The ISME Journal (2015) 9, 2329–2335

www.nature.com/ismej

MINI REVIEW

Volatile affairs in microbial interactions

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Microorganisms are important factors in shaping our environment. One key characteristic that has been neglected for a long time is the ability of microorganisms to release chemically diverse volatile compounds. At present, it is clear that the blend of volatiles released by microorganisms can be very complex and often includes many unknown compounds for which the chemical structures remain to be elucidated. The biggest challenge now is to unravel the biological and ecological functions of these microbial volatiles. There is increasing evidence that microbial volatiles can act as infochemicals in interactions among microbes and between microbes and their eukaryotic hosts. Here, we review and discuss recent advances in understanding the natural roles of volatiles in microbe–microbe interactions. Specific emphasis will be given to the antimicrobial activities of microbial volatiles and their effects on bacterial quorum sensing, motility, gene expression and antibiotic resistance.
The ISME Journal (2015) **9,** 2329–2335; doi:10.1038/ismej.2015.42; published online 29 May 2015

Introduction

Microorganisms from diverse ecosystems produce a wide range of volatile organic compounds. Compared with other secondary metabolites (for example, enzymes, antibiotics and toxins), volatiles are typically small compounds (up to C20) with low molecular mass (100–500 Daltons), high vapour pressure, low boiling point and a lipophilic moiety. These properties facilitate evaporation and diffusion through both water- and gas-filled pores in soil and rhizosphere environments. Hence, microbial volatiles have important roles in marine and terrestrial environments (Schulz *et al.*, 2010; Romoli *et al.*, 2014). To date, the chemical structure of ~1000 volatiles have been described originating from a wide range of bacterial and fungal genera and species (Effmert *et al.*, 2012; Lemfack *et al.*, 2014). Bacterial volatiles are typically dominated by alkenes, alcohols, ketones, terpenes, benzenoids, pyrazines, acids and esters, whereas fungal volatiles are dominated by alcohols, benzenoids, aldehydes, alkenes, acids, esters and ketones (Piechulla and Degenhardt, 2014). Most microbial volatiles are considered as side-products of primary and secondary metabolism. They are formed mainly by oxidation of glucose from various intermediates (Korpi *et al.*, 2009). The underlying biosynthetic pathways are aerobic, heterotrophic carbon metabolism, fermentation, amino-acid catabolism, terpenoid biosynthesis, fatty acid degradation and sulphur reduction (Peñuelas *et al.*, 2014). The main metabolic pathways for microbial volatiles are summarised in Figure 1.

Although there are common volatiles produced by different, often unrelated, microorganisms, other volatiles are unique for certain strains (Schulz and Dickschat, 2007; Garbeva *et al.*, 2014a,b). The amount and composition of volatiles produced by microorganisms can vary according to culturing conditions (Claeson, 2007; Blom *et al.*, 2011; Garbeva *et al.*, 2014a,b). Other important factors influencing the production of volatiles are the physiological state of the producing microorganism, oxygen availability, moisture, temperature and pH (Insam and Seewald, 2010; Romoli *et al.*, 2014).

The importance of microbial volatiles for the ecology of microorganisms has been overlooked for a long time, probably due the lack of appropriate detection techniques. However, in the last 10 years the number of studies on microbial volatiles has increased substantially in different research areas such as food, medical, agricultural and environmental sciences. In this review, we focus on the ecological role of volatiles in microbe–microbe interactions. For more information on techniques used for volatile analyses and their role in microbe interactions with their eukaryotic hosts, we refer to several recent reviews (Effmert *et al.*, 2012; Farag *et al.*, 2013; Junker and Tholl, 2013; Peñuelas *et al.*, 2014).

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Received 4 December 2014; revised 15 February 2015; accepted 23 February 2015; published online 29 May 2015

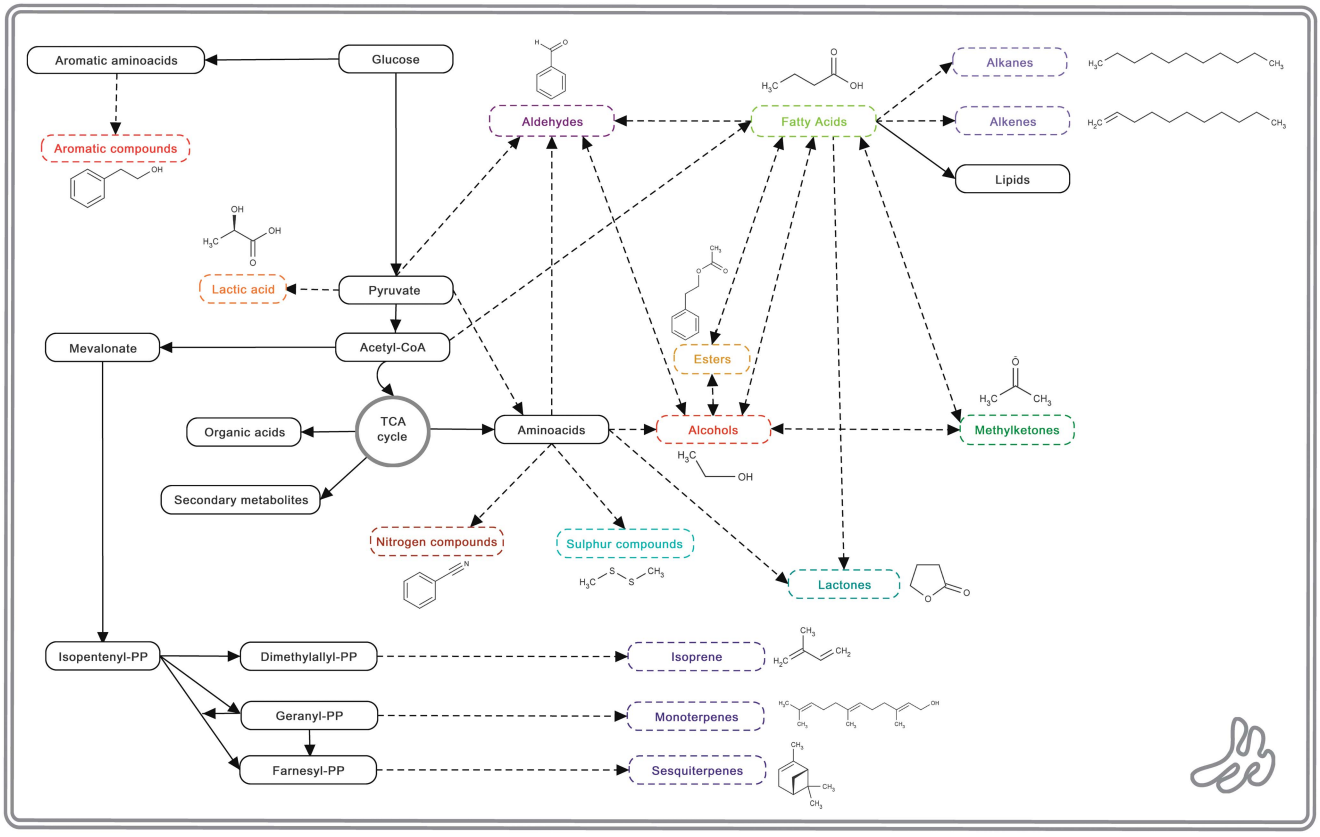

Figure 1 Main metabolic pathways for the production of microbial volatiles. Volatiles are depicted in coloured dashed rectangles indicating different chemical classes. Representative examples are given per class: alcohols (for example, ethanol), aldehydes (for example, benzaldehyde), alkanes (for example, undecane), alkenes (1-undecene), aromatic compounds (for example, 2-phenylethanol), esters (for example, 2-phenylethyl ester), fatty acids (for example, butyric acid), isoprene, lactic acid, lactones (for example, gamma-butyrolactone), methylketones (for example, acetone), monoterpenes (for example, farnesol), nitrogen compounds (for example, benzonitrile), sesquiterpenes (for example, pinene) and sulphur compounds (for example, dimethyl disulphide).

Ecological roles of microbial volatiles in antagonistic interactions

Microbial volatiles can have a significant role in antagonistic interactions between microorganisms occupying the same ecological niche. Here, we will focus on the antimicrobial activity of volatiles with specific emphasis on their antifungal and antibacterial activities.

Volatile-mediated antifungal activity

It is well known that germination of fungal spores as well as hyphal growth can be inhibited by bacterial volatiles (Herrington *et al.,* 1985, 1987). Furthermore, exposure to bacterial volatiles has been reported to change fungal morphology, enzyme activity and gene expression (Wheatley, 2002; Vespermann *et al.*, 2007; Minerdi *et al.*, 2008, 2009; Kai *et al.*, 2009; Garbeva *et al.*, 2011, 2014b). For example, activity of laccases and tyrosinases can be strongly affected by bacterial volatiles (Wheatley, 2002).

Fungal volatiles can also have inhibitory effects on other fungi. For example, the endophytic fungi *Muscodor albus* and *Oxysporus latemarginatus* strongly inhibited growth of several plant pathogenic fungi, including *Botrytis cinerea* and *Rhizoctonia solani* (Strobel *et al.*, 2001). Moreover, *M. albus* volatiles were shown to kill the fungal human pathogens *Aspergillus fumigatus* and *Candida albicans* (Strobel *et al.*, 2001). Fungi often live in symbiosis with bacteria. For *Fusarium oxysporum,* hyphae-associated bacteria were shown to produce the volatile sesquiterpene caryophyllene, which repressed the expression of two virulence genes. When cured from the bacterial symbionts, caryophyllene was not detected and *F. oxysporum* became pathogenic (Minerdi *et al.*, 2008).

Sensitivity to volatiles can strongly differ between fungal species and the extent of inhibition depends on the individual bacteria–fungus or fungus–fungus interaction (Kai *et al.*, 2007, 2009; Vespermann *et al.*, 2007; Garbeva *et al.*, 2014b). Several independent studies have reported that *F. solani* is not much affected by bacterial volatiles, whereas *Pythium* species (oomycetes) are highly sensitive to bacterial volatiles (Kai *et al.*, 2009; Effmert *et al.*, 2012; Garbeva et al., 2014a,b). *F. oxysporum* was also reported to be rather resistant to volatiles produced

by the fungus *O. latemarginatus*, whereas *Magnaporthe grisea* was sensitive. High sensitivity to bacterial volatiles was recently reported for the late blight oomycete pathogen *Phytophthora infestans*. Two volatiles, hydrogen cyanide and 1-undecen, were indicated as the main compounds responsible for the growth inhibition (Hunziker *et al.,* 2015). The apparent high sensitivity of oomycetes to volatiles may be related to their cell wall composition and structure, which is different from that of fungi. To date, however, very little is known about fungal resistance to volatiles with the exception of resistance to azole-derived compounds (Lupetti *et al*., 2002). Azole resistance commonly involves modifications of the *cyp51A* gene, the target of antifungal azoles (Lupetti *et al*., 2002, Seyedmousavi *et al*., 2014). The resistance selection is believed to occur via exposure to azole compounds in the environment (Snelders *et al*., 2009), released by humans via application of crop protections agents or by bacterial genera commonly found in soil, such as *Bacillus*, *Serratia*, *Pseudomonas* and *Burkholderia* (Lemfack *et al*., 2014).

Volatile-mediated antibacterial activity

Relatively few studies have reported on volatiles with antibacterial activity. Screenings of commonly produced volatiles with antimicrobial activity often did not reveal antibacterial activity (Schulz *et al*., 2010). Moreover, volatiles with strong antifungal activity (such as dimethyl disulphide, dimethyl trisulphide, *S*-methyl thioacetate and benzonitrile) did not exhibit antibacterial effects and even stimulated the growth of some bacteria (Garbeva *et al*., 2014a). However, some specific volatiles produced by only a few microorganisms have been indicated as potential antibacterial agents. These include volatile lactones such as γ-butyrolactones, which exhibit antibacterial activity against a broad range of Gram-positive and Gram-negative bacteria (Schulz *et al*., 2010).

An odoriferous actinomycete isolate from corn seeds, identified as *Streptomyces albidoflavus,* was shown to produce a sesquiterpene, named albaflavenone with antibacterial properties (Gurtler *et al*., 1994). More recently, albaflavenone was isolated from other *Streptomyces* species and fungi (Takamatsu *et al*., 2011; Moody *et al*., 2012). Another sesquiterpene compound with antibacterial activity, dihydro-β-agarofuran, is produced by *Streptomyces* sp. (Brana *et al*., 2014). Recently, Dandurishvili *et al.* (2011) reported that volatiles emitted by *Pseudomonas fluorescens* and *Serratia plymuthica* have bacteriostatic effects against the bacterial plant pathogens *Agrobacterium tumefaciens* and *A. vitis* and inhibited the growth of these pathogens *in planta*. The major volatile emitted by *S. plymuthica* under the tested conditions was dimethyl disulphide, whereas *P. fluorescens* emitted a mix of 1-undecene, methanthiol, methanthiol acetate and dimethyl disulphide (Dandurishvili *et al*., 2011).

Volatile-producing endophytes have recently attracted great attention due to their strong antimicrobial activity. For example, *M. albus* (an endophytic fungus of tropical tree species) emitted a number of volatiles, such as tetrohydofuran, aciphyllene and an azulene derivate (Atmosukarto *et al*., 2005). Volatiles emitted by *M. albus* as well as the artificial mixture of volatiles effectively inhibited or killed a range of plant and human-pathogenic bacteria. Another recently described endophytic fungus *M. crispans*, isolated from wild pineapple, produced a mixture of volatile compounds with strong activity against a major bacterial pathogen of citrus, *Xanthomonas axonopodis* pv. *citri,* and the human pathogens *Yersinia pestis*, *Mycobacterium tuberculosis* and *Staphylococcus aureus* (Mittchell *et al*., 2010). Five classes of volatiles (acids, alcohols, esters, ketones and lipids) were identified in *Muscodor* species and although each class had some antimicrobial effect, their collective action was required to kill a broad range of bacterial pathogens.

In the past years, a group of pyrazine volatile compounds have been attracting wide interest due to their promising antitumour, antimicrobial and insecticidal activities (Rajini *et al*., 2011). The production of pyrazines is widely distributed in plants, and only few bacteria have been reported so far to synthesize these volatile compounds (Rajini *et al*., 2011; Brana *et al*., 2014). *S. albus*, *Corynebacterium glutamicum* and *Bacillus* spp. produce tetramethylpyrazine (also known as ligustrazine), a compound that is used in traditional Chinese medicine against cystic fibrosis.

Although the mode of action of antibacterial volatiles has not been studied in detail, it is likely that hydrophobicity of some volatiles enables them to partition in the lipid layer of the cell membrane, rendering the membrane more permeable. Indeed, a study on the mechanisms of inhibitory action of three monoterpenes against *S. aureus* and *Escherichia coli* revealed a perturbation of the lipid fraction of microorganisms' plasma membrane, resulting in alteration of membrane permeability and a leakage of intracellular compounds (Trombetta *et al*., 2005).

Finally, volatile compounds may have a synergistic effect when combined with antibiotics. For example, hydrophilic antibiotics such as vancomycin and β-lactam antibiotics, which have a marginal activity on the Gram-negative bacteria *E. coli* and *Listeria monocytogenes*, exhibit an enhanced antibacterial activity when pre-treated with the volatile eugenol (Hemaiswarya and Doble, 2010). Synergistic effects of terpenes and penicillin on multiresistant strains *S. aureus* and *E. coli* have also been reported (Gallucci *et al*., 2009).

Ecological role of microbial volatiles in interspecific interactions

Volatiles have an important role in interactions between physically separated microorganisms.

Microarray analysis of *E. coli* exposed to volatiles emitted by *Bacillus subtilis* revealed that volatiles induce changes in gene expression and affect motility and biofilm formation of the exposed bacteria (Kim and Ryu, 2013). More recently, a study, using *P. putida* as a model organism, showed that indole has a role as an interspecific signalling molecule (Molina-Santiago *et al*., 2014). This compound influenced the expression pattern of *P. putida* genes involved in cell metabolism, cell wall biosynthesis and stress defence. In our research group, we have tested the effect of volatiles emitted by different soil bacteria grown in sand supplemented with artificial root exudates on the soil bacterium *P. fluorescens*. The *P. fluorescens* strain was grown on nutrient-limited agar while being exposed to volatiles produced by four phylogenetically different bacterial isolates (*Collimonas pratensis*, *S. plymuthica*, *Paenibacillus* sp. and *Pedobacter* sp.) as well as a mixture of all four bacteria. A genome-wide, microarray-based analysis revealed that volatiles of each bacterial strain affected gene expression of *P. fluorescens*, but with a different pattern for each strain. Only a small core set of 22 genes was differentially expressed by all volatile-producing bacteria, including the mixture. These genes were mainly involved in amino-acid transport and metabolism, energy production and conversion, signal transduction mechanisms, inorganic ion transport and metabolism, secretion and cell motility. Among these common, differentially expressed genes was the Pfl_0064 catalase, an important enzyme that protects the cell against damage by reactive oxygen species (Lushchak, 2001). Furthermore, the volatiles produced by *C. pratensis* triggered the production of antimicrobial secondary metabolites (Garbeva *et al*., 2014a).

Antibiotic production triggered by volatiles in microbial interactions was also observed in *P. aeruginosa* during co-culture with *Enterobacter aerogenes* and this enhanced production was due to the volatile 2,3-butanediol emitted by *E. aerogenes* (Venkataraman *et al*., 2014). Also for *Chromobacterium violaceum* and *P. aeruginosa*, several monoterpenes increased violacein and pyocyanin production, respectively (Ahmad *et al*., 2014). The fact that the production of antibiotics in these bacteria is regulated by quorum sensing (QS) suggests that volatiles may interfere with bacterial cell–cell communication. Indeed, several studies revealed that volatiles can affect QS systems in bacteria, negatively or positively (Schulz *et al*., 2010; Chernin *et al*., 2011; Ahmad *et al*., 2014). For example, volatiles produced by *S. plymuthica* can inhibit cell–cell communication mediated by acyl homoserine lactone molecules in *Agrobacterium*, *Pectobacterium* and *Pseudomonas*. Volatiles emitted by *S. plymuthica* decreased the amount of acyl homoserine lactone produced by these bacteria, leading to significant suppression of transcription of acyl homoserine lactone synthase genes (Chernin *et al*., 2011).

Volatiles may also influence fungal QS as well as fungal development and virulence. *C. albicans* and *C. dubliniensis*, well-known human opportunistic pathogenic yeasts, produce large amounts of the QS molecule (E,E)-farnesol, a sesquiterpene, that is able to modulate morphogenesis of these species. Accumulation of farnesol blocked the yeast-to-mycelium morphology switch, mycelial development and biofilm formation, important traits for virulence of *Candida* (Hornby *et al*., 2001; Martins *et al.,* 2007). Moreover, volatiles produced by *Trichoderma* were shown to function as signalling molecules regulating development and mediating intercolony communication: volatiles such as 1-octen-3-ol, 3-octanol and 3-octanone produced by conidiating colonies elicited conidiation in other colonies (Nemcovic *et al*., 2008). The underlying mechanisms of the effects volatiles on fungal development remain largely unknown.

Recently, several studies reported on the effect of volatiles on bacterial antibiotic resistance or tolerance. For example, exposure of *E. coli* to volatiles emitted by *Burkholderia ambifaria* increased its resistance to gentamycin and kanamycin by yet unknown mechanisms (Groenhagen *et al*., 2013). Exposure to the volatile compound trimethylamine was shown to modify the antibiotic resistance profiles of several Gram-positive and Gram-negative bacteria (Létoffé *et al.,* 2014). In addition, indole, a volatile that has been proposed to act as signalling molecule, can also affect antibiotic resistance. For example, *P. putida* does not produce the volatile indole itself but recognizes indole produced by other bacteria (for example, *E. coli*) and activates the expression of the gene encoding the TtgGHI efflux pump (Lee *et al*., 2010; Molina-Santiago *et al.,* 2014). Biogenic ammonia, an inorganic volatile compound, was also reported to modify antibiotic resistance in physically separated bacteria (Bernier *et al*., 2011). One of the underlying mechanisms proposed involves ammonia-induced synthesis of polyamines, which alters the permeability of the bacterial membrane or helps the bacteria to cope with oxygen radicals. A recent study reported on ammonia-mediated growth promotion of ampicillin-sensitive bacteria by means of antibiotic inactivation (Cepl *et al*., 2014). However, this phenomenon appeared to result from pH increase in the media caused by bacterial volatiles rather than by alteration of specific traits in the target bacterium. Another inorganic volatile compound, hydrogen sulphide, was suggested as a universal defence against antibiotics in bacteria as it seemed to trigger broad-spectrum antibiotic resistance, most probably due to alleviation of oxidative stress (Shatalin *et al*., 2011).

As was shown for the above mentioned *Candida* species, also virulence and fitness of microorganisms can be affected by microbial volatiles. This was for instance observed for *Pectobacterium* species, bacterial pathogens responsible for soft rot disease in potato. Disruption of the biosynthesis of the volatile

2,3-butanediol coincided with reduced virulence (Marquez-Villavicencio *et al.,* 2011).

Volatile compounds can also have a role in the attraction of other microorganisms. During interaction between *X. perforans* and *Paenibacillus vortex,* volatiles produced by *X. perforans* were found to attract the proficient swarmer *P. vortex* (Hagai *et al*., 2014). Interestingly, the volatiles released by *X. perforans* did not only attract the swarmer but also increased its dispersal without affecting its growth rate. Using fluorescent-stained *X. perforans*, Hagai *et al.* (2014) revealed that this hitch-hiking strategy also occurs on tomato leaves with different swarming bacterial species, suggesting that this might be a widespread and ecologically important phenomenon.

Conclusions and perspectives

Most studies to date have focused on the role of volatiles in plant–microbe interactions and their role in plant growth and health (Bitas *et al*., 2013; Peñuelas *et al*., 2014). However, the role of volatiles in microbe–microbe communication and competition in soils remains largely unknown. It is not completely clear why microorganisms produce volatiles and what their exact functions are. It has been proposed that volatiles represent waste material or a detoxification system of the producing microorganisms (Claeson, 2007). However, from recent studies summarised in part 2 and 3 of this review, it is clear that microbial volatiles can have two major roles in a long-distance interactions in microbial communities as: (i) infochemical molecules affecting the behaviour, population dynamic and gene expression in the responding microorganism, and (ii) competitive tools directly exerting antimicrobial activity, providing an advantage by suppressing or eliminating potential enemies.

Currently, most studies on microbial volatiles are performed *in vitro* under nutrient rich conditions (Kai *et al*., 2009; Weise *et al*., 2012) and may not represent the conditions that prevail in the microbial environment. Furthermore, as indicated by Garbeva et al. (2014a,b), the composition of volatiles produced by a mixture of bacterial species can differ from those produced by each bacterial monoculture.

Soil is a complex, highly diverse and heterogeneous environment; an important characteristic of most soils is the occurrence of air-filled pores. Hence, the gaseous phase forms an important part of the natural surroundings of soil microorganisms. It has been estimated that the area of soil particles covered by microorganisms is less than 1%, implying that the distance between microcolonies of microbial neighbours can be considerable (Young *et al*., 2008). Compared with diffusible compounds, volatile compounds can travel faster and over longer distances through both the liquid and gaseous phase of the soil (Insam and Seewald, 2010; Effmert *et al*., 2012), which facilitate the interactions between soil microorganisms. Therefore, volatiles have an important role in the communication and competitiveness between physically separated soil microorganisms (Kai *et al*., 2009; Effmert *et al*., 2012; Garbeva *et al*., 2014a). It is plausible that in soil, dormant microorganisms can sense changes in their environments via emitted volatiles and change their behaviour accordingly and in turn, influence the behaviour of other soil microorganisms (Garbeva *et al*., 2011). Although several studies have shown that volatile compounds can be used as signalling molecules in soil microbial communication, so far it is unclear how volatiles are perceived as signals by the microorganisms.

To date, little is still known about the regulatory pathways and genes involved in volatile biosynthesis, as well as the possible role of QS in the production of volatiles. Because the production of volatiles is often reported to vary depending on cell density (Weise *et al*., 2012; Groenhagen *et al*., 2013), it is tempting to reason that volatiles are regulated by QS. However, there are only few and contradictory reports regarding QS regulation of volatile production. Whereas for hydrogen cyanide in *Pseudomonas* and *Chromobacterium* species it was concluded to be QS regulated (Pessi and Haas, 2000; Blom *et al*., 2011), for *B. ambifaria*, production of volatiles appeared not to be controlled by QS as the volatile profiles of the wild-type and the QS mutant were very similar (Groenhagen *et al*., 2013). Future challenges are therefore to further elucidate the large chemical diversity of microbial volatiles, to discover regulatory pathways and genes involved in the biosynthesis of volatiles in soil bacteria and fungi, to determine biologically relevant concentrations and to resolve the importance of volatiles in ecosystem processes. Monitoring volatiles may be used as a potential indicator of microbial activity, measuring shifts in community composition in the environment and ultimately for determining the soil health status of agricultural soils.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

This work is supported by The Netherlands Organization for Scientific Research (NWO) VIDI personal grant to PG (864.11.015). This is publication 5808 of the Netherlands Institute of Ecology (NIOO-KNAW). We wish to thank the anonymous reviewers for their helpful comments.

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