Title

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Authors

Härer, Andreas
Rennison, Diana J

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Title: The biogeography of host-associated bacterial microbiomes: revisiting classic biodiversity patterns

Running title: Open questions in bacterial microbiome biogeography

Andreas Härer (AH)[1] ahaerer@ucsd.edu

Diana J. Rennison (DJR)[1] drennison@ucsd.edu

[1] School of Biological Sciences, Department of Ecology, Behavior, & Evolution, University of California San Diego, La Jolla, California, USA

Corresponding author

Andreas Härer, ahaerer@ucsd.edu

ABSTRACT

Background: The question of which ecological and evolutionary processes structure the distribution of biodiversity has intrigued scientists for centuries, and historically, inferences have been predominantly gained by studying animals and plants. While substantial progress has been made towards understanding the multitude of factors that shape host-associated microbial communities (i.e., microbiomes), it remains largely unknown if large-scale geographic patterns in diversity observed for macroorganisms also apply for their microbiomes and whether microbiomes are shaped by the same processes that appear key for determining biogeographic patterns in their hosts.

The geographic distribution of microbiome diversity: We discuss challenges and potential approaches for studying microbiome biogeography, with the goal of inspiring future lines of research that can stimulate the development of novel ecological and evolutionary theory in the microbiome field. The theory and examples presented here specifically focus on bacterial microbiomes, and we give an overview of host-associated bacterial microbiome research beginning to examine some of the classic biodiversity patterns central to the fields of ecology and evolution.

Potential impacts of microbiome variation for host ecology and evolution: Microbiome diversity patterns are particularly important to consider as microbes are crucial for many aspects of their hosts' biology. We discuss how a more comprehensive knowledge on the geographic variation of microbiome diversity at the host individual and population levels might be critical for understanding host ecology and evolution.

Keywords: environmental gradients, diversity-area relationship, elevational diversity gradient, latitudinal diversity gradient, island biogeography, host-microbiome interaction, macroecology, microbial diversity

INTRODUCTION

The question of which factors structure the geographic distribution of biodiversity is central to the fields of ecology, evolutionary biology, and conservation, and large-scale geographic surveys have revealed a range of intriguing patterns. One striking pattern is the latitudinal diversity gradient, where diversity peaks at lower latitudes and declines towards the poles (Fischer, 1960; Hillebrand, 2004). Insights into biogeographic patterns and the processes that generate them have been predominantly obtained from animals and plants (Hillebrand, 2004; Lomolino, 2001a), which is unsatisfactory since microbes are likely the most diverse and abundant group of organisms on our planet (Oren, 2004; Whitman, Coleman, & Wiebe, 1998). Thus, if our goal is to understand general processes that structure biodiversity and community assemblage, inclusion of microbes in the development of biogeographic and ecological theory is crucial (Martiny et al., 2006; Shade et al., 2018). Knowledge of microbial biogeography thus far has largely been limited to free-living microbial communities (reviewed in Dickey et al., 2021; Martiny et al., 2006), and studies have shown that microbial abundance, composition, and diversity vary along environmental gradients (e.g., Bryant et al., 2008; Ladau et al., 2013). Yet, host-associated microbial communities (hereafter referred to as 'microbiomes') have been mostly neglected with very few studies having explored microbiome biogeography (e.g., Morelan, Gaulke, Sharpton, Thurber, & Denver, 2019; Neu, Allen, & Roy, 2021). This is particularly true for bacteria, whereas we have a better understanding for other microbes such as plant-associated fungi (Kivlin, Lynn, Kazenel, Beals, & Rudgers, 2017). A recent meta-analysis investigated the biogeography of free-living and host-associated microbes (i.e., archaea, bacteria, fungi, protozoa), but only a small fraction, 6 of 156 included studies, were on bacterial microbiomes (Dickey et al., 2021). Hence, it remains generally unknown whether the diversity patterns observed for macroorganisms, free-living microorganisms, or plant-associated fungi are also found for bacterial microbiomes (Table 1). Host-microbe associations appear to be universal across animals (McFall-Ngai et al., 2013) and plants (Trivedi, Leach, Tringe, Sa, & Singh, 2020). Host-associated microbes (and bacteria in particular) are important for their hosts' biology (Pieterse et al., 2014; Youngblut et al., 2019), e.g., nutrient metabolism (Turnbaugh et al., 2006) and immune system function (Lathrop et al., 2011), which can even affect host ecology and evolution (Rudman et al., 2019; Zepeda Mendoza et al., 2018). If we want to understand how host-microbiome interactions can shape their hosts' evolutionary trajectories, we also need to understand the factors that shape the geographic distribution of microbial diversity (Shade et al., 2018).

But should we actually expect to find congruent diversity patterns for hosts and their microbiomes? Ultimately, the geographic distribution of microbes is shaped by the same macroecological mechanisms as for plants and animals: dispersal, environmental filtering, microbial responses, diversification, and local extinction (see Xu et al., 2020 for a detailed discussion of these mechanisms). Environmental filtering can occur through abiotic conditions and biotic interactions that affect microbial diversity (Burns et al., 2017; Sepulveda & Moeller, 2020; Trivedi, Batista, Bazany, & Singh, 2022). Variation in these ecological factors could generate biogeographic patterns of microbiome diversity across latitudes (***latitudinal diversity gradient***) or elevations (***elevational diversity gradient***). Environmental heterogeneity and exposure to more varied environmental microbes and resources across larger habitats might also shape microbiome structuring (***diversity-area relationship, island biogeography***). Further, demographic factors such as connectivity (***geographic isolation***), density (**center-periphery dynamics**), size and diversity (***population bottleneck and founder effect***) of host populations may affect the geographic distribution of microbiome diversity (Figure 1A). In addition, other important host factors such as genetics, phylogeny, ecology, physiology, and immune function have been shown to structure bacterial microbiome composition (Amato et al., 2019; Benson et al., 2010; S. P. Brown, Grillo, Podowski, & Heath, 2020; Reese & Dunn, 2018; Song et al., 2020; Woodhams et al., 2020); these factors may not necessarily covary along environmental gradients and might therefore affect observed patterns of microbiome biogeography. Clearly, many of these patterns and processes concurrently shape the geographic distribution of microbiome diversity. Systematic biogeographic studies of diverse host lineages, their microbiomes, and free-living microbes along the same transects will allow us to make inferences about the generality of processes hypothesized to structure the distribution of biodiversity (e.g., historical contingencies and contemporary ecological conditions).

Microbes differ physiologically and ecologically from macroorganisms, which could result in distinct biogeographic diversity patterns. For example, bacterial communities are highly dynamic and complex, and community composition is strongly determined by co-dependency (e.g., syntrophy) (Morris, Henneberger, Huber, & Moissl-Eichinger, 2013) and interspecies communication (e.g., quorum sensing) (Miller & Bassler, 2001). Hence, microbial ecology and community assembly should be considered in combination with host and environmental factors when studying microbiome biogeography. Comprehensive surveys are necessary to disentangle the relative contributions of these factors, which will likely differ across study systems. Yet, it is quite possible that due to the complex interactions between microbes, their hosts, and the environment (McDonald, Marchesi, & Koskella, 2020), there may be no consistent biogeographic patterns of bacterial microbiome diversity (Table 1). Investigating these potential outcomes is intriguing as it will help us understand the macroecological processes that shape microbiomes

(Xu et al., 2020), and also provide insights into how bacterial microbiome biogeography might affect host ecology and evolution e.g., by altering their metabolic capability (Moran, Ochman, & Hammer, 2019; Zepeda Mendoza et al., 2018).

The major aim of this article is to highlight the importance of understanding how environmental and host factors together shape the geographic distribution of bacterial microbiome diversity. To this end, we present general issues to consider when studying microbiome biogeography. Next, we summarize our current knowledge on a selection of large-scale geographic patterns and host population characteristics that might be particularly relevant for collectively structuring microbiome biogeography, but note that other such patterns exist that are not addressed in our study (Dickey et al., 2021; Shade et al., 2018). We then discuss potential effects of bacterial microbiome biogeography on host ecology and evolution. As they are not our focus, the geographic patterns of free-living microbes are only briefly mentioned to discuss their relevance for structuring microbiome diversity. Due to the particular importance of bacteria for their hosts' biology, we specifically focus on biogeographic patterns for bacterial microbiomes associated with animal and plant hosts. Yet, ideas presented here should be relevant for a broad range of microbes and a diversity of host organisms, and biogeographic patterns have been studied extensively in other microbial groups such as fungi (Kivlin et al., 2017). For a comprehensive meta-analysis investigating microbial biogeography of (mostly) free-living and (few) host-associated microorganisms including archaea, fungi, and protozoa, and bacteria, we refer to Dickey et al. (2021). Since we are interested in the geographic distribution of the microbiomes' taxonomic diversity, we solely consider biogeographic patterns at the community level, but not at the organismal level (see Dickey et al., 2021 for a discussion of such patterns). Two studies included here are concerned with human microbiomes, and we note that the patterns observed in these studies are likely confounded by a range of human-specific factors such as processed diets, urbanization, travel, and the widespread use of antibiotics.

GENERAL CONSIDERATIONS FOR STUDYING THE GEOGRAPHIC DISTRIBUTION OF MICROBIOME DIVERSITY

To facilitate investigating the biogeography of microbiome diversity and the underlying eco-evolutionary processes, we provide a non-exhaustive list of relevant considerations for future studies (Figure 1B).

Diversity patterns across microbiomes with different levels of exposure to the abiotic environment

Microbial communities associated with different host tissues can vary considerably in their exposure to fluctuating abiotic conditions (e.g., temperature, pH, humidity, UV light), which is important since abiotic factors can affect microbiome composition (Sepulveda & Moeller, 2020; Trivedi et al., 2022). Thus, it could be predicted that microbiome biogeography differs across tissues with varying levels of exposure. A meta-analysis on animal and plant hosts detected evidence of this; internal bacterial microbiomes were found to be mostly affected by host factors whereas external bacterial microbiomes were mostly affected by environmental factors (Woodhams et al., 2020). Similarly, the bacterial gut microbiome of intertidal barnacles is more stable than the bacterial microbiome associated with cirri (feeding appendages), suggesting stronger environmental effects on more exposed microbiomes (Brown, Nunez, & Rand, 2020). Abiotic conditions also fluctuate more strongly for microbes associated with the plant phyllosphere, leading to more dynamic microbial communities (reviewed in Cordovez, Dini-Andreote, Carrion, & Raaijmakers, 2019). Based on these results, we could predict that geographic variation in environmental factors drives diversity patterns in both the host organisms and their microbiomes, and that biogeographic patterns are more pronounced for external microbiomes (e.g., animal skin, plant phyllosphere) compared to internal ones (e.g., animal gut, plant endosphere). Additional studies investigating geographic variation of microbiomes associated with multiple tissues of the same host can aid in developing novel ecological theory about microbiome assembly and stability along environmental gradients. If external microbiomes are indeed more unstable with varying abiotic conditions, this could have important implications in the context of climate change.

Effects of host physiology and morphology on microbiome diversity patterns

Different aspects of the host's physiology and the morphology of host tissues can affect microbiome composition and diversity (Amato et al., 2019; Greene et al., 2022; Huang et al., 2019). For example, foregut and hindgut fermenters show higher gut bacterial diversity compared to animal hosts with simple guts (Reese & Dunn, 2018), strongly suggesting that host physiology should be considered when studying microbiome biogeography. Microbial communities associated with ectothermic animals might also show stronger geographic variation compared to those associated with endothermic animals due to differences in body temperature variability. This would be of particular importance when studying latitudinal or elevational transects along which temperatures can vary drastically, since temperature can strongly affect animal and plant microbiomes (Aydogan, Moser, Muller, Kampfer, & Glaeser, 2018; Sepulveda & Moeller, 2020). The hypothesis of more stable microbiomes in endotherms could be tested across wild populations but also by experimentally exposing host lineages to fluctuating temperatures, where stronger microbiome variation would be expected for ectothermic hosts.

Diversity patterns across varying spatial scales

Microbiome diversity could also be differently structured across varying spatial scales, ranging from few kilometers across elevations to potentially thousands of kilometers across latitudes. Latitudinal diversity gradients of bacterial microbiomes are commonly investigated across hundreds to thousands of kilometers, but ranges vary substantially among studies (e.g., between 8-24 degrees of latitude in Morelan et al., 2019; Neu et al., 2021), and variation across such studies could be leveraged to test whether geographic scale affects the likelihood of observing biogeographic microbiome patterns. Dispersal rates also vary considerably across host species, raising the question of whether stronger microbiome structuring along environmental gradients might be expected for hosts with lower dispersal. For example, when investigating latitudinal diversity gradients across the same geographic range for different host lineages, one could expect to observe such gradients in sessile hosts (e.g., plants) with strong population structuring compared to mobile hosts with higher levels of gene flow.

Diversity patterns across varying phylogenetic scales for host and their microbes

Research across phylogenetically diverse host lineages comes with a range of confounding factors, e.g., ecology, physiology, and genetics. For example, stronger genetic and ecological divergence in more distantly related host lineages could have substantial effects on microbiomes, thereby potentially obscuring biogeographic patterns. Phylogenetic comparative methods could be used to control for host phylogeny (Felsenstein, 1985). Alternatively, studies on geographically dispersed populations of the same species would combat confounding host effects and provide crucial insights into microbiome biogeography.

It has also been argued that by studying diversity patterns for whole bacterial communities, one might overlook patterns in certain bacterial clades (Neu et al., 2021). One approach to overcome this issue would be to determine microbiome biogeography for certain microbial lineages rather than at the overall community level. However, it is not clear if diversity patterns differ based on the taxonomic level considered for the microbes (e.g., genus vs. phylum). Future studies could strive to compare the consistency of results across multiple microbial taxonomic levels. If biogeographic patterns vary depending on taxonomic resolution, this will be important to consider when inferring general patterns and mechanisms of microbiome biogeography.

Temporal variation in microbiome composition and diversity

Microbiomes are very complex communities, consisting of up to billions of members from hundreds to thousands of microbial lineages, but they are also highly dynamic (David et al., 2014; Sender, Fuchs, & Milo, 2016). Thus, any microbiome study has to acknowledge that each sample merely represents a snapshot of microbial diversity. Besides random fluctuations and short-term changes, animal-associated bacterial microbiomes can vary seasonally associated with availability of food resources (Baniel et al., 2021; Smits et al., 2017). At the same time, abiotic conditions (e.g., precipitation, temperature) can also show strong annual variation. Hence, we argue that such seasonal changes should be considered when studying geographic gradients in microbiome diversity. Seasonality in ecological conditions, and particularly in food availability, might covary across elevations and latitudes, emphasizing the complexity of factors necessary to consider when studying microbiome biogeography. Further, if seasonal environmental changes are shared among host species (e.g., higher diet diversity & abundance during a certain season), one could even expect correlated, and temporally variable, geographic microbiome patterns. Seasonal microbiome changes might be particularly pronounced in migratory species that are exposed to a wider range of abiotic and biotic conditions, and it would be interesting to study potential effects of host migration on microbiome diversity. For example, one could ask whether migratory species show a higher microbiome diversity and stronger temporal variation compared to non-migratory species.

OPEN ECO-EVOLUTIONARY QUESTIONS IN MICROBIOME RESEARCH

With the aim of stimulating further research, we present three major biogeographic patterns and three host population characteristics that could structure the geographic distribution of microbiome diversity. We summarize our current, mostly limited, knowledge of each pattern for host-associated microbial (and mostly bacterial) communities and compare them to macroorganisms and free-living microbial communities, when available. We further discuss whether patterns observed for host organisms might be expected to extend to their microbiomes. Determining the relative contributions of host and environment in shaping microbiome biogeography should be a major goal of future studies and collecting comprehensive environmental data will be instrumental in this endeavor. Coordinated surveys of host-associated and free-living microbial communities, as well as host organisms will be pivotal for furthering our knowledge on the geographic distribution of biodiversity across the tree of life.

Biogeographic diversity patterns

Latitudinal diversity gradient: Are microbiomes more diverse at lower latitudes?

The latitudinal diversity gradient (LDG) describes the decrease in biodiversity from the equator (lower latitudes) towards the poles (higher latitudes) (Figure 2A). It represents one of the most pervasive biogeographic patterns and has been described for animal and plant species from marine, freshwater, and terrestrial habitats (Fischer, 1960; Hillebrand, 2004). The possible mechanisms underlying the LDG include environmental factors (e.g., temperature, precipitation, productivity), evolutionary history (e.g., diversification and extinction rates), spatial dynamics (e.g., dispersal rates), and climatic stability (Jablonski, Huang, Roy, & Valentine, 2017; Table 1). The LDG appears to be strongest for animals and plants with larger body mass (Hillebrand, 2004), raising the question whether the LDG would be detected in microbes, that are extremely small, highly abundant, and widely distributed. For microbes, testing of the LDG has mainly been limited to free-living communities, with highly variable results (reviewed in Dickey et al., 2021). For example, diversity of marine microbial communities can decrease (traditional LDG; Fuhrman et al., 2008; Ibarbalz et al., 2019) or increase (inverse LDG; Raes, Bodrossy, van de Kamp, Bissett, & Waite, 2018) with higher latitudes, increase from Arctic to Antarctic waters (Moss, Henriksson, Pakulski, Snyder, & Jeffery, 2019), or peak in mid-latitudinal regions (Ladau et al., 2013; Milici et al., 2016).

Fewer studies have investigated the LDG in host-associated bacterial communities. Some evidence was found in the human gut microbiome (Dikongue & Segurel, 2017), but results might be confounded by the degree of urbanization and industrialization. In wild house mice from the Americas, gut microbiome composition and the relative abundance of some bacterial lineages are affected by latitude (Suzuki, Martins, Phifer-Rixey, & Nachman, 2020). A meta-analysis across animal and plant hosts detected opposing patterns: a traditional LDG for plant microbiomes and an inverse LDG for animal microbiomes (Thompson et al., 2017; note that this study also included archaea). Plant microbiomes (especially external microbes associated with the phyllosphere and rhizosphere) may be more exposed to abiotic conditions compared to animal microbiomes (especially those associated with internal organs), potentially explaining these distinct patterns. Differences in the geographic range surveyed may further affect the consistency of observed patterns (Thompson et al., 2017). Studies in anemones (Morelan et al., 2019) and fruit flies (Corby-Harris et al., 2007) spanning limited latitudinal ranges (8 and 10 degrees, respectively) found no differences in bacterial microbiome diversity. In contrast, geographic patterns were found in the California blue mussel across a latitudinal range of 24 degrees (Neu et al., 2021). However, results depended on the tissue type, diversity metric, taxonomic scale, and varied across bacterial clades (Neu et al., 2021).

Based on this limited data, bacterial microbiomes *can* vary with latitude, but patterns differ considerably among host taxa and do not appear to *consistently* follow the LDG. However, current data is not sufficient to draw general conclusions, and previous studies come with certain limitations: sampling across relatively small geographic ranges, long divergence times among host taxa or the multifaceted effects of urbanization and industrialization in humans (Corby-Harris et al., 2007; Dikongue & Segurel, 2017; Morelan et al., 2019; Thompson et al., 2017). Yet, some interesting observations have already emerged. For example, bacterial diversity patterns seem to vary across host taxonomy (e.g., animals vs. plants), tissues with varying levels of exposure to abiotic conditions (e.g., gill vs. shell surface), and latitudinal range. Latitudinal gradients could also be affected by habitat type (e.g., marine vs. terrestrial) as these habitats often differ in the magnitude of variation in abiotic factors or the presence of geographic barriers affecting dispersal. To formulate more comprehensive hypotheses on the geographic distribution of microbiome diversity, we need to disentangle the effects of host-associated and environmental factors associated with latitude. Many questions remain, but additional research will allow us to overcome the limitations outlined above.

Elevational diversity gradient: Are microbiomes more diverse at lower altitudes?

Elevational gradients in animal and plant communities were first reported over a century ago by Linnaeus, Darwin and Wallace, among others (Lomolino, 2001a), and have been crucial for the development of ecological and evolutionary theory (McCain & Grytnes, 2010). Elevational diversity gradients exist in mountain ranges across the planet and commonly show one of two shapes: a constant decline in diversity with elevation or a peak in diversity at intermediate elevations (McCain, 2005; Rahbek, 2005) (Figure 2A). Similar to the LDG, explanations include abiotic factors (e.g., temperature, precipitation, area), biotic factors (e.g., competition), evolutionary history (e.g., diversification rates, time since first colonization) and spatial dynamics (e.g., dispersal rates) (McCain, 2005; Wiens, Parra-Olea, Garcia-Paris, & Wake, 2007; Table 1). Due to differences in climatic variability, patterns are expected to differ between temperate and tropical regions (Ghalambor, Huey, Martin, Tewksbury, & Wang, 2006; Janzen, 1967). According to Janzen's hypothesis, smaller annual climatic variation and lower seasonal overlap across altitudes in the tropics should select for narrower physiological tolerance. Hence, elevational dispersal of host organisms is predicted to be limited, resulting in smaller distribution ranges on tropical mountains. Smaller elevational distribution ranges of host organisms in the tropics could lead to higher microbiome divergence due to decreased interhost dispersal. Latitudinal variation in type and shape of elevational gradients has indeed been described, a greater proportion of elevational gradients showed diversity peaks at intermediate elevations at lower-mid latitudes and elevational diversity peaks declined with latitude (Guo et al., 2013), but it is not clear whether these patterns also apply to microbiomes.

Our current knowledge on bacterial elevational diversity gradients comes almost exclusively from free-living soil and stream bacteria, which have yielded mixed results: decreasing diversity with increasing elevation, diversity peaks at mid-elevations or no diversity gradients depending on the study (Fierer et al., 2011; Shen, Ni, Liang, Wang, & Chu, 2015; Shigyo, Umeki, & Hirao, 2019; Singh, Takahashi, Kim, Chun, & Adams, 2012). Comparisons of bacterial and eukaryotic diversity gradients found that they often differ (Bryant et al., 2008; Fierer et al., 2011; Wang et al., 2011), suggesting that different factors structure biodiversity in these two domains of life. Perhaps this is not surprising as free-living bacterial diversity appears to be strongly affected by abiotic factors such as pH or carbon supply, which may not necessarily vary with elevation (Bryant et al., 2008; Wang et al., 2011).

For microbiomes, in Anna's hummingbirds the relative abundance of certain bacterial lineages and the overall composition of fecal microbiomes vary with elevation, but microbiome diversity on the individual host level (e.g., the number of bacterial lineages) does not (Herder, Spence, Tingley, & Hird, 2021). A decrease in diversity with elevation was detected in bacterial communities associated with sheep tick (Aivelo, Lemoine, & Tschirren, 2021). Skin microbiome diversity also decreases with elevation in humans (Li et al., 2019), but increases with elevation in salamanders (Wolz, Yarwood, Grant, Fleischer, & Lips, 2018) and shows no elevational trend in Puerto Rican frogs (Hughey et al., 2017). These studies are mostly limited to animal microbiomes with high levels of exposure to the abiotic environment, and patterns might differ for other microbiomes (note that elevational diversity gradients have been extensively studied for plant-associated fungal microbiomes, see Kivlin et al., 2017). There is also potential for elevational gradients in host ecology (e.g., diet) or demography (e.g., population size), which might shape microbiome diversity (exemplified in Figure 2B).

Diversity-area relationship & island biogeography: Do larger habitats harbor more diverse microbiomes?

The species-area relationship (SAR) is a classic ecological concept stating that biodiversity is positively associated with the area of a given environment (Arrhenius, 1921) (Figure 2A), which was recently extended with the diversity-area relationship that incorporates information on species abundance (DAR; Ma, 2018). The theory of island biogeography represents an expansion to the SAR that has been applied to a range of diverse environments (MacArthur & Wilson, 1967). The focus of this section is specifically on the diversity-area relationship; hence, we will mostly discuss effects of habitat size rather than the extent of geographic isolation among habitats, another important aspect of the theory of island biogeography (potential effects of geographic isolation on microbiome diversity are discussed further below). Many factors have been proposed to explain the DAR, including habitat diversity, resource availability, immigration and extinction rates, as well as the potential for internal geographic isolation (summarized in Lomolino, 2001b; Table 1). Tests of the SAR/DAR have largely been restricted to larger organisms (e.g., Harte, Smith, & Storch, 2009; Helmus, Mahler, & Losos, 2014), but some studies in free-living bacteria have generally confirmed that diversity tends to increase with habitat area (Horner-Devine, Lage, Hughes, & Bohannan, 2004; Noguez et al., 2005; Reche, Pulido-Villena, Morales-Baquero, & Casamayor, 2005).

There are two ways in which the DAR could be tested for microbiomes. First, habitat area can be defined as the size of the *host tissue* that microbes inhabit (e.g., total gut length or phyllosphere area), which largely depends on host size. Thus, a positive association between host size and microbiome diversity might be expected, but tests of this hypothesis remain rare. Such a positive association was detected for bacterial microbiomes of animal guts (Godon, Arulazhagan, Steyer, & Hamelin, 2016), but effects can strongly depend on host physiology (diversity increased with body mass in ruminants, but decreased in animals with simple guts) (Reese & Dunn, 2018) and trophic ecology (e.g., diversity increased with body mass in herbivores but not in predatory carnivores) (Nishida & Ochman, 2018). One limitation of such meta-analyses is that comparisons across host species might be confounded by phylogeny. A few studies in house mice have overcome this limitation by studying populations of the same host species that vary in body size. Here, a positive correlation between body mass and gut bacterial diversity was detected among wild populations (Suzuki et al., 2019; Weldon et al., 2015) and under common garden conditions (Suzuki et al., 2020). A few studies in plants found positive and negative associations between host size and microbiome diversity in Acacia trees (Dinnage et al., 2019) and oak trees (Meaden, Metcalf, & Koskella, 2016), respectively. One technical consideration that might complicate testing the DAR is the complexity of large and structured host tissues, which can consist of several microhabitats harboring distinct microbiomes and may be difficult to consistently sample across hosts. This will strongly depend on the host species and tissue, and we recommend taking such spatial heterogeneity of host tissues into account when testing the DAR for microbiomes. Further, body size is commonly associated with age, and age-associated changes in bacterial microbiomes have been detected in different animal hosts (reviewed in Kim & Benayoun, 2020). Thus, host age should be considered when studying bacterial DAR and, ideally, hosts of the same age that vary in body size should be compared. This might be complicated for many organisms when studying natural populations, but experimental studies controlling for host age could help avoid confounding effect of age-associated microbiome variation.

Second, habitat area can be defined as the geographic range a *host population* inhabits. Generally, more environmental variation across larger geographic areas could promote microbiome diversity. For example, higher diversity in a host population's trophic ecology due to a broader range of resources in larger habitats might translate to higher microbiome diversity since diet can strongly affect gut bacterial communities (Youngblut et al., 2019). Similarly, more variation in abiotic conditions across larger habitats could also shape microbiome diversity. To the best of our knowledge, no studies have investigated microbiome DAR considering the area inhabited by host populations. Reliable knowledge on host populations' geographic range will be crucial, e.g., by studying host populations inhabiting differently sized islands or lakes. Such settings commonly also limit dispersal, and hence, microbiome exchange between geographically isolated populations. In sum, many questions regarding the generality of microbiome DAR remain unanswered, and it is currently unclear whether to expect a positive correlation between microbiome diversity and habitat area.

Host population dynamics

Geographic isolation: Is microbiome diversity affected by population connectivity (sympatry vs. allopatry)?

Host populations/species occur in different geographic settings, ranging from complete overlap (sympatry) to no overlap (allopatry). The degree of geographic isolation can influence organismal divergence, including ecology, morphology, life history, and behavior (Adams & Rohlf, 2000; Porter & Benkman, 2019). Geographic structure also contributes to the probability of reproductive isolation evolving (Tripp, Dexter, & Stone, 2021), and differences in the underlying mechanisms (Edwards et al., 2005). Often, adaptation to similar environmental conditions with shared selection pressures leads to phenotypic convergence (Rosenblum, Parent, Diepeveen, Noss, & Bi, 2017). However, for some traits, exaggerated divergence is seen among sympatric lineages, a pattern known as ecological character displacement (W. L. Brown & Wilson, 1956). Ecological character displacement is assumed to be a signature of decreased overlap in resource use, thereby reducing competition (Schluter, 2000). At this point, it is not clear how geographic context might affect microbiome diversity; the degree of host geographic isolation could either be positively (‘*microbiome convergence*’) or negatively (‘*microbiome displacement*’) associated with the extent of microbiome divergence (Figure 1A).

Host organisms inhabiting the same environment could have more similar microbiomes due to shared abiotic conditions, leading to ‘*microbiome convergence*’ (Sepulveda & Moeller, 2020; Trivedi et al., 2022). A shared biotic environment could also increase microbiome similarity due to environmental acquisition of microbes (Mulder et al., 2009). Thus, one could predict that sympatric hosts have more similar microbiomes compared to allopatric hosts, which was indeed found for the bacterial gut microbiome of chimpanzees and gorillas (Moeller et al., 2013) and 17 terrestrial mammalian species throughout the Americas (Moeller et al., 2017) These results suggest that microbiome divergence is, to some extent, explained by the extent of geographic isolation. Yet, studies on fishes have shown that gut bacterial community composition differs strongly from the bacterial communities of their environment (e.g., Härer et al., 2020; Sevellec, Derome, & Bernatchez, 2018). Thus, homogenizing effects of a shared environment may not necessarily be expected universally. Physical interactions among individuals, which would only be possible in sympatry, can also increase microbiome similarity via interhost dispersal (Burns et al., 2017), potentially contributing to ‘*microbiome convergence*’.

Stronger microbiome divergence among sympatric host lineages due to shifts in resource use and the accompanying ecological character displacement also seems plausible. For example, if two recently diverged and ecologically similar host lineages compete for the same diet, selection to avoid competition could lead to a reduction in trophic niche overlap. This, in turn, could promote '*microbiome displacement*' since diet is a strong predictor of bacterial gut microbiome composition (Youngblut et al., 2019). The studies on primates and terrestrial mammals from the Americas (Moeller et al., 2013; Moeller et al., 2017) investigated species with substantial ecological and phylogenetic divergence (2.4 - 94 my), but geographic microbiome dynamics may differ for recently diverged and ecologically more similar populations/species.

These two hypotheses have not been tested to date, but it could be done in closely related populations/species that show repeated ecological divergence in sympatry and allopatry (e.g., benthic and limnetic threespine stickleback; Bell & Foster, 1994). It will be crucial to determine the extent of divergence in host-associated (e.g., trophic ecology) and environmental factors (e.g., abiotic and biotic conditions) to assess their relative contributions to microbiome divergence. Alternatively, experimental evolution could be leveraged to test for '*microbiome convergence*' or '*microbiome displacement'* associated with ecological divergence of their hosts. We would like to emphasize that the theory of island biogeography could also be utilized in the context of geographic isolation, e.g., by specifically testing for effects of the extent of spatial and temporal isolation and, predominantly, unidirectional dispersal from mainland to islands on microbiome diversity (MacArthur & Wilson, 1967).

Center-periphery dynamics: Does microbiome diversity differ with population density?

Based on the center-periphery hypothesis, genetic variation and demographic performance is predicted to decrease from the center towards the edges of a species' geographic range (reviewed in Pironon et al., 2017). Accordingly, the abundant-center hypothesis states that population abundance and density decreases from the distribution center towards the range edges (Brown, 1984), but evidence varies substantially across study systems (Sagarin & Gaines, 2002). When population densities differ across a host population's geographic distribution, this might significantly affect microbiome diversity by altering the frequency of physical interactions among hosts and, thus, the potential for interhost dispersal (Figures 1A & 2B). Indeed, higher population density and physical interactions among hosts have been shown to be positively associated with bacterial gut microbiome diversity in controlled experiments (Burns et al., 2017; Li et al., 2016). However, it remains to be tested whether microbiome diversity covaries with host density across the geographic distribution of natural populations. Testing this hypothesis in natural settings would require taking into account abiotic and biotic factors across a host species' distribution, since spatial variation in such factors could also affect patterns of microbiome diversity. Alternatively, experiments with controlled environmental conditions and host density gradients could be instrumental to reliably estimate the contribution of host density in shaping microbiome diversity.

Bottleneck and founder effect: Is microbiome diversity lower in smaller populations?

Reductions in host population size and diversity (e.g., population bottlenecks after colonization of novel environments) can lead to a loss of genetic variation due to random subsampling of alleles (i.e., founder effect; Mayr, 1942). Similarly, the random subsampling of host-associated microbes that are brought into a new environment by a small number of hosts could lead to reduced microbiome diversity ('*microbiome founder effect*'). Such an effect has been observed in Drosophila, where a reduction in population size led to a loss of host genetic variation and decreased bacterial microbiome diversity, which together might lead to geographic variability in hosts' adaptive capacity associated with population size differences (Orsted, Yashiro, Hoffmann, & Kristensen, 2022). More experimental studies manipulating host population size as well as studies in natural settings where host lineages recently colonized novel environments (accompanied by a reduction in population size) will be necessary to infer how common '*microbiome founder effects*' are across diverse host lineages.

POTENTIAL IMPACTS OF MICROBIOME VARIATION FOR HOST ECOLOGY AND EVOLUTION

Determining the factors that shape bacterial microbiome biogeography is central to understanding how geographic variation in bacterial diversity might affect host ecology and evolution. To this end, it is also important to consider free-living bacteria since host organisms can acquire bacteria from the environment (Mulder et al., 2009) or by interacting with other organisms (Burns et al., 2017), which are then filtered by the host (Mazel et al., 2018). Thus, geographic variation of free-living microbes might affect microbiomes and, subsequently, their hosts' biology.

Geographic variation in microbiome diversity at the individual host level might generate ecological effects by affecting an individual's performance and survival (Moran et al., 2019). For example, geographic patterns in bacterial microbiome diversity leading to higher diversity could facilitate metabolization of a broader range of nutrients and exploitation of different trophic niches (Moran et al., 2019; Zepeda Mendoza et al., 2018) or increase capacity for energy harvest (Turnbaugh et al., 2006). This process might be aided by microbiome plasticity, the capacity of a host-associated microbial community to adjust in response to changes in host physiology or the external environment (Alberdi, Aizpurua, Bohmann, Zepeda Mendoza, & Gilbert, 2016; Kolodny & Schulenburg, 2020). It remains to be determined whether geographic variation in host-associated and free-living microbial diversity, which collectively represents the pool of microbes available to a host, can affect host performance (Figure 2B).

If host ecology is affected by geographic variation in microbiome diversity, this could shape a host population's evolutionary trajectory. For example, microbiome-mediated exploitation of a broader range of ecological niches could facilitate adaptation to changing conditions (Alberdi et al., 2016), potentially enabling host population establishment and persistence. The potential impact of the microbiome on host evolution is further highlighted by its ability to shape genomic diversity; experimental microbiome manipulation in *Drosophila* can result in extremely rapid genomic divergence among host populations (Rudman et al., 2019). Since microbes can directly affect certain host traits (reviewed in Henry, Bruijning, Forsberg, & Ayroles, 2021), the level of microbiome diversity *within* a population can impact the mean and variance of such traits. This could substantially affect a population's ability to respond to shifting selection pressures, thereby shaping a population's evolutionary trajectory (Figure 2B). In laboratory settings, bacterial gut microbiome variation has been shown to be associated with host fitness in fruit flies and mice (Gould et al., 2018; Rosshart et al., 2017). Thus, it seems reasonable to assume that fitness effects due to geographic variation in microbiome diversity might also be found in wild populations, although this has not yet been demonstrated.

Geographic gradients in microbiome diversity could further lead to stronger divergence of microbial communities *among* host populations (Thompson et al., 2017), which may directly affect the extent of reproductive isolation through hybrid breakdown or hybrid lethality (Brucker & Bordenstein, 2013; A. K. Miller, Westlake, Cross, Leigh, & Bordenstein, 2021). We may be able to augment our general understanding of speciation by considering host-associated microbial communities (A. K. Miller et al., 2021), but it remains to be determined whether geographic structuring of microbiome diversity contributes to reproductive isolation. Yet, it is becoming increasingly evident that microbes can be crucial for their hosts' ecology and evolution and determining the effects of geographic patterns of microbiome diversity represents an exciting prospect.

CONCLUDING REMARKS

We still lack a general understanding of the factors that shape the geographic distribution of microbiomes, and many questions remain to be answered (Antwis et al., 2017; Xu et al., 2020). While a few studies have begun to explore bacterial microbiome biogeography (e.g., Godon et al., 2016; Morelan et al., 2019; Neu et al., 2021), they come with limitations and there is currently not sufficient data to infer general patterns. Future studies could strive to investigate microbiome biogeography in host lineages with varying divergence times, concurrently survey geographic variation in abiotic factors and host characteristics and compare patterns of host-associated and free-living bacterial communities. Contrasting diversity gradients across microbiomes with varying levels of exposure to the external environment might be particularly illuminating. Translocation experiments, which are commonly undertaken in plants and to a lesser extent in animals, have rarely involved microbiomes (but see Bletz et al., 2016). Yet, such transplants might be instrumental in overcoming the confounding effect of genetic divergence among host populations, and in disentangling environmental and host effects. Studying their biogeography will help advance our understanding of the factors that shape microbiome diversity, and of the effects of microbiome variation for their hosts' ecology and evolution.

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Data Accessibility Statement

This manuscript does not have accompanying data

TABLES

Table 1: Summary of three biogeographic patterns described for macroorganisms, examples of explanatory factors, a summary of our current knowledge for microbiomes, and potential expectations for microbiome biogeographic patterns.

Biogeographic pattern (Macroorganisms)	**Explanatory factors**	**Studies on microbiome biogeography**	**Possible expectations for microbiome biogeography**
Latitudinal diversity gradient Decrease in diversity with latitude	Temperature, productivity, diversification and extinction rates, dispersal rates	Traditional LDG (Dikongue & Segurel, 2017; Neu et al., 2021; Suzuki et al., 2020; Thompson et al., 2017) Inverse LDG (Neu et al., 2021; Thompson et al., 2017) No LDG (Corby-Harris et al., 2007; Morelan et al., 2019)	• Stronger LDG for external microbiomes • Stronger LDG across larger latitudinal range • LDG differs for aquatic & terrestrial environments
Elevational diversity gradient Decrease in diversity with elevation or diversity peak at intermediate elevations	Temperature, precipitation, habitat area, competition, time since first colonization, dispersal rates	Lower microbiome diversity at higher elevation (Aivelo et al., 2021; Li et al., 2019) Higher microbiome diversity at higher elevation (Wolz et al., 2018) No effect of elevation (Hughey et al., 2017)	• Stronger EDG for external microbiomes • Decrease in diversity with elevation • EDG driven by variation in host ecology & demography
Diversity-area relationship Increase in diversity with geographic area	Habitat diversity, immigration and extinction rates, biotic interactions	Positive DAR (Dinnage et al., 2019; Nishida & Ochman, 2018; Reese & Dunn, 2018; Suzuki et al., 2020; Weldon et al., 2015) Negative DAR (Meaden et al., 2016; Reese & Dunn, 2018)	• Stronger DAR in more heterogeneous habitats • DAR driven by variation in host demography (e.g., population size)

FIGURES

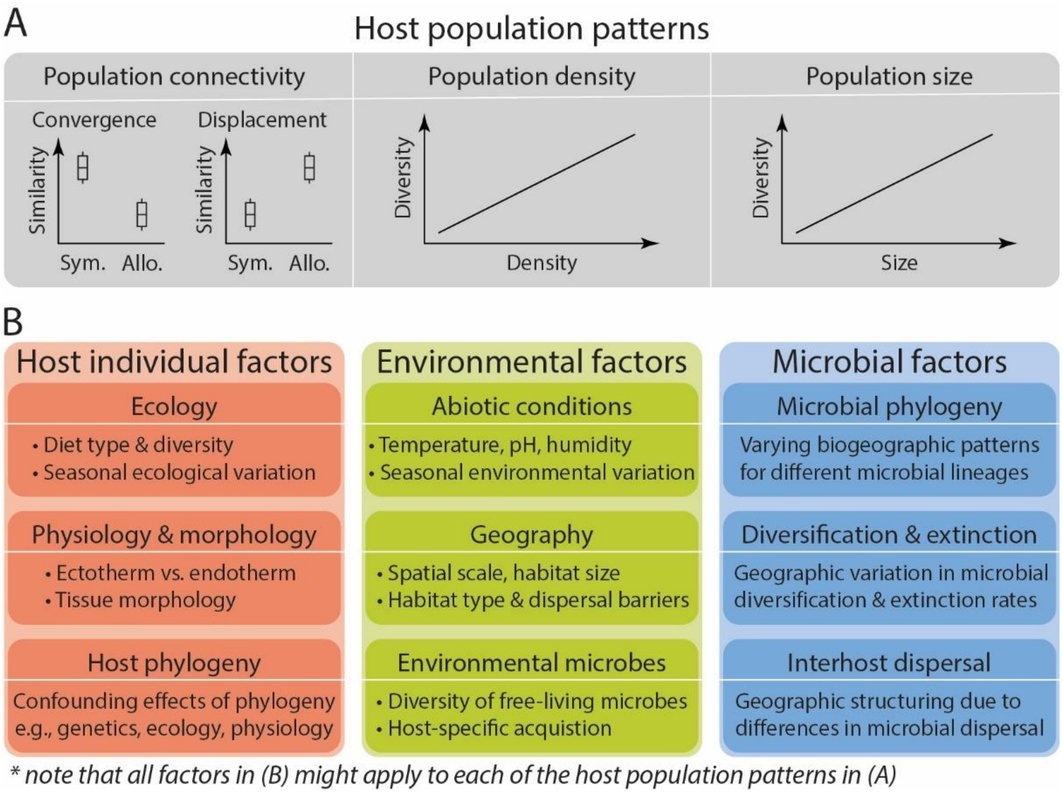

Figure 1: (A) Different patterns of geographic variation in microbiome diversity and divergence could be expected based on host population characteristics. (B) A combination of different host-associated, environmental, and microbial factors is hypothesized to shape the biogeographic distribution of microbiome diversity. The relative contributions of these factors most likely vary across study systems and geographic settings and will need to be determined in future studies.

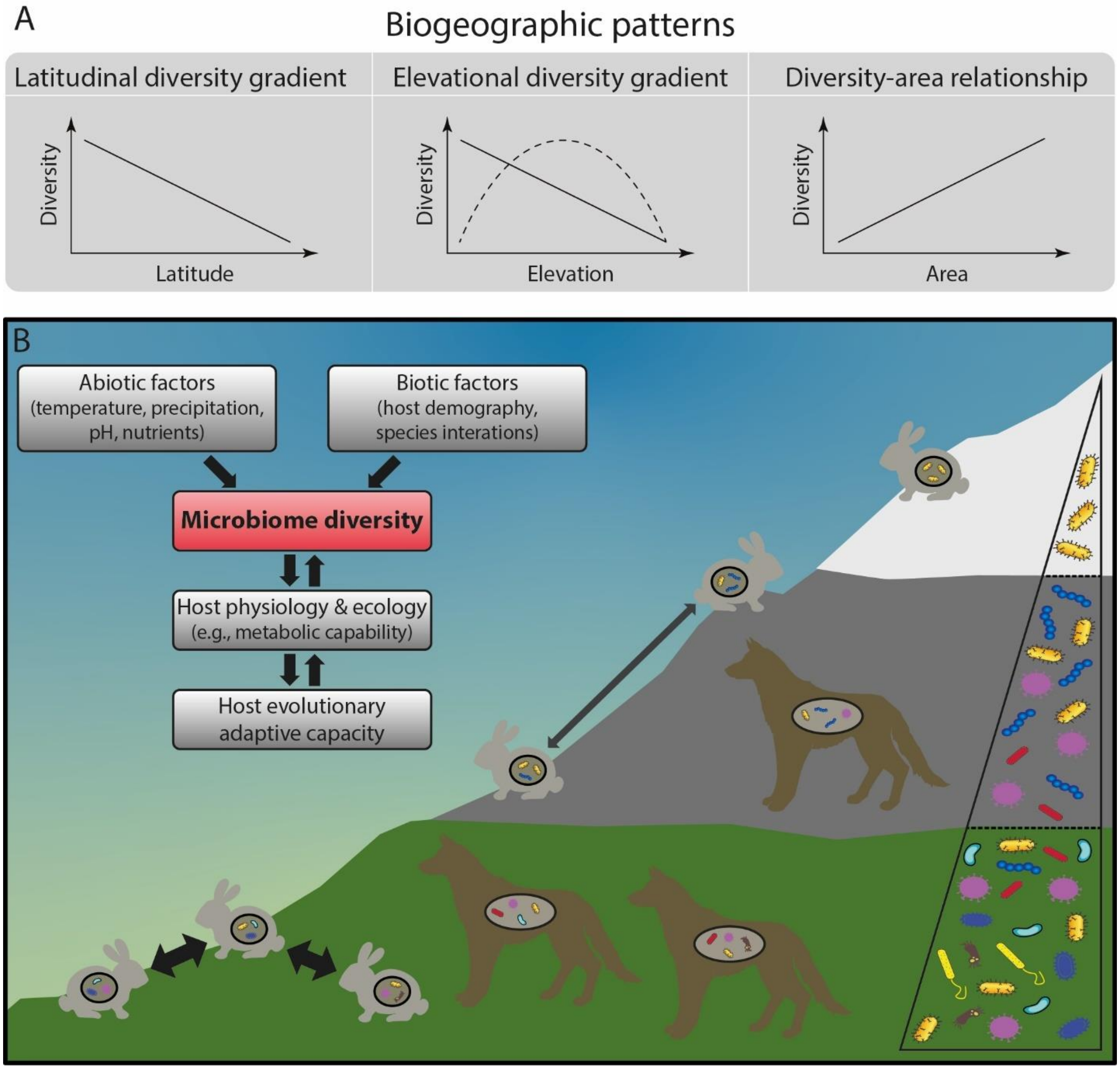

Figure 2: (A) The three biogeographic patterns exemplified in our article as they have been described for macroorganisms. (B) Hypothetical elevational diversity gradients in the bacterial gut microbiome of two different host species and free-living soil bacteria (triangle on the right). At each elevation, the pool of microbes available to a focal host organism (wolf) consists of environmental microbes (separated by dashed lines), prey-associated microbes (rabbits), and microbes associated with conspecifics. Each microbial pool is assumed to be affected by abiotic factors (e.g., a decline in temperature with altitude) and biotic factors (e.g., reduced host population size and density) that vary geographically. Such variation

could have important implications for microbial dispersal (indicated by black arrows) and, consequently, microbiome diversity on the individual and population levels. Geographic differences in microbiome diversity could affect host ecology, e.g., by modifying metabolic capability. This, could influence a host's ability to exploit novel ecological niches and alter the likelihood of host population persistence, thereby affecting host evolutionary trajectories. Please note that while this figure illustrates bacterial microbiomes, the patterns and processes presented should also apply to other microbes.