Spearman's rank correlation coefficient,  $r_s$  (routine  
237 “scipy.stats.spearmanr” of the scipy package for Python), to analyze correlations between tolerance  
238 quantified as the slope  $\kappa$  and resistance quantified as the average number of pycnidia per leaf (Karisto  
239 et al., 2018). We chose to use the Spearman's correlation instead of Pearson's correlation, because it is  
240 computed in a non-parametric fashion based on relative ranks of the estimates. It does not assume any

241 specific functional form of the relationship between the two variables and thereby is not influenced  
242 by the widths of their distributions. To test whether the correlation is significantly different from zero,  
243 the routine uses a t-test that requires a number of assumptions to be fulfilled such as the normality of  
244 the probability distribution of the correlation coefficients.

245 To determine whether these assumptions hold and the conclusions based on this test are valid,  
246 we conducted a series of statistical tests based on a more robust bootstrap t-test (Davison et al., 1997).  
247 We generated a large number of bootstrap samples ( $n_{bs}=10^5$ ) by resampling with replacement the  
248 estimates of leaf tolerance and resistance for each of the 335 cultivars and used them to compute the  
249 95 % confidence interval (CI) of  $r_s$ . We then generated the same number of bootstrap samples based  
250 on the estimates of tolerance and resistance separately in each of the two groups of cultivars, tolerant  
251 and intolerant cultivars. This allowed us to compute the confidence intervals of  $r_s$  estimates in each of  
252 the two cultivar groups. Finally, we tested whether  $r_s$  was significantly different from zero in each of  
253 the groups and whether one of the groups had a significantly higher  $r_s$  than the other group.

254

## 255 **Results**

### 256 **A novel component of tolerance**

257 Recent studies (Karisto et al., 2018; Stewart et al., 2016a) demonstrated that factors responsible for  
258 leaf damage during the infection are largely uncoupled from the pathogen's capacity to reproduce on  
259 leaves. Based on this knowledge, we devised a simple mathematical model that describes the change  
260 in the green leaf area corresponding to an increase in the number of pycnidia on a leaf (for more  
261 details see Notes S1).

262 The following differential equation governs the relationship between the number of pycnidia  
263 and the green leaf area remaining on the leaf:

$$264 \quad \frac{dH}{dN_p} = -a_p, \quad (1)$$

265 where  $a_p$  is the area of the lesion that corresponds on average to a single pycnidium. Equation (1)  
266 represents mathematically a rather general statement that the green area remaining on leaves  
267 decreases with increasing numbers of pycnidia. If  $a_p$  depends neither on  $H$ , nor on  $N_p$ , then the  
268 solution of Eq. (1) is a linear function:

$$269 \quad H(N_p) = H_0(1 - \kappa N_p), \quad (2)$$

270 where  $\kappa = a_p/H_0$  and  $H_0$  is the green leaf area in the absence of infection. Alternatively, if  $a_p$  is

271 proportional to the green leaf area  $H$ , i.e.  $a_p = \kappa H$ , then the solution of Eq. (1) is an exponential  
272 function:

$$273 \quad H(N_p) = H_0 \exp(-\kappa N_p). \quad (3)$$

274 In both its linear and exponential versions, the model predicts that the leaf loses its green area as it  
275 carries higher numbers of pycnidia. We consider the green leaf area,  $H$ , as a quantity representing  
276 plant fitness and the number of pycnidia per leaf,  $N_p$ , as a proxy for the pathogen population present  
277 on the leaf (pathogen burden). Consequently, the slope of the decrease,  $\kappa$ , characterizes the tolerance  
278 of wheat to *Z. tritici*: it measures the amount by which the green leaf area decreases when a single  
279 pycnidium is added to the leaf. We call  $\kappa$  the intolerance parameter, as the cultivars with higher  $\kappa$ -  
280 values will lose their green leaf area at a higher rate than cultivars with lower  $\kappa$ -values when the  
281 number of pycnidia is increased.

282 Using this model we developed a novel way to measure tolerance of wheat to *Z. tritici* that  
283 operates on the scale of individual leaves (“leaf tolerance”) as opposed to the “whole-plant tolerance”  
284 that was studied previously in this pathosystem (Eyal & Ziv, 1974; Parker et al., 2004; Foulkes et al.,  
285 2006; Collin et al., 2018). We demonstrated in Notes S2 that these two components of tolerance  
286 contribute to overall tolerance as multiplicative factors (under the assumption that the relationships  
287 between the yield and the damaged leaf area and between the yield and the number of pycnidia per  
288 leaf are both linear). Based on two sets of biological assumptions, we formulated two hypotheses  
289 about the shape of the relationship between the green leaf area and the number of pycnidia on the leaf  
290 represented by Eq. (2) and (3). We next tested these hypotheses using the empirical data gathered  
291 from wheat leaves naturally infected by *Z. tritici*.

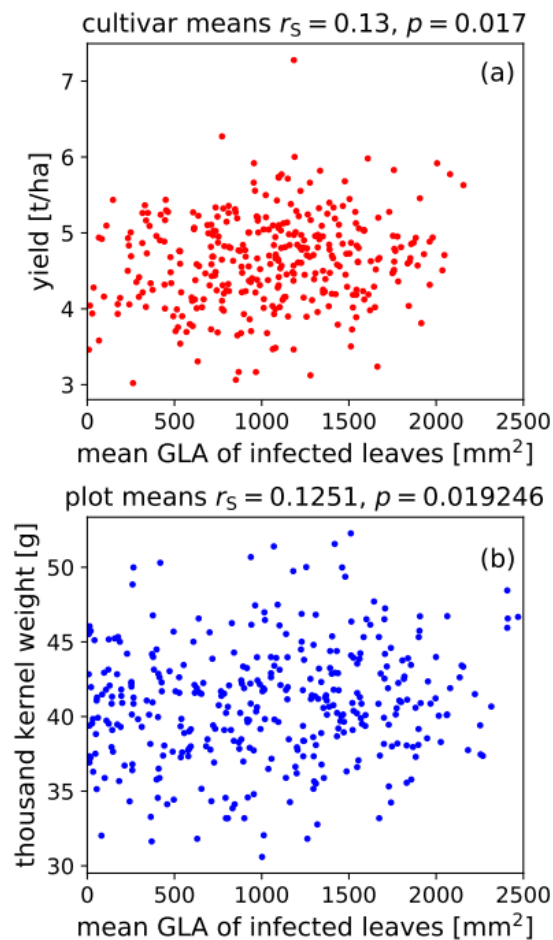
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### 293 **Relationship between green leaf area and yield**

294 To determine whether the green leaf area in our experiment can be considered a good measure  
295 of plant fitness, we studied the correlation between the green leaf area measured on infected leaves  
296 and yield measured as the weight of grains per unit area of land [tons per hectare (t/ha)] and as the  
297 thousand kernel weight (TKW). Figure 2 illustrates the outcomes: green leaf area averaged over  
298 leaves belonging to the same cultivar correlates weakly, but significantly, with the yield of the  
299 corresponding cultivar ( $r_s = 0.13$ ,  $p = 0.017$  for yield measured in t/ha and  $r_s = 0.13$ ,  $p = 0.019$  for  
300 yield measured as TKW).

301 We would like to emphasize that in our experiment, the green leaf area was recorded only on

302 infected leaves, while yield was measured from plants sampled without regard to their infection  
303 status, hence the yield measures comprised both healthy and infected plants. If in addition to the  
304 green area of infected leaves, we were able to also measure the STB incidence (that is the proportion  
305 of second leaves that were infected), then the product of the green leaf area on infected leaves times  
306 the STB incidence would give us the average green leaf area on all second leaves. This quantity  
307 would likely explain a much larger percentage of variation in yield. This has been convincingly  
308 demonstrated in a large number of field experiments, in which the reduction in wheat yield was  
309 strongly correlated with the reduction in the green leaf area of second leaves due to STB (e.g., King et  
310 al., 1983; Shaw & Royle, 1989b).  
311



312 **Figure 2** Correlation between the green leaf area (GLA) and wheat yield. (a) Yield in tons per hectare  
313 is plotted against the GLA of infected leaves measured at GS 75-85. Each value on the x-axis

314 represents the average value over approximately 30 leaves originating from two different plots  
315 belonging to the same cultivar. Each value on the  $y$ -axis represents the yield averaged over two plots  
316 planted with the same cultivar. (b) Yield measured as thousand kernel weight is plotted against the  
317 GLA. Each value on the  $x$ -axis represents the average value over approximately 15 leaves originating  
318 from a single plot belonging to the same cultivar. Each value on the  $y$ -axis represents the yield  
319 measured in a single plot.

320

### 321 **Green leaf area decreases nonlinearly with the number of pycnidia**

322 Figure 3a shows 11,152 individual leaf measurements of the number of pycnidia per leaf,  $N_p$ ,  
323 and the green leaf area,  $H$ . Overall, leaves lose more of their green area when they carry a larger  
324 number of pycnidia. The exponential function, Eq. (3), provided a better fit (standard error of the  
325 estimate  $s=472$ , coefficient of determination  $R^2=0.37$ ) than the linear function, Eq. (2) ( $s=508$ ,  
326  $R^2=0.28$ ). For this reason, we estimated the overall slope using the exponential function and obtained  
327 the best-fit parameter values: for the slope  $\kappa=0.00172$  and the intercept  $H_0=1816$  mm<sup>2</sup>. The spatial  
328 block had a significant effect on  $\kappa$  (likelihood ratio 6.9,  $p=0.008$ ) and  $H_0$  (likelihood ratio 41,  
329  $p=1.4 \times 10^{-10}$ ), but the cultivar had a much greater effect on  $\kappa$  (likelihood ratio 856,  $p=1.3 \times 10^{-47}$ )  
330 and  $H_0$  (likelihood ratio 2636,  $p<10^{-50}$ ).

331 There does not appear to be a clear pattern in terms of the goodness of fit neither for cultivars  
332 with different levels of tolerance nor for cultivars with different levels of resistance. To illustrate this,  
333 we present the goodness of fit metrics for both fit functions for four cultivars representing contrasting  
334 levels of tolerance and resistance. In a more tolerant cultivar Intact (blue curve in Fig. 3c), the linear  
335 fit yields  $s=349$ ,  $R^2=0.26$ , while the exponential fit yields  $s=345$ ,  $R^2=0.28$ . But in a less tolerant  
336 cultivar Lynx (red curve in Fig. 3c), the linear fit gives  $s=430$ ,  $R^2=0.59$  compared to the exponential  
337 fit that gives  $s=415$ ,  $R^2=0.62$ . In a more resistant cultivar Element the linear fit gives  $s=450$ ,  $R^2=0.2$   
338 and the exponential fit gives  $s=448$ ,  $R^2=0.21$ ; in a less resistant Arack the linear fit gives  $s=496$ ,  
339  $R^2=0.37$ , while the exponential fit gives  $s=490$ ,  $R^2=0.4$ . The fits for these two cultivars are shown in  
340 Fig. S2.

341

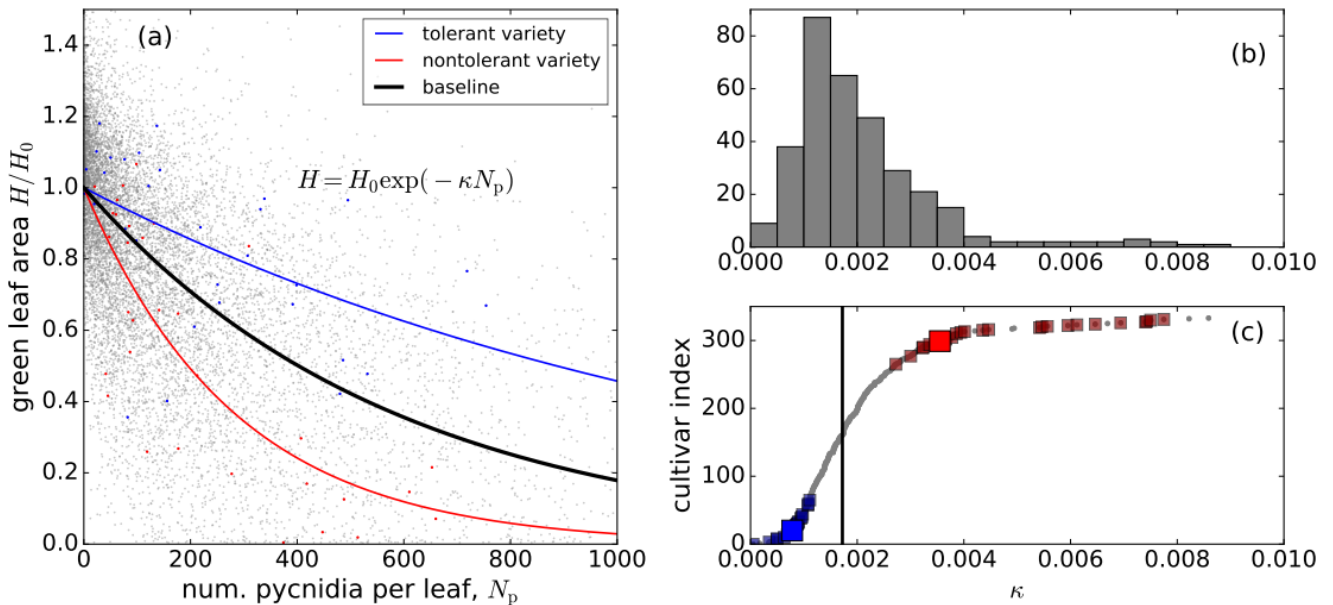
### 342 **Ranking of cultivars according to their tolerance to *Z. tritici***

343 We estimated  $\kappa$  for each cultivar by fitting the empirical dependency of the green leaf area on



344 the number of pycnidia with the exponential function [Eq. (3)], i.e. we obtained tolerance curves for  
 345 each cultivar (such as the two tolerance curves depicted Fig. 3a in blue and red). The distribution of  
 346 the  $\kappa$ -estimates is shown in Fig. 3b. Next, we ranked the cultivars according to their tolerance to *Z.*  
 347 *tritici* (see Fig. 3c and Table S1). Smaller  $\kappa$ -values corresponded to more tolerant cultivars. We also  
 348 compared  $\kappa$ -estimates for each cultivar to the baseline value (black vertical line in Fig. 3c). We found  
 349 that 22 cultivars were significantly more tolerant than the baseline (blue squares in Fig. 3c) and 25  
 350 cultivars were significantly less tolerant than the baseline (red squares in Fig. 3c). Thus, the cultivars  
 351 that we investigated in our field experiment exhibited significant differences with respect to leaf  
 352 tolerance.

353 To determine to what extent the ranking of cultivars with respect to their  $\kappa$ -estimates was  
 354 conserved between the two replicate blocks, we estimated the  $\kappa$ -values for each cultivar separately in  
 355 each of the blocks. The  $\kappa$ -estimates exhibited a positive and significant correlation between the two  
 356 replicates ( $r_s=0.18$ ,  $p=0.001$ ). In addition, we obtained similar data for a subset of 38 cultivars in  
 357 2015 (Stewart et al., 2016), which allowed us to evaluate the robustness of the outcomes. The  $\kappa$ -  
 358 estimates exhibited a positive but a non-significant correlation between the two years ( $r_s=0.3$ ,  
 359  $p=0.07$ ).



361 **Figure 3** Tolerance of wheat to *Z. tritici* measured on the scale of individual leaves. (a) Green  
 362 (Healthy) leaf area normalized by the leaf area in the absence of disease,  $H/H_0$ , is plotted versus the



363 number of pycnidia per leaf  $N_p$ . 11152 individual leaf measurements are shown using grey points.  
364 Best fit curves based on the exponential function  $H/H_0 = \exp[-\kappa N_p]$  are shown for all data (black  
365 curve) and for two example cultivars, a tolerant cultivar (Intact, blue curve), and an intolerant cultivar  
366 (Lynx, red curve). (b) The distribution of the 335 cultivars with respect to their  $\kappa$ -estimates. The most  
367 tolerant cultivars are those with the lowest  $\kappa$ -estimates at the left of the distribution. (c) Ranking of  
368 wheat cultivars according to their tolerance.  $\kappa$ -estimates for the 335 cultivars are shown in order of  
369 decreasing tolerance, that is increasing slope  $\kappa$  (grey points). Cultivars with tolerance significantly  
370 different from the baseline tolerance (black line) are marked with blue points (more tolerant) and red  
371 points (less tolerant), according to one-sided bootstrap t-tests with the confidence threshold of 0.05.  
372 Cultivars illustrated in panel (a) are marked using larger blue (cultivar Intact) and red (cultivar Lynx)  
373 squares.

374

## 375 **Relationship between tolerance/resistance and the year of cultivar** 376 **registration**

377 In a subset of 205 out of 335 cultivars, we had information on cultivar registration years. In  
378 those cultivars, tolerance increased with the year of cultivar registration: the correlation between the  
379 intolerance parameter  $\kappa$  and the cultivar's registration year was negative and significant ( $r_s = -0.17$ ,  $p$   
380  $= 0.02$ ). In contrast, resistance did not exhibit a significant correlation with the cultivar's registration  
381 year ( $r_s = -0.06$ ,  $p = 0.36$ ).

382

## 383 **Evidence for a tradeoff between leaf tolerance and resistance**

384 We found that the estimates of tolerance,  $\kappa$ , for each of the 335 cultivars correlated negatively  
385 with the mean number of pycnidia per leaf,  $N_p$ , the measure of resistance to STB, with  $r_s = -0.27$ ,  
386  $p = 5.8 \times 10^{-7}$  (Fig. 4). Interestingly,  $\kappa$ -estimates correlated positively with mean PLACL values in  
387 each cultivar ( $r_s = 0.31$ ,  $p = 8.6 \times 10^{-9}$ ).

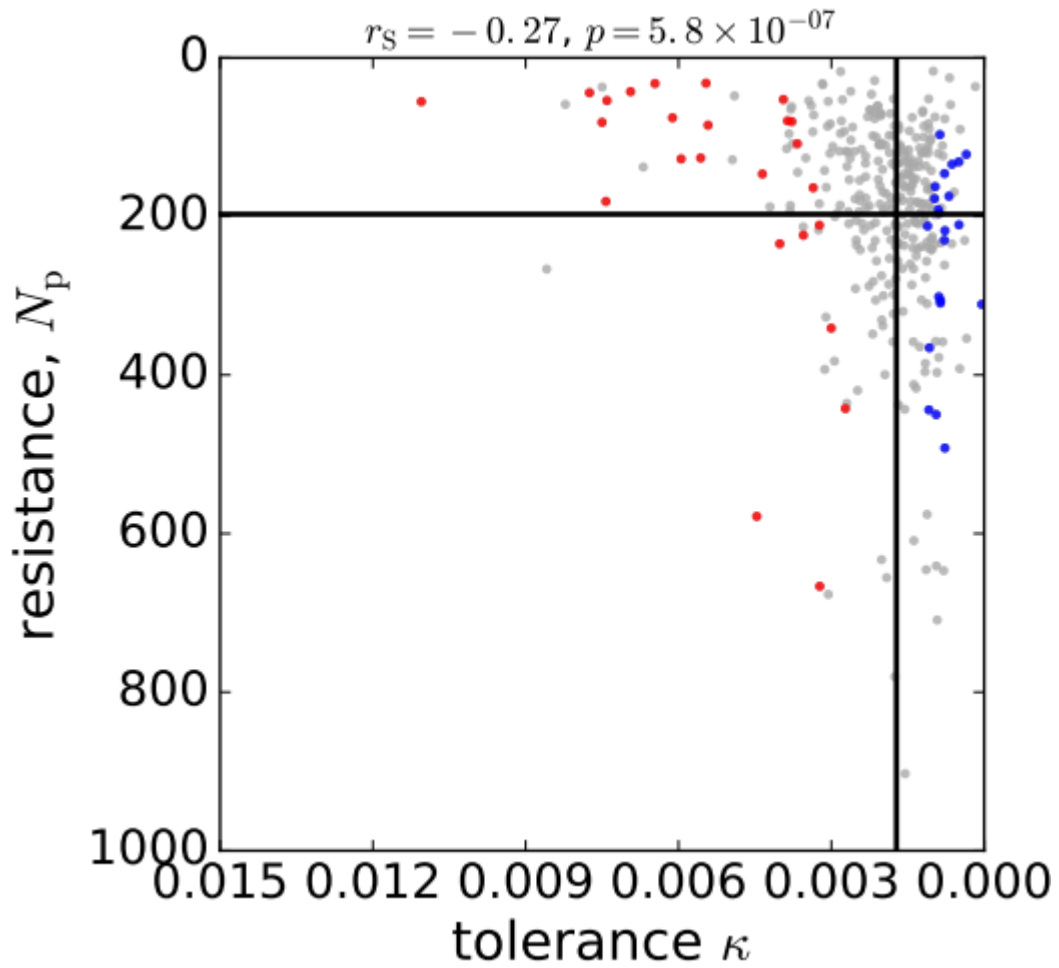
388 Why are more tolerant cultivars on average less resistant? In other words, why do more  
389 tolerant cultivars carry more pycnidia on their leaves than less tolerant cultivars? A possible  
390 explanation is that since the leaf area is limited, this places a constraint on the maximum number of  
391 pycnidia that a leaf can carry. This constraint should lead to a negative relationship between  $N_p$  and  $\kappa$   
392 in cases where the number of pycnidia on leaves belonging to the same cultivar approach the

393 maximum allowed by the leaf area. A less tolerant cultivar suffers a larger necrotic area forming, on  
394 average, per pycnidium [parameter  $a_p$  in Eq. (1)]. Consequently, the maximum number of pycnidia  
395 per leaf is lower in a less tolerant cultivar than in a more tolerant cultivar. Therefore, the limitation in  
396 the leaf area should affect more strongly pathogen populations infecting less tolerant cultivars, where  
397 the green leaf area decreases more steeply with increasing numbers of pycnidia (Fig. 5a). If the  
398 limitation in the leaf area is indeed the dominant factor responsible for the negative relationship  
399 between tolerance and resistance, then the negative correlation should be present in intolerant  
400 cultivars, but absent in tolerant cultivars. This is because only intolerant cultivars have a high  
401 proportion of their leaf area covered by lesions already at rather modest numbers of pycnidia (red  
402 curves in Fig. 5a).

403 To test this expectation in a more quantitative fashion, we subdivided all cultivars into two  
404 groups according to their tolerance estimates using the baseline tolerance ( $\kappa=0.00172$ ) as the  
405 threshold. Next, we conducted the Spearman's correlation test (based on a t-test) in each of the groups  
406 separately. We found that intolerant cultivars exhibited a significant correlation between tolerance  
407 and resistance ( $r_s = -0.34$ ,  $p = 4.3 \times 10^{-6}$ ), while tolerant cultivars showed no significant correlation  
408 between the two traits ( $r_s = -0.09$ ,  $p = 0.27$ ). To test the validity of this outcome, we performed a  
409 series of more robust tests based on a bootstrap t-test. We first computed the uncertainty in the  
410 estimate  $r_s = -0.27$  for all cultivars in the form of the 95 % confidence interval: CI, -0.37 to -0.16.  
411 We also computed the uncertainties in  $r_s$ -estimates for the two groups of cultivars, tolerant (  
412  $r_s = -0.09$ , CI, -0.25 to 0.07) and intolerant ( $r_s = -0.34$ , CI, -0.47 to -0.2). Figure S1 visualizes the  
413 bootstrap distributions of  $r_s$  and the CIs of  $r_s$ -estimates. The bootstrap t-test confirmed the outcome  
414 of the conventional t-test: the correlation between tolerance and resistance was significant among  
415 intolerant cultivars ( $p = 4.0 \times 10^{-6}$ ) and not significant among tolerant cultivars ( $p = 0.28$ ).  
416 Furthermore, we used a more stringent bootstrap t-test to compare the  $r_s$ -estimates among tolerant  
417 and intolerant cultivars and found that the correlation among intolerant cultivars was significantly  
418 more negative than among tolerant cultivars ( $p = 0.019$ ).

419 Figure 5 illustrates why intolerant cultivars should be more strongly affected by the limitation  
420 in the leaf area than tolerant cultivars. Figure 5a shows the tolerance curves for tolerant (blue) and  
421 intolerant (red) cultivars. We determined the maximum number of pycnidia that can be reached in  
422 each cultivar by computing the number of pycnidia,  $N_{pm}$ , at which 95 % of the green leaf area is lost

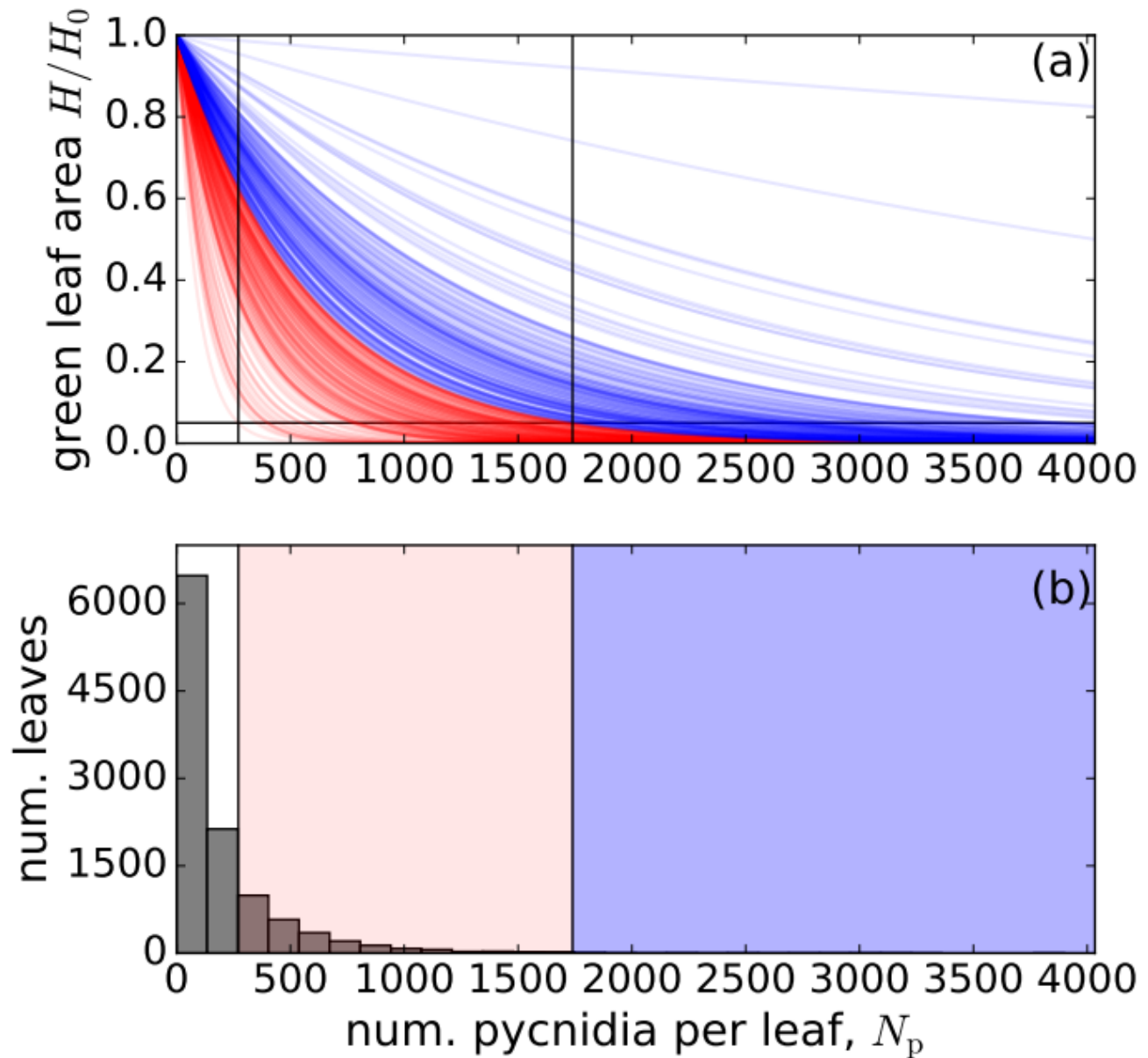
423 on average (this is given by the intersection of each tolerance curve with the horizontal line  $H$ /  
424  $H_0=0.05$  in Fig. 5a). Next, we computed the ranges in terms of  $N_{pm}$  corresponding to tolerant cultivars  
425 (blue-shaded area in Fig. 5b) and intolerant cultivars (red-shaded area in Fig. 5b). To determine the  
426 extent to which pathogen populations infecting tolerant and intolerant cultivars could be affected by  
427 the limitation in the leaf area, we compared these ranges with the overall distribution of leaves with  
428 respect to the numbers of pycnidia they carry (cf. the histogram in Fig. 5b and the blue- and red-  
429 shaded areas). While the blue-shaded area in Fig. 5b contained 38 leaves that constitute only about  
430 0.3 % of the total number of 11,152 infected leaves, the red-shaded area contained a much more  
431 substantial proportion (22 %) of the leaves (2,485 leaves out 11,152). Therefore, the intolerant  
432 cultivars contained a much greater proportion of the leaves on which pathogen populations were  
433 likely to be affected by limitations in the leaf area compared to the tolerant cultivars. Combined with  
434 the observation that only intolerant cultivars exhibited a negative relationship between tolerance and  
435 resistance, these data support our hypothesis that the negative relationship between tolerance and  
436 resistance arises largely due to a limitation in the leaf area.



438 **Figure 4** Correlation between leaf tolerance and resistance of wheat to STB. The measure of  
 439 resistance,  $N_p$  is plotted against the measure of tolerance,  $\kappa$ , for each of 335 wheat cultivars (grey  
 440 circles). Horizontal line shows the mean resistance and vertical line shows the baseline tolerance;  
 441 blue/red circles mark the cultivars that are significantly more/less tolerant than the baseline.

442

443



445 **Figure 5** Limitation in the leaf area in tolerant and intolerant wheat cultivars. (a) Tolerance curves  
 446 fitted to individual leaf data (raw data points are shown in Fig. 3a) for 335 wheat cultivars, blue  
 447 curves correspond to cultivars more tolerant than the baseline (black curve) and red curves  
 448 correspond to cultivars less tolerant than the baseline. The horizontal line shows the threshold  $H/H_0=0.05$ .  
 449 (b) Distribution of 11,152 individual infected leaves with respect to the number of pycnidia  
 450 per leaf,  $N_p$ . Shaded areas illustrate the ranges of  $N_p$ -values in which the pathogen population  
 451 infecting tolerant (blue) and intolerant (red) wheat varieties is affected by the limitation in the leaf  
 452 area.

## 453 **Discussion**

454 We discovered a novel component of tolerance in wheat to *Z. tritici* that operates on the scale of  
455 individual leaves (leaf tolerance). We devised an approach to quantify leaf tolerance empirically  
456 based on automated measurements of the green leaf area and the numbers of pycnidia on individual  
457 leaves. We gathered data from 11,152 individual infected leaves and characterized leaf tolerance in  
458 335 elite European wheat cultivars. Cultivars exhibited significant differences in leaf tolerance,  
459 suggesting that this trait is at least partially under genetic control. We also found a negative  
460 relationship between leaf tolerance and resistance to *Z. tritici*, indicating that there is a tradeoff  
461 between tolerance and resistance. Our study presents the first clear evidence for such a tradeoff in the  
462 context of plant-pathogen interactions. We discuss the consequences of this possible tradeoff for the  
463 selection of tolerance/resistance in agricultural host populations.

464 Surprisingly, the nature of this tradeoff turned out to be different from what we expected  
465 based on ecological theory. Our analysis shows that the tradeoff is only present in cultivars with less  
466 than average tolerance (intolerant cultivars) and that the limitation in the leaf area is the dominant  
467 factor responsible for its occurrence. This mechanism differs from the host metabolic constraints that  
468 are usually implicated in the tradeoff between resistance and tolerance. We expect this novel  
469 mechanism underlying a tradeoff between tolerance and resistance could operate across a large class  
470 of infectious diseases in plants and animals, in which tolerance to the pathogen can be measured and  
471 the amount of host resources available to the pathogen can limit the pathogen population within the  
472 host. A key conceptual outcome of our study is that observing a negative relationship between  
473 tolerance and resistance is not necessarily indicative of a metabolic tradeoff, whereby tolerance and  
474 resistance confer fitness costs. Instead, as we show here, a tradeoff can arise via an entirely different  
475 mechanism, namely a limitation in the amount of host tissue or resources available to the pathogen  
476 (or more generally a limitation in the degree of fitness a host can lose because of infection). In the  
477 two prominent examples of a negative relationship between tolerance and resistance found in the  
478 literature (herbivory in plants, Fineblum & Rausher, 1995; malaria in mice, Råberg et al., 2007), the  
479 mechanisms underlying this relationship remain unknown.

480 The limitation in the leaf area is expected to constrain the evolution of pathogen populations  
481 towards higher reproductive fitness on intolerant cultivars, but the pathogen may overcome this  
482 limitation by evolving lower virulence (Anderson & May, 1982). According to our current  
483 understanding in ecological theory, a metabolic tradeoff between tolerance and resistance is expected

484 that arises due to limitation in resources available to the host. Our data does not exclude the  
485 possibility of a metabolic tradeoff, but its detection may require an even more comprehensive dataset  
486 than what we have at hand. Evidence for the metabolic tradeoff is more likely to be found in the  
487 future by considering a larger number of sufficiently tolerant cultivars, because as we demonstrated  
488 here, in more tolerant cultivars the relationship between tolerance and resistance is not dominated by  
489 the limitation in the leaf area.

490 Jackson et al. (2014) reported that mature male voles were more tolerant to macroparasite  
491 infection compared to young males. Zeller & Koella (2017) found that the availability of nutrients  
492 influenced the magnitude of tolerance to microsporidian parasites in mosquito populations: mosquitos  
493 that had a restricted food supply were generally less tolerant to infection. It is plausible that both of  
494 these factors influence the tolerance of wheat leaves to *Z. tritici*. First, only the STB-induced damage  
495 on the three upper-most wheat leaves correlates strongly with yield loss (e.g., Thomas et al., 1989).  
496 Hence leaf tolerance may confer a fitness advantage to plants only during the later developmental  
497 stages when these leaf layers have already emerged. As a result, selection may have favored tolerance  
498 to manifest only during this late stage of development (similar to the adult plant resistance that is well  
499 known for several plant diseases). Second, the severity of STB epidemics is known to increase with  
500 increased rates of nitrogen fertilization (Leitch & Jenkins, 1995). This may result from an improved  
501 nutritional or physiological status of the leaves or a more disease-conducive physical environment.  
502 Hence leaf tolerance and its relationship with resistance may be affected by changing the rate of  
503 nitrogen application. Empirical investigation of both of these factors is feasible in the *Z. tritici*-wheat  
504 pathosystem and would improve our understanding of the ecological determinants of tolerance.

505 The dataset we used to characterize tolerance to a plant pathogen is unusually large compared  
506 to previous studies. For example, the number of different wheat genotypes used to study tolerance of  
507 wheat to STB in earlier studies ranged from 2 to 25 (Eyal & Ziv, 1974; Zuckerman et al., 1997;  
508 Parker et al., 2004; Foulkes et al., 2006; Collin et al., 2018). Råberg et al. (2007) investigated  
509 tolerance of mice to malaria infection using five mouse strains and three strains of *Plasmodium*  
510 *chabaudi*. Only the study of human tolerance to HIV (Regoes et al., 2014) and the study of tolerance  
511 in the wild population of Soay sheep to a gastrointestinal nematode infection (Hayward et al., 2014)  
512 had comparably large datasets that included thousands of infected individuals. Remarkably, as we  
513 demonstrated here, both tolerance and resistance can be readily quantified from digital images of  
514 infected leaves.

515 Our analyses and interpretations are based on two important assumptions: (i) the reduction in  
516 the green area of the second leaf is a major driver of yield loss induced by STB, and; (ii) the number  
517 of pycnidia per leaf is a good measure of the size of the pathogen population on a leaf. We justify  
518 these assumptions as follows: (i) Compared to infected leaves that have a large fraction of their  
519 surface area covered by lesions, leaves with a larger green area intercept a larger fraction of the  
520 incoming radiation, which contributes to plant yield. There is overwhelming empirical evidence  
521 showing that the reduction in the green leaf area is a major driver of yield loss for many leaf-affecting  
522 diseases of wheat (for example, Teng and Gaunt, 1980; Seck et al., 1991; Gaunt 1995; Bhathal et al.,  
523 2003), including STB (Eyal & Ziv, 1974; King et al., 1983; Forrer & Zadoks, 1983; Shaw & Royle,  
524 1989b; Thomas et al., 1989). In particular, these studies conclude that the reduction in yield is  
525 strongest for the three upper leaves (including the second leaf on which we focused in this study) if  
526 the green leaf area is measured during the critical phase of seed development. In our field experiment,  
527 we could not determine yield corresponding to each individual infected leaf that we sampled.  
528 However, we measured overall yield per plot and found significant correlations between the green  
529 leaf area of second leaves (sampled at GS 75-85) and yield, measured both as tons per hectare and as  
530 thousand kernel weight ( $r_s=0.13$ ,  $p=0.017$  for yield measured in t/ha and  $r_s=0.13$ ,  $p=0.019$  for  
531 yield measured as TKW, see Results, Fig. 2). Note that the green leaf area was recorded only on  
532 infected leaves, while the yield was measured from plants sampled without regard to their infection  
533 status, hence the samples used to calculate yield comprised both healthy and infected plants.  
534 Therefore, the correlation coefficients we obtained here are likely to considerably underestimate the  
535 actual correlations between the green leaf area and yield, consistent with previous studies that found  
536 much stronger correlations (Eyal & Ziv, 1974; King et al., 1983; Forrer & Zadoks, 1983; Shaw &  
537 Royle 1989b). In particular, Thomas et al., (1989) reported that STB severity on second (flag-1)  
538 leaves had a particularly strong effect on yield. Thus, there is compelling empirical evidence in the  
539 existing literature and also an indication in the present study showing that the reduction in the green  
540 leaf area of second leaves contributes substantially to the yield loss induced by the disease.

541 To justify (ii) we first note that in this study we investigate tolerance and resistance from an  
542 evolutionary perspective. Hence, the measure of pathogen burden should reflect the reproductively  
543 active population of the pathogen. Measuring the total number of spores produced per leaf may  
544 provide a better way to quantify pathogen burden, but was not possible in our experiment because it  
545 could not be automated. However, we believe that the number of pycnidia is a reasonable proxy of



546 pathogen burden because the number of pycnidia was shown to be the main factor determining the  
547 number of pathogen spores produced on an infected leaf (Stewart et al., 2016a). In addition, a recent  
548 field experiment showed that the proportion of the leaf area covered by STB lesions was largely  
549 independent from the number of pycnidia produced on a leaf (Karisto et al., 2018). Combining these  
550 two findings led us to conclude that the number of pycnidia per leaf is a better measure to quantify  
551 the pathogen population inhabiting a leaf than the area of a leaf damaged by infection.

552 According to our statistical analysis, an exponential decrease better fits the empirical  
553 dependency of the green leaf area on the number of pycnidia per leaf than a linear decrease,  
554 demonstrating that leaf tolerance curves were nonlinear. This deviates from what was reported in  
555 earlier analyses of wheat tolerance to *Z. tritici*: tolerance curves were typically fitted using linear  
556 functions (Eyal & Ziv, 1974; Parker et al., 2004; Foulkes et al., 2006), with the notable exception of  
557 the study by Shaw & Royle (1989b) that used a family of nonlinear curves. It was important to  
558 establish the departure from linearity in our study for two reasons. First, it allowed a more accurate  
559 comparison of tolerance estimates in different cultivars against the baseline. Second, it provided  
560 additional insight into the biology of the infection, because the linear model and the exponential  
561 model are based on different biological assumptions.

562 Our analysis of the model (Notes S1) demonstrates that the linear function Eq. (2)  
563 approximates well the relationship between the green leaf area and the number of pycnidia on the leaf  
564 when the number of pycnidia on the leaf is sufficiently low. This implies that the number of lesions  
565 on the leaf is also likely to be low, with the necrotic area covering only a small proportion of the total  
566 leaf area. Under this scenario, lesions develop mostly independently of each other. However, when  
567 lesions start to occupy a large proportion of the total leaf area, they become more likely to influence  
568 each other's development due to limitations in space and/or resources. Under this scenario, Eq. (2) is  
569 no longer a good approximation and the necrotic area  $a_p = a_l/n_p$  that corresponds to a single  
570 pycnidium may depend on both green leaf area  $H$  and the number of pycnidia  $N_p$  already present on  
571 the leaf (i.e., a density dependence). Above, we considered the simplest case of this dependency when  
572  $a_p$  is proportional to  $H$ , which resulted in the exponential solution [Eq. (3)]. This dependency may  
573 result from the lesion area  $a_l$  being proportional to the remaining green leaf area  $H$ . Biologically, this  
574 means that as more of the green leaf area becomes occupied by lesions, lesions tend to grow to a  
575 smaller size due to limitations in available green space and/or resources in the leaf. Alternatively, this  
576 dependency may arise due to the number of pycnidia per lesion  $n_p$  being inversely proportional to the

577 remaining green leaf area  $H$ . This may occur due to an increased activation of plant defenses as more  
578 of the leaf area becomes occupied by lesions. Since our analysis shows that Eq. (3) is better supported  
579 by the data we collected for *Z. tritici* than Eq. (2), we conclude that density dependence contributes to  
580 the relationship between the number of pycnidia and the green leaf area, and is therefore expected to  
581 influence epidemiological dynamics on the scale of individual leaves. However, dedicated  
582 experiments under controlled conditions will be needed to reveal the mechanism behind the density  
583 dependence.

584 We recently identified several chromosomal regions and candidate genes in the wheat genome  
585 associated with resistance to STB (quantified as the mean pathogen burden, i.e. the mean number of  
586 pycnidia per leaf) using the same phenotypic dataset (Karisto et al., 2018) and a genome-wide  
587 association study (GWAS; Yates, et al., 2019). We hypothesize that a GWAS based on the leaf-level  
588 tolerance estimates that we report here could also identify significantly associated chromosomal  
589 regions. This would indicate that leaf-level tolerance has an underlying genetic basis and is subject to  
590 evolutionary processes, and potentially elucidate molecular mechanisms affecting leaf-level  
591 tolerance. One possible mechanism could be related to additive actions of toxin sensitivity genes  
592 carried by different wheat cultivars that interact with host-specific toxins produced by the pathogen,  
593 as demonstrated for *Parastagonospora nodorum* on wheat (Friesen et al., 2008; Oliver et al., 2012).  
594 This mechanism would contribute to tolerance if the number of actively interacting toxin - toxin  
595 sensitivity gene pairs exceeds a threshold beyond which the removal of a single gene pair does not  
596 impair the pathogen reproduction, but nevertheless reduces the host damage, thereby decreasing the  
597 average necrotic area per pycnidium and increasing leaf tolerance.

598 Breeding for resistance to STB disease is based on disease assessments that do not quantify  
599 pathogen reproduction on the leaves. The amount of disease is typically assessed visually using a  
600 categorical scale of severities corresponding to different ranges in terms of the proportion of necrotic  
601 area on the leaves (or PLACL). As a result, breeders are likely to select for cultivars with lower  
602 PLACL. But as we have shown above, cultivars with lower PLACL are on average more tolerant.  
603 Hence, by focusing on PLACL wheat breeders may have inadvertently selected for increased  
604 tolerance. Due to the tradeoff between tolerance and resistance, this simultaneously favors lower  
605 levels of STB resistance. Some support for this hypothesis is given by our preliminary analysis of the  
606 relationship between tolerance/resistance and the year of cultivar registration. In a subset of 205 out  
607 of 335 cultivars, we found that estimates of tolerance increased with the year of cultivar registration,

608 while estimates of resistance did not exhibit a significant change over time  $\kappa$ . This pattern suggests  
609 that the selection practices used by plant breeders have led to wheat populations in Europe with  
610 higher tolerance but lower resistance to STB over time.

611 The method to quantify leaf tolerance presented here can potentially be used to measure  
612 tolerance to other pathogens that infect plant leaves. The necessary condition is that digital images of  
613 infected leaves should enable quantitative measurements of both the damage to the plant induced by  
614 the pathogen and the size of the pathogen population on the leaf. This should be possible for many  
615 necrotrophic pathogens that form visible fruiting bodies on the leaf surface. Using this approach may  
616 facilitate the discovery of similar tradeoffs between tolerance and resistance across a wide array of  
617 plant-pathogen systems.

618

619

## 620 **Acknowledgements**

621 We thank P. Karisto, D. Dos Santos Pereira, S. Fouché, and L. Meile for help in collecting and  
622 processing leaf samples; H. Zellweger for managing the wheat trial; and A. Hund and J. Anderegg for  
623 providing data on wheat yield. A. Mikaberidze would like to thank P. Karisto and R. Regoes for  
624 fruitful discussions. A. Mikaberidze gratefully acknowledges financial support from the Swiss  
625 National Science Foundation through the Ambizione grant PZ00P3\_161453.

626

## 627 **Author Contributions**

628

629 AM and BAM conceived and designed the experiment. AM supervised the field collection and  
630 processing of leaf samples. AM analyzed the data in discussions with BAM. AM wrote the  
631 manuscript. AM and BAM revised the manuscript.

632

## 633 **Data Accessibility Statement**

634 Raw data is available from the Dryad Digital Repository: <https://doi.org/10.5061/dryad.171q4>. We  
635 confirm that, should the manuscript be accepted, additional data supporting the results will be  
636 archived in an appropriate public repository such as Dryad or Figshare, and the data DOI will be  
637 provided at the end of the article.

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## 907 **Supporting Information**

908

909 The following Supporting Information is available for this article:

910 **Notes S1.** Simple model of leaf tolerance

911 **Notes S2.** Two components of tolerance

912 **Figure S1.** Detailed statistical analysis of the correlation between tolerance and resistance among  
913 tolerant and intolerant cultivars.

914 **Figure S2.** Example fits for cultivars with contrasting levels of resistance.

915 **Table S1.** Ranking of wheat cultivars according to their tolerance to *Zymoseptoria tritici*.

916

917

918 **Notes S1.** Simple model of leaf tolerance

919 Here we derive a simple model of infection of wheat leaves by *Z. tritici*. We assume that each lesion  
920 has an area  $a_l$  and contains  $n_p$  pycnidia. How much will the green leaf area  $H$  diminish under a small  
921 increase in the number of pycnidia  $\Delta N_p$ ? To find out, we express a small decrease in the green leaf  
922 area  $\Delta H$  in terms of a small increase in the number of lesions:  $\Delta H = -a_l \Delta N_l$ . At the same time, the  
923 increment in the number of pycnidia  $\Delta N_p$  is related to the increment in the number of lesions:  
924  $\Delta N_p = n_p \Delta N_l$ . A simple rearrangement yields the relationship between the increment in the number  
925 of pycnidia and the decrease in the green leaf area:  $\Delta H = -a_l/n_p \Delta N_p$ . By taking the limit  $\Delta N_p \rightarrow 0$   
926 and  $\Delta H \rightarrow 0$  we obtain the differential equation:

927 
$$\frac{dH}{dN_p} = -a_p, \quad (4)$$

928 where  $a_p = a_l/n_p$  represents the area of the lesion that corresponds to a single pycnidium.

929

930 **Assumption 1.**

931 We first assume that  $a_p$  depends neither on  $H$ , nor on  $N_p$ . In this case, the solution of Eq. (4)  
932 is a linear function that can be written as:

933 
$$H(N_p) = H_0(1 - \kappa N_p), \quad (5)$$

934 where  $\kappa = a_p H_0$  and  $H_0$  is the green leaf area in the absence of infection.

935

936 **Assumption 2.**

937 Here, we relax Assumption 1 and consider the case when the area  $a_p$  is proportional to the  
938 green leaf area  $H$ , i. e.

939 
$$a_p = \kappa H. \quad (6)$$

940 In this case, the solution of Eq. (4) is an exponential function that can be expressed as:

941 
$$H(N_p) = H_0 \exp(-\kappa N_p). \quad (7)$$

942 Note, that when  $\kappa N_p$  is small, we can expand the function  $H(N_p)$  Eq. (7) in the Taylor's series with  
943 respect to its argument  $\kappa N_p$ . Retaining the zeroth and the first terms of the series yields the linear  
944 dependency Eq. (5).

945

946 **Notes S2.** Two components of tolerance

947 Here we demonstrate mathematically that the novel component of tolerance of wheat to STB that we  
948 measured in this experiment and the tolerance components that were measured previously contribute  
949 to overall tolerance as multiplicative factors. We use the critical point model (King et al.,1983; Shaw  
950 & Royle, 1989a) to relate the grain yield to the loss in the green leaf area in the three upper-most  
951 leaves:

952 
$$Y = Y_0 - \sum_{i=1}^3 \kappa_{0i} I_i, \quad (8)$$

953 where  $Y$  is the yield in the presence of disease (measured for example in tons per hectare),  $Y_0$  is  
954 the yield in the absence of disease and  $I_i$  is the area of the  $i$ th leaf ( $i=1$  for flag leaf,  $i=2$  for flag-1  
955 leaf,  $i=3$  for flag-2 leaf) that became chlorotic or necrotic as a result of infection, measured during  
956 the critical stage of grain development (around GS 75). The slope  $\kappa_{0i}$  represents the intolerance  
957 parameter that may have different values in different leaf layers. We call this component of  
958 tolerance "whole-plant tolerance", because it includes various mechanisms of compensation for the  
959 leaf damage at the level of the whole plant.

960 In this study, we argue that the number of pycnidia per leaf,  $N_{pi}$ , corresponding to the  $i$ th

961 leaf layer allows for a more accurate quantification of the pathogen population than the area of the  
 962 leaf  $I_i$  damaged due to disease. Similarly to Eq. (8), this leads to the following relationship between  
 963 the yield and the number of pycnidia per leaf:

$$964 \quad Y = Y_0 - \sum_{i=1}^3 \kappa_{toti} N_{pi}, \quad (9)$$

965 where  $\kappa_{toti}$  is the total intolerance parameter and as in Eq. (8), we perform a summation over the  
 966 three upper-most leaf layers. Further, we assume for simplicity that the linear model Eq. (2)  
 967 describes well the relationship between the green leaf area,  $H_i$ , and the number of pycnidia per leaf  
 968  $N_{pi}$ . The damaged leaf area,  $I_i$ , can then be determined from Eq. (2), but for each individual leaf  
 969 layer  $i$ , according to

$$970 \quad I_i = H_{0i} - H_i = a_{pi} N_{pi}, \quad (10)$$

971 where  $a_{pi}$  is the damaged leaf area that corresponds on average to a single pycnidium, which  
 972 quantifies the degree of tolerance on the scale of individual leaves that we measured in this study  
 973 for the second leaf (i.e., flag-1 leaf). Here we used the linear approximation of the dependency of  
 974 the green leaf area on the number of pycnidia, which works well when the number of pycnidia per  
 975 leaf is sufficiently low. In this case,  $a_{pi}$  is related to the intolerance parameter,  $\kappa_i$ , that we measured  
 976 here through  $H_{0i}$ , the green leaf area in the absence of disease:  $a_{pi} = H_{0i} \kappa_i$ . To establish the  
 977 relationship between the overall tolerance quantified by  $\kappa_{tot}$ , whole-plant tolerance quantified by  $\kappa_0$   
 978 and leaf tolerance quantified by  $\kappa$ , we substitute  $I$  from Eq. (10) in Eq. (8)

$$979 \quad Y = Y_0 - \sum_{i=1}^3 \kappa_{0i} a_{pi} N_{pi}, \quad (11)$$

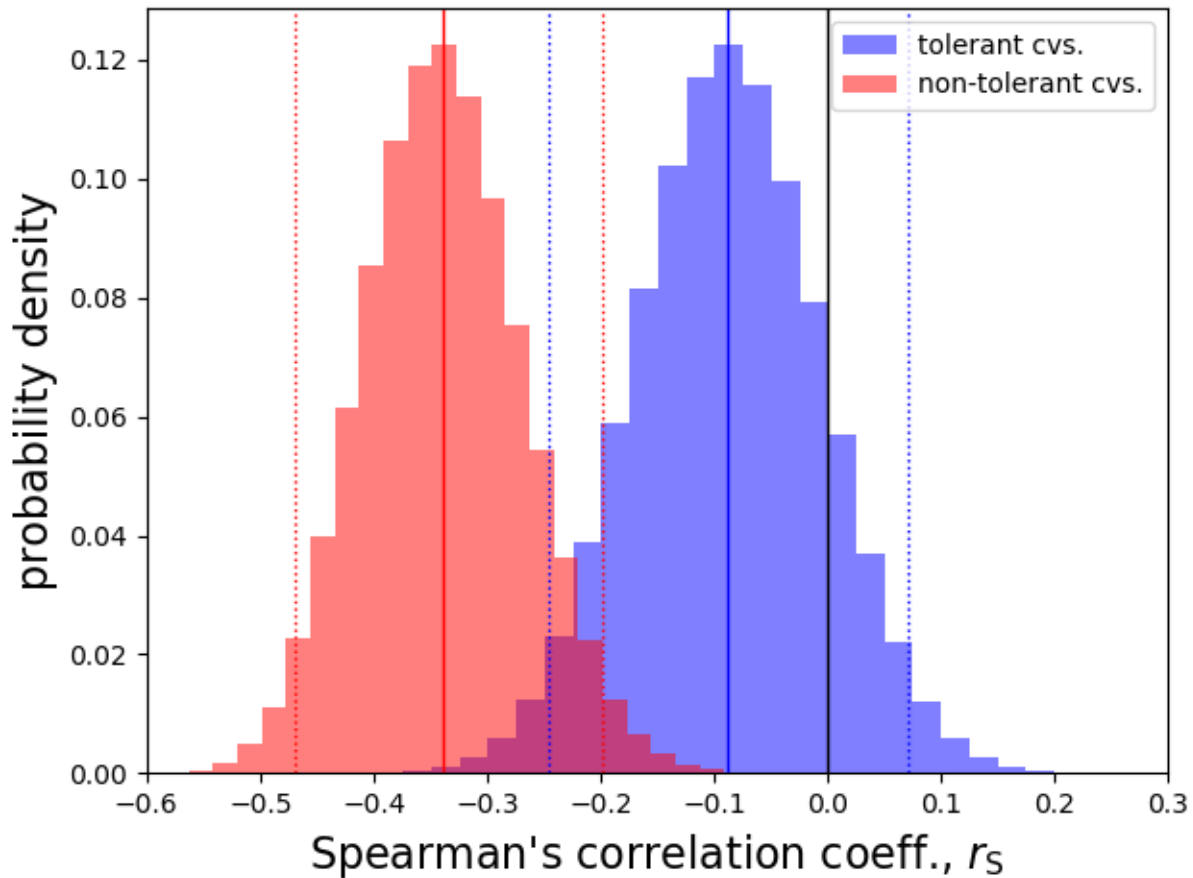
980 Comparison of Eq. (11) and Eq. (9) reveals that for each leaf layer  $i$

$$981 \quad \kappa_{toti} = \kappa_{0i} a_{pi}, \quad (12)$$

982 the total intolerance parameter is a product of the whole-plant and leaf intolerance parameters. If  
 983 the relationships between the yield,  $Y$ , and the damaged leaf area,  $I_i$ , and between the yield,  $Y$ , and  
 984 the number of pycnidia per leaf,  $N_{pi}$ , are not linear, then the yield would still be a decreasing, but a  
 985 nonlinear function of the number of pycnidia per leaf, and the multiplicative relation between the  
 986 total tolerance and the two components of intolerance in Eq. (12) will not be retained.

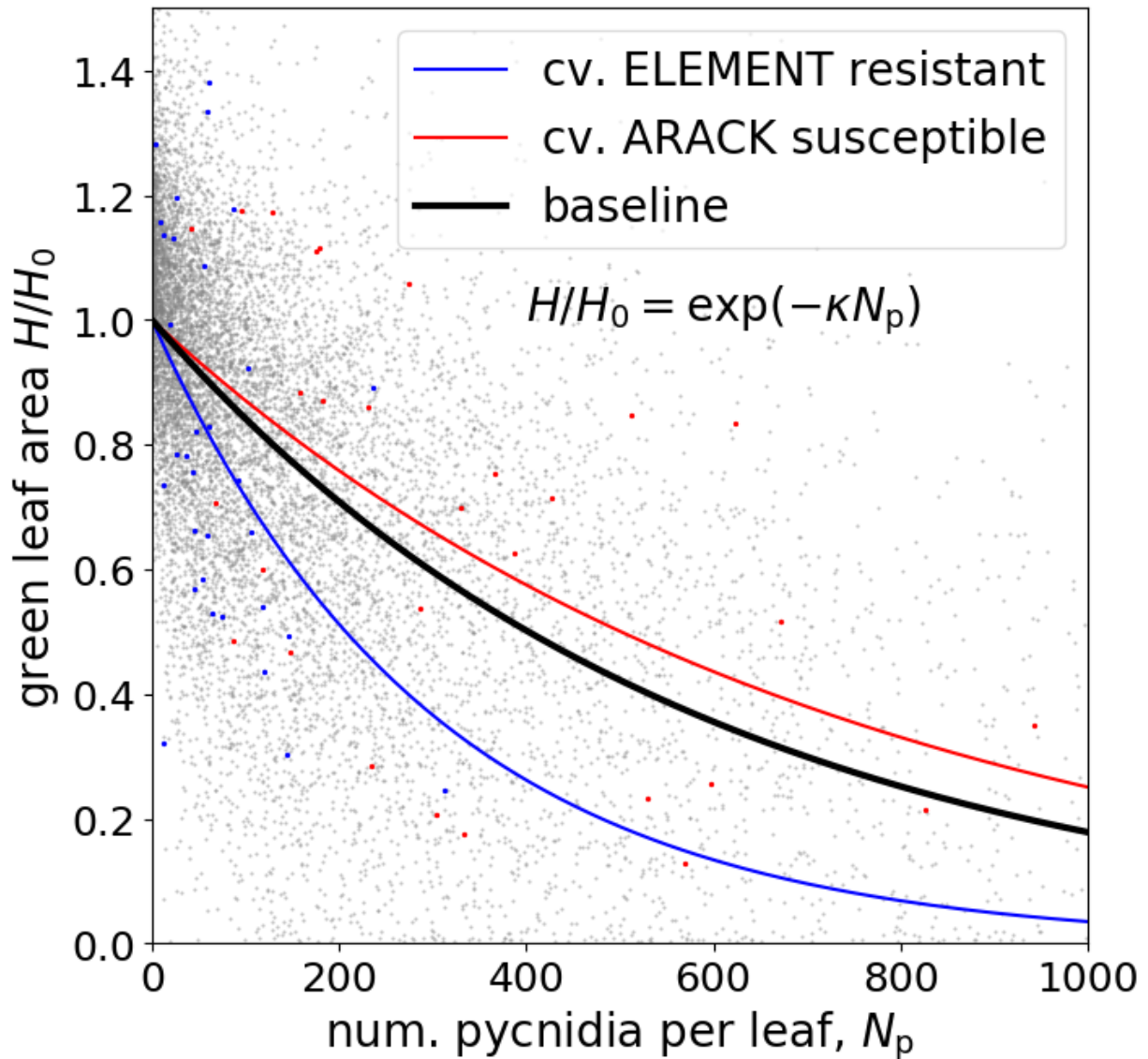
987

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991 **Figure S1** Detailed statistical analysis of the correlation between tolerance and resistance among  
 992 tolerant and intolerant cultivars. The analysis is based on creating a large number of bootstrap  
 993 samples ( $n_{bs}=1'000'000$ ) on the basis of the estimates of tolerance and resistance in 335 wheat  
 994 cultivars shown in Fig. 3 of the main text. The histogram shows the distributions of the values of the  
 995 Spearman's correlation coefficient,  $r_s$ , among tolerant (blue) and intolerant (red) cultivars. These  
 996 distributions approximate the underlying probability distributions. Solid vertical lines show the  
 997 point-estimates of  $r_s$  among tolerant (blue) and intolerant (red) cultivars. Dotted vertical lines show  
 998 the 95 % confidence intervals of the corresponding point estimates.





1001 **Figure S2** Example fits for cultivars with contrasting levels of resistance. Cultivar Element (estimate  
 1002 of resistance  $N_p = 66$  estimate of tolerance  $\kappa = 0.0033$ , ) is more resistant than cultivar Arack (estimate  
 1003 of resistance  $N_p = 412$ , estimate of tolerance  $\kappa = 0.0014$ ). However, in terms of tolerance the two  
 1004 cultivars are not significantly different from the baseline (black curve).