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Improving the design of sustainable crop protection strategies thanks to population genetics concepts

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Running title:

Enhancing Plant Resistance Durability

Abstract

Cropping genetically resistant plants allows to control pathogen populations while substantially reducing chemical inputs. However, resistances are often quickly defeated by pathogens. In this context, how can sustainable crop protection be achieved? This question has shaped the debate about the durability of genetic resistances in agriculture for decades, and, despite active research efforts, has not been satisfactorily answered yet. Here we demonstrate from a bibliography analysis that the research field of resistance durability evolved into two non-overlapping directions: (i) the subfield of '*epidemiology and evolution*', which aims to forecast and explain pathogen population dynamics; (ii) the subfield of '*molecular interactions*', which studies the molecular processes involved in the overcoming of resistance and in the dialogue between plants and pathogens. After reviewing briefly these two subfields and the gap between the corresponding research communities, we propose strategies to merge these approaches into one by using the concepts of population genetics. Ultimately, such new eco-evolutionary studies could be used to determine the best strategy for the deployment of genetically resistant cultivars by integrating, from gene to landscape, all relevant and contextual biological knowledge into sound theoretical models.

Main text

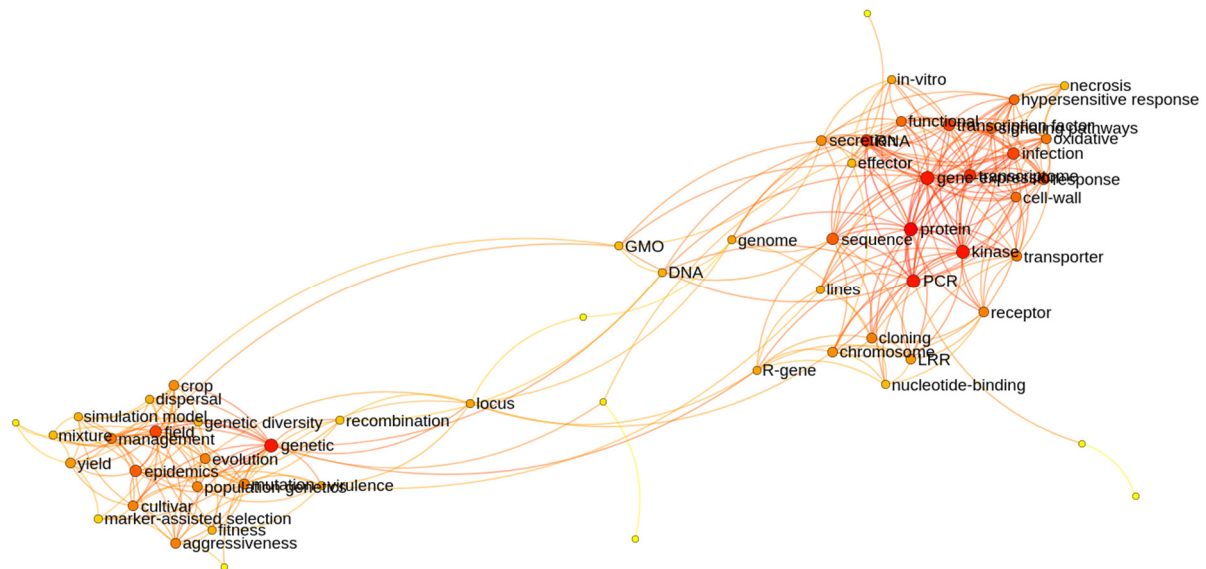
1- The question of the durability of genetic resistances

Cropping genetically resistant plants helps regulating pathogen populations while considerably reducing chemical inputs. Plant resistances are extensively used in crops to confer partial or complete host immunity. However, such resistances might be quickly defeated by pathogens, inducing their loss of efficiency (Brown, 2015; REX Consortium, 2016). A typical example is the use of qualitative resistances that often rely on the recognition of a specific pathogen molecule (e.g. an effector protein, called avirulence protein when recognised by a cognate resistance protein) by a plant receptor that confers host immunity according to the gene-for-gene model (Flor, 1971). In such cases, pathogens can easily evolve by losing or modifying the recognized molecule and thus escape host recognition, thereby restoring infectivity. Nevertheless, the overcoming of genetic resistance is not systematic (García-Arenal et al., 2003; Nilusmas et al., 2020). The timeliness of overcoming sets the duration of the use of a given resistance (the so-called resistance durability; Johnson 1984). In recent years, quantitative resistances that confer to the plant only a partial level of resistance has received increased attention. Indeed, since quantitative resistances reduce selection pressure, an increased length of resistance durability is expected. However, evolution of pathogen populations in the face of quantitative resistance can lead to more crop damages (Gandon et al., 2000). A crucial question is thus how to use plant resistances to prevent rapid pathogen adaptation, and enhance resistance durability? This question has been driving the debate about the durability of genetic resistances for decades and, despite active research efforts, has not been satisfactorily answered yet.

2- The plant resistance durability literature groups into two distinct subfields

This opinion note was prompted by an analysis of the literature addressing the issue of plant resistance durability (Annex). This analysis reveals a split among studies addressing the question of the durability of plant resistances. The fragmentation within this research field was already documented for the resistance to pesticides (REX Consortium, 2010). The persistence of this division results in a gap between two scientific communities. We believe that this gap impedes an integrated view of evolutionary processes and ultimately compromises the sustainable management of genetic resistances. Indeed, nowadays, based on cross citations and co-publications, two areas of research can be distinguished, each focusing on a different scale of the process leading to the overcoming of resistance by plant pathogens. On the one hand, a scientific community aims at elucidating the molecular dialogue that rules plant pathogen interactions. On the other hand, another scientific community aims at elucidating the fate of pathogen populations facing the selection pressure(s)

exerted by resistant plants. For the sake of clarity, these two subfields are thereafter referred to as ‘*molecular interactions*’ and ‘*epidemiology and evolution*’. The ultimate goal of these two research subfields is to explain and understand the global processes and detailed mechanisms of plant-pathogen interactions, to improve plant health and achieve durable crop protection. In this respect, both subfields evolved from the pioneering work of Flor (1971) but they no longer form a continuum of research activities. Nowadays, they tackle the question of resistance durability in very different ways.



Network of the articles’ keywords. This representation was drawn with the Network Mapping tool on Cortext manager, based on the refined list of 61 keywords and articles from the ‘*epidemiology and evolution*’ and ‘*molecular interactions*’ clusters (Annex). All other parameters were set to default values. Nodes represent the keywords; lines between nodes represent the links that measure the mutual occurrence of the keywords among articles. The closer the nodes are, the tighter the association is. An interactive version of this figure is available online:

<https://documents.cortext.net/lib/mapexplorer/explorerjs.html?file=https://assets.cortext.net/docs/7b064e776c8c4a90bc9e159b7e6d52c2#>

On the one hand, ‘*molecular interactions*’ studies examine how plant pathogens promote infection by inhibiting or alleviating plant defence reactions, and how plants recognize pathogens and trigger immunity. These studies focus on various well-defined aspects of the plant immune system and infection mechanisms by using theoretical concepts (e.g. recognition models between effectors and receptors) and experimental approaches. Prominent organisms are used, and major research topics dominate, such as the investigation of the inducible immune response of plants, or the exploration of infection processes, from the trafficking to the functional characterization of pathogen effectors. Technological innovations (i.e. genomics, bioinformatics) and strong conceptual models (i.e. recognition-based immunity called zig-zag model; Jones & Dangl, 2006) nurture this research subfield.

In particular, they promote the identification of key molecular players by allowing functional genomics approaches and by integrating knowledge gained from molecular works that otherwise remain parcelled out. On the pathogen side, cloning of avirulence genes recognized by specific resistance genes has led to several important discoveries that could help managing resistances and predicting their durability (Janzac et al., 2009). First, while an increasing number of avirulence genes are identified in pathogens infecting agronomically important crops, more and more “unconventional” gene-for-gene interactions are reported between avirulence and resistance genes. For instance, the recognition of one avirulence gene by several resistance genes, the epistatic interactions between avirulence genes, or the requirement of two avirulence genes to induce recognition by a resistance gene. All these interactions have different consequences on the switch from avirulence to virulence and hence on resistance gene management (see for review Petit-Houdenot & Fudal (2017)). Second, inactivation of avirulence genes or generation of near isogenic strains of fungi differing by the presence / absence of one avirulence gene allowed to measure fitness costs associated to a switch to virulence, costs that differ depending on the avirulence (Huang et al., 2006; Nováková et al., 2016). These fitness costs have major consequences on resistance durability and therefore on management strategies (Fabre et al., 2012; Leach et al., 2001). Third, several molecular mechanisms are involved in the switch to virulence. This includes deletion, inactivation or down-regulation of the avirulence gene, point mutations allowing recognition to be evaded while sometimes maintaining the function of the effector, or the acquisition of new effectors that suppress recognition (Gómez et al., 2009; Rouxel & Balesdent, 2017; Sánchez-Vallet et al., 2018). Some of these events being favored by sexual reproduction (Daverdin et al., 2012). Noteworthy, the number of mutational events necessary for the switch from avirulence to virulence may be linked to the durability of resistance, as observed for viruses (Gómez et al., 2009; Lecoq et al., 2004).

On the other hand, *‘epidemiology and evolution’* studies decipher the evolutionary causes and consequences of resistance overcoming at the population scale. In order to improve resistance durability, these studies first aim to identify the key drivers of the so-called durability. Several strategies can be distinguished, differing by the type of resistances used, and their deployment in time and / or space (Brown, 2015; REX Consortium, 2016). While the progression of knowledge in the *‘molecular interactions’* field is stirred by technological advances brought about in the -omics era, *‘epidemiology and evolution’* studies are mostly driven by field observations and includes a large corpus of modelling works (Brown, 2015; Rimbaud et al. 2021). A major change in *‘epidemiology and evolution’* studies is the progressive integration of quantitative resistance studies, as evidenced in our bibliography analysis (Annex). Indeed, epidemiological studies historically focused on plants bearing a single qualitative resistance. The observation of major resistance overcomings after qualitative

resistance deployments prompted the field to increasingly investigate the contribution of multiple and quantitative resistances on resistance durability (Lo Iacono et al., 2012; Rimbaud et al., 2018a; Zhan et al., 2015). Some studies compare both resistance types with different deployment strategies like resistance mixtures or pyramiding (REX Consortium, 2016; Rimbaud et al. 2018b). In addition, experimental studies also highlight the importance of the association of both resistance types (Brun et al., 2010; Fournet et al., 2013; Palloix et al., 2009). Overall, this research subfield has led to three main conclusions: First, it is of prime importance to take pathogen population biology into account. In particular, the review of McDonald & Linde (2002) drew a typology of risk of resistance breakdown depending on pathogens' life cycle. This study highlights that pathogens with large population sizes, mixed reproductive modes (i.e. both sexual and asexual reproduction), and massive, long-distance dispersals, are those with the highest evolutionary potential. Second, given this pathogen variability, there is no absolute rule about the best deployment strategy promoting resistance durability. All else being equal, gene pyramiding will perform better in case of de novo mutations, whereas other strategies (e.g. crop rotations and mixtures) are better suited for impeding evolution from standing genetic variation (Djidjou-Demasse et al., 2017; REX Consortium, 2016; Rimbaud et al., 2021b). In that respect, the dispersal ability of the pathogen will condition the spatial scale for landscape management. Paying attention to the key roles of survival and dispersal could be done within the metapopulation theory (Bousset & Chèvre, 2013; Lo Iacono et al., 2013). Third, there may be antagonisms between short-term disease control and long-term control of pathogen evolution (Brown, 2015; Papaïx et al., 2018), which parcel out research advances in this subfield.

Therefore, despite a common objective (the understanding of the causes and consequences of resistance loss of efficacy to improve plant health and achieve durable crop protection), there is a clear gap between these two research subfields. This gap originates from different sources: the biological scale considered, the methods used, and of course the cited literature. In summary, the question of resistance durability is tackled by two communities that lie at two extreme levels of the organization of the living. How would it be possible to gather these approaches?

3- Population genetics provides a conceptual link between these two research subfields

The field of population genetics is conceptually dedicated to link molecular investigations of biological evolution and studies at the population scale. By definition, population genetics deals with the distribution of genetic variability within and between populations. As such, it enables to expand the

reasoning from the gene to the population scale and conversely provides a sound approach to investigate molecular evolution.

Population genetics is a research field with a long and productive history. Our goal here is not to draw a detailed picture of it. We rather summarize the main points of interest to the reader for the proper understanding of this opinion note. Population genetics has been a key element of the evolutionary synthesis conducted notably by Fisher (1930), Wright (1930) and (Haldane, 1924-1934). As a theoretical field, population genetics is deeply rooted in mathematical modelling but it also has important ramifications in experimental sciences. At the origin, its main contribution has been to show that a phenotype, even if it is continuously distributed, could be explained by the contribution of discrete entities called genes (Fisher, 1930). Evolution thus results from the changes in the frequencies of gene states (alleles) by the combined action of evolutionary forces, namely selection, migration, mutation, and drift. Drift is often overlooked compared to other evolutionary forces, but it plays an important role in the evolution by chance of allelic frequencies. With the development of molecular markers and more recently the burst of the new generation sequencing approaches, population genetics has gained increasing attention for an even broader community of researchers. These empirical studies challenged the former theoretical predictions, which led to new theoretical developments. Thus, there is still a strong interest and need for conceptual developments, even concerning the original link between genetic determinism and population dynamics, in particular to explore transient evolutionary trajectories (Day & Gandon, 2007; Djidjou-Demasse et al., 2020). This is the way we want to prompt the use of population genetics for the sustainability of plant genetic resistances. Studies on '*molecular interactions*' build up a comprehensive knowledge on the determinisms of plant pathogen interaction that has to be better taken into account in '*epidemiology and evolution*' modelling works. Conversely, evolutionary studies could highlight constraints that need to be further illuminated by molecular studies.

4- The current use of population genetics disregards this conceptual link

Contrary to what we expected from the conceptual definition of population genetics, our analysis of the literature addressing plant resistance durability did not illustrate population genetics as a field that merges '*molecular interactions*' and '*epidemiology and evolution*' subfields (Annex). As such, our bibliography analysis showed that only 43 out of 1783 studies (less than 3% of the corpus) explicitly refer to population genetics. Moreover, most of these studies employ population genetics as a specific and simplified tool in most studies, and not as a conceptual discipline.

On the one hand, the most significant part of the articles focusing on plant resistance durability and referring to population genetics investigate pathogen population structures using neutral molecular markers. These articles reflect the main body of population genetic studies, which aim to infer key elements of pathogen biology from neutral population structure analyses (e.g. the extent of gene flow as a proxy for migration rate or the variation of within-population indices as an indicator of reproductive mode). The knowledge of these key biological aspects is of paramount importance to feed into epidemiological models and, ultimately, to forecast the risk of resistance breakdown (Hessenauer et al., 2021; Milgroom & Peever, 2003). However, such neutral population genetics studies too often disregard selection as an evolutionary force.

On the other hand, some articles from the '*molecular interactions*' subfield focus on plant resistance durability and study the genetic variability of genes under selection (e.g. those coding effectors) in pathogen populations. These articles do not necessarily stand out in the bibliographic analysis because they do not use the term 'population genetics' in their main keywords (e.g. Daverdin et al., 2012). Their analyses are based on classical population genetics tools and concepts but do not associate genetic structures at selected loci to neutral genetic diversity during the overcoming of a resistance.

These different uses of population genetics concepts strengthen the gap between '*molecular interactions*' and '*epidemiology and evolution*' subfields. As both subfields share the same underlying concepts, the use of population genetics not only as a tool but also as a conceptual discipline would permit to bridge the gap between these subfields.

5- Bridging the gap between '*molecular interactions*' and '*epidemiology and evolution*' studies by using the field of population genetics

The main issue is therefore how to use the population genetics discipline on both sides to bridge the gap between these two subfields. The ultimate goal is to present a framework to study how molecular mechanisms of host-pathogen interactions can lead to resistance overcoming at the individual level and loss of efficacy at the population level, shaping the evolutionary trajectories of pathogen populations.

First, we propose that '*epidemiology and evolution*' studies take more systematically into account demographic fluctuations of pathogen populations, and focus on genetic trajectories instead of equilibrium states (as in e.g. Djidjou-Demasse et al., 2020). This issue cannot be tackled without a proper definition of resistance durability. Among the articles combining plant resistance durability and

population genetics, the study by Van den Bosch & Gilligan (2003) is distinctive. This modelling study, which is mainly in line with those of the '*epidemiology and evolution*' studies, proposes several measures of resistance durability. In particular, it includes the time to fix a virulent allele in the pathogen population, a concept and vocabulary derived from population genetics. Beyond this definition, the study used several indicators of resistance durability defined as the time to reach a given virulence frequency in the population. They showed that the evaluation of resistance durability can differ depending on the indicator considered. This conclusion prompts biologists to better evaluate resistance durability by using the dynamics of virulence evolution, rather than from arbitrary thresholds for virulence frequency in the population. This corresponds to the change in paradigm observed in the literature, from the short-term control of pathogen populations by means of epidemiology driven regulations to the long-term control of the evolutionary trajectories of pathogen populations (Brown, 2015; Papaïx et al., 2018). This raises the question of how to better characterise these evolutionary trajectories. This question is all the more relevant as pathogen populations are characterised by large demographic fluctuations. In this respect, evaluating evolutionary outcomes at equilibrium states is inappropriate, especially in agroecosystems (Nilusmas et al., 2020). Moreover, the selection pressures exerted on pathogens (e.g. resulting from the deployment of resistance genes) change at a fast pace in agricultural landscapes (Stukenbrock & McDonald, 2008; Zhan et al., 2015). The most recent theoretical models consider the stochasticity of pathogen evolutionary trajectories thanks to demo-genetic models. However, few modelling works consider the effect of genetic drift (Rimbaud et al., 2021). Some studies consider that pathogen effective population sizes are very high (e.g. Walker et al. (2017) and Zhan et al. (2001)), which leads to a negligible genetic drift. This is especially true for pathogens with horizontal transmissions (Bergstrom et al., 1999). Nonetheless, some recent experimental studies highlighted the non-negligible effect of genetic drift on the dynamics of adaptation of diverse pathogens, including viruses (Rousseau et al., 2017) and nematodes (Jan et al., 2016; Montarry et al., 2019). Drift should therefore be better considered in modelling works (e.g. as in Rousseau et al. 2019), as a direct consequence of demographic fluctuations that should be monitored through time and not only at an equilibrium state, as equilibrium state is never reached in agricultural landscapes. It has then been highlighted that some quantitative resistances can decrease pathogen population sizes, hence increasing the durability of qualitative resistance when used in association (Brun et al., 2010; Rousseau et al., 2017).

Second, '*epidemiology and evolution*' studies should take into account the molecular mechanisms underlying resistance overcomings. Such loss of resistance efficacy results from a genetic change in the pathogen population. A modelling framework has been proposed by Day & Proulx (2004) and Day & Gandon (2007) to investigate evolutionary trajectories of pathogen populations based on

population and quantitative genetics. Yet, this framework has seldom been applied. A reason for this is that it can lead to complex mathematical models, especially when dealing with quantitative resistances (Djidjou-Demasse et al., 2020). Still, new models have yet to be developed, even considering the simpler genetic determinisms that rule qualitative interactions. For example, few evolutionary epidemiology models compare haploid and diploid pathogens, and often neglect the role of sexual reproduction (Rimbaud et al., 2021). Yet, following the gene-for-gene model, the recessivity of the virulence allele increases the magnitude of drift in diploids (Saubin et al., 2021). Likewise, no theoretical model considers epistatic interaction among avirulence gene loci, although molecular investigations proved that it can occur (Plissonneau et al., 2017). It could also be worth considering other theoretical frameworks, such as evolutionary rescue (Alexander et al., 2014) to shed new light on the effect of landscape management strategies on the changes in pathogen population sizes. Developing more contextualised models (e.g. as in Nilusmas et al., 2020) would thus tighten the links with molecular characterisation studies.

Third, '*molecular interactions*' studies should focus on temporal samplings to better understand the evolutionary trajectories resulting from the molecular interactions studied. The recent advances in molecular studies, promoted by omic approaches, enabled to decipher the diversity of effectors and the multiplicity of evolutionary mechanisms that can lead to the emergence of virulent individuals (Fouché et al., 2018; Rouxel & Balesdent, 2017; Stergiopoulos et al., 2007; Stukenbrock & Bataillon, 2012). More detailed studies have examined the diversity of virulence determinisms within pathogen populations (Daverdin et al., 2012; Huang et al., 2014) or evolutionary patterns in effector diversification (Stukenbrock & McDonald, 2009). Yet, the temporal dimension in pathogen population surveys is often lacking or too narrow to trace evolutionary dynamics in detail, as can be done using phylogenomic approaches about human diseases. Examining genetic variation on a snapshot sample can only give access to a restricted part of the evolutionary history and hides phenomena that remain unsuspected without the use of temporal samples (e.g. population replacement as evidenced in Persoons et al. (2017)). Pathogens offer the unique opportunity to study contemporaneous evolution (McDonald, 2010) and to disentangle the interplay among evolutionary forces at work.

Finally, the use of population genetics concepts allows to associate studies of genetic variability at effector and neutral loci, and temporal sampling data. This would permit deciphering evolutionary trajectories compared to focusing on equilibrium states only. Therefore, it would lead to a better understanding of the evolutionary forces at stake by bridging the gap between previously described '*molecular interactions*' and '*evolutionary epidemiology*' studies.

Concluding remarks

To conclude, population genetics is a central concept to tackle the durability of plant resistance. It enables ‘*molecular interactions*’ and ‘*epidemiology and evolution*’ analyses to be linked. However, this research field is still underrepresented, both empirically and theoretically, and often used only as a simplified tool. Studies on the variability of molecular determinisms associated with resistance overcoming could better integrate the population genetics toolbox. This would enable retracing the dynamics of genetic changes thanks to temporal samplings. ‘*Evolutionary epidemiology*’ studies would also gain to consider the use of population genetics on selected loci and better consider molecular determinisms associated with genetic changes in pathogen populations. We believe that this enhanced dialogue between ‘*molecular interactions*’ and ‘*epidemiology and evolution*’ will pave the way to an enhanced knowledge on the evolutionary trajectories of pathogen populations, and ultimately improve the sustainable management of genetic resistances.

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