Response to the comments

Manuscript PCIEvolBiol#628

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

by Loup Rimbaud, Julien Papaïx, Jean-François Rey, Benoît Moury, Luke G. Barrett and Peter H. Thrall

We are grateful to the reviewers and the recommender for showing interest in this article, as well as their constructive and insightful comments. In this improved version of our article, we have taken these comments into account by especially:

- including a supplemental Text S1 containing a full description of the mathematical model;
- detailing the computation of model outputs in the main text;
- moving some paragraphs of the 'results' section into 'methods' for improved understanding of the model and numerical experiments, as suggested.

Please find below a point-by-point response to the comments (the original comments are cited in blue italic font). Our new submission includes a version of the article in track-change mode, as well as a "clean" version online (https://www.biorxiv.org/content/10.1101/2022.08.30.505787v2). In our responses, line numbers refer to the article in track-change mode.

Reviewer #1

We thank Jean-Paul Soularue for his meticulous review and numerous suggestions to improve our manuscript.

I have only minor suggestions for improvement:

My main concern is that I find the current manuscript difficult to follow in places. The introduction is fine but the methods are too succintely explained. Current model description contains a short mix of statements that do not allow the reader to understand and evaluate the model. I agree with the authors that there is no need to give, again in this new paper, all the details of the model. Yet, the model proposed in this paper is not exactly the same as the model by Rimbaud et al. (2018 c). Adding more information about the composition of the fields, the traits targeted by the resistance, the host pathogen interaction, and mutation is necessary (see some remarks below).

Action: Supplemental text S1 now fully describes the mathematical equations of the model used in this study.

Some elements, essential for model understanding, are given in Results section; they should be moved in Methods section.

Action: Done as suggested (see details in specific comments).

As the model proposed is complex and the experimental design ambitious, it is not easy for the reader to get an integrative picture of all the results produces. That being said, the manuscript does a good job with regard to showing and commenting disease development in susceptible and resistant fields, and resistance durability. But I find the results section lacks of a more detailed presentation of the

total damages caused by the pathogen (as given for instance in figure S5), that could help in the interpretation of the results, and that would inform the reader about the overall yield of the landscape depending on the deployment strategy implemented.

Response: With regard to the total damages caused by the pathogen, there may be a misunderstanding in the direction of the output variable (better disease control for higher Green Leaf Area, GLA). In fact, in figure S5, we do not see any result on total damage that contrasts with the results presented in the main text (see the related specific comment below for details).

Action: A full description of the computation of output variables in the Methods section (l. 287-303) will help get a better interpretation of the results.

In the discussion, the authors propose comparisons with existing litterature and descriptions of the mechanisms leading to the patterns predicted. The discussion is overall efficient, although the part about the combination of major resistance genes with adult plant resistance genes is not easy to follow. The mention of a competition effect among the different pathogen strains was also sometimes a bit vague, as it does not always give the reader a good understanding of what happened in the simulations. This overall feeling may be the consequence of an insufficient understanding of the model.

Response: We hope that model description in Text S1 will improve the understanding of the model.

Action: In addition, the Discussion paragraph on the competition effect has been extended to give a more mechanistic description, as suggested (l. 536-556, see also specific comments below).

Below are my specific comments on the paper:

l. 106, 108, and further. «hard» and «soft» selection recalls the dichotomy proposed by Wallace (1975, Evolution) (see also Reznick, 2015, Heredity)). If the aim of the authors is to quantify the strength of the selection undergone by the pathogen, I recommend to use « strong » and « weak » selection, largely used in the litterature (e.g. Whitlock 2008, Molecular Ecology).

Response: Thanks for this remark. We indeed aim to quantify the strength of the selection.

Action: we replaced “hard” by “strong” and “soft” by “weak” selection throughout the manuscript.

l. 108. The constraint imposed on pathogen populations by delayed resistances and partial resistances are not exactly the same. Delayed resistances induce, at the plant scale, a sudden change in the direction of the selection pressure, with an intensity that can be strong. By contrast, partial resistances impose constant but relatively weak selection pressure on the pathogen population.

Response: this is totally correct.

Action: we mention this point in Introduction (l. 109-112).

l. 131. As sexual reproduction is not simulated here, I would remove the beginning of the sentence.

Action: done.

l. 136. Unlike the model by Rimbaud et al. (2018c), I understand that there is here no aggressiveness quantitative component, is it correct? Few sentences describing the traits, the interaction between host and pathogen and how mutation affects the expression of the traits are necessary here. For instance, does the transformation of a ‘wt’ genotype into a ‘rb1’ a genotype or a ‘rb12’genotype require the same number of mutations?

Response: this is correct: there is no quantitative interaction between the host and the pathogen.

Action: A full description of pathogen-host interaction is present in Text S1. In addition, in the main text we explain more in details the effect of resistance on different pathogenicity traits (l. 166-177, see also the comment below on l. 177-181). In addition, we now mention clearly in the main text that mutation from wt to rb1 or rb2 requires a single mutation (l. 143 & 217 & 271) and that two distinct mutations are required from wt to rb12 (l. 273).

l. 142. I understand that each field is assumed to be perfectly mixed, and that the density of hosts is assumed to be globally homogeneous. Therefore, the probability that a fungal genotypes carried by a spore reaching field i penetrates an healthy host depends on the proportion of healthy hosts in field i and the composition of the cloud of spores. I would add these important elements to the text.

Response: this is correct.

Action: these elements are now clear in Text S1. We also mention in the main text (l. 145) that the spatial unit is the field.

l. 177 to 181. This part is also at the heart of the model and not specific to the experiment. I suggest to transfer these lines to model description. How resistance activation operate on latent period duration is well explained, but how does resistance activation influence other traits ? For instance I am not sure to understand correctly: what happens when the resistance targeting pathogen infectivity is activated within a host already infected? Nothing?

Response: this is correct, nothing happens when resistance targeting infectivity activates in an already infected host.

Action: we moved the lines as suggested. We also detailed what happens when resistance targets all pathogenicity traits (l. 166-177).

l.186 : « off season survival » is mentionned for the first time here. Mentionning this important component of the model earlier in overall model description (l. 144?) would facilitate the overall understanding of the structure of the model.

Action: done as suggested.

l. 250 to 258. I would move these lines to Methods.

Action: done as suggested.

l. 285 to 287. I would move these lines to Methods.

Action: done as suggested.

l. 304 « Critical zone ». Please define here this term, using for instance the definition given l. 465.

Action: done as suggested.

l. 306. Unremarked on here is the fact that the overall epidemiological control (damage in S and R fields) is worst when the activation of strong resistance is delayed (If I understand correctly figure S5...). My impression is that this result, difficult to extrapolate from the main figures, deserves more comments.

Response: There may be a misunderstanding on the direction of the epidemiological output (Green Leaf Area, GLA), which is higher for better control (i.e. less diseased plants). In Fig. S5, the overall epidemiological control (red curve) is higher in scenario 3 (strong delayed resistance) than in the

other scenarios (weak delayed resistance & strong early resistance). We hope that the description of the computation of the GLA in the Methods section improves its interpretation.

l. 354 to 361. Should be explained in Methods section.

Action: done as suggested.

l. 426 to 434. These sentences about the generality of the predictions could be moved to the last paragraph of the discussion.

Action: done as suggested.

l. 446. Is there a difference between the severity of epidemics and the level of epidemiological control monitored in the simulations?

Response: no.

Action: "severity of epidemics" has been removed.

l. 462 and l. 486. As mentioned by the authors, the infection of many resistant cultivars (before resistance activation) decreases the quantity of available host tissue, because of many infections and as a consequence of an indirect effect on hosts growth (equation 2 Rimbaud et al. 2018 c). After resistance activation 'wt' genotypes have few chances to infect resistant hosts, while both the requency of 'rb' genotypes in pathogen population and the availability of healthy resistant hosts are low. I agree with the authors that there is, formally, competition between the two pathogen strains, but, If my understanding is correct, this competition takes different forms depending on the delay of resistance expression, the efficiency of the resistance, the mutation rate and the range of dispersal of spores. As this competition effect is mentionned several times in the discussion, I think the paper would benefit here from a slightly more mechanistic and detailed description of how competition occurs.

Responses & actions: thank you for highlighting this point. There are, indeed, two different forms of competition depending on the combination of efficiency and age of resistance activation. First (1), when resistance is strong and delayed, "The delay in resistance activation allows the wt genotype to infect resistant hosts early in the season, more efficiently than potential rb genotypes which suffer a fitness cost while resistance is inactive. As soon as it activates, resistance is strong enough to select for rb genotypes, but many hosts are, at this time, already infected by the wt genotype". Second (2), when resistance is weak but activated early, "the wt genotype is (slightly) limited on the resistant cultivar (due to early resistance activation), while the rb genotype is (slightly) limited on the susceptible cultivar (due to the fitness cost of adaptation)." We give more details on these two forms of competition (l. 536-556) and enrich these elements with parallels with (1) rotations and induced resistance; and (2) competition between specialist genotypes for limited resources; including associated references (Calonnec et al 1996, Mikaberidze et al 2015, Clin et al 2021, Clin et al 2022).

With respect to the effect of mutation rate and dispersal of spores, we cannot quantify their impact as these parameters were not allowed to vary in this study. But we now mention what influence these parameters could have on our results in the Discussion section (l. 694-698).

l. 551 « hard selection » should be replaced by « strong selection ».

Action: done as suggested.

Reviewer #2

General comments. The manuscript is concerned with the role of adult plant resistance (APR) in short and long-term disease control through a modelling approach. The manuscript is well written in general and addressing such a question is relevant compared to the existing literature on the subject.

My main concern is the lack of more details on the model formulation within the current manuscript. We need to refer to the authors' previous publications to be able to precisely follow the model overview used here. Such a point seems particularly relevant because the main results of the manuscript are based on the numerical simulations of that model (whatever the target audience of the journal).

Response: We thank the reviewer for his/her helpful comments.

Action: Text S1 now gives all details to fully understand the model.

More specifically.

1. *The term 'age to resistance expression' seems more relevant than 'time to resistance expression' (eg, line 6). Indeed, this is useful to distinguish the 'time' (viewed as the dynamical time) from the plant age at which the resistant gene is expressed (the 'age to resistance expression').*

Response: This is very relevant.

Action: We replaced "time to expression" by "age of resistance activation" throughout the manuscript as well as in all figures.

2. *Similarly, 'time to expression' can be replaced by 'plant age for RG (resistant gene) expression'.*

Response: ok, see above.

3. *What is the actual meaning of the full activation of APR gene (eg, lines 84-86)?*

Response: We mean the time when the APR gene reaches its maximal efficiency.

Action: Rephrased accordingly (l. 86).

4. *The plant age for RG expression is modelled by a gamma distribution. Please, can you precisely detail how this gamma distribution is parameterized? Instead of Figure 1 (which I think is not so helpful), those details will help draw a 2D figure with the x-axis (the age of the plant) and the y-axis (the resistant efficiency). More precisely, how can I find the resistance efficiency when the age of the plant is known?*

Response: There may be a misunderstanding. Resistance efficiency and age of activation are considered independent in this study. Thus, in the numerical experiments, these parameters could vary independently (efficiency from 0% to 100% and age of activation from 0 day to 90 days) within a complete factorial design. In other words, resistance efficiency does not depend on age of activation (and vice versa). All figures (except S5 and S6) illustrate the output (resistance durability or disease control) as a function of the two parameters, positioned on the x-axis for the age of activation and the y-axis for the resistance efficiency.

Action: The parameterization of the gamma distribution is better explained in the main text, especially how the usual shape and scale parameters of the Gamma distribution can be retrieved

from its expectation and variance (l. 162-165). In addition, Text S1 now fully describes the underlying equations.

5. *Moreover, Figure 2 seems to come before Figure 1 in the manuscript (line 170). Please, check.*

Action: Figure 1 now comes before Figure 2.

6. *A formula is welcome in lines 265-267 to help understand how green leaf area is quantified by the model presented here. This will help to give some details on the model used here, without necessarily referring to the authors' previous paper.*

Action: The computation of outputs is now fully described in Methods (l. 283-303).

7. *Lines 250-258 seem more relevant at the beginning of the section 'Numerical experiments'.*

Action: Done as suggested.

8. *Please, explain why for the latent period, multiplicative coefficients are 1 + and 1 + instead of 1 and 1 (Table 1).*

Response: This is because latent period is lengthened when targeted by plant resistance, whereas other pathogenicity traits are reduced.

Action: captions of Tables 2 and 3 now explain that latent period varies in a direction opposite to the other traits (l. 222-227 & 245-251).