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The functional microbiome of grapevine throughout plant evolutionary history and lifetime

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Abstract

European grapevine is a complex holobiont composed of two plant genomes, that of the scion (*Vitis vinifera* L.) and the rootstock (*Vitis* spp.), and a multiude of microbial genomes that collectively form the microbiome. The grapevine microbiome has been extensively described over the last decade, primarily using metabarcoding approaches. Unfortunately, metabarcoding data provide little information on microbial functions and outcomes of plant-microbe interactions. Here we review knowledge about the microorganisms that have a demonstrated influence, positive or negative, on the performance of the grapevine holobiont. Our review encompasses bacteria, filamentous fungi, yeasts, oomycetes and viruses. We focus on taxa and functions that protect the plant against pathogens and pests, promote growth, increase tolerance to abiotic stresses and highlight those involved in disease and decline. As the outcomes of plant-microbe interactions are labile, we examine the dynamics and functions of grapevine-microbiome interactions over both the plant lifetime and the plant evolutionary history, beginning with plant domestication. Based on the knowledge and gaps we identified, we suggest field sampling designs, culture-based experiments, molecular tools and theoretical analysis methods, including shotgun metagenomics and network models, that could be used in future research to uncover and leverage the full functional potential of the grapevine microbiome.

Keywords

plant-microbe interaction, biogeography, coevolution, *Vitis*, bacteria, fungi, oomycete, virus, metagenomics, microbial network

INTRODUCTION

European cultivated grapevine is a complex and dynamic system of plant-microbe interactions that has been shaped by humankind to produce grapes and wine. Each plant individual is generally composed of the assembly of two plant genomes, that of the rootstock (*Vitis* spp.) and the scion (*Vitis vinifera* L.), to which are linked a multitude of microbial and viral genomes. The set of microbial genomes forms the microbiome (Berg et al., 2020; Compant et al., 2019; Saikkonen et al., 2020), while the set of viral genomes forms the virome (Roossinck, 2010). The whole, including the plant genomes, forms the hologenome (Bettenfeld et al., 2021; Zilber-Rosenberg and Rosenberg, 2008; Theis et al., 2016). This conceptualization of each grapevine individual as a complex and dynamic system of plant-microbe interactions (i.e. an holobiont; Bettenfeld et al., 2021; Vandenkoornhuyse et al., 2015) has not been necessary, for most of human history, to grow vines and produce wine. But it could provide solutions in the future, to maintain grapevine cultivation in a context of climate change (Gambetta et al., 2020) and reduced use of phytosanitary products (Jacquet et al., 2022; Pertot et al., 2017).

The objective of this chapter is to present the state of art about the dynamics of grapevine-microbiome interactions, from the evolutionary time scale to the seasonal scale, and to propose some research avenues to increase knowledge on the functions of the grapevine microbiome. The chapter first gives an overview of the evolution of the grapevine microbiome, starting with grapevine domestication (Section 1), and then describes the microbiome dynamics during the lifetime of each plant, from the grafting stage in the nursery to the decline in the vineyard (Section 2). In both sections, we specifically highlight those microorganisms and viruses that have a demonstrated influence, positive or negative, on the performance of the grapevine holobiont (health, growth and berry quality). Based on this state of art, we suggest experimental and theoretical approaches that could lead to a better understanding of the functions of the grapevine microbiome (Section 3). We propose some experiments to identify the microbial taxa and functions that play a key role in grapevine performance under drought conditions and in agro-ecological settings. We describe how to decipher the microbial interaction networks to which these key taxa belong, to understand how they maintain in the system and regulate grapevine performance. We also provide recommendations about the biogeographic regions that could be explored in the future to isolate beneficial microbial taxa, which could then be inoculated to drive the system.

1. THE GRAPEVINE FUNCTIONAL MICROBIOME THROUGHOUT EVOLUTIONARY HISTORY

This section reviews the knowledge and gaps regarding microbiome evolution during grapevine domestication and breeding, as well as the microbiome dynamics triggered by microbial fluxes across geographic regions and between members of the *Vitis* genus. Based on this state of art we hypothesize which geographic regions and plant genetic material are most likely to be associated with beneficial microbial taxa and functions (Fig. 1 and 2).

1. Microbiome evolution during grapevine domestication and breeding

Transcaucasus (i.e. the geographic region between Black and Caucasian Sea, which today corresponds to Armenia, Georgia, and Azerbaijan) is the cradle of viticulture (Fig. 1). It is the

most probable region of domestication of grapevine 6.000 to 8.000 years ago (This et al., 2006; Zohary and Hopf, 1993), even if secondary domestication probably occurred later in western Europe (Arroyo-García et al., 2006; Sivan et al., 2021; Terral et al., 2010). *Vitis vinifera* L., 1753 subsp. *vinifera*, is nowadays the main *Vitis* species used for the production of wine, table grape and raisin in the world. It has been domesticated from its wild ancestor, *Vitis vinifera ssp. sylvestris* (Gmelin) Hegi (hereafter referred to as sylvestris) which naturally occurs in Mediterranean Europe (Fig. 1) and southwestern Asia (Di Vecchi-Staraz et al., 2009). In the wild, sylvestris is a liana that climbs trees, and has very small, black and acidic berries produced by dioecious flowers. During domestication, grape has undergone marked changes, the most important being the evolution of sex (from dioecious to hermaphroditic flowers), the increase in size of berries and bunches, and changes in berry chemical composition (This et al., 2006).

From Transcaucasus, cultivated grape spread to Europe, first to the Mediterranean region following the main civilizations (Greeks, Romans, Etruscans, Egyptians), then to northern Europe following the Christian Church. At the beginning, cultivars experienced introgressions from local wild grapes (Myles et al., 2011). Genetic flows in the other direction, from cultivated grapes to wild populations, also occurred (Di Vecchi-Staraz et al., 2009). From the medieval period onwards, cultivars evolved by crossings within *Vitis vinifera* subsp. *vinifera*, most likely in a fortuitous way at the beginning (Bowers et al., 1999), then in a directed manner, particularly after the emergence of mildews and phylloxera in Europe (Section 1.2). Nowadays *Vitis vinifera* genetic diversity is huge, with 6,000 to 7,000 cultivars in the world. However, the total number of cultivars commonly used is much less, since half the world's plantings were accounted for by 16 varieties in 2016 (Anderson and Aryal, 2013).

In addition to genetic and phenotypic changes on the plant side, grapevine domestication was accompanied by an evolution of fermentative microorganisms, particularly *Saccharomyces cerevisiae*. *S. cerevisiae* is the main agent of wine fermentation and one of the best models for understanding the eukaryotic cell (Botstein and Fink, 2011). It is naturally part of the berry microbiome (Section 2.4) and colonizes many other ecological niches (Schacherer et al., 2009). *S. cerevisiae* strains naturally occurring in cultivated grapevines are often referred to as vineyard yeasts or domesticated yeasts. The comparison of vineyard and non-vineyard *S. cerevisiae* strains revealed that the oldest lineages and greatest genetic variability are found in the non-vineyard strains (Fay and Benavides, 2005). This is consistent with the hypothesis that *S. cerevisiae* originated in natural environments and was subsequently domesticated by humans. Molecular analyses revealed that domesticated *S. cerevisiae* strains have a single origin. The initial domestication event probably occurred in Mesopotamia, concomitantly with the grapevine domestication event (Legras et al., 2007). Domestication was followed by a marked phenotypic divergence between vineyard and non-vineyard yeasts. For instance, vineyard yeasts show greater resistance to copper sulfate (Fay et al., 2004; Warringer et al., 2011), a chemical compound used as a fungicide against downy mildew since the 1880s, confirming that vineyard yeast populations evolved in response to agricultural practices.

How has the microbiome of European cultivated grapevine, *Vitis vinifera* subsp. *vinifera*, evolved during grape domestication? Little is known apart from *S. cerevisiae* (reviewed above). Several studies suggested that grapevine domestication yielded a decrease in microbiome diversity and a change in microbiome functions. Wild sylvestris grapes are inhabited by a greater diversity of endophytic bacteria, epiphytic yeasts and arbuscular mycorrhiza than domesticated grapes (Campisano et al., 2015; Cordero-Bueso et al., 2017; Ocete et al., 2015).

Moreover, microbial communities of wild and domesticated grapes differ in their potential for pathogen biocontrol and plant growth promotion (Campisano et al., 2015; Cordero-Bueso et al., 2017). Finally, microorganisms generally associated with humans may have been integrated into the grapevine microbiome during domestication (Campisano et al.; 2014; Youssaf et al. 2014). After the initial domestication event, the grapevine microbiome kept changing as new varieties were created. Molecular analysis of parental relationships among grapevine varieties identified Heunisch weiss, Pinot noir N or Riesling B as the oldest and less evolved varieties, and also the main progenitors of other varieties (Lacombe et al., 2013). Microbiome taxonomic composition of Pinot and Riesling grape varieties has been compared to that of more recent varieties (Bao et al., 2022; Zhang et al., 2020). The bacterial genera *Bacillus*, *Turicibacter* and *Romboutsia* were enriched in the leaf microbiome of Pinot noir (Zhang et al., 2020), while *Pseudomonas* and *Rhizobium*, which include plant growth-promoting strains (Section 2.2), were enriched in the rhizosphere microbiome (Bao et al., 2022). Rhizosphere microbial communities of Pinot and Riesling varieties were more similar to one another than those of more recent grape varieties (Bao et al., 2022).

Several studies hypothesized that wild populations of *V. vinifera* subsp. *sylvestris* constitute a reservoir of useful microbial strains because wild plants often harbor beneficial endophytes that are absent, or less abundant, in domesticated plants (Ofek-Lalzar et al., 2016; Sun et al., 2020). They explored the microbiome of sylvestris and obtained promising results. For instance, the analysis of the root microbiome showed that sylvestris roots were colonized by ectomycorrhizal fungi and that fungal pathogens were completely absent from roots colonized by these fungi (Radić et al., 2021). The analysis of the berry microbiome of sylvestris revealed a high diversity of yeasts, with some of them having promising prospects for use in oenology (Cordero-Bueso et al., 2022, 2017; Puig-Pujol et al., 2016). Yeast strains belonging to four species (*Meyerozyma guilliermondii, Hanseniaspora uvarum, H. clermontiae, and Pichia kluyveri*), all isolated from sylvestris, reduced growth of molds caused by *Botrytis cinerea*, *Aspergillus carbonarius*, and *Penicillium expansum* (Cordero-Bueso et al., 2017). Finally, endophytic bacterial strains with biocontrol properties against several pathogens were isolated from sylvestris (Campisano et al., 2015), including strains belonging to *Pantoea* spp. and *Pseudomonas* spp. that showed antagonistic activity against crown gall agents (*Agrobacterium tumefaciens* and *Allorhizobium vitis*) (Asghari et al., 2019).

To identify and isolate beneficial microorganisms that may have been lost during the domestication process, future research should continue exploring the microbiome of *Vitis vinifera* subsp. *sylvestris* and that of ancestral grapevine varieties. We recommend focusing on sylvestris populations in the center of origin of cultivated grapevines (i.e. the Transcaucasus region; Fig. 1), where beneficial microbes may have co-evolved with wild progenitors, before being lost during the range expansion of cultivated grapevines. Such analysis could allow the isolation of plant growth-promoting bacteria (Gutierrez and Grillo, 2022), that might confer tolerance to abiotic stresses and grapevine pathogens of Eurasian origin (such as *Botrytis cinerea*). The case of pathogens introduced form North America is different and is discussed herafter (Section 1.2).

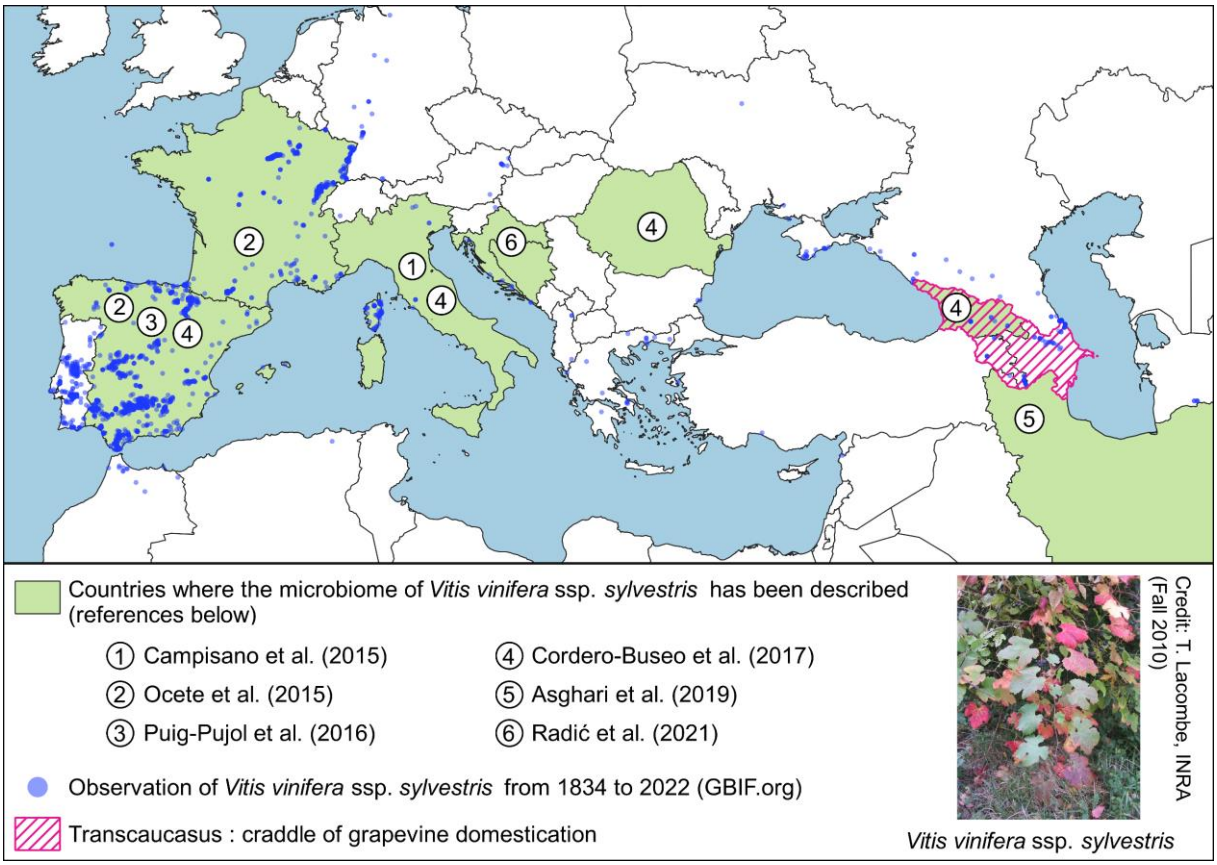


Figure 1 - Area of domestication of European cultivated grapevine, *Vitis vinifera* subsp. *vinifera* (area hatched in pink), and countries where the microbiome of its wild ancestor, *Vitis vinifera* subsp. *sylvestris*, has been described (in green). Campisano et al. (2015) isolated bacterial endophytes from wild grapevine shoots (1). Ocete et al. (2015) explored taxonomic diversity of arbuscular mycorrhizal fungi in wild grapevine rhizosphere (2). Puig-Pujol et al. (2016) isolated yeast strains at the end of spontaneous fermentations of wild grapes (3). Cordero-Buseo et al. (2017) studied yeasts associated with wild grape berries (4). Asghari et al. (2019) analyzed bacterial endophytes in healthy roots, stems, leaves and fruits of wild grapevines (5). Radić et al. (2021) characterized fungal communities associated with wild grapevine roots with a focus on mycorrhizae (6). For future research, we recommend exploring the center of origin of cultivated grapevines (in pink), studying both the microbiome wild grapevine and that of ancestral grapevine cultivars. Map created using the Free and Open Source QGIS.

2. Microbial interactions in the center of origin of major grapevine pathogens

In the middle of the 19th century, several fungal pathogen and insect pest species of North American origin crossed the Atlantic and reached Europe, causing the destruction of a large proportion of vineyards (Gessler et al., 2011). These American species included grape phylloxera (introduced in 1863), and the agents of powdery mildew (1848), downy mildew (1878) and black-rot (1885). Phylloxera is caused by the insect *Daktulosphaira vitifoliae* (Fitch), powdery mildew by the fungi *Erysiphe necator* (Schwein.), downy mildew by the oomycete *Plasmopara viticola* ((Berk. & M.A. Curtis) Berl. & De Toni), and black-rot by the

fungi *Phyllosticta ampelicida* ((Engelm.) Aa) (asexual stage) or *Guignardia bidwellii* ((Ellis) Viala & Ravaz) (sexual stage). Scientists who established collections of wild American *Vitis* species in botanical gardens in the early 19th century probably brought these pathogen species. From there, the diseases spread to other European regions and are now reported in most wine-producing regions (Bois et al., 2017; Fontaine et al., 2021; Pirrello et al., 2019).

European viticulture was saved by the introduction of native American *Vitis* species (such as *V. riparia*, *V. rupestris* and *V. berlandieri*; Fig. 2) that were resistant to grape phylloxera. Moreover, sulfur, copper and later on, phytopharmaceutical treatments, have been and are still used extensively to protect vines from downy and powdery mildews. The American *Vitis* species have first been used to produce rootstocks resistant to phylloxera. Since the end of the 19th century, most European cultivated vines are therefore grafted plants composed of a rootstock tolerant to phylloxera and a scion used to produce berries (Section 2.1). The rootstock and the scion are genetically different and may even belong to different *Vitis* species, which makes European cultivated grapevine an interesting holobiont (Biget et al., submitted). *Vitis* species of American of Asian origin (Fig. 2) have also been used to produce interspecific hybrids cultivated on their own roots (This et al., 2006). More recently, they have been used as sources of disease-resistance genes in breeding programs (Merdinoglu et al., 2018) since they are not only resistant to phylloxera but also to other pests and diseases (Cadle-Davidson et al., 2011; Merdinoglu et al., 2018; Staudt and Kassemeyer, 1995; Villano and Aversano, 2020). However, these new disease-resistant varieties are already threatened by pathogen strains able to overcome resistance genes (for downy mildew: Peressotti et al., 2010, for powdery mildew: Feechan et al., 2015).

As for other plant spevies, the grapevine microbiome offers tremendous genetic variability that hardly been used in breeding programs until now (Gopal and Gupta, 2016). What if American and Asian *Vitis* species still had something to offer to European vineyards? Although this hypothesis has not yet been tested in grapevine, the higher resistance of some American *Vitis* accessions to pathogens of North American origin (Fig. 2) could be due an increased ability of the plant to select a protective microbiome (Gopal and Gupta, 2016; Lyu et al., 2021), in addition to the acquisition of resistance genes in the plant genome. This higher disease-resistance may be the result of a longer coevolution with the pathogens (Jürges et al., 2009). The resistance of some Asian *Vitis* species (Fig. 2) to mildews is more difficult to explain. The resistance of *V. amurensis* to downy mildew, *Plasmopara viticola*, might be due to the presence in Asia of a related pathogen species, *P. amurensis*, which has similar infection mechanisms (Jürges et al., 2009). Recent genetic analyses reopened the question of a possible origin of powdery mildew from Asia (Gur et al., 2021) and might account for resistances to powdery mildew.

Several studies characterized the microbiome of American and Asian *Vitis* species. They found a high richness of endophytes (Fan et al., 2020; Kernaghan et al., 2017) and isolated strains with biocontrol properties against pathogens of North-American origin, as well as other pathogens. For instance, *V. amurensis* cv. Shuangyou in China hosted *Alternari*a strains effective against downy mildew (Musetti et al., 2006). Fungal endophytes isolated from leaves of *V. riparia* in eastern Canada showed high levels of inhibition of gray mold (caused by *Botrytis cinerea*) and black-foot disease (*Cylindrocarpon destructans*). Fungal strains inhibiting gray mold belonged to *Ramularia pratensis*, *Phoma aliena* and *Fusarium*

acuminatum, while strains inhibiting black-foot belonged to *Ramularia* spp., *Phoma* spp., and *Biscogniauxia mediterranea* (Kernaghan et al., 2017). Similarly, endophytes isolated from *V. labrusca* leaves in Brazil showed *in vitro* antagonistic activity against several grapevine pathogens (Brum et al., 2012; Felber et al., 2016). Isolates of *Flavodon flavus* and *Colletotrichum gloeosporioides* strongly inhibited the root pathogen *Fusarium oxysporum f.* sp *herbemontis* (Brum et al., 2012). Isolates belonging to *Phoma* spp. inhibited the growth of the causal agent of leaf blight (*Alternaria* spp.), isolates of *Fusarium culmorum* regulated anthracnose (*Sphaceloma* spp.) and *Sordariomycetes* isolates controlled ripe rot of grapes (*Glomerella* spp.) (Felber et al., 2016). Finally, the fungal species *Acaromyces ingoldii*, previously reported for its plant protection functions, was found to be the most abundant taxon in the berry microbiome of muscadine grape (*Muscadinia rotundifolia* Michx.) in China (Sun et al., 2021). In addition, the bacterial genus *Rahnella* was detected in the microbiome of *M. rotundifolia* and might play a role in the biological control of grapevine crown gall, caused by *Agrobacterium vitis* (Chen et al., 2007).

To identify microorganisms that protect against diseases of North American origin (powdery mildew, downy mildew and black-rot), future research should continue exploring the microbiome of American *Vitis* species. We recommend analyzing their microbiome in their native range (Fig. 2), where they have co-evolved with the pathogens and the rest of the microbiome. It could also be relevant to analyse the microbiome of resistant Asian *Vitis* species (Fig. 2) in areas where they have co-evolved with pathogens related to pathogens of North-American origin. The level of disease-resistance should first be evaluated and the microbiome of all plant compartments colonized by pathogens should be characterized. To highlight microbial taxa that play a role in disease resistance (Section 3.1), the microbiomes of resistant accessions could then be compared to that of sensitive ones in the same geographic region. The inference of microbial interaction networks in resistant *Vitis* species could also generate hypotheses about the microbial taxa or consortia conferring disease resistance (Section 3.3).

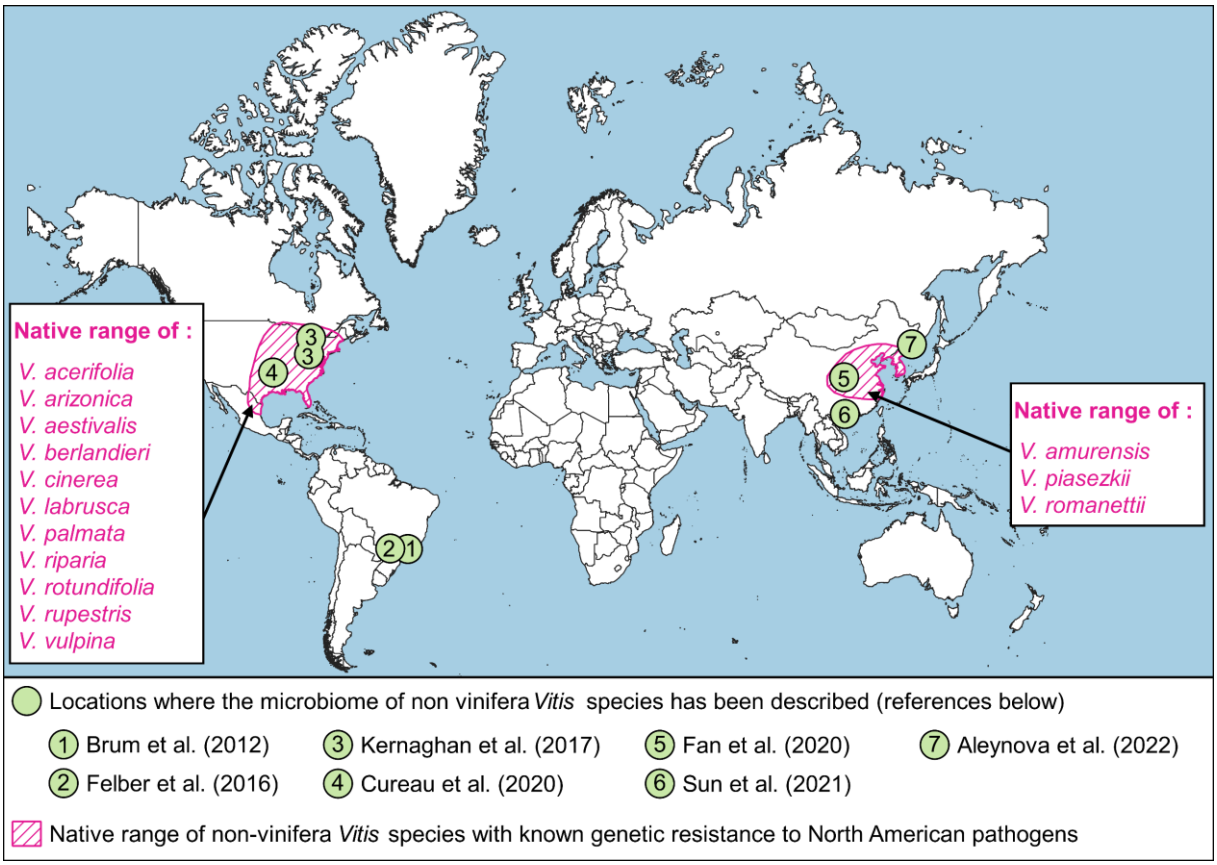


Figure 2 - Geographic locations where the microbiome of American and Asian *Vitis* species, partially or totally resistant to pathogens of North American origin (*Plasmopara viticola*, *Erysiphe necator* and *Phyllosticta ampelicida*), has been described (green circles), as well as the native range of these resistant *Vitis* species (area hatched in pink) (from Wan et al., 2013). Brum et al. (2012) isolated foliar fungal endophytes from *V. labrusca* cv. Niagara Rosada collected in Brazil (1). Felber et al. (2016) isolated foliar endophytic fungi from grapevine cultivars Bordô and Concord (*V. labrusca*) in Brazil (2). Kernaghan et al. (2017) analyzed foliar fungal endophytes of a cultivated hybrid grape variety (L'Acadie blanc) and one of its native progenitors (*V. riparia*) in eastern Canada (3). Cureau et al. (2021) explored the taxonomic diversity of berry fungal communities in *V. vinifera*, *V. rotundifolia*, *V. aestiva*lis, and in hybrid *Vitis* grape varieties grown in different vineyards in Arkansas (4). Fan et al. (2020) compared endophytic fungi of *V. vinifera* cv. Red Globe (cultivated grape) with those of *V. amurensis* cv. Shuangyou (wild grape) grown in a nursery in China (5). Sun et al. (2021) studied the berry microbiome of six muscadine (*Muscadinia rotundifolia* Michx.) cultivars grown in Guangxi, China (6). Aleynova et al. (2022) compared endophytic bacterial communities of a wild grape population of *V. amurensis* in Russia with those of domesticated *V. vinifera* cultivars from Germany and California (USA) (7). Studies that focused on microorganisms isolated during or at the end of spontaneous grape fermentations are not reported on this map. For future research to identify microbial biocontrol candidates against mildews and black rot, we suggest further exploration of the microbiome of these resistant *Vitis* species in their native range (area hatched in pink), where they have co-evolved with pathogens or with related pathogens. Map created using the Free and Open Source QGIS.

3. Microbial fluxes across geographic regions and *Vitis* species

As described above, cultivated grapevine is a complex holobiont that incorporates plant and microbial genomes of European, American and Asian origin (Sections 1.1 and 1.2). To understand how this complex system has assembled since grapevine domestication (Section 1.1), it is necessary to understand the origin and migratory routes of grapevine-associated microbes. Up to now, research focused on the migratory flows of the oenological yeast *Saccharomyces cerevisiae* as well as those of major pathogens of grapevine (*Plasmopara viticola*, in particular).

Molecular evidence for the historical presence of *Saccharomyces cerevisiae* in wine fermentation was obtained from pottery jars hidden in the tomb of King Scorpio I, one of the earliest kings of Egypt, dating back to 3150 BC (Cavalieri et al., 2003). At that time, fermentations were only spontaneous (Marsit and Dequin, 2015), suggesting that *S. cerevisiae* was already an integral part of the berry microbiome. Legras et al. (2007) analyzed migration routes of *S. cerevisiae* and showed that they correspond to the known migration routes of cultivated grapevine (Grassi and De Lorenzis, 2021). From Lebanon, yeast migration may have taken place across the Mediterranean region towards Italy, Spain and France, through three main routes: (1) the Rhône Valley-Burgundy-Alsace and Nantes route that goes along the Rhône and Loire rivers, (2) the Italy-Cognac route and (3) the Danube Valley route. This migration of vineyard yeast strains is accounted for, at least in part, by the trade of grape varieties. For instance, the Muscadet grape variety was imported from Burgundy to Nantes during the 15th century, while Ugni blanc, the dominant grape variety in the French Cognac region, originated from Italy. Genetically-distant Austrian yeast strains were domesticated from local wild sylvestris populations (Section 1.1).

Plasmopara viticola is a complex of five species, each with a unique degree of host specialization within the American Vitaceae (Fontaine et al., 2021; Rouxel et al., 2014, 2013). Fontaine et al. (2021, 2013) found that all invasive grapevine downy mildew populations worldwide belonged to the small clade *P. viticola* f. sp. *aestivalis*, which parasitizes *Vitis aestivalis* in Northeast America (Fig. 1). *P. viticola* was first introduced into Western Europe in the middle of the 19th century (Section 1.2), then it spread to Central and Eastern Europe. European populations of downy mildew then served as a source for secondary introductions into other viticultural regions of the world, including China, South Africa, and Australia. A third introduction event occurred later, that spread the disease from Australia to Argentina. Fontaine et al. (2013) and Gobbin et al. (2006) observed a low diversity and weak structure in European populations of *P. viticola*, suggesting that the strains initially introduced into Europe came from a single source population of North American origin.

Migration routes of *Erysiphe necator* and *Phyllosticta ampelicida* have been less studied than those of *Plasmopara viticola*. According to Brewer and Milgroom (2010), populations of *E. necator* in Europe are derived from two separate introductions from Eastern United States. These initial introductions into Europe were followed by secondary introductions from Europe into the Western United States and Australia. Recently, Gur et al. (2021) proposed an additional non-American (possibly Asian) origin of *E. necator*. There is even less knowledge on the invasion pathways of *P. ampelicida* (Narduzzi-Wicht et al., 2014). Rinaldi et al. (2017) suggested that the pathogen was introduced into Northeastern Italy from Eastern Europe and

that two introductions occurred in Portugal, one from France or Italy, and another from America. Interestingly, these American pathogens did not only colonize the European cultivated grapevine *Vitis vinifera* subsp. *vinifera*, but also incorporated the microbiome of its wild ancestor *Vitis vinifera* subsp. *sylvestris* (Section 1.1). As a result, the distribution of wild grapevines has been greatly reduced over the last 150 years and it is now considered an endangered plant species in Europe (Arnold et al., 2005).

Future research should continue unravelling the migratory routes of grapevine pathogens and extend these efforts to other member of the functional microbiome (Section 2). This is crucial to identify accurately the geographic locations where grapevine-pathogen-microbiome co-evolution has occurred, as well as the *Vitis* species involved in this coevolutionary process (Fig. 2). This knowledge is necessary to design microbiome studies informed by the biogeography and evolutionary history of grapevine. Microbiome dynamics on a smaller temporal scale should also be considered and is discussed below (Section 2).

2. THE GRAPEVINE FUNCTIONAL MICROBIOME THROUGHOUT PLANT LIFETIME

This section describes how the microbiome assembles, functions and changes over the course of grapevine life. It highlights the plant-microbe interactions that have a proven, direct and significant influence on the grapevine performance (growth, health and berries quality) at every life stage (Fig. 3). The section deals with both the microbiome (bacteria, filamentous fungi, yeasts and oomycetes) and the virome, including phytoviruses (plant-infecting viruses), mycoviruses (fungi-infecting viruses) and phages (bacteria-infecting viruses).

1. Initial microbiome and virome at the graft stage

The life of cultivated grapevine generally begins in a nursery with a graft (Fig. 3). The two components of the graft, the scion and the rootstock, are produced in nursery "mother" plots. Mother plants produce stems that are pruned during the dormant stage in winter to make cuttings, which are then stored in a cold room. Rootstock and scion cuttings on the one hand, and grafted plants on the other hand, undergo different treatments depending on the country and the nursery (Gramaje and Armengol, 2011). Most often, immediately after grafting, the scion and the graft zone are dipped in a wax solution, which may contain plant growth regulators (mainly auxins) and fungicides. The grafted plants are then incubated for two to three weeks under controlled temperature (28°C) and high humidity (90%), to promote callusing. A second waxing step is then performed, before planting in pots in the greenhouse, or in nursery fields. Potted plants can be shipped directly to winegrowers and planted in the field next autumn, while plants kept in nursery fields are usually shipped as one-year-old bare-root plants to be planted in spring.

Many steps in the grafting process are highly critical to obtain quality plants. First, the choice of the two plant genomes is crucial. Not counting losses due to incompatibility between genotypes (Tedesco et al., 2022), about 50% of the plants produced are unmarketable because of the low quality of the graft (Carrere et al., 2022). Second, it is fundamental for nurseries to produce plants that do not carry diseases (Waite et al., 2015), in particular phytoviruses. Viruses trigger both graft incompatibility and decline of young vines. For instance, the transmission of

grapevine leafroll-associated virus 2 (GLRaV-2; Fig. 3) from scion to rootstock results in graft incompatibility (Rowhani et al., 2017). Rootstock susceptibility to infection depends on the genotype, with genotypes 1616 Couderc, Kober 5BB, 1103 Paulsen being the most susceptible rootstocks (Alkowni et al., 2011; Rowhani et al., 2017; Uyemoto et al., 2001, 2000). Reverse incompatibility, where the rootstock is the source of a latent virus, has not been observed in grapevine yet. Decline of young vines triggered by joint infection with GLRaV-2 and grapevine virus B (GVB) infection, or GLRaV-1 and grapevine virus A (GVA), were also observed (Rowhani et al., 2017). The mechanisms underlying such decline have not been clearly determined yet, but they might involve the production of viral small interfering RNAs (vsiRNAs) by the plant cell machinery, which in turn would affect plant gene expression (Smith et al., 2011). Management of these phytoviruses relies primarily on preventive measures (such as the use of clean propagation and planting materials) and robust diagnostics (Maliogka et al., 2015; Martelli, 1999). In addition, hot water treatment (HWT) of the grafted plant (Eichmeier et al., 2018) is sometimes performed to reduce infection by phytoplasmas (flavescence dorée, bois noir, grapevine yellows) and by fungi responsible for grapevine trunk diseases (Section 2.5). *Trichoderma* spp., which are soil microbes with an antagonistic activity against some pathogenic fungi, are sometimes inoculated by nurseries (Eichmeier et al., 2018; Jaarsveld et al., 2021). Finally, mycorrhiza (*Rhizophagus irregularis*, in particular) can also be inoculated at the nursery stage (Fig. 3), to increase grapevine resistance to biotic and abiotic stresses by promoting the structure and development of the root system (Bettenfeld et al., 2021).

All the manipulations and treatments experienced by scions and rootstocks in the nursery can influence the initial grapevine microbiome and its future trajectory of assembly. Gramaje et al. (2022) analyzed the fungal microbiome associated with rootstocks harvested in two mother plots located 800m appart. No difference in fungal community composition between these two locations was detected, but the fungal communities varied along the grafting process (after cutting from mother plants, after cold storage and hydration, after grafting and callusing, and in dormant grafted plants). The core fungal microbiome was composed of the genera *Cadophora*, *Cladosporium*, *Penicillium* and *Alternaria* in both rootstocks. Numerous genera associated with grapevine trunk diseases (*Cadophora, Dactylonectria, Diaporthe, Diplodia, Ilyonectria, Neofusicoccum, Phaeoacremonium and Phaeomoniella*; Section 2.5) and potential biocontrol activities (*Aureobasidium pullulans*) were identified (Fig. 3). The pathogenic genus *Neofusicoccum* was persistent throughout the propagation process (Fig. 3), confirming the role of rootstock as a primary source of many pathogens. Lade et al. (2022) compared the contribution of nursery, scion variety and rootstock variety to fungal community composition in the graft zone and found that the nurseries (i.e. plant production practices) played a major role, followed by rootstocks and scion varieties.

Future studies should explore further the concept of microbial community coalescence (i.e. the joining of previously separate communities, forming a new entity that is not easily separable and with properties distinct from the parts it joins) in the context of grapevine grafting (Rillig et al., 2015). Indeed, at the graft stage, major physiological changes occur (Cookson et al., 2013; Prodhomme et al., 2019), including vascular connection between rootstock and scion that influences sap flow and associated fluxes of microorganisms (Deyett and Rolshausen, 2020). These processes have hardly been studied so far although they might have a significant impact on the assembly of the grapevine microbiome.

2. Recruitment of the root microbiome from the soil reservoir

Winegrowers usually receive grafted vines (potted or bare-rooted) from nurseries (Section 2.1) and plant them in the vineyard. The young plants then start recruiting microorganisms from the soil (Fig. 3), which is the major reservoir of microorganisms for the plant microbiome (Griggs et al., 2021; Liu et al., 2019; Swift et al., 2021). Recruitment is based on the active release by the roots of a wide range of carbon-containing compounds known as rhizodeposits (Chaparro et al., 2014; Martínez-Diz et al., 2019). The rhizodeposits represent nearly 40% of the photosynthates produced by a plant (Bais et al., 2006). These compounds serve as a substrate for the development of microorganisms and make the rhizosphere (i.e. the transition zone between soil and plant roots) much more attractive for microbes than surrounding soil. The nature and quantity of rhizodeposits depend on the plant genotype and vary across seasons and throughout plant life, allowing the plant to actively shape the composition of rhizosphere microbial communities (Berlanas et al., 2019). Beneficial microorganisms may for instance be recruited under stressful conditions, a mechanism known as the "cry for help" reaction (Rizaludin et al., 2021). Some rhizospheric microorganisms develop physical interactions with the root (case of mycorrhizae, for instance) and some of them can even enter the root endosphere. Once in the root endosphere, some microorganisms colonize the vascular tissues and disseminate in the aerial parts of the plant (Fig. 3), sometimes reaching leaves and berries (Darriaut et al., 2022; Liu et al., 2019). Not all microorganisms can colonize the plant internal tissues from surrounding soil, which creates a decreasing gradient of microbial diversity from the outside of the root towards the inside (Marasco et al., 2018; Martínez-Diz et al., 2019; Zarraonaindia et al., 2015).

Many studies have examined the taxonomic composition of the grapevine rhizosphere and root microbiome. The same major taxonomic groups are generally represented. Proteobacteria, Actinobacteria or Acidobacteria are the dominant bacterial phyla, followed by Firmicutes and Bacteroidetes (Bettenfeld et al., 2021; Dries et al., 2021; Novello et al., 2017; Zarraonaindia et al., 2015). Ascomycota, followed by Basidiomycota, are the dominant fungal phyla (Bettenfeld et al., 2021; Liu and Howell, 2021). On a finer taxonomic scale, the microbiome composition varies with soil physical and chemical features (Bettenfeld et al., 2021), geography and climate (Hernandez and Menéndez, 2019; Liu et al., 2019), plant age and rootstock genotype (Berlanas et al., 2019; Ji et al., 2019), and vineyard management practices (Likar et al., 2017) including applications of plant protection products and fertilizers (Canfora et al., 2018; Zaller et al., 2018) and the presence of vegetation cover (Vukicevich et al., 2018).

Root-microbe interactions can foster vine growth and productivity through various mechanisms. Plant Growth-Promoting (PGP) microbes (Fig. 3) can for instance solubilize and make nutrients available to the roots (Darriaut et al., 2022). The mineral elements needed by the plant (phosphorus, nitrogen and phosphate) are indeed naturally present in the soil but cannot be efficiently or directly assimilated by plants because they are complexed with other molecules. Some PGP bacteria produce enzymes (phosphatases) or organic acids (e.g. hydrogen cyanide; Rijavec and Lapanje, 2016) that solubilize inorganic phosphate, while others produce ammonium (NH_4^+) or convert nitrites (NO_2^-) to nitrates (NO_3^-), that are easily absorbed by the plant. Some bacteria, including *Bacillus herbersteinensis*, *Bacillus licheniformis*, *Micrococcus* spp., *Pseudomonas* spp., and *Pantoea agglomerans*, can combine these mechanisms (Asghari et al., 2020; Baldan et al., 2015). In the grapevine rhizosphere, the

bacterial genera *Pseudomonas*, *Streptomyces* and *Rhizobia* are those most involved in phosphorus and nitrogen cycles (Bona et al., 2018). Some fungal genera are also involved in phosphate solubilization, such as the genus *Mortierella* (Carbone et al., 2021; Liu and Howell, 2021). Rhizosphere PGP bacteria (Fig. 3) can also produce hormones, such as auxin, which directly stimulates plant growth (Morales-Cedeño et al., 2021). For instance, *Agrococcus baldri* and *Paenibacillus* spp. produce hormones that, even at low concentration, cause root elongation, branching and increase root diameter and density (Baldan et al., 2015). Bacterial species, such as *Bacillus amyloliquefaciens*, can produce microbial siderophores, which bind with iron, and contribute to plant iron nutrition (Mardanov et al., 2019). Other endophytic bacteria associated with root tissues (*Pseudomonas* spp., in particular), produce enzymes (ACC-deaminases) that cleave ACC (1-aminocyclopropane-1-carboxylic acid), which is the immediate precursor of ethylene in plants. This reduces the production of ethylene and limits the damage caused by biotic and abiotic stresses (Marasco et al., 2018; Saraf et al., 2010).

Arbuscular mycorrhizal fungi (AMF) also play an important role in water and nutrient absorption. Belonging mainly to the *Glomeromycota* phylum, these endomycorrhizal fungi establish symbioses with vine roots (Balestrini et al., 2010). Hyphae increase the exchange surface between vine roots and soil. They also activate phosphorus and nitrogen transporters in root cortical cells (Trouvelot et al., 2015). AMF are the most abundant mycorrhizae associated with grapevine roots and include species belonging to the genera *Acaulospora, Diversispora, Funneliformis, Glomus* and *Rhizophagus* (Darriaut et al., 2022; Liu and Howell, 2021). They are actively recruited by vine roots during water stress (Carbone et al., 2021).

Grapevine roots are not only colonized by beneficial microorganisms such as PGP and AMF, but also by bacterial, fungal and viral pathogens (Fig. 3). The bacterial pathogen *Allorhizobium vitis*, the causal agent of crown gall, is frequently isolated from diseased plants in the vineyard (Habbadi et al., 2020). The bacteria harbors tumor-inducing plasmids (pTi), part of which integrate into the plant genome (Transfert-DNA, T-DNA) to induce the development of root or crown galls and the synthesis of opines, which the bacteria utilizes as nutrients. The spread of pTI plasmids can be facilitated by bacteria belonging to the *Novosphingobium* genus, which are therefore pathogen stimulants (Gan et al., 2019). Black-foot disease, caused by *Ilyonectria* spp. (*I. liriodendri*, in particular), is responsible for root necrotic lesions, with a reduction in root biomass, besides other symptoms that include reduction of internodes, loss of vigor, patchy foliage and smaller leaves (Bleach et al., 2021). The fungal genus *Ilyonectria* is found in many metabarcoding analyses of vineyard soil because it can persist for several years after the removal of infected vines (Brito et al., 2019; Deyett and Rolshausen, 2020; Liu and Howell, 2021; Rivas et al., 2022). Several fungal genera associated with grapevine trunk diseases (*Botryosphaeria* and *Diplodia*; Section 2.5), Petri disease (*Cadophora, Phaeoacremonium* and *Phaeomoniella*) and Diaporthe dieback (*Diaporthe*) have been detected in asymptomatic root tissues (Deyett and Rolshausen, 2020; Liu and Howell, 2021; Martínez-Diz et al., 2019; Rivas et al., 2022). *Candidatus phytoplasma* spp., the causal agent of bois noir disease, was also detected in healthy root tissues (Marasco et al., 2018), indicating that the root endosphere is a reservoir for latent pathogens (Liu and Howell, 2021; Martínez-Diz et al., 2019). Finally, grapevine roots can be infected by phytoviruses, some of which are transmitted by soil nematodes. For instance, grapevine fanleaf virus (GFLV) and arabis mosaic virus (ArMV), the main causal agents of grapevine fanleaf disease, are transmitted by the nematode species *Xiphinema index* and *Xiphinema italiae* in the case of GFLV, and *Xiphinema diversicaudatum*

in the case of ArMV (Oliver and Fuchs, 2011). The nematodes feed on the tips of growing roots by pricking them with a stylet. By successively feeding on neighboring vines, they disseminate the virus retained in their esophageal tracts (Maliogka et al., 2015). This is why virus-infected vines often have a patchy distribution in vineyards.

The root microbiome also harbors microorganisms that directly inhibit pathogen growth, through antagonistic microbial interactions, or indirectly limit disease severity or frequency by stimulating the plant immune system or by acting on vector populations (Fig. 3). Microbial interactions responsible for pathogen biocontrol include antibiosis, hyperparasitism, spatial and nutritional competition, interference with pathogen signaling, and disease symptom reduction by degradation of pathogen toxins or virulence factors (Compant et al., 2013). For instance, the biocontrol activity of *Bacillus amyloliquefasciens* mainly relies on antibiosis. This bacteria synthesizes a wide range of antimicrobial compounds (surfactin, plantazolicin, macrolactin, bacillaene, fengycin, difficidin, bacillibactin, and bacilysin) that regulate the growth of several grapevine pathogen species, including *Botrytis cinerea*, *Phaeoacremonium aleophilum*, *Phaeomoniella chlamydospora* (Mardanov et al., 2019). Root microbes also stimulate plant defenses, by inducing oxidative bursts, activating signaling pathways (salicylic acid, ethylene/jasmonic acid), and increasing the synthesis of pathogenesis-related (PR) proteins, lytic enzymes, polyamines and phytoalexins (Héloir et al., 2019). This stimulation increases the plant capacity to react to ongoing infections, or to future ones through pre-activation of the immune system (immune priming). For instance, bacteria of the *Burkholderia* genus increase the production of PR proteins when inoculated on the roots of grapevine infected with *B. cinerea* (Esmaeel et al., 2020). In addition, the strain *Burkholderia phytofirmans* PsJN can migrate to the aerial parts of grapevine and form biofilms that directly limit the spread of *B. cinerea* (Miotto-Vilanova et al., 2016). Many other root microorganisms have a proven negative influence on grapevine pathogens but their mode of action is not always known. Other bacteria with a biocontrol activity include *Streptomyces* spp, that reduce young grapevine decline and black-foot disease (González-García et al., 2019; Pilar Martínez-Diz et al., 2021), and *Bacillus subtilis*, which directly limits the growth of fungal pathogens related with grapevine trunk diseases (Berlanas et al., 2019). The latter also stimulates plant defenses, similar to *Pseudomonas fluorescens*, *Pantoea agglomerans*, *Acinetobacter lwoffii* (Aziz et al., 2020, 2016; Magnin-Robert et al., 2007). Root fungi, in particular AMF, also play a role in disease biocontrol. AMF of the *Glomus* genus and *Rhizophagus irregularis* reduce the severity of black-foot disease (Berlanas et al., 2019; Darriaut et al., 2022). AMF may also protect grapevines from GFLV by inhibiting the proliferation and penetration of its nematode vector (*X. index*) in roots (Hao et al., 2018). In addition, the fungal species *Trichoderma atroviride* and *Aureobasidium pullulans* are antagonists of the fungal pathogens associated with Petri disease (*Phaeomoniella chlamydospora and Phaeoacremonium minimum*), and of *Diplodia seriata* which is associated with Botryosphaeria dieback (Martínez-Diz et al., 2019). *T. atroviride* also fosters plant defenses (Stempien et al., 2020). Finally, the oomycete *Pythium oligandrum* has mostly indirect negative effects on fungal pathogens associated with Petri disease (Yacoub et al., 2016).

Overall, this state of art indicates that grapevine roots constitute a rich microbial compartment that is quite well understood from a functional point of view. Many microorganisms that have a positive (such as PGP bacteria, AMF and biocontrol agents) or negative (such as *Allorhizobium vitis* or phytoviruses) influence on grapevine have been identified and their mode

of action has been described. Shotgun metagenomics and metabolic network modeling (Section 3.3) could further advance this understanding. Future research should also focus on belowground-aboveground relationships, assessing the influence of soil and root microbiomes on leaf and berry microbiomes (Sections 2.3 and 2.4) and the consequences on grapevine health and wine quality.

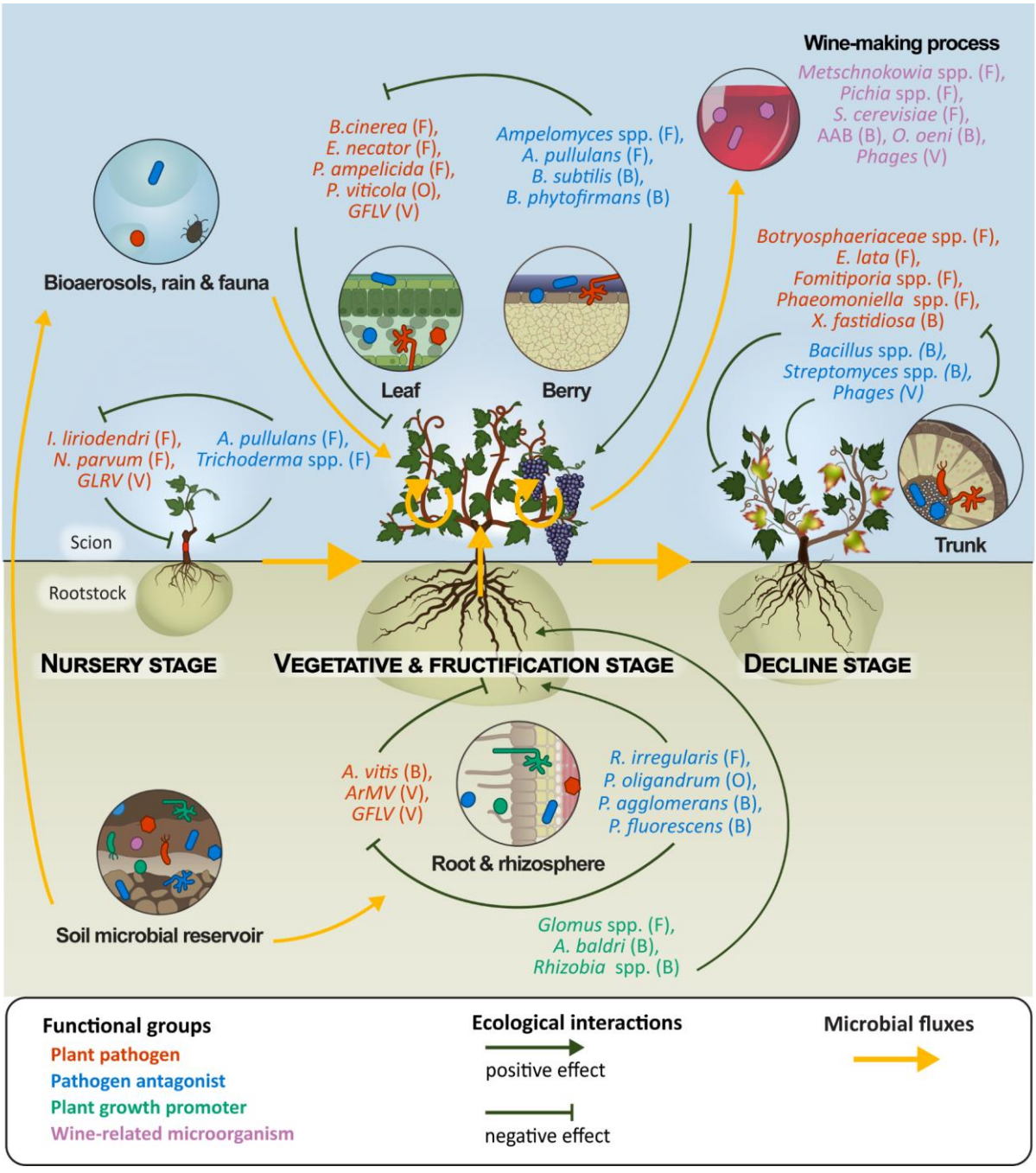


Figure 3 - Microbial functional groups that colonize cultivated grapevine from the nursery to plant decline, as well as ecological interactions (black arrows) and microbial fluxes (yellow arrows) that drive the microbiome dynamics during plant lifetime. Plant-microbe-microbe ecological interactions form complex networks (Section 3) that could not be represented here for clarity. Only a few ecological interactions are represented. For the same reason, we could not represent all the fungal (F), bacterial (B), oomycete (O) species and viruses (V) that

significantly influence grapevine performance and wine-making process. We only represented a few well-studied species or species groups. AAB, Acetic Acid Bacteria; GFLV: Grapevine Fanleaf Virus; GLRV, Grapevine Leafroll associated Virus; Other species names: *Agrococcus baldri, Allorhizobium vitis, Aureobasidium pullulans, Bacillus subtilis, Botrytis cinerea, Burkholderia phytofirmans, Candidatus phytoplasma, Erysiphe necator, Eutypa lata, Ilyonectria liriodendri, Neofusicoccum parvum, Oenococcus oeni, Pantoea agglomerans, Phyllosticta ampelicida, Plasmopara viticola, Pseudomonas fluorescens, Pythium oligandrum, Rhizophagus irregularis, Saccharomyces cerevisiae, Xylella fastidiosa.*

3. Seasonal assembly of the leaf microbiome in interaction with leaf pathogens

Grapevine leaf microbiome has a cyclic dynamic: it assembles in spring, changes during the vegetative season and then disassembles during leaf senescence. In spring, the buds burst and let the first shoots appear. As vines are lianas, the shoots hang on to the trellis with their tendrils and grow by producing new leaves, at a rate of about one every three days in the Bordeaux area (Calonnec et al., 2008). At a given time, each vine thus displays a mosaic of leaves of different ages. The leaves at the distal end of the twigs are the youngest and the leaves near the stock are the oldest (see Fan et al., 2020). As the shoot grows, the young leaves expand, become mature, and are colonized by epiphytic microorganisms (the phyllosphere microbiome *sensu stricto*; Behrens and Fischer, 2022; Vacher et al., 2016) and endophytic microorganisms (Pacifico et al., 2019) that collectively form the leaf microbiome. The latter is largely dominated by fungi belonging to the Ascomycota and by bacteria belonging to the Actinobacteria, followed by Proteobacteria and Firmicutes (Bettenfeld et al., 2021; Fort et al., 2016; Singh et al., 2018). The fungal species *Aureobasidium pullulans* was dominant at the end of growing season in several independent metabarcoding studies, representing more than half of the fungal community in old leaves (Grube et al., 2011; Knapp et al., 2021).

Leaf microbiome dynamics depends on many factors, and first and foremost on the specific growth pattern of grapevine (Calonnec et al., 2018, 2008). Indeed, the date at which a leaf emerges determines its morphology and physiology (Chitwood et al., 2016; Majer and Hideg, 2012) and also the microbial fluxes and environmental perturbations to which it will subsequently be exposed. Leaves that emerge first are colonized by microorganisms that overwintered in buds or on woody parts (case of primary infections by the fungal pathogen *Erysiphe necator*, Gadoury et al., 2012), or in senescent leaf debris that remained on the soil (case of primary infections by the oomycete pathogen *Plasmopara viticola*, Burruano, 2000). They are also colonized by microorganisms circulating in the xylem or in the phloem (Fig. 3). These circulating microorganisms may be benefic (case of the bacterium *Burkholderia phytofirmans*, Compant et al., 2008) or they may be pathogens (case of the bacterial pathogen *Xylella fastidiosa*, Deyett and Rolshausen, 2019, and of viruses and phytoplasmas, Laimer et al., 2009; Zherdev et al., 2018). Wind and rain disseminate microorganisms from multiple sources (vines, soil, adjacent semi-natural and natural habitats) (Fig. 3) and may also contribute to the initial colonization of the phyllosphere (Abdelfattah et al., 2019; Griggs et al., 2021). In contrast, leaves that emerge later in the season are in direct contact with other grape leaves that already have a more developed microbiome. Leaf-to-leaf transmission of the microbiome (Fig. 3), which may transiently involve the atmosphere or other plant organs, is the dominant microbial colonization pathway in grapevine leaves (Abdelfattah et al., 2019). This

transmission is responsible for secondary infection cycles in leaf pathogens. Late-emerging leaves also face greater activity from fauna (arthropods, birds) that are underestimated microbial vectors (Griggs et al., 2021; Stefanini and Cavalieri, 2018). Finally, it should be noted that leaves of different ages do not provide the same habitat for microorganisms. Leaf age determines the structure of the cuticle and epicuticular waxes, the amount of available nutrients, the concentration of secondary metabolites, all of which regulate the growth of microbial populations (Griggs et al., 2021; Shakir et al., 2021). Leaf age also determines immune status as microbial colonization can stimulate defenses and make the leaf more resistant to subsequent infection (Chaudhry et al., 2021; Shakir et al., 2021), a mechanism known as immune priming (Section 2.2). The effect of leaf age on disease development is well known and is termed ontogenic resistance. It has been demonstrated for several grapevine leaf pathogens (Calonnec et al., 2018; Qiu et al., 2015; Steimetz et al., 2012). All of these factors lead to intra-canopy variation in the composition of the grapevine leaf microbiome (Calonnec et al., 2008; Fan et al., 2020) as well as strong seasonal dynamics. Seasonal dynamics, however, are less pronounced in bacterial communities than in fungal communities, whose diversity decreases markedly over the growing season (Fort et al., 2016; Gobbi et al., 2020; Liu and Howell, 2021; Pinto et al., 2014; Singh et al., 2018).

In addition to seasonal intra-canopy dynamics, the grapevine leaf microbiome exhibits high spatial variability. Its composition changes significantly from one geographical region to another (Oliveira et al., 2018; Singh et al., 2018) and from one vineyard plot to another (Barroso-Bergadà et al., 2021 but see Knapp et al., 2021). These spatial variations are explained by vine-related (scion variety, cultural practices) and environmental factors (climate and microclimate, landscape structure) (Bettenfeld et al., 2021). Several studies have attempted to establish a hierarchy between these factors. For example, variety has a significant effect on leaf microbiome composition (Singh et al., 2019, 2018; Zhang et al., 2020), but its effect is much smaller than that of geographic and climatic factors (Singh et al., 2018). The effect of phytosanitary treatments appears to be less important than seasonal dynamics (Gobbi et al., 2020), in agreement with results demonstrating high resilience of the phyllosphere microbiome to phytosanitary treatments (Perazzolli et al., 2014). The cropping system as a whole, however, has a substantial influence on the diversity and composition of leaf microbiome, with significant differences found between organic and conventional farming (Barroso-Bergadà et al., 2021; Castañeda et al., 2018; Kernaghan et al., 2017; Miura et al., 2019). Finally, several studies investigated whether forest patches or orchards adjacent to grapevine plots structure the grapevine leaf microbiome, with varying results (Castañeda et al., 2018; Castañeda and Barbosa, 2017; Chandra et al., 2020; Fort et al., 2016; Miura et al., 2019).

Among the multitude of microorganisms that colonize grapevine leaves, some affect plant health and growth. Pathogens and their mode of action have been the most studied (Armijo et al., 2016) Powdery and downy mildews (respectively caused by the fungal species *Erysiphe necator* and the oomycete species *Plasmopara viticola*; Fig. 3) are the most important diseases of grapevine (Bois et al., 2017). Black-rot (caused by the fungi *Phyllosticta ampelicida*, Fig. 3) is a foliar disease that is becoming increasingly important in Europe, concomitant with efforts to reduce fungicide use (Molitor and Beyer, 2014). All three pathogens are introduced species of North-American origin (Sections 1.2 and 1.3). When these fungal pathogens colonize the grapevine leaf, they encounter the resident microbiome and virome, which can act as a barrier to their growth through direct ecological interactions (Chaudhry et al., 2021; Hacquard et al.,

2017), such as exploitative competition, interference competition (antibiosis), and hyperparasitism. Once this first barrier is overcome, pathogens are confronted to the plant's immune system, which is itself stimulated by the microbiome, especially the root microbiome (Section 2.2).

Natural antagonists of downy mildew (Fig. 3) have been identified using culture-dependent methods. Several bacterial and fungal species, isolated from grapevine leaves or previously detected in the leaf microbiome, have a negative effect on *Plasmopara viticola* under experimental conditions. For fungi these include *Acremonium byssoides*, *Alternaria alternata*, *Beauveria bassiana*, *Epicoccum nigrum* (Burruano et al., 2016, 2008; Kortekamp, 1997; Musetti et al., 2006; Rondot and Reineke, 2019; Taguiam et al., 2021; Zanzotto and Morroni, 2016), and several *Fusarium* species (Bakshi et al., 2001; Falk, 1996). The genus *Bacillus*, including *B. subtilis* and *B. pumilus*, predominates among *P. viticola* antagonistic bacteria (Bruisson et al., 2019; Dagostin et al., 2011; Zanzotto and Morroni, 2016; Zhang et al., 2017). Moreover, root colonization by the arbuscular mycorrhizal fungus *Rhizophagus irregularis* (Sections 2.1 and 2.2) increases grapevine resistance to *P. viticola* (Cruz-Silva et al., 2021). Finally, the virome of *P. viticola* has been analyzed using metatranscriptomics in search for hypovirulence-inducing mycoviruses (Chiapello et al., 2020). However, despite the description of many new mycoviruses (283 new viruses associated with lesions caused by *P. viticola*), the limited availability of phenotypic data on fungal hosts has so far prevented the association of particular viruses with variations in fungal virulence.

Pathogen-microbiome-virome interactions are not so well documented in powdery mildew (Panstruga and Kuhn, 2019) but some antagonistic interactions (Fig. 3) have been experimentally demonstrated. Several natural hyperparasites of *Erysiphe necator* have been identified among the *Ampelomyces*, *Lecanicillium*, and *Acremonium* genera (Falk, 1995; Ghule et al., 2019; Kiss, 2003). As with downy mildew, powdery mildew growth is reduced by *B. subtilis* and *B. pumilus* (Compant et al., 2013; Crisp et al., 2006). Network inference (Section 3.3) suggested an antagonistic interaction between powdery mildew and the yeast *Buckleyzyma aurantiaca* (Pauvert et al., 2020), which remains to be experimentally validated with culture-dependant approaches (Section 3.4). Moreover, as for *Plasmopara viticola*, the virome of *E. necator* has been studied in search of hypovirulence-inducing mycoviruses (Pandey et al., 2018). Mycoviruses have been detected but their influence on fungal virulence and disease development has not been demonstrated yet.

Future studies should continue searching for members of the resident microbiome and virome that naturally regulate mildews, and identify the biodiversity management practices that favor these natural antagonists. Such results are urgently needed as mildews are currently controlled by chemical pesticides whose use should be drastically reduced to preserve environmental and human health (Jacquet et al., 2022). To identify biocontrol candidates against mildews, we recommend exploring the microbiome and the virome of mildew-resistant *Vitis* species in their native range (Fig. 2), where they have co-evolved with pathogen species (Section 1.2). Deciphering the microbial interaction networks (Section 3.3) in these resistance zones could also provide interesting insights into the natural regulation of mildews.

4. Dynamics of the berry microbiome until ripening and winemaking

Like the leaf microbiome (Section 2.3), the berry microbiome varies significantly in abundance and composition throughout the season. Population sizes of both fungal and bacterial communities on the berry surface increase with ripening and reach a maximum when the berries become overripe. The community composition varies significantly during the season, with a decrease in *Basidiomycota* (*Aureobasidium, Cryptococcus and Rhodotorula* spp.) and an increase in *Ascomycota* (*Hanseniaspora, Metschnokowia, Pichia* spp.) (Barata et al., 2012). As the season progresses, Gram-negative bacteria (mostly *Pseudomonas spp.*) decrease in abundance whereas Gram-positive communities (mostly *Micrococcus* spp.) increase (Martins et al., 2012). The morphology and chemical composition of berries are major drivers of these seasonal variations in microbiome composition (Liu and Howell, 2021). Indeed, the water activity on grape berry skin and the composition of exudates change along the grape berry ripening process, with an increase in sugar content, a decrease in pH and acidity (Griggs et al., 2021; Martins et al., 2014, 2020). Other drivers include the agricultural practices during the fructification period (phytosanitary treatments, pruning), as well as the climatic conditions from fruit set to harvest (Belessi et al., 2022; Bokulich et al., 2014; Cordero-Bueso et al., 2011a, 2011b; Ding et al., 2021; Martins et al., 2014, 2020; Pinto et al., 2014). In addition to these seasonal variations, the berry microbiome varies markedly in space. In the last decade, many studies conducted at different spatial scales (world, countries, regions and vineyards) gave evidence of a biogeographic differentiation of the berry microbiome (Bokulich et al., 2014; Gobbi et al. 2022; Jara et al., 2016; Li et al., 2022; Miura et al., 2017; Vitulo et al., 2019). Based on these findings, the authors developed the concept of "*microbial* terroir" that proposes a causal relationship between grape microbial biogeography and regional wine characteristics.

At the ripening stage, the grape berries harbor fermentative microorganisms that will subsequently contribute to the winemaking process and to wine quality (Fig. 3). These microorganisms include *Saccharomyces cerevisiae* (Sections 1.1 and 1.3), non-*Saccharomyces* yeasts and Lactic Acid Bacteria (LAB). *S. cerevisiae* is the main species responsible for alcoholic fermentation. Although its populations reach their higher level at berry maturity (10^4 to 10^6 cfu/g), the yeast remain rare at the grape berry surface, thus raising questions on its origin (Mortimer and Polsinelli, 1999 ; Börlin et al., 2020). The abundance and diversity of fermentative yeasts on the grape berry surface is impacted by fungicide treatments (Cordero-Bueso et al., 2014) and infection by *Botrytis cinerea*, which modifies sugar availability (Fleet et al., 2003 ; Nisiotou and Nychas, 2007). Low numbers ($<10^3$ cfu/g) of cultivable LAB are also present on sound fruit and end up in must during the early stages of wine processing. Within this group of bacteria, *Oenococcus oeni* (Fig. 3) is responsible for a crucial process called malo-lactic fermentation (MLF), where L-malic acid in wine converts to softer L-lactic acid. The reduction of acidity, which spontaneously occurs after alcoholic fermentation, is beneficial to the quality of wines made in cool winegrowing regions. Yet, MLF only starts when the *O. oeni* population reaches 10^6 cfu/ml. Factors reducing the bacterial biomass are thoroughly studied to avoid slow or blocked MLF. Phages (Fig. 3) are part of these factors, as they may modulate *O. oeni* population size, and a number of temperate and virulent phages infecting *O. oeni* have been recently isolated from crushed grapes and later winemaking stages (Claisse et al., 2021).

The berry microbiome may also contain microorganisms that alter wine quality, such as Acetic Acid Bacteria (AAB) or fungi that produce off-flavors or mycotoxins. AAB (*Acetobacter* spp.,

Gluconobacter spp.) (Fig. 3) are wine spoilage bacteria that are naturally present in the microbiome of grape berries (Fleet, 1993). They cause pre- and post-harvest yield losses and render berries unsuitable for wine production. A relevant example is sour rot of grape (Lleixa et al., 2018), which is a polymicrobial disease requiring the presence of *Drosophila* flies (disease vector), wounded fruits, various yeasts that convert grape sugars to ethanol, and AAB that subsequently oxidize the ethanol to acetic acid. AAB co-exist with phages on ripe grapes and a member of the *Tectiviridae* family has been recently characterized (Philippe et al., 2018). The control of AAB is challenging as these bacteria show great capacities to persist during wine making. Phages and their derived enzymes called endolysins may offer new solutions.

Fungi naturally present on ripened grape berries can also produce off-flavors, in particular earthy or moldy odors in grape juice and wines. This is the case of *Botrytis cinerea* (Figure 3), the necrotrophic fungal pathogen responsible for grey mold (Armijo et al., 2016). *B. cinerea* produces cellulases, pectinases, proteases and a *p*-phenol oxygen oxidoreductase able to oxidize phenolics compounds, which is at the origin of severe alteration of wine color. *B. cinerea* also causes an enhancement of phenylpropanoid metabolism, terpenes and fatty acid aroma precursors at the grape berry level. It can be associated with *Penicillium expansum*, then leading to the production of geosmin, an earthy off-aroma (La Guerche et al., 2007, 2005). However, *B. cinerea* can also colonize berries under its "noble rot" form which positively develops the grape aroma potential (Thibon et al., 2011, 2010). Natural antagonists of *B. cinerea* have been searched for within the leaf and berry microbiome to develop microbial biocontrol. They include *Aureobasidium pullulans*, which acts against *B. cinerea* through nutritive and spatial competition and antibiosis (Carmichael et al., 2019; Martini et al., 2009, p. 200; Rathnayake et al., 2018). They also include some bacteria (*Bacillus* spp., Actinomycetes) and yeasts (*Metchnikovia* spp., *Pichia* spp.) (Loqman et al., 2009; Raspor et al., 2010; Santos and Marquina, 2004). Mycoviruses infecting *B. cinerea* (Pearson and Bailey, 2013; Ruiz-Padilla et al., 2021) have been searched for to foster biocontrol. Although a rich virome was discovered, only a few mycoviruses were associated with a reduced virulence of the fungal pathogen (i.e. an hypovirulence phenotype) (Khalifa and MacDiarmid, 2021; Wu et al., 2010; Yu et al., 2015). These mycoviruses belonged to several families, including *Narnaviridae* (single-stranded RNA virus) and *Genomoviridae* (single-stranded DNA virus). An unclassified double-stranded RNA virus was also found. Finally, fungal pathogens producing mycotoxins (*Aspergillus carbonarius*, *Aspergillus niger*) can also develop in mature berries. Mycotoxin contamination can be limited by specific practices (Hocking et al., 2007; Perera et al., 2021), including biocontrol by *A. pullulans* (Bozoudi and Tsaltas, 2018).

Future research should continue investigating the dynamics of microbial interactions and functions on the grape berry surface (Section 3.3), to elucidate their impact on berry quality and wine properties. Conversely, the impact of the winemaking process on the berry microbiome dynamics could be studied. Indeed, during winemaking, fermentative microorganisms reach very high population levels in cellars and can be disseminated in the vineyard through CO_2-extraction systems and insect vectors.

5. Wood microbiome dysbiosis during grapevine aging and decline

Cultivated grapevines are perennial plants that age and are eventually removed when they are no longer productive. Nowadays, a major cause of grapevine decline (Fig. 3) are Grapevine

Trunk Diseases (GTDs), a group of diseases which re-emerged in the late 1990s and cause wood degradation and necrosis within the inner structures of mature grapevines (Bertsch et al., 2013; Bruez et al., 2013; Mugnai et al., 1999). GTDs include *Botryosphaeria* dieback, *Diaporthe* dieback, *Eutypa* dieback, *Phomopsis* dieback, Petri disease, black-foot disease and Esca complex diseases. Pathogenic fungi associated with GTDs belong to several genera, including *Phaeomoniella, Phaeoacremonium, Fomitiporia, Eutypa*, and to the *Botryosphaeriaceae* family (Cobos et al., 2022; Fig. 3). However, these fungi have been isolated from both healthy and necrotic wood tissues of both GTD-symptomatic and asymptomatic grapevines. Their role in GTDs has therefore been questioned (Hofstetter et al., 2012) and other microorganisms potentially involved in GTDs have been isolated using culture-dependent methods (Elena et al., 2018; Kraus et al., 2019). Cobos et al. (2022) reported that in 2018, 133 fungal species belonging to 34 genera (mainly ascomycetes and basidiomycetes) had been associated with GTDs worldwide, this number increasing yearly. Bacteria inhabiting grapevine wood have also been isolated, identified and their functions studied. For instance, Bruez et al. (2015) identified 26 bacterial genera inhabiting the various wood tissues, the most abundant being *Bacillus* (34% of the bacterial strains), then *Pantoea* (12%), *Paenibacillus* (9%), and *Enterobacter* (6%). Bacterial communities differed between anatomical parts (i.e. trunk or cordon) and tissue types (i.e. necrotic or non-necrotic). Functions of bacteria colonizing necrotic and non-necrotic tissues differed, as they metabolized differently the carbon substrates. Over the last decade, next-generation sequencing (Del Frari et al., 2019; Eichmeier et al., 2018; Gramaje et al., 2022; Lade et al., 2022) and metatranscriptomic analyses (Nerva et al., 2022; Paolinelli et al., 2022) provided deeper resolution in the grapevine wood fungal and bacterial microbiomes. Depending on the grapevine organs, years, seasons and wood health status (i.e. healthy or necrotic), variations in the wood microbiome composition were observed, for both fungi and bacteria (Bruez et al., 2020, 2014).

Wood necrosis is often observed in mature grapevines (15 to 25-year-old), the difference between healthy and GTDs-plants being the quantity of wood necrosis. White-rot necrotic wood, is in particular, more abundant in diseased plants (Maher et al., 2012; Ouadi et al., 2021, 2019). This observation raised a key question: why does a substantial percentage of wood become necrotic in mature plants? This question has recently been investigated in the case of Esca, the most frequent GTD. Microbiome changes occurring at the onset of Esca were investigated using metabarcoding approaches (Bruez et al., 2020). The results showed a decrease in the diversity of the fungal microbiome in the white-rot of diseased trunks, linked with the tissue colonization by the fungal pathogen *Fomitiporia mediterranea*. Because fungi and bacteria coexist in the wood, the authors hypothesized that fungal-bacteria associations were involved in the wood degradation. In agreement with this hypothesis, associations between GTD-fungal pathogens (*F. mediterranea* and *Phaeomoniella chlamydospora*) and bacterial species (*Sphingomonas* spp. and *Mycobacterium* spp.) were detecetd in the cordons of young grapevines expressing Esca-foliar symptoms. More recently, Haidar et al. (2021) showed that *F. mediterranea* and a novel species of bacteria isolated from grapevine wood (Haidar et al., submitted) acted synergistically to enhance wood structure degradations associated with Esca.

Plant-microbe and microbe-microbe interactions responsible for other GTDs (*Botryosphaeria* dieback, *Diaporthe* dieback) have also been studied. Several fungal pathogens of the genera *Botryosphaeria*, *Diplodia*, *Lasiodiplodia* and *Neofusicoccum* have been identified as causal agents of *Botryosphaeria* dieback. This complex of xylem-inhabiting fungi can remain latent

in the roots before producing phytotoxic compounds and degrading enzymes (xylanases, cellulases, β-glucanases) in stems and symptomatic leaves (Gramaje et al., 2018; Marais et al., 2021; Martínez-Diz et al., 2019). Fungi of the genus *Diaporthe* are responsible for *Diaporthe* dieback, a disease that causes, among others, cane bleaching, swelling arms, trunk cankers, shoots breaking off at the base, loss of vigor, and reduced bunch size (Guarnaccia et al., 2018; Martínez-Diz et al., 2019). These symptoms can allow the implantation of opportunistic microorganisms such as *Didymella negriana*, which is capable of producing mycotoxins (Liu and Howell, 2021; Stranska et al., 2022).

Wood bacteria, fungi and mycoviruses with potential biocontrol activities against fungal pathogens associated GTDs have been searched for (Haidar et al., 2021; Marais et al., 2021; Mondello et al., 2018; Rezgui et al., 2016). Fotios et al. (2021) analyzed the wood microbiome of asymptomatic and symptomatic plants in three Greek grapevine varieties, using differential abundance analysis (Section 3.1) and network inference methods (Section 3.3). Their results showed that *Bacillus* and *Streptomyces* genera dominated the bacterial microbiome of asymptomatic plants and had a negative co-occurrence pattern with GTD-pathogens belonging to the *Phaeomoniella*, *Phaeoacremonium* and *Seimatosporium* genera. The authors concluded that these bacterial taxa may play a role in the suppression of GTDs. The suppressive role of the wood microbiome was also suggested by Bruez et al. (2016), as they noticed that pathogenic and non-pathogenic fungi reach an equilibrium in the functional tissues of old grapevines. Mycoviruses may also play a role in the suppression of GTDs. For instance, mycoviruses were detected in *Neofusicoccum parvum* isolates from grapevines without symptoms of Esca (Nerva et al., 2019) and in hypovirulent isolates (Marais et al., 2021), suggesting that mycoviruses may reduce the aggressiveness of this *Botryosphaeriaceae* species. It is noteworthy tha viruses could also be helpful to fight pathogenic bacteria that colonize xylem vessels, like *Xylella fastidiosa* (Fig. 3), the causal agent of Pierce's Disease, and *Xylophilus ampelinus*, the causal agent of bacterial blight. Biocontrol protocols using virulent phages have been successfully implemented *in planta* in Texas, USA, to control *Xylella fastidiosa* (Das et al., 2015). This approach is promising, especially since the pathogen is vectored by an insect (the glassy-winged sharpshooter, *Homalodisca vitripennis*) (Bhowmick et al., 2016) which has the capacity to uptake *X. fastidiosa* phages (Clavijo-Coppens et al., 2021).

Future research should therefore continue to decipher plant-microbe-virus interactions in grapevine wood, and more specifically the dynamics of these interactions in relation to the onset of disease symptoms (Section 3.3). For instance, the wood microbiome and microbial networks could be analyzed just before the appearance of the first Esca-foliar symptoms to answer the following questions: (i) is the onset of the disease marked by an increase in the heterogeneity of the microbiome between grapevines, as stated in the 'Anna Karenina principle' (Zaneveld et al., 2017)? (ii) is the onset of the disease marked by a change in microbial interaction networks? (iii) is there a change in the functional composition of the microbiome, marked by an increase in the abundance of pathogenic species? Some of the tools to answer these questions are described in the next section (Section 3).

3. LET'S MAKE THE GRAPEVINE MICROBIOME MORE FUNCTIONAL

This section proposes experimental and computational approaches that could help uncover the functioning of the grapevine microbiome. *Experimental designs* exploit what we know of the evolution and dynamics of the grapevine microbiome (Sections 1 and 2) and aim to identify microbial taxa or consortia that may play a role in vine performance and vineyard ecosystem health. *Molecular tools* and *computational approaches* work together to analyze the grapevine holobiont as a dynamic, interactive, and functional system. We emphasize throughout the need for *culture-dependent approaches* to validate the effects of specific microbial taxa and functions on vine performance and vineyard ecosystem functioning. Each subsection sets out research hypotheses or questions about microbiome functioning, describes methodological frameworks that exist or could be developed to address these questions, and finally suggests how to apply them to the grapevine system.

1. Field sampling designs and statistical approaches to identify beneficial microbial taxa

Grapevine hosts several hundreds of microbial taxa (Knapp et al., 2021; Morgan et al., 2017; Zarraonaindia et al., 2015 and Section 2) of which only a few dozen have known roles and modes of action (Fig. 3). Here we propose field sampling designs and statistical approaches that could be applied to metabarcoidng datasets to elucidate the links between the presence or abundance of particular microbial taxa, and functional traits measured at the plant- or ecosystem-scale. In the current context of climate change and pesticide use decrease (Jacquet et al., 2022), we ask, which field sampling designs ans statistical approaches are suitable to identify microorganisms enhancing plant tolerance to drought or providing a barrier effect against microbial pathogens?

Question #1: How to identify microbial taxa enhancing plant tolerance to drought or providing a barrier effect against microbial pathogens from metabarcoding data?

To address this question, the composition of grapevine microbiome samples can be analyzed using metabarcoding approaches and then statistically related to measurements of grapevine physiology or vineyard ecosystem functioning. For example, the microbiome can be related to ecophysiological traits that indicate grapevine tolerance to drought (Gambetta et al., 2020; Vacher et al., in press), or to the frequency and intensity of diseases at the plot level in epidemiological surveys (Chen et al., 2019), or to more integrative agricultural variables such as yield potential. The grapevine microbiome can then be considered as an explanatory factor of the variation in the functional trait of interest (e.g. drought tolerance, disease resistance, yield). This variation can be analyzed at different temporal and spatial scales (Fig. 4): within the lifetime of a cultivated vine individual (Fig. 3), between vines planted in the same plot (e.g. Darriaut et al., 2021), between vineyard plots, between cultivated vines and their wild ancestors (Section 1.1), or between cultivated vines and disease-resistant *Vitis* species (Section 1.2).

Field sampling design should anticipate the statistical analyses. Grapevine individuals or vineyard plots can be selected along a gradient of a previously measured functional trait of

interest. Pairs of individuals, or pairs of plots, contrast in the functional trait of interest (e.g. drought-tolerant vs. drought-sensitive, disease-resistant vs. disease-susceptible, high- vs. low-yielding) while being otherwise similar (same rootstock and scion cultivars, similar plant age, soil type and farming system) can also be selected. These two sampling strategies (Fig. 4) rely on spatial variation in the functional trait of interest. The first maximizes the variation in the trait along the gradient, while the second reduces the environmental heterogeneity within a pair. Time series longitudinal surveys (Fig. 4) complete this picture to highlight joint temporal variations between the microbiome and the functional trait of interest. This combination is highly relevant for grapevine given the strong dynamics in the microbiome at multiple timescales (Sections 1 and 2).

Several statistical tools can then be applied to metabarcoding data to assess the contribution of microbiome composition to variation in the functional trait of interest, and identify the properties of the microbiome that are the most explanatory. These explanatory properties can be the occurrence or abundance of particular microbial taxa or microbial functional groups (Section 3.2), or aggregated properties at the community or network levels (such as community alpha-diversity or microbial network connectance) (Barroso-Bergadà et al., 2021). The compositional dissimilarity matrix between samples (community beta-diversity) can be converted into explanatory vectors using the method of PCNM eigenvectors, developed for spatial distance matrices (Borcard and Legendre, 2002). The statistical model will have the functional trait of interest as the dependent variable and the microbiome properties and environmental factors as explanatory variables (e.g. Asad et al., 2022 for yield; Cambon et al., 2022 for drought tolerance; Pérez-Valera et al., 2020 for an example of paired samples). When the microbiome contributes significantly to the functional trait of interest, identifying which microbial taxa are the main players can be done using the TITAN2 method (Baker et al., 2015) or differential abundance analysis methods (Nearing et al., 2022; Weiss et al., 2017). Machine learning or deep learning methods can also be applied (Xu et al., 2022); for example, the Random Forest algorithm has been used to identify combinations of microbial taxa indicative of yield (Yergeau et al., 2020). Finally, to test specific hypotheses on the direct and indirect effects of the explanatory factors (including microbiome) on the functional trait of interest, structural equation models (SEM) can be developed (Jassey et al., 2018).

For grapevine, SEM would be highly relevant for assessing the direct effects and indirect effects (through the microbiome) of variety and environmental factors (drought, agricultural practices) on disease severity and frequency. Moreover, statistical identification of subsets of microbial taxa potentially involved in disease resistance would be relevant to set up experimental, culture-dependant approaches to analyze the effects of microbial consortia on grapevine pathogens (Sections 3.4).

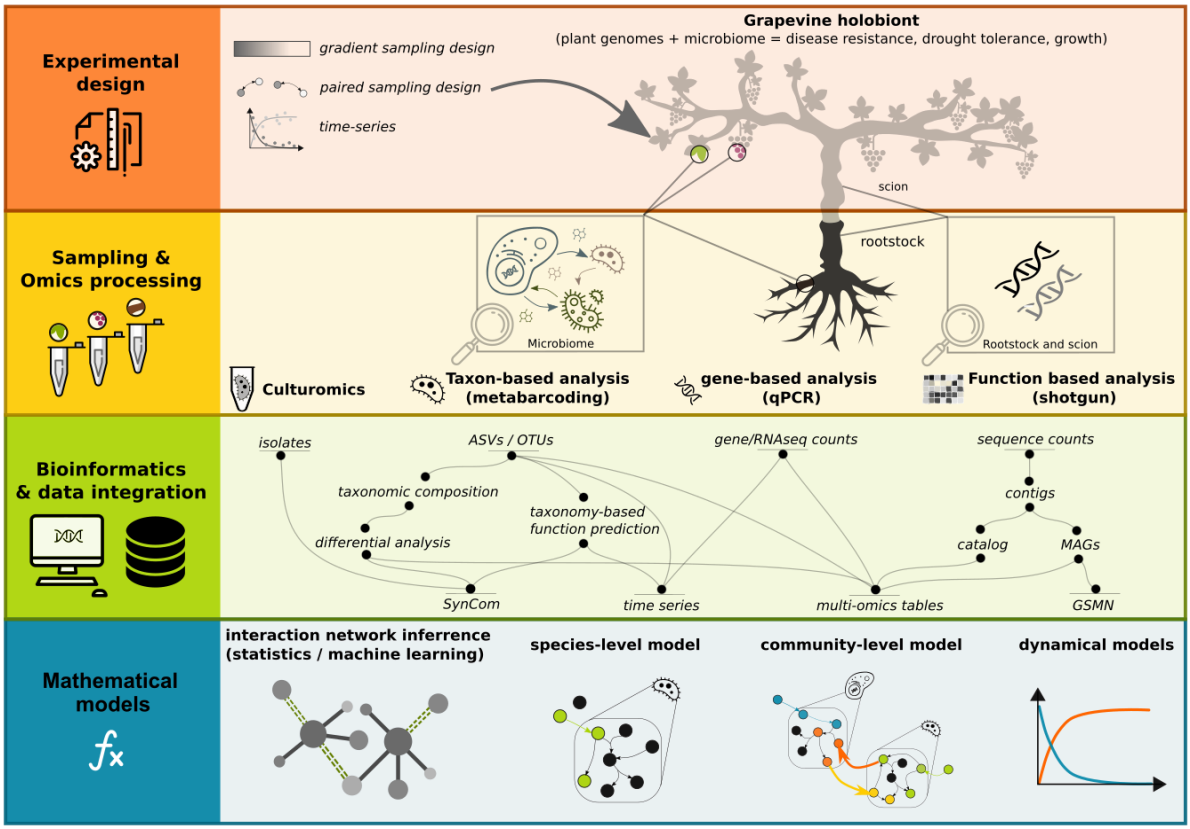


Figure 4 - Workflow, from field experiments to mathematical models of omics data, to decipher the complex plant-microbe-microbe interactions forming the grapevine holobiont and to identify beneficial microbial taxa. The experimental design sets up the sampling plots, hosts, compartments and time-points, according to spatial and temporal variations in a functional trait of interest (e.g. grapevine drought tolerance, disease resistance, yield). Grapevine samples (roots, trunk, leaves or berries) are then collected, cultivated, amplified and sequenced, and omics data are processed. Omics approaches can be culture-based (culturomics), taxon-based (metabarcoding), gene-based (microfluidic qPCR chips, for instance) or function-based (shotgun metagenomics). Bioinformatic analysis and data integration pipelines result in multi-omics tables, time series, SynComs or GSMN construction. This data can be used as input data for interaction network inference, species or community-level models and dynamical systems representing microbial populations' dynamics under various environmental conditions. ASV, Amplicon Sequence Variant; GSNM, Genome-Scale Metabolic Network; MAG, Metagenome-Assembled Genomes; OTU, Operational Taxonomic Unit; SynCom, Synthetic Community.

2. Molecular tools to uncover the functional potential of the microbiome

Microbiome samples collected from contrasted environments following the field sampling designs described above (Section 3.1) can be further analyzed using culture-independent molecular tools to uncover the microbial genomes present in the sample, analyze the microbial functions they carry, estimate precisely variation in their abundance and link this variation with plant gene expression patterns. We review the molecular tools that could be used to address the following questions: How to characterize the functional potential of the grapevine microbiome

with shotgun metagenomics? How to decipher the functional coupling between grapevine and its microbiome with quantitative approaches?

Question #2 : How to characterize the functional potential of the grapevine microbiome with shotgun metagenomics?

Metataxonomics using metabarcoding of amplified marker DNA sequences has been widely used to inventory the microbial taxa present in a sample (Marchesi and Ravel, 2015), including in grapevine (Sections 1 et 2). Bioinformatic tools exploit this data to generate abundance tables of microbial Operational Taxonomic Units (OTUs) or Amplicon Sequence Variants (ASVs) in samples (Callahan et al., 2017, 2016; Estaki et al., 2020; Hildebrand et al., 2014; Pauvert et al., 2019; Schloss et al., 2009). However metabarcoding has strong limitations, including primer amplification bias, copy number variation of the target sequence across taxa, and limits to taxonomic resolution, which may prevent the accurate characterization of taxa composition and abundance. Insight into the functional potential of a microbiome can nevertheless be obtained from metabarcoding data (Belcour et al., 2022; Douglas et al., 2020; Louca et al., 2016; Nguyen et al., 2016; Wemheuer et al., 2020; Zanne et al., 2020), using taxonomy-based function prediction methods. These methods build upon the association of taxonomic clades to known functional guilds, or to metabolic functions or pathways obtained from public databases of annotated genomes (Section 3.3).

In contrast to metabarcoding approaches, shotgun metagenomics (Fig. 4) does not sequence DNA markers but the total DNA material of a sample. Significant data processing is required (Bickhart et al., 2022). Reference-based profiling (Section 3.3) compares these reads to reference genomes. In genome-resolved metagenomics, quality-filtered reads are assembled into contigs (Li et al., 2015; Nurk et al., 2017), which can be parsed into genes that are binned into metagenome-assembled genomes (MAGs) (Borderes et al., 2021; Kang et al., 2019; Wu et al., 2016; Yue et al., 2020). Genomes can be resolved for uncultured bacterial and eukaryotic members of the microbiome, and the precise function carried by a species in the sample can be investigated. The limitations of MAG reconstruction are due to the diversity of species found in the same sample (Lemos et al., 2021; Nayfach et al., 2020). Improvements to long-read sequencing such as PacBio or Nanopore technologies lead to better metagenome assembly. They can be combined synergistically with low error rate short reads to accurately retrieve repetitive genome regions (Chen et al., 2021; Damme et al., 2021). Long reads using the most recent technologies can suffice alone for reconstructing high-quality MAGs (Sereika et al., 2022). The principal bias in shotgun metagenomics is taxonomic incompleteness in reference databases that can noise the taxonomic assignment for underrepresented species. In addition to shotgun metagenomics, metabolomics and metatranscriptomics (Paolinelli et al., 2022) identify metabolites or expressed genes, respectively, in the host and the microbiome.

While genome-resolved metagenomics applications to soil and plants are becoming more frequent (Wu et al., 2022a, 2022b), few studies have yet applied it to grapevine. Metagenomics has been used to analyze the microbial composition of grape berries and to reconstruct 13 near-complete draft genomes (Salvetti et al., 2016). Azevedo-Silva et al. (2021) discussed the feasibility of applying shotgun metagenomics to grapevine leaf, rhizosphere and soil characterization and proposed a protocol. For grapevine, we recommend using metataxonomics before shotgun metagenomics to first target the environmental samples worthy of deeper

sequencing (Fig. 4). We argue that, while metagenomics has some biases, it has fewer than amplicon sequencing and the substantial amount of information it brings makes it worthy of consideration for deeper analyses of the grapevine microbiome.

Question #3 : How to decipher the functional coupling between grapevine and its microbiome with quantitative approaches?

Metabarcoding and metagenomics data are by nature compositional, measuring the relative abundance of microbial taxa or functions within a sample but not their absolute abundance. To produce absolute counts requires complementary, quantitative methodologies (Props et al., 2017). Real-time quantitative PCR (RT-qPCR) has developed into a powerful and accurate technique for measuring absolute abundance by assessing quantitative changes in taxonomic or phylogenetic marker genes across spatial and temporal scales (Heid et al., 1996), supplanting the classical colony counting method, which is hindered by the low proportion of cultivable microorganisms (Lou et al., 2018). Development of automated, high-throughput qPCR platforms (Fig. 4) have increased tenfold the number of qPCR reactions that can be simultaneously performed on a single instrument. Microfluidic qPCR chips with the Biomark® HD system, for example, can perform 9216 qPCR reactions (96 samples amplified with 96 primer sets) in only 4 hours.

Different microfluidic qPCR chips have been used in pioneer studies of gene expression in grapevines. The NeoVigen chip (Dufour et al., 2016), developed to quantify defense gene expressions in grapevine, quantifies plant genes involved in pathogenesis-related protein synthesis, secondary metabolites synthesis, the indole pathway, the oxidoreduction system, the salicylic acid, ethylene, and jasmonic acid pathways, and cell wall reinforcement. The BioStim chip (Bodin et al., 2020) has extended the gene set by including, among others, genes involved in primary pathways and phytohormones pathways (auxin, cytokinin, gibberellin, abscisic acid). These chips have been used to decipher the mechanisms underlying the effects of biostimulants on grapevine resistance to multiple stresses. The workflow can be adapted to different types of microbial marker genes, whether taxonomic (Dreier et al., 2021; Kleyer et al., 2017) or functional (Crane et al., 2018). The technology could therefore provide simultaneous quantitative snapshots of the microbiome taxonomic and functional composition and of the host response (Noman et al., 2021; Zolti et al., 2020).

For grapevine, to decipher the functional coupling between host and its microbiome, we recommend parallel development of microfluidic chips targeting plant genes involved in plant growth or stress resistance, and chips targeting specific microbial taxa and functions. Considerable progress has been made for the plant side (Bodin et al., 2020; Dufour et al., 2016), but a chip has yet to be created for microbiomes. Several challenges must be overcome to choose the most relevant microbial targets, design primer sets, and validate the chip. Target selection must deal with the multitude of microbial taxa colonizing the plant and the multitude of functions they carry (Section 2). Chip validation must use reference species and synthetic microbial communities (Section 3.4) before applying the chip to environmental samples. Once developed, this tool could associate microorganisms with plant health biomarkers, for instance to identify beneficial (phyto-probiotic) microbial agents that foster plant health or stimulate plant immunity, or potential antagonists of vine pathogens that are candidates for next-generation biocontrol products.

3. Computational approaches to understand the grapevine holobiont as a functional and dynamic network

Computational methods exploit the wealth of -omics data produced by high-throughput methods (Sections 3.2) to infer networks of ecological interactions between microbial taxa, unravel the trophic and metabolic relationships that underlie them, and analyze how they drive microbiome dynamics at different time scales (Sections 1 and 2). Our questions here are: How to characterize ecological interactions between grapevine-associated microorganisms using metabarcoding data? How to decipher metabolic interactions within the grapevine microbiome? How to infer the microbial interactions that shape microbiome dynamics from time-series data?

Question #4 : How to identify and characterize ecological interactions between grapevine-associated microorganisms using metabarcoding data?

Microbial ecologists have long used metabarcoding to learn ecological interactions between microbial taxa. They assume that since past or ongoing interactions between microbial taxa may impact their frequencies, patterns in relative shifts in frequency may provide information about the structure of the ecological interaction network (Cobo-Díaz et al., 2022; Jakuschkin et al., 2016; Kerdraon et al., 2019; Poudel et al., 2016; Vacher et al., 2016). However, this process is not straightforward: metabarcoding data can be biased by amplification and sequencing artifacts, and are always compositional (Gloor et al., 2017; Section 3.2). One of the first tools for inferring interaction networks from relative sequence counts was SparCC (Friedman and Alm, 2012), which avoided the compositional effect by using log-transformation components to obtain correlation. Other tools like SPIEC-EASI (Kurtz et al., 2015) or CCLasso (Fang et al., 2015) refined correlation-based measures. PLN (Chiquet et al., 2019) enhances inference accuracy by exploiting sample covariance, while MPLasso (Lo and Marculescu, 2017) introduces the use of prior microbiological knowledge through data-mining of external sources of information. HMSC (Ovaskainen et al., 2017) also integrates covariates on samples and taxa and was recently used to infer microbial networks (Abrego et al., 2020; Fort et al., 2021). These tools are extremely robust to noise in experimental data and can be run rapidly on even quite large datasets. Most of them are available in R, which facilitates their use (Dohlman and Shen, 2019; Tikhonov et al., 2020). However, these tools define no clear link between the positive and negative interactions they find, and the ecological mechanisms that may generate them (Röttjers and Faust, 2018).

Explainable machine learning can associate ecological mechanisms with the inferred interaction networks (Tamaddoni-Nezhad et al., 2021). Different interaction types, such as competition and mutualism, lead to different changes in species frequency (Fig. 4), and can be learned (Derocles et al., 2018; Tshikantwa et al., 2018). Explainable machine learning transcribes these criteria into logical rules that directly infer ecological interactions, with little to no human intervention in the interpretation step (Barroso-Bergada et al., 2022). Hypotheses of ecological interactions between taxa pairs are generated through a process that simultaneously detects interactions and classifies them as competition, mutualism, amensalism or commensalism. This direct approach is particularly valuable for reconstructing microbial networks in previously unstudied ecosystems, where human knowledge for interpretation may effectively be lacking.

For grapevine, this approach was recently applied to microbial communities sampled from symptomatic and asymptomatic leaves of European cultivated grapevine during downy mildew

epidemics. After a thorough assessment of the method using simulated datasets (Weiss et al., 2016), preliminary interaction networks were computed and showed potential antagonists of the causal agent *Plasmopara viticola* —some known, some new— constituting options to control mildew development. We expect that this approach will identify sub-networks of interest, centered on pathogen species and their direct antagonists or facilitators, whose subsequent modeling could lead to better understanding of pathogen-microbiome interaction dynamics.

Question #5: How to decipher metabolic interactions within the grapevine microbiome?

The microbial functions present in a given sample can be assessed from shotgun metagenomic surveys or from metataxonomic data after taxonomy-based function prediction (Section 3.2). An advantage of the former is functional profiling of communities, using assembly-independent reference-based approaches, or de-novo reference-free assembled sequences (Quince et al., 2017). Both delineate microbial species and strains, needed for deciphering microbial metabolic interactions in communities. Metabolic networks allow kinetic and discrete models.

Assembly-independent reference-based profiling directly compares reads to reference databases (Beghini et al., 2021) to identify genes and thus functions. Functions or pathways associated with samples are then compared or used in statistical learning in order to reveal higher level functional patterns between sample groups (Raguideau et al., 2016). Unfortunately, reads cannot be linked to their genome of origin, impeding the interpretation of these patterns in terms of metabolite-mediated trophic interactions between microbial taxa. Moreover, plant and grapevine-associated reference catalogs are less available than, for instance, the gut microbiome. Hence, genome-resolved metagenomics, below, seems to be a better option for grapevine.

Reference-free de novo assembly allows functional annotation of genes (Cantalapiedra et al., 2021; Seemann, 2014), functional characterization of the corresponding organisms, and genome-scale metabolic network (GSMN) reconstructions (Fig. 4). GSMN consist of all biochemical and transport reactions predicted from an individual microbial genome (Gu et al., 2019) and can be reconstructed by different tools (Arkin et al., 2018; Karp et al., 2019; Seaver et al., 2020) or even directly connected to MAG reconstruction (Zorrilla et al., 2021). In most cases, GSMN reconstruction involves manual curation to ensure the quality of the predictions they provide (Karp et al., 2018). GSMN can be associated with mathematical models to predict the metabolism of a species or a community of organisms in an environment. The main difficulty is to achieve high-quality GSMNs, since i) MAGs are frequently incomplete, even worse so when under-studied microbiota are under-represented in the gene annotation databases; and ii) GSMN reconstruction from the MAG can be imperfect. Manually curated GSMNs are best but the number of genomes in a microbiota and limited knowledge about the microorganisms argues in favor of automatisation (Belcour et al., 2020). Fortunately, the multiplication of shotgun sequencing studies of the grapevine microbiome will increase the size and quality of grapevine-related annotated gene catalogs and favor better MAGs-based GSMN automatic reconstruction.

Kinetic modeling uses differential equations models of the kinetics of biochemical reactions throughout the metabolic network of an organism (Ross and McMeekin, 1994), permitting microbial phenotype prediction that accounts for enzyme and metabolite concentration

dynamics. While it has been applied to model organisms such as *Escherichia coli*, it is not widely applied due to the need to obtain biochemical measurements to parameterize the models (Khodayari et al., 2014). An alternative are stoichiometric models, also known as constraint-based models. They translate a GSMN into a linear system of constraints for an optimization problem used to predict metabolic fluxes across the GSMN under simplificatory assumptions such as steady state in the system, i.e. the non-accumulation of internal metabolites and their constant concentration over time. Flux Balance Analysis (FBA) or Flux Variability Analysis (FVA) compute the activity rates of metabolic reactions while optimizing an objective function, typically the maximization of the microbial population growth (Orth et al., 2010). FBA models can be coupled with differential equations through dynamic FBA (dFBA) (Mahadevan et al., 2002). These methods have been widely used and extended to the study of microbial communities (Biggs et al., 2015; Frioux et al., 2020) and to study the metabolism of enological yeasts (Eder et al., 2020; Nidelet et al., 2016).

Discrete models are an alternative to constraint-based models to capture the metabolic potential of a GSMN, in a nutritional environment ideally characterized by metabolomics. Network expansion (Ebenhöh et al., 2004) computes the set of reachable metabolites from a given set of metabolic seeds and has been used as a building block for screening the metabolism of microbial communities (Belcour et al., 2020). Complexity is reduced by selecting minimal communities that satisfy a metabolic objective, which may take the host metabolism into account (Frioux et al., 2018). Hypotheses arising from these minimal communities can be tested using synthetic communities (SynComs; Marín et al., 2021) selected to provide a targeted function. These approaches can be coupled with dFBA: discrete models are used for systematic screening and selection of SynComs, then dFBA is used on the selected SynComs to decipher the dynamics of the community at a molecular level.

GSMN were used to study soil and rhizosphere microbiome (Jacoby et al., 2017), and to model winemaking process (Mendoza et al., 2017). However, to our knowledge, GSMNs of grapevine phyllosphere or berry microbiomes remain an open challenge, of great potential for improving functional characterization of microbiomes. For grapevine, kinetic modeling would permit, for example, integration of multi-omics data to decipher and validate the dynamical interactions between a microbial pathogen and putative antagonists. Minimal communities identified by discrete modeling, for example to compete against microbial grapevine pathogens, or to promote enological yeast growth by maintaining a tailored nutritional niche, can be tested with SynComs (Section 3.4).

Question #6: How to infer microbial interactions shaping microbiome dynamics from time-series?

Four fundamental, intrinsically dynamical ecological processes drive microbial communities: evolutionary diversification, selection, dispersal, and ecological drift (Nemergut et al., 2013; Vellend, 2010). The contribution of these deterministic and stochastic processes, complementary to historical contingency and priority effects, can now be evaluated cost-effectively using -omics time-series data (Ning et al., 2019; Vass et al., 2020; Zhou and Ning, 2017). Longitudinal time-series data enable the study of the dynamical interactions that determine selection in the microbial ecosystem.

One increasingly common approach is the use of Generalized Lotka-Volterra models (GLV) to decipher the dynamic interactions shaping community dynamics (Faust et al., 2018). GLV models decompose microbial growth into an intrinsic growth rate that models population fitness and interspecies interactions modeling ecological processes such as competition or parasitism (Fig. 4). These interactions are fitted to reproduce temporal data, which permits an ecological interpretation of the community dynamics. Despite simplifying assumptions such as constant environmental constraints, GLV models are suitable for studying microbiome stability, microbial population persistence and microbial community robustness (Gonze et al., 2018). They model dynamics that correlation-based methods cannot (Carr et al., 2019). They have been used to study the dynamics of the gut microbiome during primary succession (Marino et al., 2014) and pathogenic infection (Stein et al., 2013), and to identify the assembly rules that determine the long-term composition of synthetic communities (Friedman et al., 2017). Computational tools for inferring GLV interactions have been proposed by Bucci et al. (2016) and Kuntal et al. (2019).

GLV models need specific experimental design to guarantee accuracy of microbial network inference (Remien et al., 2021). GLV models describe the evolution of absolute population, so model parametrization requires time-series of absolute counts (e.g. qPCR or flux cytometry, Section 3.2). Abundance proxies can be used, such as compositional metabarcoding data renormalized in each sample by the dosage of total DNA (Stein et al., 2013). The need for absolute population counts has been relaxed with an alternative GLV formulation for compositional data (Joseph et al., 2020). GLV models are better suited to analyze marked changes of the microbial community, for example after strong perturbations such as pesticide treatment or colonization by exogenous microbes such as pathogens (Remien et al., 2021), although Xiao et al. (2017) does address the steady-state microbiome.

GLV models have intrinsic limitations. First, growth and interspecies interactions are treated phenomenologically without regard to their underlying mechanisms, contrary to other models that supplement pairwise ecological interactions with metabolite-mediated interactions (Momeni et al., 2017). Second, microbial populations are treated as well-mixed microbial without regard to spatial structures caused by nutritional niches (Prosser et al., 2007), which can impair GLV estimates (Armitage and Jones, 2019). Other population dynamics modeling frameworks avoid these drawbacks: GSMN, above, are particularly suitable for describing the metabolism of species subject to trophic interactions such as competition for resources, or cross-feeding in small consortia (Widder et al., 2016); spatially explicit microbial population dynamics models can take into account spatial heterogeneities (Labarthe et al., 2019). These models require, for parameterization, experimental measurements of reduced synthetic communities in controlled environments.

For grapevine, GLV models have not yet been used, but have been to model microbial dynamics in other plant species (Becerra-Lucio et al., 2021). GLV models could be coupled with machine-learning approaches to select pathogen-associated sub-networks before studying their dynamics. They could also be used to study the dynamics of minimal communities identified by discrete modeling.

4. Culture-dependent approaches to validate microbial interactions and functions

All statistical and computational approaches described above generate hypotheses about the microbiome and its dynamics that must be experimentally validated. Thefore, we ask, how to isolate and culture microorganisms from a microbiome to study their functions and their interactions?

Question #7: How to isolate and culture microorganisms from the grapevine microbiome to study their functions and their interactions?

Culturomics, a high-throughput combination of multiple culture conditions and rapid identification of microorganisms (Fig. 4), has revitalized culture-dependent methods. The landmark studies by Lagier et al. (2018, 2016, 2015) combined high-throughput cultivation with cost-effective rapid identification by Matrix-Assisted Laser Desorption/Ionization Time Of Flight Mass Spectrometry (MALDI-TOF MS), and increased the number of microorganisms identified in the human gut microbiome by more than 50%. Large-scale isolation strategies have since been developed, including new culture media and advanced cultivation technologies. Specific protocols consisting of successive dilutions of a microbial population to the point of no growth, and technologies such as microdroplet and microfluidics, have been proposed to enhance isolation efficiency (Button et al., 1993; Kaminski et al., 2016; Zhang et al., 2021). For the plant microbiome, plant-based media that isolate microorganisms in environmental and nutritional conditions close to their natural habitats have been successfully developed to improve cultivability (Mourad et al., 2018; Sarhan et al., 2019, 2018).

The success of culturomics in improving the catalog of isolated human bacteria and plant endophytic bacterial communities (Bilen et al., 2018; Riva et al., 2022) holds promise for the grapevine microbiome, but the task ahead is huge. Fewer than 3000 plant-associated bacterial genomes are available, out of 70 000 known bacterial genomes (Joint Genome Institute Integrated Microbial Genomes (https://img.jgi.doe.gov/); Trivedi et al., 2021). High-quality sequencing, assembly, and annotation of pure microbial strain genomes is needed to improve gene and protein databases and knowledge of the genome-based mechanisms underlying plant-microbe interactions (Levy et al., 2018; Sarhan et al., 2019; Section 3.3). Genome-resolved metagenomics produces uncurated draft genomes whose gaps, assembly errors and contamination from other genomes limit their usefulness (Chen et al., 2020); obtaining reference bacterial genome sequences (Trivedi et al., 2021; Section 3.3) will improve quality. Microbial culture collections make it possible to screen for microbial phenotypic traits that foster plant growth (growth promoting bacteria) and plant health (biocontrol agents) and they are imperative for validation of candidate genes. Cultivation and co-cultivation strategies are needed for experimental validation of predictive models of plant-microbiome and pathogen-microbiome interactions, and to provide deeper insight into the functional potential of beneficial plant-associated microbes (Nai and Meyer, 2018; Trivedi et al., 2020).

CONCLUSION AND PERSPECTIVES

The grapevine microbiome has developed over thousands of years, integrating taxa from Asia, Europe and America, under the pressures of human selection and pathogen invasions. There are

many gaps in this history, but the numerous studies of the grapevine microbiome show that it contains beneficial microorganisms (growth promoters, biocontrol agents, microorganisms of oenological interest) whose mode of action is sometimes well documented. In order to better understand and manage this beneficial microbiome, we propose the following research avenues:

A. Design microbiome studies informed by evolutionary history

- Analyze the microbiome of wild grapevine and ancestral grapevine varieties to discover beneficial microorganisms that may have been lost during domestication and breeding
- Analyze the microbiome of American *Vitis* species to discover potential antagonists of North-American pathogens

B. Consider grapevine as a dynamic system of interactions

- Investigate how rootstock-scion interactions in the graft zone shape the microbiome of the whole plant
- Decipher the microbial interactions that regulate the dynamics of pathogen populations
- Assess the cascading effects of the soil microbiome on the root, trunk, leaf and berry microbiome, and their consequences on vineyard health
- Analyze the microbial fluxes that govern the seasonal dynamics of the berry microbiome, and their consequences on wine properties
- Identify the microbiome changes that precede the development of trunk diseases
- Identify the viruses that shape the dynamics of the grapevine microbiome

C. Combine metagenomics, culturomics and computational approaches

- Use field experiments and metabarcoding data to highlight small microbial consortia related to variations in grapevine functional traits
- Create and maintain microbial culture collections to perform controlled experiments with the identified consortia
- Develop shotgun metagenomics and metabolic network modeling to understand the functionning of the target microbial consortia
- Monitor target microbial populations with quantitative approaches to model and predict their dynamics in response to environmental changes or management scenarios.

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