From Animalcules to an Ecosystem: Application of Ecological Concepts to the Human Microbiome

Noah Fierer,[1,2] Scott Ferrenberg,[1] Gilberto E. Flores,[2] Antonio González,[3] Jordan Kueneman,[1] Teresa Legg,[1] Ryan C. Lynch,[1] Daniel McDonald,[4] Joseph R. Mihaljevic,[1] Sean P. O'Neill,[1,5] Matthew E. Rhodes,[1] Se Jin Song,[1] and William A. Walters[6]

[1]Department of Ecology and Evolutionary Biology, [2]Cooperative Institute for Research in Environmental Sciences, [3]Department of Computer Science, [4]Biofrontiers Institute, [5]Institute of Arctic and Alpine Research, and [6]Department of Molecular, Cellular, and Developmental Biology, University of Colorado, Boulder, Colorado 80309; email: Noah.Fierer@colorado.edu

Annu. Rev. Ecol. Evol. Syst. 2012. 43:137–55

First published online as a Review in Advance on August 28, 2012

The *Annual Review of Ecology, Evolution, and Systematics* is online at ecolsys.annualreviews.org

This article's doi: 10.1146/annurev-ecolsys-110411-160307

1543-592X/12/1201-0137$20.00

Keywords

bacterial diversity, host-associated bacterial communities, microbial diversity, microbial ecology

Abstract

The human body is inhabited by billions of microbial cells and these microbial symbionts play critical roles in human health. Human-associated microbial communities are diverse, and the structure of these communities is variable across body habitats, through time, and between individuals. We can apply concepts developed by plant and animal ecologists to better understand and predict the spatial and temporal patterns in these communities. Due to methodological limitations and the largely unknown natural history of most microbial taxa, this integration of ecology into research on the human microbiome is still in its infancy. However, such integration will yield a deeper understanding of the role of the microbiome in human health and an improved ability to test ecological concepts that are more difficult to test in plant and animal systems.

1. INTRODUCTION

Like nearly all plants and animals, humans host a large number of microorganisms, both on and in our bodies. As we go about our daily lives, we are continually in the process of acquiring and shedding microbes, exchanging microbes directly and indirectly with friends, family members, strangers, and any environment with which we come into contact. However, the resulting structure of our microbial communities is not simply a product of this immigration and emigration of microbes. Current and past conditions of our body habitats, conditions that are largely a product of our anatomy, physiology, behavior, and immune system function, also affect the structure of our microbial communities. The converse is also true; the microbial communities living on and in our bodies can shape the characteristics of the human body in a myriad of ways.

Collectively, the human microbiome, which we define here as those microorganisms associated with the human body, is represented by 10^{14} to 10^{15} microbial cells and the majority of these cells are found in the large intestine (Bäckhed et al. 2005). In terms of numerical abundance, bacterial cells likely outnumber human cells by at least an order of magnitude (Savage 1977). The bacterial contribution to the total genetic diversity found within the human body is perhaps a more important consideration as the number of bacterial genes clearly outnumbers the number of genes in the human genome by several orders of magnitude (Qin et al. 2010). Although many of these bacterial genes may have no direct relevance to the health of the human host, the human microbiome has the potential to endow us with a large number of traits or characteristics that are not encoded in our own genome. In other words, our health is not simply a product of the genetic or epigenetic potential of human cells, but also a function of the structure and activities of our associated microbial communities.

Understanding the structure and function of the human microbiome requires knowledge from a wide range of disciplines—from immunology to genomics to microbial metabolism. Here we examine the human microbiome from an ecological perspective, exploring how ecological concepts derived largely from research on plant and animal communities may help us understand the structure and function of the human microbiome. We recognize that ours is not the first attempt to delve into the ecology of the human microbiome; there are a number of excellent reviews on the topic (e.g., Dethlefsen et al. 2007, Gonzalez et al. 2011, Robinson et al. 2010). We also recognize that the ecology of the human microbiome is an impossibly large topic to summarize in this space. Essentially every topic in the field of ecology, from autecology to biogeography, is relevant to understanding the spatial and temporal patterns exhibited by human-associated microbes. We focus on selected topics that represent key knowledge gaps in our understanding of the ecology of the human microbiome. Although we primarily focus on bacteria, we recognize that the human body is also home to other microbial taxa, including fungi, microeukaryotes, and archaea, which can have important effects on the health of the human host. Likewise, we do not devote a lot of attention to viruses as researchers are only now beginning to document the diversity of viruses found in the human body and their role in the human microbiome (e.g., Minot et al. 2011, Reyes et al. 2010).

2. RELEVANCE OF THE MICROBIOME TO HUMAN HEALTH

Research on the human microbiome is as old as the field of microbiology. The first person to observe and formally describe microbes was Antonie van Leeuwenhoek, who in the late seventeenth century looked at his own saliva through a rudimentary microscope and noted: "I then most always saw, with great wonder, that in the said matter there were many very little living animalcules, very prettily a-moving." In subsequent centuries, research on the human microbiome expanded as

microbiologists began to discover that specific bacterial taxa caused diseases, with many of these pathogens fulfilling Koch's postulates. Although the limitations of Koch's postulates are well known, they remain a cornerstone of medical microbiology because they provide a useful framework for the identification of new pathogens. However, the reliance on Koch's postulates (or variants thereof, see Fredericks & Relman 1996) may have directed the focus of medical microbiology toward diseases that could be linked to a specific taxon and away from diseases associated with changes in multiple taxa within a microbial community. The recent launch of the Human Microbiome Project (**http://commonfund.nih.gov/hmp/**), MetaHIT (**http://www.metahit.eu/**), and other related large-scale research efforts signals a shift of focus as both medical professionals and research microbiologists are increasingly recognizing the importance of the underlying structure of the entire human microbiome for human health.

The human microbiome can affect human health in many ways, and new functions of the human microbiome are being discovered on a regular basis. For example, we know that the human microbiome can alter host susceptibility to microbial pathogens, aid in the digestion of complex polysaccharides, produce metabolites required by the host (e.g., vitamins or specific amino acids), modulate and educate the immune system, regulate environmental conditions within body habitats, and influence tissue development (Gill et al. 2006, Pflughoeft & Versalovic 2011, Robinson et al. 2010). Host-microbiome interactions span the spectrum of being beneficial to the host, having no detectable influence on host health (a commensal relationship), or having a net negative effect on the health of the host. For example, the pathogenic bacterium *Clostridium difficile* can, in some cases, become more abundant and permanent members of the human microbiome (McFarland 2008). Likewise, there is a wide range of diseases that have been linked to dysbioses, causing changes in resident microbial communities that are associated with negative effects on host health. Such diseases include bacterial vaginosis, Crohn's disease, psoriasis, gingivitis, obesity, antibiotic-associated diarrhea, and irritable bowel syndrome (Frank et al. 2011, Pflughoeft & Versalovic 2011). However, causality for dysbiosis is often difficult to determine; the microbiome could be causing the disease or the resident microbial communities could be reflecting changes in the host brought about by the disease state. In either case, ecological investigations of human-associated microbial communities have the potential to directly affect the way in which we prevent diseases, identify onset of disease, design treatments, and track disease recovery.

3. DESCRIBING DIVERSITY IN THE HUMAN MICROBIOME

Only in the past few decades have microbiologists begun to fully appreciate the extent of microbial diversity found within the human body. Although we have known for centuries that the mouth, for example, harbors large numbers of bacteria (van Leeuwenhoek's animalcules), until recently, our understanding of their taxonomy and function was drawn almost entirely from pure culture studies of individual bacterial isolates grown in vitro. Most microbes are difficult to culture in isolation, leading to biases in culture-dependent surveys of microbial diversity (Pace 1997). Moreover, although culture-based investigations are vital to understanding the ecology, physiology, and genetics of individual taxa, microorganisms may exhibit different characteristics in vitro than in vivo. For example, streptococci, which are often associated with dental caries, rely on a suite of other bacteria in order to effectively colonize and reproduce on tooth surfaces (Jenkinson 2011). Thus, streptococcal ecology cannot be understood by solely studying these organisms in pure culture.

The development of culture-independent tools, particularly 16S rRNA gene sequence analysis, has greatly expanded our understanding of the microbial diversity in the human microbiome. We now know that the human mouth, for example, contains hundreds of microbial taxa, most of

which have yet to be cultured (Jenkinson 2011). This revolution in our ability to describe human-associated microbial communities continues unabated. New tools that enable detailed examination of the human microbiome across large numbers of individuals are introduced nearly every month, including both sequencing platforms and data analysis approaches. Reviews of the methodological advances in human microbiome research (Hamady & Knight 2009, Kuczynski et al. 2012) point out that it is increasingly feasible for researchers to rapidly characterize microbial communities in thousands of samples. These advances enable us to move research on the human microbiome into the realm of ecology, describing and predicting the inter- and intraindividual variability in microbial communities and their functional capabilities.

Many of the approaches microbiologists use to describe the variability in microbial communities are conceptually similar to those approaches long used by plant and animal ecologists. However, there are important distinctions between microbial and "macrobial" (i.e., plant and animal) diversity surveys. Studies of plant and animal systems often rely on visible observations of taxa and their responses to biotic and abiotic stimuli. However, modern microbiome studies typically rely on DNA or RNA sequencing to infer the presence or relative abundance of organisms because visual observation of microbial taxa in situ is often difficult. Also, though microbiologists do have extensive knowledge about a limited number of well-studied, cultured organisms, we lack basic knowledge about the natural histories of most microbial taxa, even those taxa commonly found in the human body. Furthermore, because the average sizes and generation times of plant and animal species are orders of magnitude larger or longer than those of bacterial taxa, microbial ecologists need to address a unique set of spatial and temporal issues. These limitations make it difficult to directly compare those ecological phenomena observed in macrobial versus microbial systems. Nevertheless, they should not prevent us from applying ecological concepts (which were largely derived from plant and animal systems) to the study of the human microbiome.

4. ALPHA DIVERSITY IN THE HUMAN MICROBIOME AND HOST HEALTH

Alpha diversity is a key metric used by community ecologists and may provide important insight into community assembly patterns and the interactions between the microbiome and its human host. Alpha diversity is generally defined as richness (the number of taxa or lineages in a given sample), evenness (the relative abundance of taxa present within a given sample), or a metric that combines these two parameters (e.g., Shannon-Weiner diversity index). Although ecologists are increasingly describing alpha diversity patterns using metrics that incorporate phylogenetic (Faith & Baker 2006) and functional or trait-based information (Petchey & Gaston 2007), we focus here on the taxonomic diversity of human-associated microbial communities as this is the alpha diversity metric most commonly applied in microbial community analyses.

To an ecologist more familiar with plant and animal communities, the alpha diversity observed in human-associated bacterial communities is immense. Individual body habitats typically harbor dozens of bacterial phyla and hundreds, if not thousands, of individual bacterial phylotypes, canonically referred to as operational taxonomic units (OTUs). The notion of an OTU is essential as there is no consensus definition of what constitutes a bacterial species (Zhi et al. 2012). However, most of these OTUs are rare, and the majority of body habitats are dominated by just a few bacterial phyla (**Figure 1**). We also know that alpha diversity levels can vary dramatically between individuals, across body habitats, and within an individual body habitat over time (Caporaso et al. 2011, Costello et al. 2009). From a long history of research on the alpha diversity patterns exhibited by plant and animal communities, we know that a wide range of processes could generate the alpha diversity patterns observed within the human microbiome. Such

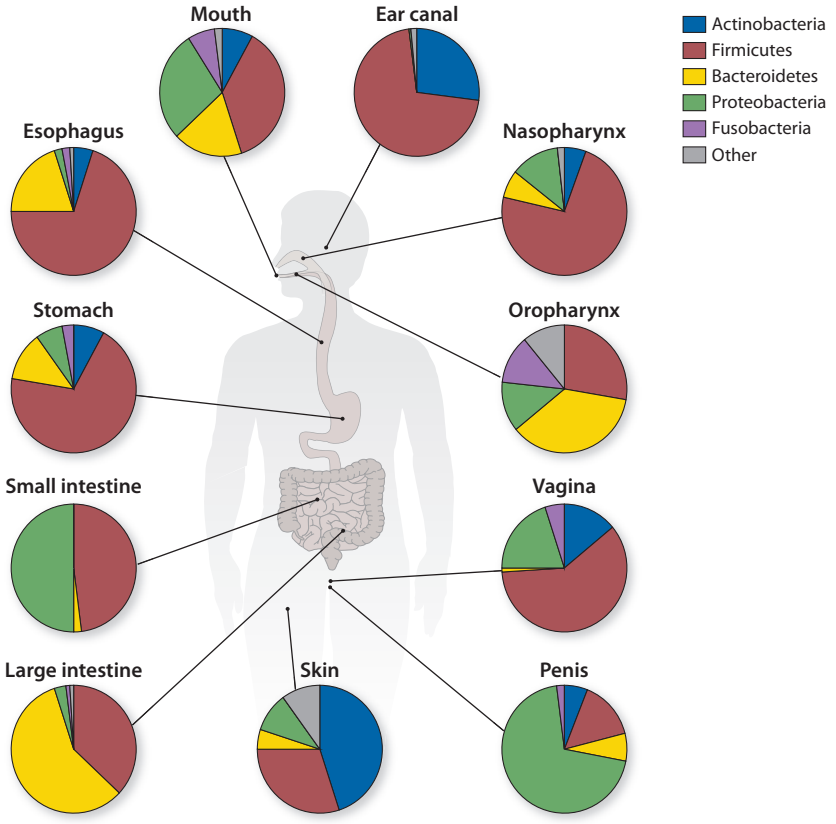

Figure 1

General patterns in the composition of bacterial communities in various body habitats. Pie charts illustrate percentage of 16S rRNA gene sequences representing the dominant bacterial phyla. Data compiled from Charlson et al. 2010, Costello et al. 2009, Dicksved et al. 2009, Frank et al. 2003, Hayashi et al. 2005, Kim et al. 2009, Pei et al. 2004, Price et al. 2010.

processes include environmental gradients, disturbance regimes, resource competition, predator-prey interactions, and niche differentiation (Ricklefs & Schluter 1993, Rosenzweig 1995), in addition to neutral processes (Hubbell 2001). Unfortunately, there are surprisingly few studies of the human microbiome that explicitly examine how these factors can influence alpha diversity patterns even though understanding the relationship between the alpha diversity of microbial communities and a disease state is one of the key questions in human microbiome research (Frank et al. 2011).

We know that certain diseases are associated with pronounced changes in alpha diversity within affected body habitats. However, the directional change associated with the disease state is not consistent across all diseases. Cystic fibrosis appears to cause an increase in the diversity of bacteria in patients' lungs (Harrison 2007), whereas Crohn's disease often results in a decrease in the microbial diversity of the intestine (Manichanh et al. 2006). Furthermore, it is often difficult to determine whether changes in alpha diversity are the cause or consequence of the disease state. For example, a study of human gut microbial communities found that there were differences in bacterial diversity between healthy individuals and those with inflammatory bowel disease (IBD; Frank et al. 2007); yet it was not clear if the healthy individuals were less susceptible to IBD

because they had a diverse gut microbiota to begin with or if IBD caused a lower alpha diversity. For these reasons, alpha diversity may be a poor predictor of disease status (or susceptibility to disease). Nevertheless, changes in alpha diversity could provide a useful indicator of health status just as changes in plant diversity (Balvanera et al. 2006, Loreau et al. 2001) or animal diversity (Hudson et al. 2006) can sometimes be used as indicators of ecosystem health or function. Work on bacterial vaginosis lends support to this idea. In many cases, the onset of vaginosis is preceded by a large increase in bacterial diversity levels within the vagina (Lamont et al. 2011).

Although it is difficult to determine how shifts in alpha diversity within human-associated microbial communities may impact human health, we can apply concepts derived from research on plant and animal communities to speculate on possible linkages. In particular, we hypothesize that changes in alpha diversity may impact the stability of human-associated microbial communities and their susceptibility to invasion from microbial pathogens. Ecologists have long hypothesized that biodiversity might relate to these community-level properties of stability and invasibility (Elton 1958, MacArthur 1955). Despite some debate on this topic, there is increasing evidence from research in both terrestrial and aquatic systems that increases in alpha diversity may promote community stability and reduce invasibility. For example, higher alpha diversity tends to decrease the susceptibility of a wide range of ecosystem-level processes to disturbance events or environmental stressors (Cadotte et al. 2008, Cardinale et al. 2011, Hooper et al. 2005). Likewise, more diverse communities may be more resistant to invasion (Ives & Carpenter 2007). However, this is not always the case and ecologists have hypothesized that diverse communities may, in some cases, facilitate invasion by creating more niches than the endemic taxa can fill (Fridley et al. 2007). In addition, environmental conditions that favor highly diverse communities could also favor colonization by invasive taxa (Stohlgren et al. 2003). Still, a review of studies investigating links between plant community diversity and invasion found that higher alpha diversity was typically correlated with the reduced invasibility of communities at more local scales (Stohlgren et al. 2003).

There is some evidence that, within the human microbiome, more diverse communities may be less prone to microbial invaders. Blaser & Falkow (2009) have suggested that decreases in microbial diversity could create niches for microbial invaders including human pathogens. For example, antibiotic treatments typically reduce bacterial species richness, which may open up niches for pathogens such as *C. difficile* in the human gut (McFarland 2008) and *Pseudomonas aeruginosa* in the pulmonary tract (Flanagan et al. 2007). Unfortunately, we are not aware of any empirical studies that directly demonstrate a link between an increase, or decrease, in microbiome diversity and the onset of a disease in humans. Similarly, there is a dearth of empirical data indicating whether people with high or low diversity microbiomes are more prone or resistant to disease, although there is some evidence suggesting that such relationships may exist (Chang et al. 2008, Mazmanian et al. 2008, Packey & Sartor 2009).

5. BETA DIVERSITY IN THE HUMAN MICROBIOME

The human microbiome is frequently characterized as having high beta diversity, defined as the taxonomic or phylogenetic difference in community composition between samples [see Anderson et al. (2011) and Graham & Fine (2008) for an overview of the various beta diversity metrics]. Recent high-throughput studies reveal that even within a given body habitat, any pair of individuals share remarkably few bacterial taxa. For example, though the composition of gut microbial communities is more similar between family members than unrelated individuals, the relative abundances of the taxa found within the communities of family members can still vary by two orders of magnitude (Turnbaugh et al. 2009a). In addition, less than 30% of the microbial taxa

sampled daily from specific habitats in a person's body were consistent community members in that body habitat over one month; after 120 days, less than 10% were consistent members (Caporaso et al. 2011). Although it is not a surprise that different body habitats harbor distinct bacterial communities (Costello et al. 2009), it is worth noting that the variability in bacterial communities across skin sites on one person, for example, exceeds the variability in community composition for a given skin location between individuals (Costello et al. 2009, Grice et al. 2009). All of this evidence suggests that at the finer levels of taxonomic resolution, a "core microbiome" (sensu Turnbaugh et al. 2007) is not likely to exist. Thus, one of the central questions in human microbiome research is: What mechanisms are responsible for these differences in the composition of human-associated microbial communities? As noted above, there is a long list of factors that can influence species diversity and cause high levels of beta diversity. For simplicity, we focus on niche and neutral theories that provide opposing explanations for beta diversity within and between individuals.

5.1. Niche Processes in the Human Microbiome

The majority of human microbiome studies conducted to date have focused on the role of niche processes in shaping beta diversity patterns. The niche perspective stresses the roles of environmental variables in driving patterns in community assembly and diversity. In fact, many human microbiome studies have found evidence supporting the role of niche-based processes in explaining beta diversity patterns. The significant differences between the microbial community structures of different body habitats provide a compelling example of niche differentiation in human-associated microbial communities (Costello et al. 2009). Within the skin body habitat, differences in microbial community composition are related to moisture content and pH of the skin (Grice et al. 2009). In addition, dietary habits (Ley et al. 2006) and obesity (Turnbaugh et al. 2006) have been shown to be correlated with differences in gut microbial community composition and phylogenetic structure.

However, there are limitations to niche-based approaches in human microbiome research. In most internal body habitats, it is difficult to accurately measure all of the environmental parameters, such as oxygen concentrations or moisture levels, which could be essential for defining microbial niches. Methodological constraints aside, one can imagine the difficulties associated with accurately characterizing the niches within the five to eight meters of the small intestine (for example) given that individual microbes are typically only a few microns in size. In particular, consider the environmental heterogeneity created by changes in the mucosal layers from the duodenum to the ileum, as well as the complexity created by villi and the continual breakdown of contents. For this reason, most studies of the gut rely on fecal samples, which are assumed to be representative of the average microbial community across the myriad of niches in the entire human gut. Consequently, it is not only difficult to determine the strength of niche processes in body habitats, it is also difficult to understand how niches influence the observed levels of beta diversity.

5.2. Neutral Processes in the Human Microbiome

It is possible that stochastic processes may also strongly influence beta diversity patterns in the human microbiome because microorganisms have high dispersal rates onto/into the human body and microbial taxa are subject to rapid evolutionary changes owing to relatively short generation times and horizontal gene transfer. In the neutral theory of biodiversity, interspecific trait differences are assumed irrelevant, and community structures arise via primarily stochastic processes (Hubbell 2001). In brief, neutral theory posits that stochastic extinction, immigration, and

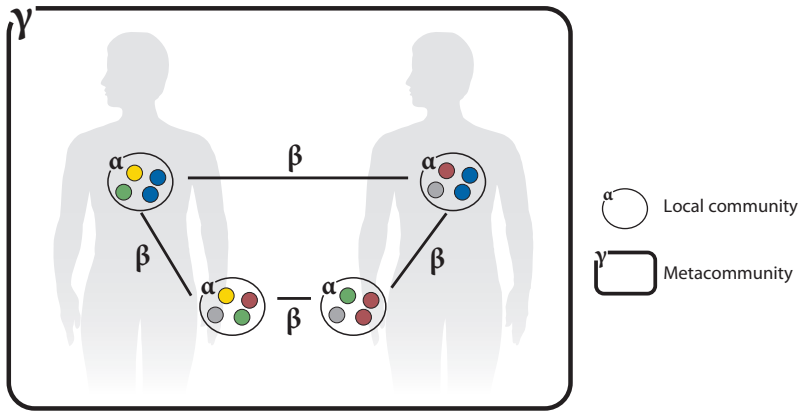

Figure 2

Three levels of diversity as defined by Whittaker et al. (2001) and applied to the human microbiome. Alpha diversity (α) describes the biodiversity found in one sample or a community (e.g., the microbes sampled from the skin on one's palm); beta diversity (β) describes the dissimilarity in communities or samples (e.g., the phylogenetic diversity difference between the group of microbes found on the skin of one's palm and chest, or between the palms of individuals); gamma diversity (γ) is the collective diversity of all samples, i.e., the grouped alpha diversity, (e.g., the total biodiversity found in all skin samples of one or more individuals).

speciation events can explain community composition within or between sites without knowledge of species-level traits. The appeal of these simple models is their parsimony or ability to accurately predict biodiversity while including few parameters or assumptions (e.g., Hubbell 2001). In studies of plants and animals, neutral models, though not always providing the best fit, have been able to predict species abundance curves, species area relationships, and distance-decay patterns across a variety of systems with similar accuracy as niche models that incorporate species-level traits and variability (McGill et al. 2006, Rosindell et al. 2011).

Neutral models pose unique challenges and opportunities in the study of the human microbiome. For example, defining the size and composition of the bacterial source pool (metacommunity; **Figure 2**), as well as determining the dispersal rates within the metacommunity, is conceptually and empirically challenging. Although initial studies have proposed elegant mathematical solutions to these challenges in model-fitting studies (Ofiteru et al. 2010, Sloan et al. 2006), empirical testing and validation of neutral model assumptions in bacterial communities remains difficult. Still, neutral models can be used to generate testable hypotheses of community patterns, which can then help us understand the relative roles of niche versus neutral processes in structuring the human microbiome [see discussions by Ofiteru et al. (2010) and Rosindell et al. (2011)].

Although the exploration of neutral processes in the human microbiome is relatively nascent, stochastic processes do seem to be significant predictors of the bacterial community composition within certain body habitats. For example, dispersal rates and the size of the bacterial source pool have been shown to be important in shaping the relative proportions of bacteria observed in human lungs, but not necessarily of communities found in fecal samples (Sloan et al. 2006). The same processes can also be important in structuring bacterial communities of lake and sewage treatment waters, as shown by theoretical and empirical studies (Lindström & Ostman 2011, Ofiteru et al. 2010). These results show that the influx of bacteria to certain habitats can be high, and stochastic departures and arrivals of bacterial community members can influence the variation observed between human body cavities and between human hosts.

Both niche and neutral processes are likely important for assembling the bacterial communities of humans, a pattern already reported for some plant and animal communities (Chase 2007, Chase & Myers 2011) and microbial communities (Cadotte 2007, Fukami et al. 2007, Zhang et al. 2009). Nevertheless, determining which process is most important under which conditions, or if these processes work simultaneously or conditionally, is imperative for the effective design of more targeted studies. For example, if neutral processes dictate community structure in the microbiome, it is important to empirically test the effect of dispersal rates among communities, as well as to determine the size and diversity of the relevant metacommunity. Alternatively, where niche processes are most important, research should focus on measuring community structure in response to variation in local environments and processes, as well as focusing on the role of interspecific and intraspecific trait variation in coexistence and community structuring (e.g., Clark et al. 2010). Finally, determining the relative strength of niche and neutral processes across spatial and temporal scales in the human microbiome is necessary in order to disentangle the effects of deterministic and stochastic processes on beta diversity. Considering beta diversity in the context of niche and neutral processes is particularly important for understanding how the microbiome responds to, and recovers from, disturbances. Also, we can use both niche and neutral approaches to refine our understanding of how community assembly in the microbiome is influenced by environmental heterogeneity and competition/facilitation, factors long considered by community ecologists and covered in greater detail below.

6. SUCCESSION AND DISTURBANCE

As with all biological communities, the composition and structure of the human microbiome is not static. The types of changes observed in the human microbiome can vary from small fluctuations around a relatively stable microbial community to complete shifts in community membership to alternate stable states. Furthermore, these variations in microbial community structure can occur over timescales ranging from hours to decades. Although some of the changes observed in the human microbiome occur during specific life stages and are thus predictable, other shifts are seemingly random or are triggered by specific disturbance events. In these regards, concepts borrowed from community ecology, such as succession and the temporal stability in community structure, may offer insights into the factors driving the temporal variability within the human microbiome.

Microbial colonization of the human body begins at birth, and delivery mode largely determines the pioneer colonizers (Dominguez-Bello et al. 2010). For example, the different body habitats of babies born vaginally are first colonized by *Lactobacillus* and *Prevotella* species originating from the mother's vagina. In contrast, babies born via Cesarean-section (C-section) are first colonized by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* species that originate from human skin. Interestingly, the pioneer microbiota of C-section babies differ from the skin communities of their mother, suggesting that these skin-associated taxa came from other people (nurses, doctors, the father) or from surfaces that the babies contact shortly after being born (Dominguez-Bello et al. 2010). These differences in initial colonization have a lasting effect on community composition as the intestinal microbiota of C-section babies remains distinct from vaginally delivered babies several months after birth (reviewed by Dominguez-Bello et al. 2011). This phenomenon is conceptually similar to the "priority effect" observed in other types of communities (Fukami & Nakajima 2011) and may be partially responsible for the higher occurrence of certain atopic diseases later in life. For example, the human microbiome can train the immune system to respond to various pathogens (Björkstén 2004), possibly contributing to the increased susceptibility of babies born via C-section to the development of allergies and asthma later in life (Salam et al. 2006).

Following initial colonization, our microbial communities continue to develop and diversify through the first couple of years of life (reviewed by Dominguez-Bello et al. 2011). During this life stage, bacterial communities change rapidly in response to our environment, health, and diet (Spor et al. 2011). For example, the intestinal community of an infant can switch from an *Actinobacteria*- and *Proteobacteria*-dominated community to an adult-like state dominated by *Firmicutes* and *Bacteroidetes* upon the introduction of plant-derived foods like peas (Koenig et al. 2011). Adolescents have distinct distal colon microbiota from adults (Agans et al. 2011), and shifts in the composition of the oral microbiota have been associated with the development of secondary sexual characteristics during puberty (Gusberti et al. 1990). This evidence indicates that some microbial communities undergo succession in concert with the developmental stages of the human host.

Until recently, there was a general consensus that healthy adults harbored a relatively stable, climax microbiome. Stability, however, is a relative term and means different things depending on the body habitat in question and the age of the individual. Furthermore, there is little empirical data to support this consensus, as only a few studies have examined temporal variability in the microbiome associated with healthy adults (e.g., Caporaso et al. 2011, Costello et al. 2009, Grice et al. 2009). From these studies, it is apparent that the adult microbiome is in a constant state of flux as microbial community composition on and in an individual varies substantially over time. Moreover, our body habitats exhibit differing degrees of variability; skin is the most variable, whereas the mouth appears to be the least variable (Caporaso et al. 2011). The differing degrees of variability observed across body habitats is likely dependent on a wide range of factors including the stability of environmental conditions, the turnover rate of the community, and the immigration rate from external sources. However, intraindividual variation is nearly always less than interindividual variation, and body habitats harbor distinct microbial communities (Caporaso et al. 2011, Costello et al. 2009). So, though there are variations in microbial community composition over time, each body habitat appears to exist in its own stability domain.

Although the healthy human microbiome is temporally variable and animal-associated microbiomes may transition between alternate stable states (Costello et al. 2010, Ravel et al. 2011), variation due to stressors may have detrimental effects on the function of our native microbiome. Stressors such as pathogenic invasions and exposure to broad-spectrum antibiotics (Dethlefsen et al. 2008, Hoffmann et al. 2009) can rapidly and dramatically alter the structure of the human microbiome. The recovery time after removal of the stress can be weeks to months, although evidence suggests that the microbial communities in some body habitats may never return to their prior state (Antonopoulos et al. 2009). In these cases, certain treatment measures, such as cohabitation with healthy individuals or intentional inoculation, may expedite the recovery process (Khoruts et al. 2010). In contrast, there are a wide range of stressors, such as hand washing, teeth brushing, and dieting, that have more transient effects on the skin, mouth, and gut microbiomes, respectively, and the residual populations rapidly recover after removal of the stressor (Fierer et al. 2008, Turnbaugh et al. 2009b).

Generally, the response of microbial communities to perturbations can be characterized by their resistance, resilience, and whether their stable states are changed (Allison & Martiny 2008) (**Figure 3**). Communities that are resistant change composition comparatively little in response to a disturbance. Although specific bacterial populations are resistant to certain disturbances (e.g., antibiotic-resistant taxa), it is likely that community-level resistance is dependent on the severity of the disturbance and is not a defining feature of the human microbiome. Instead, human-associated microbial communities appear to be highly resilient as there are numerous examples of communities either rapidly returning to a state that resembles the predisturbance community or moving to an entirely different stable state following a disturbance. For example, the gut communities of three individuals returned to their initial state after a single treatment with the antibiotic ciprofloxacin

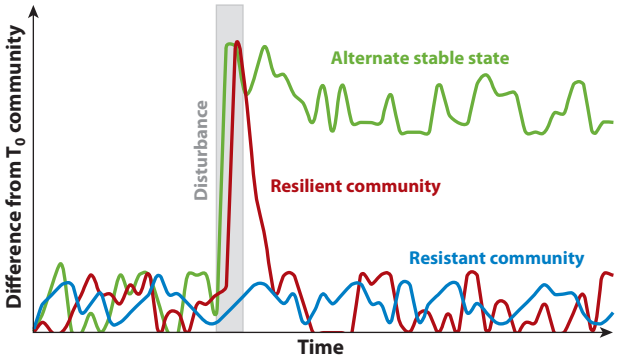

Figure 3

Biological communities respond to disturbances in at least three distinct ways. Resistant communities (*blue*) do not deviate considerably from an initial state following a disturbance. Resilient communities (*red*) deviate considerably but then return to resemble the initial community in time. Finally, communities may respond to a disturbance by moving to an alternate stable state (*green*), where community composition and structure stabilizes in a regime distinct from the initial stable state.

(Dethlefsen & Relman 2011). However, after a second treatment with the antibiotic, the communities stabilized around states different from their preantibiotic state. In this example, the impacts on the health of the hosts after the state change were unknown. However, other studies indicate that alternate states are not always healthy for the host, as illustrated by polymicrobial infections like bacterial vaginosis (Lamont et al. 2011). Moreover, care is needed in determining whether or not a community has entered an alternative stable state. This is because what appears to be an alternative stable state may actually represent an alternative transient state, and the conditions that promote alternative transient states can be different from those that promote alternative stable states (Fukami & Nakajima 2011).

7. MICROBE-MICROBE INTERACTIONS

Microbial diversity and function are driven to a large extent by biotic interactions occurring at the local scale (Lindström & Langenheder 2011). These include interactions between microbial taxa and, in the human microbiome, between microbes and the host. Host-microbe interactions play a significant role in regulating microbial community structure and function, and these relationships are reviewed in detail elsewhere (e.g., Bäckhed et al. 2005). Here we focus on the types of antagonistic and cooperative microbe-microbe interactions that are likely to play an important role in shaping both our health and the structure of our microbiome.

7.1. Antagonistic Interactions

Microbe-microbe competition for limited resources is likely a common occurrence in human-associated body habitats, and such competition may be an important driver of community structure and overall diversity through niche diversification. In the human gut, for example, many microbes are specialists in terms of nutrient sources despite the availability of a wide array of substrates, suggesting that competition for resources may be a strong driver of niche diversification in the gut environment. Studies show that different *Bacteroides* species exhibit corresponding changes in population size with the availability of specific substrates (Sonnenburg et al. 2010), and one study of two *Lactobacillus* strains in the mouse gut showed that resource specialization can allow for

coexistence despite apparent overlap in resource requirements (Tannock et al. 2011). In a unique example, one strain of *Salmonella enterica* has been shown to have evolved a unique capacity to utilize ethanolamine, a byproduct of intestinal inflammation induced by virulence factors secreted by *S. enterica*. By stimulating an inflammation response, *S. enterica* is able to indirectly create a novel niche and thereby avoid competition for more commonly used redox combinations (Thiennimitr et al. 2011).

Microbial diversity within a given community may result from other types of antagonistic interactions besides the direct competition for resources. In the vagina, *Lactobacillus* spp. can lower the pH of the environment, thereby inhibiting the growth of potentially competitive microbes (Lamont et al. 2011). In addition, gut microbiota release molecules that trigger the mounting of antibacterial defenses such as defensins, mucin, and secretory IgA by host cells (Salzman 2011). These types of interactions between microbes and host can benefit both the resident microbiota and the host by protecting against invasive microbes that may compete for resources and/or function as host pathogens.

Predator-prey interactions, which are traditionally a major focus in population and community ecology, are also likely to be important in structuring the human microbiome. Gut microbial studies of predator-prey interactions have typically focused on bacteriophages (i.e., viruses) and their effects on bacterial population structure (Reyes et al. 2010). Viruses fulfill a unique and important role in the microbial trophic system because they can cause high levels of microbial mortality and also may promote horizontal gene transfer between bacterial lineages. New work detailing the effects of the predatory bacteria, such as *Bdellovibrio*-and-like organisms (BALO), in the gut adds yet another layer to our understanding of trophic interactions in the human microbiome. These studies suggest that predatory bacteria could be used in medical treatments to control pathogens in the human body (Schwudke et al. 2001, Van Essche et al. 2011).

7.2. Mutualistic Interactions

Cooperation between microbes is also important in structuring communities in the human microbiome. This is particularly true in the gut where low O_2 conditions promote syntrophic interactions—groups of microorganisms combining metabolic reactions to improve total energy yield (Stams & Plugge 2009). For example, the human gut archaeon *Methanobrevibacter smithii* reduces CO_2 to CH_4 with electrons from H_2 produced by bacteria such as *Bacteroides thetaiotaomicron* (Hansen et al. 2011). Removal of H_2 by *M. smithii* can accelerate *B. thetaiotaomicron* respiration, thereby accelerating the growth rates of both microbes (Samuel & Gordon 2006). Additionally, the augmented *B. thetaiotaomicron* levels lead to increased production of short-chain fatty acids, which can be used as source of nutrition by the human host. Alternatively, gut communities that lack methanogens can instead process excess H_2 through acetogenesis (Rey et al. 2010). In this case the acetogen *Bacteroides hydrogenotrophica* fills the role of H_2 consumer, with similar benefits to both the microbes involved in the syntrophic interaction and the host. More generally, these types of interactions are evidence that certain taxa, even rare taxa, can have effects on the host and on community assembly patterns that may be larger than their relative abundances might suggest.

Microbe-microbe signaling, such as quorum-sensing (QS), also demonstrates the advantage of cooperative behavior. QS is a form of chemical communication between and within species that allows for the coordination of activities according to changes in population density. Through QS, microbes such as *Vibrio cholera*, the bacterium that causes cholera, produce virulence factors and form biofilms at low cell densities, facilitating successful infection of hosts. In contrast, at higher cell densities *V. cholera* show a reduced rate of biofilm formation possibly to improve dispersal following diarrheal events (Hammer & Bassler 2003). Between microbial taxa, QS allows the

peridontal pathogen *Poryphyromonas gingivalis* to colonize the biofilm created by a commensal bacteria, *Streptococcus gordonii* (McNab et al. 2003). In addition, evidence suggests that QS is used to create biofilms between two pathogens, *Pseudomonas aeruginosa* and *Burkholderia cepacia*, that are known to cause complications in cystic fibrosis patients (Riedel et al. 2001).

Overall, bacteria appear to exhibit numerous types of cooperative behaviors, many with significant manifestations at the community level. For example, many bacterial taxa release metabolites into the environment, which help other community members access essential resources such as complex organic compounds and iron (e.g., siderophores) or protect community members against toxic substances. In particular, horizontal gene transfer (HGT) generates unique opportunities for indirect community-level cooperation, including the transfer of novel traits between microbial taxa that may be unrelated. Recent research indicates that the gut bacteria unique to Japanese populations may have acquired novel enzymes for the degradation of porphyran, a chemical in seaweed, from marine bacteria associated with edible seaweed (Hehemann et al. 2010).

As the catalog of uncultured human microbial diversity continues to explode, we are faced with the difficult task of untangling the various interactions between microbes, and between microbes and host physiology, which could involve thousands of microbial taxa. Medical advances, such as the development of antibiotic and therapeutic drugs, have relied on our growing understanding of these relationships (Firn & Jones 2003). However, given the sheer scale and variability of the human microbiome, more research is required to fully understand the underlying interactions that define the human microbiome. Currently, we have the necessary tools for describing taxonomic co-occurrence networks, and these offer starting points for identifying relationships among taxa (e.g., Barberán et al. 2012, Freilich et al. 2010). However, we are only just beginning to resolve the functional components of these networks in the human microbiome, such as pathways of metabolites and trophic levels (levels that are more easily delineated in plant and animal systems). Furthermore, these interactions are difficult to study because they are dynamic; it is likely that multiple interactions occur simultaneously and that the characteristics of the interactions change depending on biotic and abiotic conditions. Also, interaction networks may be challenging to study in microorganisms because characteristics such as QS allow for the ecological attributes of a population (including functional capabilities and gene expression) to change with population density. Given the dynamism of microbial systems, detailed time course analyses will be particularly important to unraveling these webs of interactions. Likewise, integrating culture-based experiments, metabolic modeling, and the experimental manipulation of gnotobiotic communities should help address the knowledge gap between our cataloged microbial diversity and the respective functions of these complex communities.

8. CONCLUSIONS AND FUTURE DIRECTIONS

Our understanding of the ecology of the human microbiome clearly lags behind our understanding of plant and animal ecology. This discrepancy in the maturity of macrobial versus microbial ecology is not surprising—basic surveys of microbial diversity were, until recently, difficult to conduct; the functional attributes of many microbial taxa remain unknown; and the small size of microorganisms makes it inherently problematic to understand microbe-environment and microbe-microbe interactions at the spatial scales relevant to the size of the organisms. Fortunately, these barriers are dissolving as methodologies continue to advance at a rapid pace and as interdisciplinary research groups continue to focus on the human microbiome as a study system.

However, a number of ecological concepts are actually easier to study in microbial systems, like the human microbiome, than in plant or animal communities. Microbial communities are more amenable to experimental manipulations than plant and animal communities, where

generation times are longer and logistical concerns prevent experimentation with large numbers of individuals in well-replicated studies. In addition, just as plant and animal ecologists increasingly incorporate phylogenetic information into models of community assembly and diversity patterns, microbiologists nearly always have such phylogenetic information as a product of the sequence-based diversity surveys, making such analyses even more straightforward. Likewise, with the short generation times of most microbial taxa, evolutionary processes can be directly observed during the course of studies lasting weeks to months, making it possible to assess how evolutionary processes may influence ecological processes and vice versa. Comparable studies in plant or animal communities could take decades or millennia, lengths of time far beyond the duration of most research programs.

As research on the human microbiome is advancing rapidly, it is our hope that this review will soon be rendered out of date. Thus, in lieu of a more formal conclusion, we conclude by highlighting a handful of topics that represent key knowledge gaps. This is not meant to be a comprehensive list, but rather a wish list of future research directions in the field.

- *Interactions between microbial taxa within the human body*. Bacteria, archaea, fungi, microeukaryotes, and viruses all share space within human body habitats, yet most studies focus on individual microbial groups in isolation (often just bacteria). Integrative studies that seek to understand the role of these cross-taxon interactions in shaping the structure and function of the human microbiome will be critical.
- *Moving beyond phylogenetic and taxonomic descriptions of the human microbiome*. Despite the explosion of information on the phylogenetic and taxonomic composition of the human microbiome, we often lack key information on the functional attributes of these communities and the traits of individual community members. In some cases, the phylogenetic structure of microbial communities may predict the functional characteristics of those communities, but this is clearly not true for all functional attributes. The wider application of "-omics"-based approaches (e.g., metabolomics, proteomics), together with more detailed analyses of individual taxa, may help resolve these knowledge gaps and improve our understanding of how the functional characteristics of the human microbiome shift across space and time.
- *Changes in microbial biomass within and between individuals*. Two of the fundamental metrics in community ecology are biomass (or productivity) and diversity. Researchers routinely characterize microbial diversity and changes in the relative abundances of specific microbial taxa, but it is surprisingly difficult to find robust estimates of total microbial abundances across human body habitats and how those abundances vary between individuals and over time. This is of particular importance as some disease states may not necessarily be associated with changes in diversity, but rather with changes in the absolute abundances of specific taxa or total microbial biomass levels.
- *Experimental manipulations of the microbiome*. Controlled experiments are critical for testing concepts in microbial ecology and building a more mechanistic understanding of community assembly within the human microbiome. For example, experimental manipulations could be used to determine how changes in biotic or abiotic conditions alter community composition, the role of niche versus neutral processes in governing community assembly patterns, and the importance of priority effects in diversity changes over time. Although controlled experiments and experimental treatments are logistically difficult to conduct with humans, such experiments could be conducted in model animal systems (e.g., mice) or in vitro using communities and environmental conditions that mimic those found within the human body.
- *Reconciling the disparity in scales*. We typically measure temporal and spatial patterns in microbial communities at scales that are far different from the scales at which microorganisms actually operate. For example, we assess bacterial community composition on skin regions

that are often many square centimeters, yet bacteria are typically less than a few microns in diameter and they often interact with the human host and other microorganisms at spatial scales that are orders of magnitude smaller than the sampled area. Likewise, published studies of how microbial communities change over time have typically looked at patterns across temporal scales (weeks to months to years) that are far longer than the generation time of many microorganisms (hours to days). Although methodologically difficult, characterizing microbial communities and the environmental conditions of microbial habitats at scales that more closely approximate the scales at which they operate will undoubtedly improve our ability to describe and understand the ecology of the human microbiome.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

Agans R, Rigsbee L, Kenche H, Michail S, Khamis HJ, Paliy O. 2011. Distal gut microbiota of adolescent children is different from that of adults. *FEMS Microbiol. Ecol.* 77:404–12

Allison SD, Martiny JB. 2008. Resistance, resilience, and redundancy in microbial communities. *Proc. Natl. Acad. Sci. USA* 105:11512–19

Anderson MJ, Crist TO, Chase JM, Vellend M, Inouye BD, et al. 2011. Navigating the multiple meanings of beta diversity: a roadmap for the practicing ecologist. *Ecol. Lett.* 14:19–28

Antonopoulos DA, Huse SM, Morrison HG, Schmidt TM, Sogin ML, Young VB. 2009. Reproducible community dynamics of the gastrointestinal microbiota following antibiotic perturbation. *Infect. Immun.* 77:2367–75

Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. 2005. Host-bacterial mutualism in the human intestine. *Science* 307:1915–20

Balvanera P, Pfisterer AB, Buchmann N, He JS, Nakashizuka T, et al. 2006. Quantifying the evidence for biodiversity effects on ecosystem functioning and services. *Ecol. Lett.* 9:1146–56

Barberán A, Bates ST, Casamayor EO, Fierer N. 2012. Using network analysis to explore co-occurrence patterns in soil microbial communities. *Int. Soc. Microb. Ecol. J.* 6:343–51

Björkstén B. 2004. Effects of intestinal microflora and the environment on the development of asthma and allergy. *Semin. Immunopathol.* 25:257–70

Blaser MJ, Falkow S. 2009. What are the consequences of the disappearing human microbiota? *Nat. Rev. Microbiol.* 7:887–94

Cadotte MW. 2007. Concurrent niche and neutral processes in the competition-colonization model of species coexistence. *Proc. R. Soc. Lond. Ser. B* 274:2739–44

Cadotte MW, Cardinale BJ, Oakley TH. 2008. Evolutionary history and the effect of biodiversity on plant productivity. *Proc. Natl. Acad. Sci. USA* 105:17012–17

Caporaso JG, Lauber CL, Costello EK, Berg-Lyons D, Gonzalez A, et al. 2011. Moving pictures of the human microbiome. *Genome Biol.* 12:R50

Cardinale BJ, Matulich KL, Hooper DU, Byrnes JE, Duffy E, et al. 2011. The functional role of producer diversity in ecosystems. *Am. J. Bot.* 98:572–92

Chang JY, Antonopoulos DA, Kalra A, Tonelli A, Khalife WT, et al. 2008. Decreased diversity of the fecal microbiome in recurrent *Clostridium difficile*-associated diarrhea. *J. Infect. Dis.* 197:435–38

Charlson ES, Chen J, Custers-Allen R, Bittinger K, Li H, et al. 2010. Disordered microbial communities in the upper respiratory tract of cigarette smokers. *PLoS One* 5:e15216

Chase JM. 2007. Drought mediates the importance of stochastic community assembly. *Proc. Natl. Acad. Sci. USA* 104:17430–34

Chase JM, Myers JA. 2011. Disentangling the importance of ecological niches from stochastic processes across scales. *Proc. R. Soc. Lond. Ser. B* 366:2351–63
Clark JS, Bell D, Chu CJ, Courbaud B, Dietze M, et al. 2010. High-dimensional coexistence based on individual variation: a synthesis of evidence. *Ecol. Monogr.* 80:569–608
Costello EK, Gordon JI, Secor SM, Knight R. 2010. Postprandial remodeling of the gut microbiota in Burmese pythons. *Int. Soc. Microb. Ecol. J.* 4:1375–85
Costello EK, Lauber C, Hamady M, Fierer N, Gordon J, Knight R. 2009. Bacterial community variation in human body habitats across space and time. *Science* 326:1694–97
Dethlefsen L, Huse S, Sogin ML, Relman DA. 2008. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol.* 6:e280
Dethlefsen L, McFall-Ngai M, Relman DA. 2007. An ecological and evolutionary perspective on human-microbe mutualism and disease. *Nature* 449:811–18
Dethlefsen L, Relman DA. 2011. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc. Natl. Acad. Sci. USA* 108(Suppl 1):4554–61
Dicksved J, Lindberg M, Rosenquist M, Enroth H, Jansson JK, Engstrand L. 2009. Molecular characterization of the stomach microbiota in patients with gastric cancer and in controls. *J. Med. Microbiol.* 58:509–16
Dominguez-Bello MG, Blaser MJ, Ley RE, Knight R. 2011. Development of the human gastrointestinal microbiota and insights from high-throughput sequencing. *Gastroenterology* 140:1713–19
Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, et al. 2010. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc. Natl. Acad. Sci. USA* 107:11971–75
Elton C. 1958. *The Ecology of Invasions by Animals and Plants*. London: Methuen
Faith DP, Baker AM. 2006. Phylogenetic diversity (PD) and biodiversity conservation: some bioinformatics challenges. *Evol. Bioinform.* 2:121–28
Fierer N, Hamady M, Lauber C, Knight R. 2008. The influence of sex, handedness, and washing on the diversity of hand surface bacteria. *Proc. Natl. Acad. Sci. USA* 105:17994–99
Firn RD, Jones CG. 2003. Natural products—a simple model to explain chemical diversity. *Nat. Prod. Rep.* 20:382–91
Flanagan JL, Brodie EL, Weng L, Lynch SV, Garcia O, et al. 2007. Loss of bacterial diversity during antibiotic treatment of intubated patients colonized with *Pseudomonas aeruginosa*. *J. Clin. Microbiol.* 45:1954–62
Frank DN, Spiegelman GB, Davis W, Wagner E, Lyons E, Pace NR. 2003. Culture-independent molecular analysis of microbial constituents of the healthy human outer ear. *J. Clin. Microbiol.* 41:295–303
Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. 2007. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc. Natl. Acad. Sci. USA* 104:13780–85
Frank DN, Zhu W, Sartor RB, Li E. 2011. Investigating the biological and clinical significance of human dysbioses. *Trends Microbiol.* 19:427–34
Fredericks DN, Relman DA. 1996. Sequence-based identification of microbial pathogens: a reconsideration of Koch's postulates. *Clin. Microbiol. Rev.* 9:18–33
Freilich S, Kreimer A, Meilijson I, Gophna U, Sharan R, Ruppin E. 2010. The large-scale organization of the bacterial network of ecological co-occurrence interactions. *Nucleic Acids Res.* 38:3857–68
Fridley JD, Stachowicz JJ, Naeem S, Sax DF, Seabloom EW, et al. 2007. The invasion paradox: reconciling pattern and process in species invasions. *Ecology* 88:3–17
Fukami T, Beaumont HJE, Zhang XX, Rainey PB. 2007. Immigration history controls diversification in experimental adaptive radiation. *Nature* 446:436–439
Fukami T, Nakajima M. 2011. Community assembly: alternative stable states or alternative transient states? *Ecol. Lett.* 14:973–84
Gill SR, Pop M, Deboy RT, Eckburg PB, Turnbaugh PJ, et al. 2006. Metagenomic analysis of the human distal gut microbiome. *Science* 312:1355–59
Gonzalez A, Clemente JC, Shade A, Metcalf JL, Song S, et al. 2011. Our microbial selves: what ecology can teach us. *EMBO Rep.* 12:775–84
Graham CH, Fine PV. 2008. Phylogenetic beta diversity: linking ecological and evolutionary processes across space in time. *Ecol. Lett.* 11:1265–77

Grice EA, Kong HH, Conlan S, Deming CB, Davis J, et al. 2009. Topographical and temporal diversity of the human skin microbiome. *Science* 324:1190–92
Gusberti FA, Mombelli A, Lang NP, Minder CE. 1990. Changes in subgingival microbiota during puberty. A 4-year longitudinal study. *J. Clin. Periodontol.* 17:685–92
Hamady M, Knight R. 2009. Microbial community profiling for human microbiome projects: tools, techniques, and challenges. *Genome Res.* 19:1141–52
Hammer BK, Bassler BL. 2003. Quorum sensing controls biofilm formation in *Vibrio cholerae*. *Mol. Microbiol.* 50:101–4
Hansen EE, Lozupone CA, Rey FE, Wu M, Guruge JL, et al. 2011. Pan-genome of the dominant human gut-associated archaeon, *Methanobrevibacter smithii*, studied in twins. *Proc. Natl. Acad. Sci. USA* 108:4599–606
Harrison F. 2007. Microbial ecology of the cystic fibrosis lung. *Microbiology* 153:917–23
Hayashi H, Takahashi R, Nishi T, Sakamoto M, Benno Y. 2005. Molecular analysis of jejunal, ileal, caecal and recto-sigmoidal human colonic microbiota using 16S rRNA gene libraries and terminal restriction fragment length polymorphism. *J. Med. Microbiol.* 54:1093–101
Hehemann JH, Correc G, Barbeyron T, Helbert W, Czjzek M, Michel G. 2010. Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. *Nature* 464:908–12
Hoffmann C, Hill DA, Minkah N, Kirn T, Troy A, et al. 2009. Community-wide response of the gut microbiota to enteropathogenic *Citrobacter rodentium* infection revealed by deep sequencing. *Infect. Immunol.* 77:4668–78
Hooper DU, Chapin FS, Ewel JJ, Hector A, Inchausti P, et al. 2005. Effects of biodiversity on ecosystem functioning: a consensus of current knowledge. *Ecol. Monogr.* 75:3–35
Hubbell S. 2001. *The Unified Neutral Theory of Biodiversity and Biogeography*. Princeton, NJ: Princeton Univ. Press
Hudson PJ, Dobson AP, Lafferty KD. 2006. Is a healthy ecosystem one that is rich in parasites? *Trends Ecol. Evol.* 21:381–85
Ives AR, Carpenter SR. 2007. Stability and diversity of ecosystems. *Science* 317:58–62
Jenkinson H. 2011. Beyond the oral microbiome. *Environ. Microbiol.* 13:3077–87
Khoruts A, Dicksved J, Jansson JK, Sadowsky MJ. 2010. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent *Clostridium difficile*-associated diarrhea. *J. Clin. Gastroenterol.* 44:354–60
Kim TK, Thomas SM, Ho M, Sharma S, Reich CI, et al. 2009. Heterogeneity of vaginal microbial communities within individuals. *J. Clin. Microbiol.* 47:1181–89
Koenig JE, Spor A, Scalfone N, Fricker AD, Stombaugh J, et al. 2011. Succession of microbial consortia in the developing infant gut microbiome. *Proc. Natl. Acad. Sci. USA* 108:4578–85
Kuczynski J, Lauber CL, Walters WA, Parfrey LW, Clemente J, et al. 2012. Experimental and analytical tools for studying the human microbiome. *Nat. Rev. Genet.* 13:47–58
Lamont RF, Sobel JD, Akins RA, Hassan SS, Chaiworapongsa T, et al. 2011. The vaginal microbiome: new information about genital tract flora using molecular based techniques. *Br. J. Obstet. Gynaecolog.* 118:533–49
Ley RE, Turnbaugh PJ, Klein S, Gordon JI. 2006. Microbial ecology: human gut microbes associated with obesity. *Nature* 444:1022–23
Lindström ES, Langenheder S. 2011. Local and regional factors influencing bacterial community assembly. *Environ. Microbiol. Rep.* 4:1–9
Lindström ES, Ostman O. 2011. The importance of dispersal for bacterial community composition and functioning. *PLoS One* 6:e25883
Loreau M, Naeem S, Inchausti P, Bengtsson J, Grime JP, et al. 2001. Biodiversity and ecosystem functioning: current knowledge and future challenges. *Science* 294:804–8
Macarthur R. 1955. Fluctuations of animal populations, and a measure of community stability. *Ecology* 36:533–36
Manichanh C, Rigottier-Gois L, Bonnaud E, Gloux K, Pelletier E, et al. 2006. Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. *Gut* 55:205–11
Mazmanian SK, Round JL, Kasper DL. 2008. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature* 453:620–25

McFarland LV. 2008. Update on the changing epidemiology of *Clostridium difficile*-associated disease. *Nat. Clin. Pract. Gastroenterol. Hepatol.* 5:40–48
McGill BJ, Maurer BA, Weiser MD. 2006. Empirical evaluation of neutral theory. *Ecology* 87:1411–23
McNab R, Ford SK, El-Sabaeny A, Barbieri B, Cook GS, Lamont RJ. 2003. LuxS-based signaling in *Streptococcus gordonii*: autoinducer 2 controls carbohydrate metabolism and biofilm formation with *Porphyromonas gingivalis*. *J. Bacteriol.* 185:274–84
Minot S, Sinha R, Chen J, Li H, Keilbaugh SA, et al. 2011. The human gut virome: inter-individual variation and dynamic response to diet. *Genome Res.* 21:1616–25
Ofiteru ID, Lunn M, Curtis TP, Wells GF, Criddle CS, et al. 2010. Combined niche and neutral effects in a microbial wastewater treatment community. *Proc. Natl. Acad. Sci. USA* 107:15345–50
Pace NR. 1997. A molecular view of microbial diversity and the biosphere. *Science* 276:734–39
Packey CD, Sartor RB. 2009. Commensal bacteria, traditional and opportunistic pathogens, dysbiosis and bacterial killing in inflammatory bowel diseases. *Curr. Opin. Infect. Dis.* 22:292–301
Pei Z, Bini EJ, Yang L, Zhou M, Francois F, Blaser MJ. 2004. Bacterial biota in the human distal esophagus. *Proc. Natl. Acad. Sci. USA* 101:4250–55
Petchey OL, Gaston KJ. 2007. Dendrograms and measuring functional diversity. *Oikos* 116:1422–26
Pflughoeft KJ, Versalovic J. 2011. Human microbiome in health and disease. *Annu. Rev. Pathol. Mech. Dis.* 7:99–122
Price LB, Liu CM, Johnson KE, Aziz M, Lau MK, et al. 2010. The effects of circumcision on the penis microbiome. *PLoS One* 5:e8422
Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, et al. 2010. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 464:59–65
Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SS, et al. 2011. Vaginal microbiome of reproductive-age women. *Proc. Natl. Acad. Sci. USA* 108(Suppl 1):4680–87
Rey FE, Faith JJ, Bain J, Muehlbauer MJ, Stevens RD, et al. 2010. Dissecting the in vivo metabolic potential of two human gut acetogens. *J. Biol. Chem.* 285:22082–90
Reyes A, Haynes M, Hanson N, Angly FE, Heath AC, et al. 2010. Viruses in the faecal microbiota of monozygotic twins and their mothers. *Nature* 466:334–38
Ricklefs R, Schluter D. 1993. *Species Diversity in Space and Time*. Cambridge, UK: Cambridge Univ. Press
Riedel K, Hentzer M, Geisenberger O, Huber B, Steidle A, et al. 2001. N-acylhomoserine-lactone-mediated communication between *Pseudomonas aeruginosa* and *Burkholderia cepacia* in mixed biofilms. *Microbiology* 147:3249–62
Robinson CJ, Bohannan BJ, Young VB. 2010. From structure to function: the ecology of host-associated microbial communities. *Microbiol. Mol. Biol. Rev.* 74:453–76
Rosenzweig M. 1995. *Species Diversity in Space and Time*. Cambridge, UK: Cambridge Univ. Press
Rosindell J, Hubbell SP, Etienne RS. 2011. The unified neutral theory of biodiversity and biogeography at age ten. *Trends Ecol. Evol.* 26:340–48
Salam MT, Margolis HG, McConnell R, McGregor JA, Avol EL, Gilliland FD. 2006. Mode of delivery is associated with asthma and allergy occurrences in children. *Ann. Epidemiol.* 16:341–46
Salzman NH. 2011. Microbiota-immune system interaction: an uneasy alliance. *Curr. Opin. Microbiol.* 14:99–105
Samuel BS, Gordon JI. 2006. A humanized gnotobiotic mouse model of host-archaeal-bacterial mutualism. *Proc. Natl. Acad. Sci. USA* 103:10011–16
Savage DC. 1977. Microbial ecology of the gastrointestinal tract. *Annu. Rev. Microbiol.* 31:107–33
Schwudke D, Strauch E, Krueger M, Appel B. 2001. Taxonomic studies of predatory bdellovibrios based on 16S rRNA analysis, ribotyping and the hit locus and characterization of isolates from the gut of animals. *Syst. Appl. Microbiol.* 24:385–94
Sloan WT, Lunn M, Woodcock S, Head IM, Nee S, Curtis TP. 2006. Quantifying the roles of immigration and chance in shaping prokaryote community structure. *Environ. Microbiol.* 8:732–40
Sonnenburg ED, Zheng H, Joglekar P, Higginbottom SK, Firbank SJ, et al. 2010. Specificity of polysaccharide use in intestinal bacteroides species determines diet-induced microbiota alterations. *Cell* 141:1241–52
Spor A, Koren O, Ley R. 2011. Unravelling the effects of the environment and host genotype on the gut microbiome. *Nat. Rev. Microbiol.* 9:279–90

Stams AJ, Plugge CM. 2009. Electron transfer in syntrophic communities of anaerobic bacteria and archaea. *Nat. Rev. Microbiol.* 7:568–77

Stohlgren TJ, Barnett DT, Kartesz J. 2003. The rich get richer: patterns of plant invasions in the United States. *Front. Ecol. Environ.* 1:11–14

Tannock GW, Wilson CM, Loach D, Cook GM, Eason J, et al. 2011. Resource partitioning in relation to cohabitation of *Lactobacillus* species in the mouse forestomach. *Int. Soc. Microb. Ecol. J.* 6:927–38

Thiennimitr P, Winter SE, Winter MG, Xavier MN, Tolstikov V, et al. 2011. Intestinal inflammation allows *Salmonella* to use ethanolamine to compete with the microbiota. *Proc. Natl. Acad. Sci. USA* 108:17480–85

Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, et al. 2009a. A core gut microbiome in obese and lean twins. *Nature* 457:480–84

Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. 2007. The human microbiome project. *Nature* 449:804–10

Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444:1027–31

Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. 2009b. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Sci. Transl. Med.* 1:6ra14

Van Essche M, Quirynen M, Sliepen I, Loozen G, Boon N, et al. 2011. Killing of anaerobic pathogens by predatory bacteria. *Mol. Oral Microbiol.* 26:52–61

Whittaker RJ, Willis KJ, Field R. 2001. Scale and species richness: towards a general, hierarchical theory of species diversity. *J. Biogeogr.* 28:453–70

Zhang QG, Buckling A, Godfray HCJ. 2009. Quantifying the relative importance of niches and neutrality for coexistence in a model microbial system. *Funct. Ecol.* 23:1139–47

Zhi XY, Zhao W, Li WJ, Zhao GP. 2012. Prokaryotic systematics in the genomics era. *Antonie Van Leeuwenhoek* 101:21–34

Annual Review of Ecology, Evolution, and Systematics

Volume 43, 2012

Contents

Scalingy Up in Ecology: Mechanistic Approaches
Mark Denny and Lisandro Benedetti-Cecchi 1

Adaptive Genetic Variation on the Landscape: Methods and Cases
Sean D. Schoville, Aurélie Bonin, Olivier François, Stéphane Lobreaux, Christelle Melodelima, and Stéphanie Manel 23

Endogenous Plant Cell Wall Digestion: A Key Mechanism in Insect Evolution
Nancy Calderón-Cortés, Mauricio Quesada, Hirofumi Watanabe, Horacio Cano-Camacho, and Ken Oyama 45

New Insights into Pelagic Migrations: Implications for Ecology and Conservation
Daniel P. Costa, Greg A. Breed, and Patrick W. Robinson 73

The Biogeography of Marine Invertebrate Life Histories
Dustin J. Marshall, Patrick J. Krug, Elena K. Kupriyanova, Maria Byrne, and Richard B. Emlet 97

Mutation Load: The Fitness of Individuals in Populations Where Deleterious Alleles Are Abunduant
Aneil F. Agrawal and Michael C. Whitlock 115

From Animalcules to an Ecosystem: Application of Ecological Concepts to the Human Microbiome
Noah Fierer, Scott Ferrenberg, Gilberto E. Flores, Antonio González, Jordan Kueneman, Teresa Legg, Ryan C. Lynch, Daniel McDonald, Joseph R. Mihaljevic, Sean P. O'Neill, Matthew E. Rhodes, Se Jin Song, and William A. Walters 137

Effects of Host Diversity on Infectious Disease
Richard S. Ostfeld and Felicia Keesing 157

Coextinction and Persistence of Dependent Species in a Changing World
Robert K. Colwell, Robert R. Dunn, and Nyeema C. Harris 183

Functional and Phylogenetic Approaches to Forecasting Species' Responses to Climate Change
Lauren B. Buckley and Joel G. Kingsolver 205

Rethinking Community Assembly through the Lens of Coexistence Theory
J. HilleRisLambers, P.B. Adler, W.S. Harpole, J.M. Levine, and M.M. Mayfield 227

The Role of Mountain Ranges in the Diversification of Birds
Jon Fjeldså, Rauri C.K. Bowie, and Carsten Rahbek 249

Evolutionary Inferences from Phylogenies: A Review of Methods
Brian C. O'Meara 267

A Guide to Sexual Selection Theory
Bram Kuijper, Ido Pen, and Franz J. Weissing 287

Ecoenzymatic Stoichiometry and Ecological Theory
Robert L. Sinsabaugh and Jennifer J. Follstad Shah 313

Origins of New Genes and Evolution of Their Novel Functions
Yun Ding, Qi Zhou, and Wen Wang 345

Climate Change, Aboveground-Belowground Interactions, and Species' Range Shifts
Wim H. Van der Putten 365

Inflammation: Mechanisms, Costs, and Natural Variation
Noah T. Ashley, Zachary M. Weil, and Randy J. Nelson 385

New Pathways and Processes in the Global Nitrogen Cycle
Bo Thamdrup 407

Beyond the Plankton Ecology Groug (PEG) Model: Mechanisms Driving Plankton Succession
Ulrich Sommer, Rita Adrian, Lisette De Senerpont Domis, James J. Elser, Ursula Gaedke, Bas Ibelings, Erik Jeppesen, Miquel Lürling, Juan Carlos Molinero, Wolf M. Mooij, Ellen van Donk, and Monika Winder 429

Global Introductions of Crayfishes: Evaluating the Impact of Species Invasions on Ecosystem Services
David M. Lodge, Andrew Deines, Francesca Gherardi, Darren C.J. Yeo, Tracy Arcella, Ashley K. Baldridge, Matthew A. Barnes, W. Lindsay Chadderton, Jeffrey L. Feder, Crysta A. Gantz, Geoffrey W. Howard, Christopher L. Jerde, Brett W. Peters, Jody A. Peters, Lindsey W. Sargent, Cameron R. Turner, Marion E. Wittmann, and Yiwen Zeng 449

Indexes

Cumulative Index of Contributing Authors, Volumes 39–43 473

Cumulative Index of Chapter Titles, Volumes 39–43 477

Errata

An online log of corrections to *Annual Review of Ecology, Evolution, and Systematics* articles may be found at http://ecolsys.annualreviews.org/errata.shtml