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# Our microbial selves: what ecology can teach us

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**Advances in DNA sequencing have allowed us to characterize microbial communities—including those associated with the human body—at a broader range of spatial and temporal scales than ever before. We can now answer fundamental questions that were previously inaccessible and use well-tested ecological theories to gain insight into changes in the microbiome that are associated with normal development and human disease. Perhaps unsurprisingly, the ecosystems associated with our body follow trends identified in communities at other sites and scales, and thus studies of the microbiome benefit from ecological insight. Here, we assess human microbiome research in the context of ecological principles and models, focusing on diversity, biological drivers of community structure, spatial patterning and temporal dynamics, and suggest key directions for future research that will bring us closer to the goal of building predictive models for personalized medicine.**

Keywords: human microbiome; ecological theory; microbiota; pathogenesis; microbial diversity

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## Introduction

Microbial cells outnumber human host cells by up to one order of magnitude (Turnbaugh *et al*, 2007); it is therefore unsurprising that these symbionts have an important role in human health. For example, changes in the gut microbial community are linked to metabolic disorders (Spencer *et al*, 2011), obesity (Turnbaugh *et al*, 2009a) and Crohn's disease (Eckburg & Relman, 2007). Efforts are under way to further understand and characterize the human-associated microbiota—the collection of microbes that inhabit us—and its microbiome—the collection of genes in these organisms—through international projects such as the Human Microbiome Project of the National Institutes of Health, the Metagenomics of the Human Intestinal Tract initiative, and the European-Union-funded TORNADO project. Most studies have focused so far on five areas of the body—the gut, skin, mouth, nose and vagina—with the goals of defining a core microbiome across individuals and determining the relationship between the human microbiome and health and disease. Research on the microbiome from a medical perspective has revealed the importance of human-associated microbial communities. However, viewing the human microbiome from an ecological perspective can provide the biomedical community and microbiologists with a robust framework for hypothesis testing (Dethlefsen *et al*, 2007; Ley *et al*, 2007, 2008; Robinson *et al*, 2010).

Ecological studies provide an understanding of the way in which interactions with the environment influence the distribution and abundance of species, populations and communities over space and time. Community ecologists are interested in what controls patterns in diversity and the dynamics of consortia in the same environment. As early as 1914, community ecologists sought to understand the distribution and abundance of coexisting animal species, the spatial and temporal distribution of their communities and the interactions among members of those communities (Vestal, 1914). Applying ecological theory to microbial communities has allowed the field to advance beyond basic descriptions and has allowed microbial communities to become key model systems for testing ecological hypotheses, such as neutral theory in community assembly (Dumbrell *et al*, 2010; Horner-Devine *et al*, 2007; Woodcock *et al*, 2006) and species–area relationships (Horner-Devine *et al*, 2004; King *et al*, 2010). Further extensions of ecological theory from plants and animals to other microbial communities will help us to understand our living world more comprehensively, including the ecosystem of the human body (Robinson *et al*, 2010).

Here, we suggest a foundation in traditional ecological theory that will provide a deeper understanding of the human microbiome,

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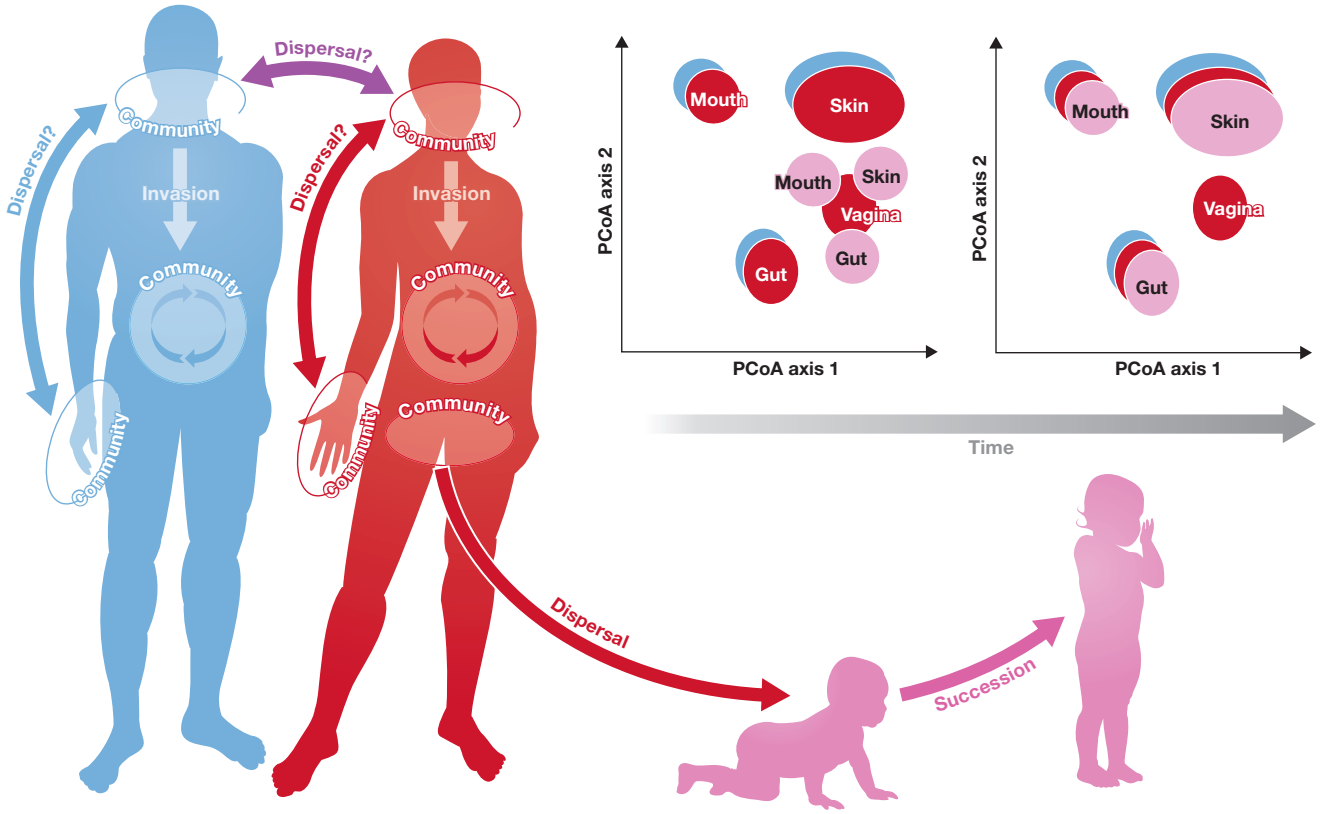


**Fig 1** | The human microbiome meets ecology. The human body can be visualized as an ecosystem that is subject to the ecological processes that structure communities, including dispersal, invasion, succession and meta-community dynamics. At the local level, interactions with members of the resident microbial and phage community, such as competition and predation, probably shape the structure of the community, whereas the meta-community structure might be more influenced by interactions among communities, such as dispersal and invasion, and stochastic events, such as disturbance. These types of interaction can extend beyond the meta-community to the ecosystem when more than one individual is considered, and they can also vary temporally. Further studies of the human microbiome will help to determine the effects of these processes on microbial interactions over space and time, including intra- and inter-personal variation and development from birth, and ultimately lead to a more-comprehensive understanding of our microbial selves.

and ultimately facilitate the prediction of microbiome dynamics in health and disease. We structure this review around four ecological topics, showing the way that each could affect human microbiome research and focusing on examples from the past five years in which data were collected by using high-throughput sequencing (Fig 1). First, we discuss diversity and its implications for the distribution and variability of human-associated microbial communities. Second, we discuss biological drivers of community structure, including interactions with invasive species, metacommunities, host ecosystems and predators. Third, we consider spatial patterning. Fourth, we consider temporal dynamics of microbial communities, highlighting implications for succession and response to disturbances. We conclude by suggesting future applications of ecology to human microbiomes that will aid in predicting responses to disturbances, and perhaps underpin new approaches to personalized medicine—just as improved understanding of the ecology of macroorganisms has led to improvements in agriculture and conservation.

## Microbial diversity

Throughout the history of microbiology, researchers have been interested in questions about the abundance, distribution and interactions of organisms, as well as the ways in which these relate to ecological processes (Fig 2). From the first observation of dental microbes by Antonie van Leeuwenhoek using the microscope, to the culturing and subsequent sequencing of specific strains approximately 300 years later, technology has provided information about the presence, abundance and biology of our microscopic residents. Now, with the recent development of high-throughput sequencing and meta-genomics, we are able to move from a purely descriptive approach to uncovering the functional relationships and interactions between genomes, taxa and communities.

One method by which to address these questions is to measure and compare diversity metrics for communities. Whittaker defined three measures to achieve this: (i) alpha diversity, to quantify the richness of the species—the number of taxa—in a niche (that is, which species are found in a single habitat); (ii) beta diversity, to compare diversity between environments, addressing the question of how different communities are structured in different niches; and (iii) gamma diversity, which measures both alpha and beta diversity of communities from different landscapes or geographical regions (Whittaker, 1972). A recurrent challenge in describing microbial diversity is how to define the relevant species unit.

 

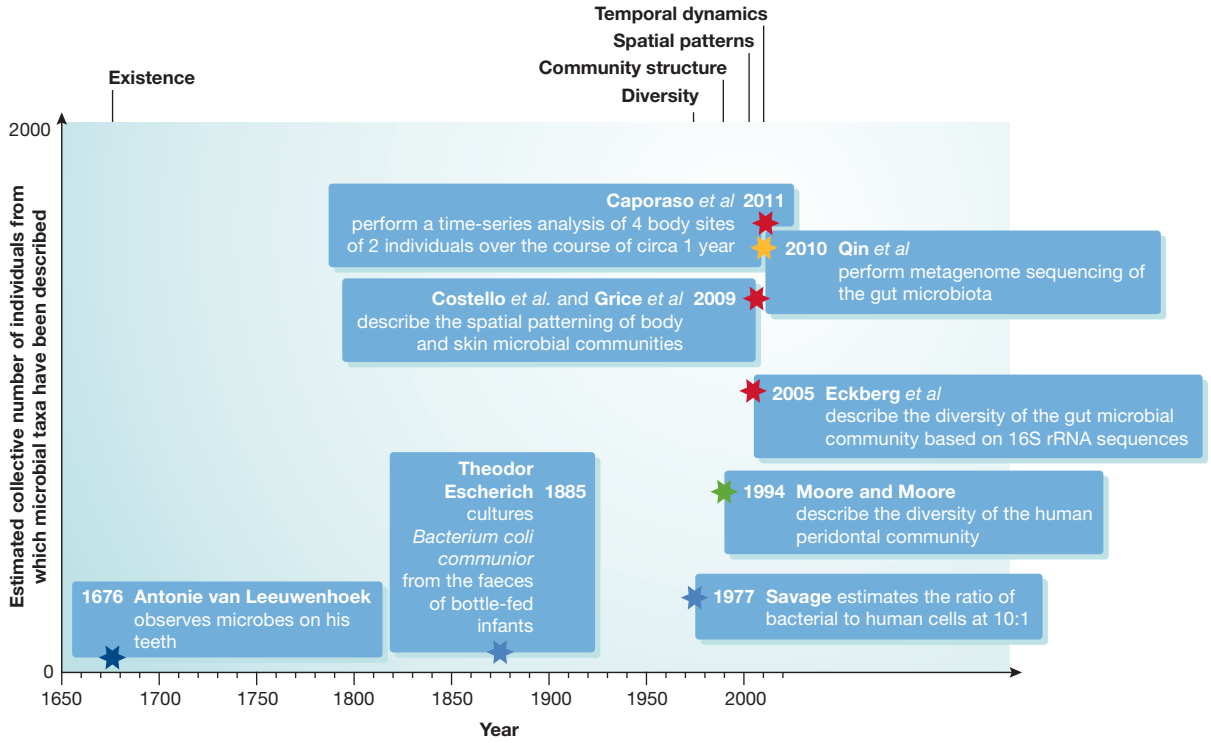


**Fig 2** | New technologies reveal new pictures of human-associated microbial communities. With the development of new technologies—including but not limited to high-throughput sequencing—the increase in the amount of data we can gather has allowed us to better test and understand the ecological processes acting within our microbial selves and, in turn, will help to frame future work within an ecological context. The colour of each star indicates the methodologies used in the different studies: dark blue, microscopic observation; blue, culturing; green, Sanger sequencing; red, pyrosequencing; yellow, metagenome sequencing (Eckburg *et al*, 2005; Moore & Moore, 1994; Savage, 1977). Estimates are based on a rough count of individuals reported in studies and articles describing human-associated microbes or communities, and are probably underestimates of the numbers of subjects.

For example, species diversity can be measured by collapsing sequences into operational taxonomic units (OTUs) and functional diversity by grouping sequences into codes in the enzyme-commission (EC) hierarchy (Bohannan & Hughes, 2003; Jensen, 2010). The resolution of such units can be specified by grouping the sequences at different levels of identity, with higher identity defining more phylogenetically resolved biological groups—strains compared with species, or protein families compared with superfamilies.

Understanding diversity is important because high species diversity can enhance ecosystem function by buffering against invasion, increasing robustness to disturbances and facilitating efficient use of resources (Cardinale *et al*, 2002; Chapin *et al*, 2000). However, higher diversity does not always result in enhanced function (Ives & Carpenter, 2007; McCann, 2000; Tilman *et al*, 1998). Diversity might also have a crucial role in ecosystem health by contributing to stability (Elmqvist *et al*, 2003; van Bruggen & Semenov, 2000). Diversity measurements have been used to infer general patterns that are true for many taxa and ecosystem scales; perhaps the most famous example is species–area curves (Schoener, 1976), which consistently show that the alpha diversity of a habitat is positively correlated with the size of the area being sampled (Magurran, 2004). Large areas reduce the risk of chance extinction and provide more niches than small areas (MacArthur & Wilson, 1967). This relationship usually fits a power-law model, in which the number of species increases as a function of the size of the sampled area. However, when comparing diversity across habitats, the opposite effect is generally observed: sampling a larger area increases the chance of observing species that are shared among the habitats, reducing the number of unique species and, consequently, overall beta diversity (Whittaker, 1972). Although these trends were inferred from the study of macroscopic organisms (MacArthur & Wilson, 1967), they might also be true for microbes (Horner-Devine *et al*, 2004; King *et al*, 2010). However, a detailed analysis of species–area relationships in the human body has not yet been performed. For example, do adults harbour a higher diversity of microbes than babies? Do molars harbour a higher diversity than incisors? Furthermore, it is essential to establish the importance of high or low diversity in the health of microbial communities from various human habitats, such as the gut or vagina.

## Drivers of community structure

Biological interactions have a role in structuring communities. They can occur within a community (such as interacting gut bacterial populations), across communities (gut compared with oral microbiota), between microbiota and the host, and between microbiota and their predators (such as bacteriophages). We select ecological examples relevant to understanding the human microbiome, focusing on invasive species and models of interaction among communities.

**Sidebar A** | In need of answers

(i) Is the success of a potential invading microbe linked to one factor —such as the characteristics of the invader, the host, the existing microbial community or the phage community—more than others? How is this reflected in the health of the host?
(ii) Over what spatial scales do microbial communities vary in humans? Are anatomical features more important than proximity, for example in the nostrils and the lips?
(iii) Over what temporal scales do human microbial communities vary most? For instance, how does daily variation compare with variation due to ageing, development and disease?
(iv) Can we use the microbiota and microbiome in one body-habitat to predict the microbiota and microbiome in other body-habitats?
(v) Which experimental and computational strategies can we exploit to find members of microbial communities that interact with each other?

*Community interactions: managing invasive microbes*. An invasive species is a non-indigenous organism that spreads from the point of introduction and becomes abundant (Kolar & Lodge, 2001). This includes both pathogenic and probiotic organisms that invade the human microbiota. The invading organism must proliferate within the native community, distinguishing it from those that merely survive in their new environment. Therefore, the success of the invader depends on its interactions with the indigenous species.

Whether a non-indigenous organism becomes invasive depends on both its ability to disperse to a new location and the outcome of the interactions with both the new ecosystem and the indigenous community (Goodwin *et al*, 1999; Kolar & Lodge, 2001), which might be affected by its relatedness to species that are already present (Webb *et al*, 2006). Here, we focus on interactions with other species. Most immigrants fail to establish themselves and will not become invasive (Kolar & Lodge, 2001). However, there is an opportunity for success in a non-native environment if a non-indigenous species escapes native predators that previously controlled population size, as stated by the enemy-release hypothesis (Keane *et al*, 2002; Torchin *et al*, 2003). As a 'predator' to foreign cells, the host immune system provides a connection to this aspect of invasion. Successful invasive microbes might also escape from native viruses, which are important in regulating bacterial populations (Gorski & Weber-Dabrowska, 2005; see Interactions with predators).

A second opportunity for immigrant success occurs if the native community is recovering from a disturbance or exists in an unstable disturbance regime. For gut-associated microbiomes, antibiotic disturbance or infections are known to alter gut communities (for examples see Dethlefsen *et al*, 2008; Hoffmann *et al*, 2009); therefore, an immigrant might become invasive if the native community is stressed. Finally, high numbers of immigrants or repeated immigration events increase the chance of a successful invasion (Mack *et al*, 2000). For many probiotics, repeated exposure seems to be important for maintaining the desired benefit, although there is conflicting evidence about their effectiveness for relieving symptoms of irritable bowel syndrome or chronic irritable bowel diseases (Gareau *et al*, 2010). Questions about the ability of a species to invade are important given the interest in stool transplantation, which seems to be an effective treatment for persistent, antibiotic-resistant *Clostridium difficile* infections (Khoruts *et al*, 2010). Fascinatingly, the intuitive idea that antibiotics will ease microbiota transfer by clearing out the original community does not seem to be true (Manichanh *et al*, 2010), and additional work in this area will have important health implications (Sidebar A).

For the indigenous community, invasion can alter community structure by reducing the abundance of or eliminating species through competition or predation, as well as by altering the habitat. For example, in patients with cystic fibrosis, invasion of the lungs by the opportunistic pathogen *Pseudomonas aeruginosa* alters the biofilm environment by blocking antimicrobials (Donlan & Costerton, 2002). The resulting environment is hidden from host immune-system phagocytes, also providing protection for less abundant non-*P. aeruginosa* community members. The cystic-fibrosis microbiome has many other characteristics of the invasive-species framework. After colonization to a non-native environment, species that become invasive typically experience an indeterminate growth lag, often followed by natural selection for mutants or phenotypes that are fitter in the new environment (Mack *et al*, 2000). These then rapidly proliferate as the 'successful' invading population. Given our understanding of invasion ecology in other ecosystems, improved understanding of biotic interactions within the cystic-fibrosis lung communities could help us to control *P. aeruginosa* invasion by introducing other microbes that block its establishment through production of the toxin *Bacterocin* (Riley & Wertz, 2002), or by selecting harmless strains to displace this pathogen.

*Community interactions: one host, many microbiomes*. Although microbial communities are often defined by geographical barriers, microbes have remarkable abilities to disperse. Thus, communities should not be considered in isolation, but as part of a regional pool of interacting communities: the meta-community (Leibold *et al*, 2004). Meta-communities are important in the context of the human microbiome, as different sites within the human body have different microbial communities (Costello *et al*, 2009; Dominguez-Bello *et al*, 2010; Grice *et al*, 2009; Ley *et al*, 2008), and these communities can directly or indirectly interact. For example, microbes in arterial plaques are linked to both the oral and gut microbiota, and macrophages provide a possible mode of dispersal (Koren *et al*, 2011). One interesting hypothesis proposes a connection between altered vaginal and oral microbiota and pre-term birth (Srinivasan *et al*, 2009). Disturbances to the 'healthy' bacterial communities of oral cavities and vaginas—caused by periodontal disease and bacterial vaginosis, respectively—are correlated with increased risk of pre-term birth. The oral and vaginal microbiomes—for example, *Fusobacterium* and *Pseudomonas* species—have similar environmental niches (squamous epithelial cells), dynamics of biofilm formation and identity of community members during dysbiosis (an imbalance of microbiota). Thus, although there is the potential for direct dispersal between these communities due to host sexual behaviour, there is also potential for indirect interactions modulated by the host immune system, as dysbiosis in one locality might elicit an immune response that affects both communities due to their similar composition. Srinivasan and colleagues suggest that during dysbiosis, the vaginal and oral communities should be considered similarly for diagnosis of individuals at risk for pre-term birth. *Salmonella typhimurium* has also been shown to interact with the host by inducing the production of tetrathionate, which can be then used as a respiratory source by *S. typhimurium* to indirectly compete with other gut microbes (Winter *et al*, 2010).

*Interactions with host ecosystems*. Ecosystems are an ongoing dialogue between chemical and physical conditions, and biology: the environment selects for organisms capable of surviving, which in

 

turn alter the environment to become more-favourable for their success. Among the most-important microbial interactions with ecosystems are nutrient and carbon cycling. For example, bacterial communities associated with soils and legumes modify forms of nitrogen ($NH_4^+$, $N_2$, $NO_2^-$, $NO_3^-$), which makes them available to plants or the atmosphere. Recent experimental research on soils from different ecosystems showed that soil microbial communities are predictably structured by the amount and quality of carbon and nitrogen available (Ramirez *et al*, 2010), as are plants (for examples, see Elser *et al*, 2011; Harpole & Tilman, 2007; Wedin & Tilman, 1996). Similarly to soil microbial communities, human microbial communities—such as gut communities—are influenced by the types and availability of electron donors and acceptors. For example, 24-h starvation of mice leads to alteration of the gut community (Crawford *et al*, 2009), and one day after a shift from a low-fat to a western-human-equivalent diet, the gut microbial community of gnotobiotic mice changed radically (Turnbaugh *et al*, 2009b). Similarly, the response of Burmese pythons to nutrition during the feeding cycle is systematic across animals (Costello *et al*, 2010). Interestingly, in all cases, increased nutrient flux causes a substantial shift in the ratio of Firmicutes to Bacteroidetes, probably reflecting competition between copiotrophs and oligotrophs, especially in carbohydrate-rich diets. The effect of nutrition on human infants—in particular the switch from breastfeeding to solid food—is also profound (see Temporal dynamics).

*Interactions with predators: microbiome and virome.* Other important interactions, especially for bacterial communities, are with their bacteriophage predators (Deveau *et al*, 2010; Pride *et al*, 2011). From oceans (Angly *et al*, 2006) to human bodies (Nelson *et al*, 2011), the number of viruses and virus-like particles outnumber bacteria by orders of magnitude. Studies of host–phage dynamics in aquatic ecosystems indicate that phages can affect the diversity and abundance of bacterial species or strains in a community (Sime-Ngando & Colombet, 2009; Suttle, 1994). However, one study on the phages of human faecal microbiota suggests that this might not always be the case (Reyes *et al*, 2010). Accordingly, the interactions between viral and microbial consortia are complex and structured by the environment (Dinsdale *et al*, 2008).

Ecological theory has been developed from other predator–prey relationships; one classic example is the 'red queen' hypothesis, named after the character in Lewis Carroll's *Through the Looking Glass*. This hypothesis refers to the evolutionary arms race that can occur between predator and prey, in which both must keep 'running'—random mutations that result in fitness advantages for predation or escape, respectively—to stay in the same place (van Valen, 1973). For example, bacteria and archaea have developed mechanisms to protect themselves from phages through the duplication of genetic material—such as clustered, regularly interspaced, short palindromic repeats (CRISPRs). CRISPRs act as genetic markers of a past immune response to phages or other exogenetic material such as plasmids. CRISPRs can be shared among environmental bacterial communities to protect them from adverse environments (Heidelberg *et al*, 2009). CRISPRs might provide an important window into the history of interactions between phage and bacteria or archaea within the human microbiota. An interesting research path is to understand the interactions between viruses, host microbiome and host genetics, and their role in the health of the host. For example, the combination of a specific virome and the gene variant *Atg16L1* in the host can lead to Crohn's disease (Cadwell *et al*, 2010) or inflammatory bowel disease (Bloom *et al*, 2011). Furthermore, commensal bacteria can modulate the host immune response against influenza A virus (Ichinohe *et al*, 2011). These studies provide an insight into the crucial role that these interactions have in the health of the host (Sidebar A).

## Spatial distributions

Understanding the distribution of species on Earth is a focus in ecology. A sub-discipline, known as biogeography, is the study of the way the distribution and abundance of species change over time at the regional or continental scales. Assessments of microbial diversity have shown that the deterministic—such as biotic and abiotic interactions—and stochastic—such as dispersal ability—processes that structure plant and animal distributions also control microbial distributions (reviewed in Martiny *et al*, 2006). Microbial biogeography has been particularly useful in mapping occurrences of disease-relevant microbes and, more recently, has helped to explain their geographical patterns of distribution, such as the spread of antibiotic resistance in *Escherichia coli*, *Salmonella enterica* and *Vibrio vulnificus* (Baker-Austin *et al*, 2009; Mirzaagha *et al*, 2011; Shulse & Allen, 2011). Additionally, biogeographical studies of soil microbes have revealed consistent patterns of distribution at both species and community levels (Bru *et al*, 2011; Costello *et al*, 2010; Fierer & Jackson, 2006; Nemergut *et al*, 2011; Van der Gucht *et al*, 2007). Similarly, determining the drivers of spatial patterns on and in the human body will require tools from the field of biogeography. Similarly to the natural environments on Earth, the human body acts as an ecological landscape by harbouring many ecosystems and meta-communities, as well as biotic and abiotic determinants and barriers that prevent, and corridors that facilitate, dispersal. For instance, in a study of transplants in which forearm and forehead skin plots were inoculated with tongue bacteria, forearm communities remained more similar to tongue communities than to native forearm communities, whereas forehead communities reverted to their native state over time (Costello *et al*, 2009). Excitingly, adaptation can occur even within a genome: for example, strains of *Methanobrevibacter smithii* are more similar in identical than non-identical twins (Hansen *et al*, 2011), and the genetic determinants of group A streptococcus that allow colonization of different parts of the body are beginning to be unravelled as more genomes are sequenced (Shea *et al*, 2011). Thus, environmental characteristics such as dispersal barriers probably also shape the geographical distribution of human-associated communities, including individual strains of species within those communities.

Ultimately, understanding why species or communities occur in particular areas can help to predict their occurrence. Predicting spatial distributions can be informed by investigating the ecological niche—the set of environmental factors that are associated with its occurrence—of a species. The abiotic conditions in which a species can survive define its fundamental niche (Hutchinson, 1957). However, only a portion of the fundamental niche is usually occupied—that is, its realized niche—because biotic interactions and dispersal ability limit the potential of a species to occupy all suitable habitats. In microbial biogeography, the predominant theory is that "everything is everywhere, but the environment selects" (Baas-Becking, 1934; O'Malley, 2007), which suggests that because dispersal is generally unlimited for microbes—in contrast to animal systems—a realized niche might be controlled by abiotic and biotic

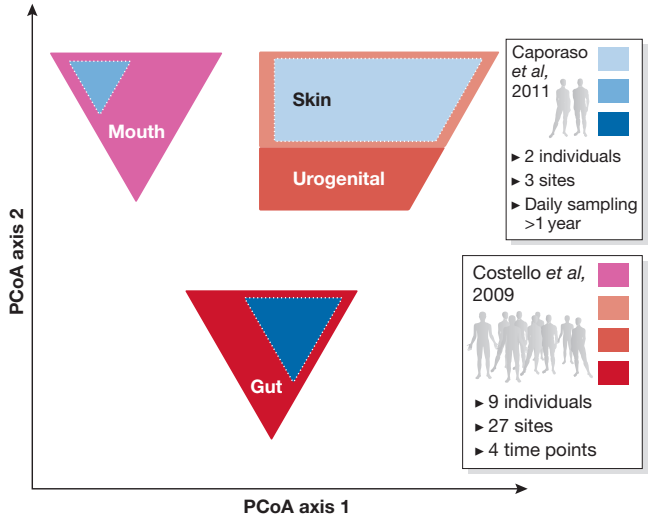


**Fig 3** | Variability of the human microbiota. The plot shows the first two axes of the principal coordinate analysis (PCoA), which capture the differences and similarities between communities in each biological sample. The area of each polygon represents the variability within clusters of the samples in each study, indicating that the human microbiome separation is due to its origin (gut, skin, mouth and urogenital) and that there is as much variation over time in one person as there is between adults in a community. Samples from Costello *et al* (2009), 27 sites in 7–9 healthy adults are shown in red and samples from Caporaso *et al* (2011a), 3 sites in two adults over 1 year, are shown in blue.

factors instead of dispersal ability. For example, studies of soil microbial communities indicate that landscape-scale spatial variation in abundances are mainly driven by environmental parameters such as pH, and that these variables can be used to accurately predict the large-scale distribution of certain communities (Bru *et al*, 2011; King *et al*, 2010; Lauber *et al*, 2009). Another study found that within local habitats, bacterial assemblages were determined by biotic interactions, exhibiting specific co-occurrence patterns (Nemergut *et al*, 2011).

Ecological-niche theory is useful for describing the spatial distribution of human-associated microbial communities. Similar patterns might emerge for microbial communities inhabiting different habitats in the body—such as gut compared with skin—and micro-habitats, such as different skin sites. Characterizing these habitats is complicated by the fact that each human harbours unique microbial consortia that are so specific that some skin sites can be used to forensically identify the host (Fierer *et al*, 2010a; Qin *et al*, 2010). As the genetics, development and behaviour, including diet, of the host contribute to the composition of individual microbiota, each person essentially functions as a unique and separate ecosystem. Despite this uniqueness, communities are grouped by body habitat—such as gut, skin or mouth—across individuals (Costello *et al*, 2009). Even within one type of body habitat, the skin, bacterial communities are more similar across physiologically comparable skin sites than in topographically close sites (Grice *et al*, 2009). These site-specific factors make it challenging to develop comprehensive niche models for the human microbiota, but studies show that micro-habitats across the skin can be quantified, as exemplified by a recent study in which measurements of skin surface temperature, surface pH and lipid content exhibited regional variations (Marrakchi & Maibach, 2007). Thus, modelling the effects of specific micro-habitats on microbial communities might be a tractable problem, although defining the niches of individual community members remains challenging.

## Temporal dynamics

In the same way that microbial communities are expected to change across a landscape, they are also dynamic in time. Community ecology provides a framework for understanding temporal dynamics, including the concepts of succession, resilience and community turnover. In general, time-series studies—in which microbial communites are sampled repeatedly at the same site over time—aim to identify deviations from an equilibrium state, and are essential for understanding the natural variability and trajectories of microbial communities. Microbial community dynamics have been characterized in time-series data from several environments, including the human body (Fig 3; Caporaso *et al*, 2011a; Costello *et al*, 2009), oceans (Gilbert *et al*, 2009), lakes (Shade *et al*, 2007) and soils (Costello & Schmidt, 2006; Griffiths *et al*, 2011). This temporal component allows for identification of both persistent and transient components of a community (Manichanh *et al*, 2010), measurement of robustness and resilience to external perturbations (Shade *et al*, 2010), and improved understanding of dispersal and migration patterns (Kerr *et al*, 2006).

Succession is a process that begins in a 'blank slate' environment; pioneer species colonize the environment first, altering it to be hospitable to secondary colonizers. This process then continues until a climax community is reached around an equilibrium composition. Succession has been widely observed, such as in microbial communities that colonize leaf surfaces (Fierer *et al*, 2010b). Primary succession—first observed in forests affected by fire—occurs as pioneer species alter the organic composition of the post-burn soil, making it suitable for subsequent colonizers. In boreal forests, a functional trajectory proceeds from herbs and forbs, shrubs, young forest (saplings), mature forest and, finally, climax forest, 150–300 years after the fire (Rowe & Scotter, 1973).

Although the functional roles of microbial-community members during succession are more difficult to discern than those of higher plants, the early colonization of the human gut provides an excellent case study for microbiota succession. Neonates are thought to develop in a microbe-free environment until delivery, when they are exposed for the first time to a variety of bacteria. During vaginal birth, the infant is first exposed to microbes present in the birth canal of the mother, an environment that is mostly colonized by *Lactobacillus* (Ravel *et al*, 2011). By contrast, babies delivered by caesarean section do not receive this initial exposure and their bacterial communities resemble those found on skin (Dominguez-Bello *et al*, 2010). A similar study demonstrated that gut diversity steadily increases from birth until two and a half years of age (Koenig *et al*, 2011). Inter-individual reproducibility of gut-community succession has also been examined in a cohort of 14 full-term infants over the first year of life (Palmer *et al*, 2007). Composition varied from infant to infant, as observed in adults (Fierer *et al*, 2010a). Although there was no common pattern of succession observed across infants, the communities in each baby showed a recognizable temporal pattern. In this study, mothers provided vaginal, milk and stool samples; the microbiomes of the milk and vaginal samples clustered with the earliest gut microbiomes of the infants.

 

The innate and adaptive immune system of the infant, which can exert pressure on the microbiota, is highly dynamic during the first year of life. The development of the infant gut microbiota is affected by passive antibodies, oligosaccharides and glycans from animal milk through the promotion of *Bifidobacterium bifidum* growth and inhibition of pathogenic species (Newburg, 2009). The function and expression of toll-like receptors (TLRs), which recognize various microbial products, rapidly change during the first year of life (Burl *et al*, 2011). At birth, the TLR response to lipopolysaccharide and CpG (cytosine–guanine dinucleotide DNA sequence) regions is impaired, leading to reduced production of proinflammatory cytokines, which can limit bacterial growth (Nguyen *et al*, 2010; Shaikh & Shaikh, 2009). In the first few months after birth, the phenotype and function of B and T cells in the *lamina propria* of the large intestine also change dramatically. The majority of B and T cells in cord blood are naive; however, in the months following birth, bacteria-specific B- and T-cell memory populations appear, begin to provide protection from pathogenic microbes, and presumably shape the commensal bacterial community within the gut. In fact, immunoglobulin-A-producing B cells—which are important for the control of microbes at mucosal surfaces—are not detected until 12 days after birth, and their density in the *lamina propria* steadily increases even after 3 months of age (Hacsek *et al*, 1999). In turn, bacterial colonization of the gut is crucial for the normal development and homeostatic maintenance of mucosal immunity (Atarashi *et al*, 2011; Gaboriau-Routhiau *et al*, 2009). Lastly, as discussed elsewhere (Favier *et al*, 2002; Koenig *et al*, 2011; Stark & Lee, 1982), the introduction of solid foods modifies the structure of the community and triggers the change towards an adult microbiota. With the advent of higher-throughput sequencing platforms (Caporaso *et al*, 2011b), we can expect to see more studies of succession at higher temporal resolution and with more subjects in the near future (Figs 2,3). These will provide insight into normal human development, recovery after antibiotic treatment or other drugs, and progression into disease states, including in some cases remission from those states.

Time-series data can also be used to investigate the responses of microbial communities to disturbances. In disturbance ecology, a robust community is one that is either resistant (changes minimally) or quickly resilient (recovers to the pre-disturbance state) to disturbance. Microbial responses to disturbance have been observed in soil, aquatic and engineered environments. For example, elevated atmospheric carbon-dioxide levels—an example of a long-term disturbance—initiated a different response in bacterial and fungal species in rhizosphere soil; specific community members were more strongly affected than others, suggesting complex response patterns that might not be uncovered using bulk-microbial measurements such as respiration and production (Drigo *et al*, 2009). Aquatic microbial communities exhibited a repeatable trajectory of response and recovery after typhoons mixed the water column in a sub-tropical lake, demonstrating a remarkable predictability in community dynamics after pulse-disturbance events (Jones *et al*, 2008). Finally, the pre-disturbance composition of methanogenic-bioreactor communities was important for functional stability after glucose amendment (Fernandez *et al*, 2000; Hashsham *et al*, 2000). These studies show that, despite similar initial performance across microbial communities, compositional differences have implications for overall functional stability after disturbance. These examples and others suggest some recovery of the post-disturbance community, either in composition or function. However, no consistent recovery has been documented, possibly because insufficient post-disturbance observation data are available (Allison & Martiny, 2008).

The principles of disturbance ecology—including response, resilience, recovery and succession—are also relevant to host-associated microbiota. An example of a perturbation with temporary effects was described in a study of patients receiving a transplant of small-bowel microbiota (Hartman *et al*, 2009). After transplant, patients harboured a higher proportion of lactobacilli and enterobacteria; however, the community eventually reverted to pre-transplantation composition—dominated by *Bacteroides* and *Clostridia*—showing resilience. Antibiotics are also known to alter bacterial composition of the gut flora (Blaser & Falkow, 2009; Dethlefsen *et al*, 2008), and prolonged use prevents recovery (Dethlefsen & Relman, 2011; Jernberg *et al*, 2007). These studies show that antibiotics can modify the gut environment by killing both pathogens and dominant community members, and that—if given an opportunity—normally non-competitive taxa can flourish. However, the eventual recovery of the gut community mimics what has been observed in other microbial communities, and suggests that prediction might be possible.

## The future: prediction and personalized medicine

The initial wave of human microbiome projects sought to describe the bacterial communities harboured in the human body. Although the fungal, viral and archeal populations have not been as deeply characterized as bacterial communities, their study is undoubtedly of great importance to better understanding their effects in the host. This initial characterization has enhanced our understanding of the differences between healthy and diseased states, such as in the distinctive nature of obesity- and lean-associated bacterial communities (Turnbaugh *et al*, 2009a). However, the large inter-individual variability of microbiota can impede diagnosis of all but the most common conditions, and more comprehensive temporal and spatial information is necessary to inform personalized medicine; several studies have begun to address this (Arumugam *et al*, 2011; Ravel *et al*, 2011).

Although species-level characterization of the bacterial communities inhabiting various body sites has provided insight into our microbial selves, current and future studies using techniques such as whole-genome shotgun sequencing will also provide a description of the functional diversity in those communities. A recent study has shown, for example, that the gut communities of different mammal species share a core set of functional genes, and that the bacterial lineages that make up a community and the gene content of that community have a similar clustering pattern (Muegge *et al*, 2011). Another active area of research aims to understand the interactions between the microbiome and the virome in the distal intestine (Reyes *et al*, 2010), the infant gut (Breitbart *et al*, 2008) and the lung (Willner *et al*, 2009).

Research in human microbial communities has already benefited from incorporating methods and concepts from ecology to collect and analyse the wealth of data generated by new sequencing technologies. The spatial and temporal characterization of the microbiota in different populations, in particular, has provided deeper insights into the dynamics of commensal bacteria and their resistance and resilience to perturbations in the human body. The ability to analyse more microbial communities at lower cost will allow us to test the reproducibility of these conclusions in subjects of different ages, diets and ethnicities, and with different

drug-exposure histories. At the same time, the ability to exploit many samples—especially in the context of time series with perturbations—will allow us to identify networks of interactions among microbial taxa and determine which species can be most-effectively targeted for therapeutic applications—either by removal with antibiotics, addition with probiotics or encouragement with prebiotics. Given the prolific and myriad types of data that are sure to emerge with the incorporation of whole-genome shotgun sequencing and viral metagenomics, continuing to frame human microbiome studies in ecological terms will be even more important. This broader and ecologically informed understanding of our microbial selves will be key for truly personalized medicine that is based not on the human genome, in which we are all 99.9% the same, but on the microbiome, in which we can differ immensely.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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