Dear Recommander,

Following your appreciation, we have revised our manuscript, entitled: '**Impact of ploidy and pathogen life cycle on resistance durability**'.
Below is a detailed response to your comments and those of the reviewers. Our replies are indicated in green. We believe they have addressed all the concerns raised. These suggestions helped us to improve our manuscript greatly. We provide you with two types of files highlighting revision marks or not in the main document. For the following responses to reviewers' comments, lines refer to the manuscript highlighting revision marks.

We hope that in its revised state the manuscript will be suitable for recommendation.

Yours sincerely,

Méline Saubin

RECOMMANDER :

Dear Dr. Méline Saubin,

We received two reviews of your preprint entitled 'Impact of ploidy and pathogen life cycle on resistance durability'. Dr. Loup Rimbaud especially is fully aware of scanty of scientific literature that investigates the effect of the important feature of plant pathogen, ploidy and life cycle, on the resistance durability, appreciates your work. At the same time, both reviewers made useful comments on the validity of the simplified model that the authors adopted. Please revise the manuscript by responding to these comments. This work is focused on the gene for gene interaction, where resistance is usually dominant and infectivity is recessive. Since this model assumption may crucially affect the result of the manuscript, I would ask the authors to include a brief literature review on the biological mechanism behind the model and the evidence sufficient for ruling out the other pattern of genetic inheritance of vir/avir alleles.
We replied point by point to all reviewers' concerns. In particular, the introduction has been modified at several instances. Concerning recessivity of the virulent allele, some lines have been added to explain the biological mechanisms behind the gene-for-gene model, and justify the assumption of a recessive virulent allele (lines 100-106). This assumption is true as long as the product of the avirulence gene is a specific molecule that can be recognised by the host (Stukenbrock & McDonald 2009).

Sincerely yours,

Hirohisa Kishino

REVIEWER 1 :

The work "Impact of ploidy and pathogen life cycle on resistance durability" by Saubin et al. aims to assess the impact of ploidy on the epidemics of plant pathogens. The study of plant pathogens is an issue of great interest in agricultural sciences and many economic implications.

After reading the abstract and the Section introduction, my first impression was that the manuscript was concerned with developing resistant host strategies to prevent resistance breakdown. The authors also highlight that the current approach couples population dynamics and population genetics. However, from my perspective, the approach used in the manuscript resembles more those of ecological models.

Metapopulation models to assess the genetic diversity of pathogens whose epidemiology follows standard dynamics such as SIR or SIS are not new. In those approaches, the hosts are represented as groups (compartments) whose states evolve, i.e. the landscape is not static.
We now precise in the “Model description” section (3.1) that the host compartments we modelled are static, i.e. their carrying capacities do not evolve during simulations. We also restructured the introduction to avoid confusion between the coevolution occurring in natural ecosystems and the pathogen evolution in agroecosystems when the hosts are selected and planted (Cf comment of reviewer 2).

Many aspects of the evolutionary dynamics of the model are unclear, and for me, it is quite challenging to understand the meaning and motivation of the results. Below I enumerate my main concerns:

1) Does the model allow the coexistence of different strains in the susceptible compartment?
This model allows the coexistence of different strains on the susceptible compartment (*avr-avr*, *avr-Avr*, and *Avr-Avr* for diploids; avr and Avr for haploids) (Figure 1 and lines 212-219).

2) As I can understand from Figure 1, the answer to question 1) is yes. In this case, the within-host dynamics, supposedly provided by Eqs. (1) and (2) is not clear.
Different strains might compete within the same host, i.e., they do not independently evolve as there is competition for "space".
It is a within-compartment dynamics and not a within-host dynamics. A sentence has been added to clarify this point (lines 172-173). At each asexual reproduction event, the logistic growth on R and S compartments (Eq (3)) indicates that individuals are in competition when the size of the population approaches the carrying capacity of the compartment (KS or KR), which corresponds to a saturated space. The number of offspring is calculated from formulas provided in Eqs (1), (2) and (3), and the genotypes of the offspring individuals are drawn randomly from the parental population, with replacement.

3) In the abstract, it is said, "A major component of deployment hosts strategies is the proportion of resistant hosts in the landscape". Nevertheless, this problem is not addressed in the paper. What is the point to not consider a consistent metapopulation model, in which the number of compartments can be made large, and not only two or three, as assumed in the current formulation?
In this non spatialised model, we chose to consider two main host compartments (S and R) regrouping all susceptible or resistant hosts that can be infected during the epidemic phase. The fixed carrying capacity of these two compartments (KS and KR) is therefore a proxy of the compartment size, i.e. the quantity of infections that a pathogen can cause on each compartment. The sum of these two carrying capacities (K = KS+KR) represents therefore the total quantity of hosts available for the pathogen.

Compartment sizes are constant during each simulation process because we modelled an agricultural ecosystem with planted hosts. In other words, we assume no negative feedback of pathogen development on host population dynamics, a common hypothesis for such studies on human-managed systems (Fabre et al., 2015; Sapoukina et al., 2009; Djidjou-Demasse et al. 2017; Rimbaud et al., 2018, 2021). We fixed the total number of hosts available (K) across simulations for the sake of comparisons. We varied the relative sizes of KS and KR, i.e. the proportion of susceptible and resistant hosts in the landscape, represented by the parameter propR = KR/K. This proportion is a key parameter of our modelling study. The results highlight the importance of propR on both the probability of fixation of the virulent allele (Figure 5), and its speed of fixation (Figure 7).

4) Different topologies (migration network) could be considered as a metapopulation model of many compartments is built. The topology of migration networks is also a significant component in epidemics, especially in plant pathogens' epidemics.
We indeed assume a simple migration regime, with regular exchanges between host compartments. It could be interesting to consider other (more complicated) migrations schemes, such as migration networks. However, this is out of the scope of our modeling study: the implementation of different topologies requires a spatialised model, which is not the case in this paper. Several non-spatial models provided insightful results for understanding how to increase resistance durability (e.g. Van den Bosch & Gilligan 2003, Pietravalle 2006). Here we focused on simple parameters and a non-spatialised migration scheme to better highlight the effect of the ploidy and life cycle of the pathogen on resistance durability in a generic approach.

5) Both pathogens and hosts are static entities. They do not effectively evolve as they do not mutate or change state. Are those assumptions reasonable in the time scale considered in the simulations?
The static state of hosts seems reasonable as we represent agricultural systems with planted hosts. Host genotypes are therefore strictly controlled, and the death of a host usually leads to its replacement by the plantation of a new host of identical genotype.
The choice of absence of mutation for the pathogen does not reflect an assumption of natural systems, but mostly represents a model simplification to study the impact on evolution from standing genetic variation only. We chose not to consider mutation to study this system as a conservative scenario. Here we demonstrated that considering a diploid pathogen generates highly stochastic behaviours. This enables us to discuss the influence of the different evolutionary forces on the evolution of pathogen populations (Discussion section). We expect that the addition of mutation would increase the stochasticity of the results, particularly for the combinations of parameters where we already observe evolutionary rescue.

REVIEWER 2 (Loup Rimbaud) :

In this article, Saubin et al. developed a simulation model to evaluate plant resistance durability for different pathogen ploidies and life histories. In particular, analyses confront haploid versus diploid pathogens, as well as absence versus presence of an alternative host (in addition to both susceptible and resistant hosts). The model is stochastic, non-spatial and accounts for pathogen evolution via selection, genetic drift, and sexual reproduction. Results highlight crucial differences in the epidemiological and evolutionary dynamics between haploid and diploid pathogens: the latter being subject to higher stochasticity and probability to extinction due to the counter-selection of heterozygous individuals in resistant hosts. The presence of an alternative host speeds the probability of invasion of resistant hosts by virulent pathogens, but slows their subsequent establishment.

The durable deployment of plant resistance is a hot topic which has been explored via numerous models. However, very few of them explored the case of diploid pathogens or the impact of alternative hosts where sexual reproduction may occur (as highlighted in one of my own article: Rimbaud et al. 2021. Models of plant resistance deployment. Annual Review of Phytopathology 59: in press). Yet, these features are potentially very influent on the epidemiological and evolutionary trajectories of the concerned pathogens(e.g. potentially numerous fungi).There is thus a gap in the scientific literature, and this article is a very nice contribution to fill it. The model is sound, results and conclusions are interesting, and the text is well written. I am very convinced by this study and only have minor comments to make to further improve the manuscript.

Loup Rimbaud

General comments:

- The word “virulence” has different meanings depending on the scientific area, I suggest to give a definition at first occurrence.

We now provide a clear definition of virulent and avirulent individuals in the introduction (lines 49-50), and of the virulence (lines 84-85). We are aware of the debate on the different meaning of the word “virulence” in evolutionation ecology and phytopathology litterature. We prefer keeping the phytopathology convention to be consistent with the molecular definition of an avirulence gene.

- In this work, resistance durability is defined in several ways:
    - apparition of a virulent pathogen in resistant hosts (line 64-65)
    - time to fixation of the virulent pathogen(line 242). “Fixation”must also be defined (I supposed it is when the frequency of the virulent pathogen exceeds a threshold? If yes, this threshold must be explicit)
    - Invasion of the resistant host(1/1000 prevalence on resistant hosts)
    - Resistance breakdown(1/100 prevalence on resistant hosts). Is there a reason for the 1/1000 and 1/100 thresholds or is it an arbitrary decision?

I think the computation of these metrics should be more explicit in the text. In addition, the two last definitions are described as two components of durability, so the status of the two first metrics is not clear.

We indeed have four metrics to examine the change in virulence frequency at different key steps from the early virulent individuals on the R compartment to the total invasion of the virulence over all compartments. A paragraph has been added in the “Model Description” section to regroup and clarify the different metrics of resistance durability (lines 227-234). Fixation has obviously no practical concern for resistance durability, as the breakdown already occured, but the time to fixation is a classical measure in population genetics to link allele dynamics and selection pressure.

Line by line comments(suggestions for additions are underlined)

Abstract

- #14 “a major component of deployment host strategies”: remove “host”
  Amended

Introduction

- #42 “...the result of the infection is determined by the interaction between a locus in the plant...”
  Amended
- Paragraph #44 to #51 needs to be slightly rephrased or re-organised. In lines #44 to #46, if the product of the avirulence gene is not recognised, it may be because the pathogen is virulent. So infection occurs,but the plant is actually resistant (broken down, though). Additionally, in lines #49 to #51, there is a mention of coevolution (which occurs in natural systems) whereas the beginning of the paragraph started with the breeding of resistance (thus cultivated crops).
  This paragraph has been rephrased and precisions have been added to distinguish resistant and susceptible hosts along with virulent and avirulent pathogens. The paragraph was split into two to highlight the distinction between natural systems (with co-evolution) and agroecosystems (without co-evolution).
- #57-58 “strategies like resistance deployment hinder this maintenance of polymorphism”: here I don’t think we can say it is a strategy, and it is definitely different from the strategies destined to improve durability. I would rather say “monocrops”, or “pure crops of resistant hosts”.
  Amended
- #64-65 “the expected time until the apparition of a virulent population of pathogens on resistant hosts (Johnson 1984)”: I am ok with this definition but this is not the same as Johnson’s one (“expected time during which a cultivar stays efficient in spite of an environment favourable to disease”).
  Since these definitions of resistance durability were indeed different, we replaced the former definition in the introduction with the one used by most authors: “the time for the virulent pathogen to reach a given threshold in the pathogen population” (lines 72-73).
- #116 “Therefore, in the absence of data, it could be more insightful not to consider fitness cost...”. I also suggest to replace “insightful” by“conservative of the risk of breakdown” (because accounting for the fitness cost is highly relevant to pathosystems where there is one!).
  Amended
- #127 it seems a bit contradictory to focus on simulations where the pathogen population “went extinct” to highlight “evolutionary rescue events”.
  We actually focused on simulations where the pathogen population went extinct for some but not all replicates. This part has been rephrased (line 145).

Model description

- #155 “the population size is considered constant”: do you mean before/after the reproduction event, or throughout the simulated period?
  The population size is constant during the sexual reproduction. The text has been amended with a new equation for clarity (lines 174-176, Eq (1)).
- #163-165: I suppose you assume here that all pathogen genotypes have the same reproduction rate. It could be worth mentioning it.
  You are right all pathogen genotypes have the same fitness (in particular because we did not consider fitness cost). This is now clearly stated (lines 186-187).

- #171-172: “even if the number of individuals on this compartment reached the maximum carrying capacity” seems contradictory with “...restricted to the carrying capacity at each reproduction event” in the sentence after. Please clarify.
  The carrying capacity of a compartment influences the population size during reproduction events, but not during migration events. The text has been modified to clarify this point (lines 194-195).
- #183: on alternative hosts, there are two reproduction events (sexual and asexual). Is there a reason for simulating an asexual reproduction here?
  Based on heteroecious life cycles of rust fungi, the sexual reproduction on the alternate host is followed by an asexual reproduction leading to the emission of spores infecting the telial host. It is the same for host-alternating aphid species.
- Paragraph starting #205: it is important to mention that homozygous avr-avr individuals are initially present.
  A sentence has been added to mention this point (lines 240-241).

Results

- #257: it could be worth mentioning here what are the sources of stochasticity (reproduction,migration, input parameters).
  We prefer to reserve the explanation of these sources of stochasticity for the discussion, in particular with the importance of genetic drift on the model outcomes.
- #278: “axes” (instead of “axis”)
  Amended
- #289-290 “higher mean generations of avr fixation”: maybe simplify by “longer time to fixation”?
  Amended
- #356 replace “theGLM results” by “the results of GLM” for fluidity
  Amended

Discussion

- The discussion is very interesting!
- #378-379 “as soon as one virulent individual invaded the resistant compartment, it was selected and the resistance breakdown occurred”. This is also because the bottleneck between seasons is large (and thus imposes soft genetic drift) and there is no host spatial structure (that could be amenable to more stochasticity and extinctions).
  Here we decided to fix the number of generations of the epidemic phase across simulations for the sake of comparisons. We agree that shortening the epidemic phase could have reduced the selection on the resistant host and led to more stochastic results and extinctions.
- #391 replace “cannot” by “poorly”and replace “only” by “mostly”(because homozygous avr-avr individuals exist).
  “This state” previously referred to the heterozygous state only, this sentence has been amended to improve its clarity (lines 420-421).
- Paragraph #436 to #438: given Figures 6 and 7, I would have said the opposite (host alternation leads to more stochastic evolution of allelic frequencies and slower speed of virulence fixation).
  The increased stochasticity with host alternation leads to fixation that can be very rapid compared to the life cycle without host alternation, especially at high values of propR. The sentence has been amended to clarify this point (lines 466-468).
- Paragraph 454 to 458: this situation may lead to high level of genetic diversity in pathogen population, as shown in a study which investigated the case where the time to immigration (“invasion” here) is well shorter than the time to colonisation (“breakdown” here) :Wingen LU, Shaw MW, Brown JKM. 2013. Long-distance dispersal and its influence on adaptation to host resistance in a heterogeneous landscape. Plant Pathology 62: 9-20

The occurrence of long-distance dispersal (LDD) events in a spatialised model would indeed lead to a higher probability of encounter of virulent pathogens originating from a susceptible host to a resistant host, and initiate founder events. It is indeed well documented that LDD events increase genetic diversity during colonization events (ex Ibrahim 1996, Bialozit et 2006, Fayard et al. 2009). Thus, this may well mirror our host alternation scenario. However, in this modelling work, we focused on the evolution of the avirulence gene only. We did not follow the identity by descent of virulent individuals. Therefore, it is not possible to speculate on any level of genetic diversity. This will be addressed in an ongoing study with the addition of neutral markers to conduct a sound population genetics analysis on the effect of resistance breakdown on the pathogen population structure.

- #523: for pyramids, the presence of an alternative host increases the probability of encounter of mono-virulent pathogens, and thus the probability of appearance of multi-virulent pathogens able to overcome the pyramid. It may be worth mentioning it.
  You are right. A sentence has been added to mention this point (lines 554-556).

Figures

- Figure 1: I suggest to indicate when(or how often) does migration occur close to the arrow, or to specify this in the caption.
  The occurrence of the migration events (at each generation) is now specified in the legend.
- Figure 2: why freq_avr is not negatively correlated with freq_Avr?
  There are three distinct and exclusive outputs: the fixation of the *avr* allele, the fixation of the *Avr* allele, and the extinction of the population. Therefore among the 100 replicates, the frequency of fixation of the *avr* allele (freq_fix_avr) is not necessarily negatively correlated with the frequency of fixation of the *Avr* allele (freq_fix_Avr): the population can also go extinct (freq_ext).
- Figure S1 (caption):“Sobol’s indices”(with a capital letter)
  Amended
- Figure S2: I hardly see the 5th colour...consider limit to 4!
  Two of the five trajectories were indeed identical and overlapped. We modified this part to consider only four replicates.
- Figure S3: year of “invasion” (instead of “invision”).
  Amended
- Figure S5 and S6: is the left part the same as in the main document? If yes, please mention it.
  The left parts are indeed the same as Figure 4 and Figure 7 in the main document. This information is now specified in the legend.

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