PERSPECTIVE
https://doi.org/10.1038/s41559-017-0340-2
nature ecology & evolution

The microbiome beyond the horizon of ecological and evolutionary theory

Britt Koskella[1]*, Lindsay J. Hall[2] and C. Jessica E. Metcalf[3]

The ecological and evolutionary study of community formation, diversity, and stability is rooted in general theory and reinforced by decades of system-specific empirical work. Deploying these ideas to study the assembly, complexity, and dynamics of microbial communities living in and on eukaryotes has proved seductive, but challenging. The success of this research endeavour depends on our capacity to observe and characterize the distributions, abundances, and functional traits of microbiota, representing an array of technical and analytical challenges. Furthermore, a number of unique characteristics of microbial species, such as horizontal gene transfer, the production of public goods, toxin and antibiotic production, rapid evolution, and feedbacks between the microbiome and its host, are not easily accommodated by current ecological and evolutionary theory. Here we highlight potential pitfalls in the application of existing theoretical tools without careful consideration of the unique complexities of the microbiome, focusing particularly on the issue of human health, and anchoring our discussion in existing empirical evidence.

A running theme across biological fields is the importance of interactions among species; whether it be human health in the face of pathogens, the disturbance of delicate ecosystems by invasive species, or the shaping of carbon cycles via microbial communities, it is clear that the biology of an individual species cannot be understood in isolation. The last decade has uncovered a further revelation: that the abundant and diverse microbial communities living in and on eukaryotic hosts are of paramount importance to the organismal phenotype, influencing everything from pathogen susceptibility[1] and autoimmunity[2], to nutrient acquisition and metabolism[3], range expansion, and an organism's ability to cope with stressful environments[4]. Owing to this far-reaching significance, scientists from across disciplines have converged on the pressing need to better understand both how the microbiome is formed and its role in shaping host phenotype, ecology, and evolution.

This flurry of research into the microbiome began with the ability to move beyond describing only culturable species to the culture-independent characterization from next-generation sequencing and metagenomic techniques. However, this sequence-based approach has come with its own unique set of challenges; for example, our ability to describe members of a microbial community based on their sequence identity remains limited by the vast number of uncharacterized species, and reliance on the highly conserved 16S rRNA gene to group taxa, which lacks resolution particularly when using short-read sequences, can be inconsistent with previous bacterial taxonomies[5]. Comparing across studies, or running meta-analyses, is further complicated by discrepancies among results obtained depending on the methods used, including DNA extraction and library preparation methods, issues with contamination, short- versus long-read sequencing technologies, and data standardization[6].

Partly as a result of the unresolved nature of microbiome composition and microbiota species identities, there has been a recent move away from describing 'who' is there towards determining what they are doing, driven by new bioinformatical and '-omic' approaches, such as metatranscriptomics and metabolomics (Fig. 1). The extreme end of the functional characterization approach is to shift focus from the organisms making up the microbiota (community composition) to the genes making up the microbiome (community function). This approach has a number of advantages — for example it is not plagued by issues of horizontal gene transfer (see Box 1 for a glossary of commonly used terminology) among species or taxonomic resolution — but is currently hindered by a basic lack of functional characterization for most microbial genes. Furthermore, such metagenomic and metatranscriptomic datasets are not easily interpreted in terms of classical community ecology.

Because the field is moving so rapidly, and data is accumulating on an unprecedented scale, the development of microbiome-specific hypotheses and predictions stemming from theory is lagging far behind the empirical work. Many studies circumvent this lack of specific theory through the incorporation of classic theories in evolution and ecology, and a number of excellent reviews have discussed how this might be done[1,7,8]. However, there are aspects of the microbiome, and host–microbiome association, that are quite distinct from other communities (including free-living microbial communities; Table 1). Ecological and evolutionary theory was broadly developed in contexts defined by higher eukaryotic communities, and contrasting features associated with free-living microbial communities (where a plethora of previous research lies) may be one avenue to disentangling the importance of particular features (such as small genome size, seasonality) and one window onto how these shifting contexts alter the application of theory. An open question in the field is therefore how these unique properties might impede the application of current ecological and evolutionary theory to decoding the complexity of microbiome establishment and dynamics (Fig. 2). In this Perspective, we emphasize the limitations of current ecological and evolutionary theory, including microbial and disease ecology, when applied to these remarkable microbial communities. We organize our ideas around four main themes:

[1]Department of Integrative Biology, University of California, Berkeley, CA 94720, USA. [2]The Gut Health and Food Safety Programme, Quadram Institute Bioscience, Norwich Research Park, Norwich NR4 7UA, UK. [3]Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08450, USA. *e-mail: bkoskella@berkeley.edu

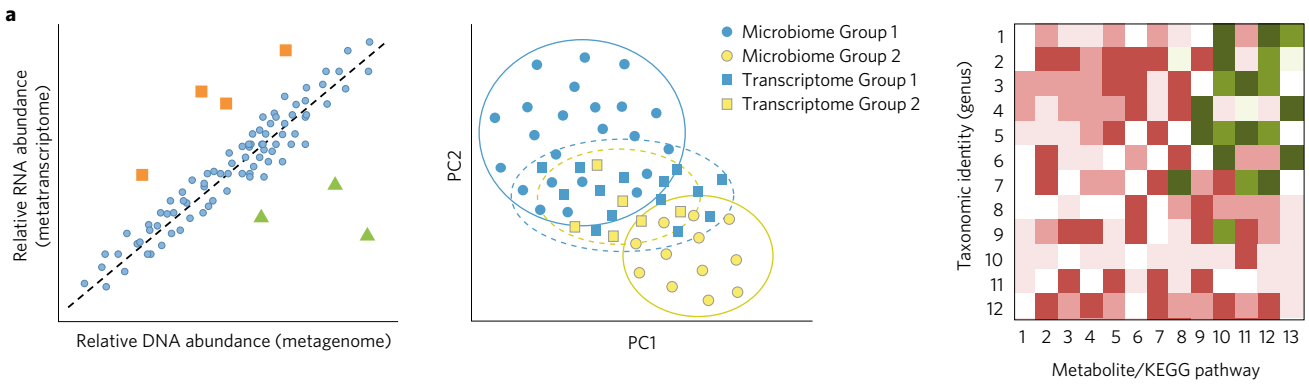

Fig. 1 | Illustration of the various -omics approaches and the advantages of combining methods to understand microbiome function. a, Comparing metagenomic and metatranscriptomic profiles allows researchers to contrast who is there (based on DNA sequence data) with what they are doing (using RNA transcript data). This approach can pinpoint genes/pathways that are overexpressed relative to expectations, as represented by the orange squares, and therefore highlight the potential importance within the host environment. Similarly, this comparison can uncover genes/pathways that are underexpressed relative to their sequence abundance, as represented by the green triangles, highlighting functions that are of lesser importance within the host. **b**, Functional redundancy among microbiomes can be uncovered by contrasting (dis)similarity among host microbiota composition with (dis)similarity among the metabolic potentials encoded by each community. This can be done, for example, by comparing Bray–Curtis dissimilarity scores for community taxonomic composition (β diversity; circles) with functional diversity (squares; illustrated together for ease of comparison) to test whether the latter is reduced relative to the former, indicative of functional redundancy, and/or whether the two metrics offer different results when comparing two groups of hosts, such as healthy and diseased individuals (represented here with blue and yellow). **c**, Correlation analyses of microbiome and metabolome data allow associations to be measured between particular taxa (genus, for example) and known metabolites or metabolic pathways. The heat map illustrates possible positive (red) and negative (green) associations.

Table 1 | Potential differences among higher eukaryotic, freeliving microbial, and host-associated microbiome communities

	Higher eukaryotic communities	Free-living microbial communities	Host-associated microbiomes[a]
Timescale of assembly	Ecological	Ecological and evolutionary	Ecological and evolutionary
Importance of neutral processes	Debated	High	Low
Species–function relationship	Typically clear	Mostly clear	Less clear
Functional redundancies	Low	Unknown	High
Genome sizes	Large	Small	Small
Generation times	Long	Short	Short
Biotic selection pressures	Competition, predation, parasitism	Competition, predation, parasitism	Competition, predation, parasitism, host defenses
Horizontal gene transfer	Rare	Less rare	Common
Production of public goods	Rare	Common	Common
Ecosystem engineering	Rare	Common	Very common
Density dependence	More negative	Both	More positive
Host control			Yes
Immigration rates	Low to high	Typically high	Mostly low, once established[b]
Seasonality	Weak (animals) to strong (plants)	Strong	Weak
Transmission			Vertical or horizontal
Community longevity	Unlimited	From seasonal to unlimited	Dependent on host lifespan

[a]Note that relative differences are mostly speculative and require direct empirical comparisons. There may also be other contexts that could be leveraged, such as existence of complex communities of parasites. [b]This is likely to be highly variable across body sites.

the issue of timescales, the question of identity, the mechanisms of heredity, and the control of microbiota by the host. We focus primarily on the human bacterial microbiome, as this is where the majority of microbiome work has thus far been concentrated, but emphasize the importance of looking across systems and the development of new model approaches in the Supplementary Information (see Supplementary Table 1 for examples of model systems that are proving particularly useful, and Supplementary Table 2 for examples of key approaches).

A mishmash of timescales

Many species that comprise the microbiome are characterized by short generation times and small genomes. As a result, community processes that are typically grounded in ecology (changes in the abundance of individuals through time) have increasing overlap with evolution (changes in gene frequencies over time) for microbiome communities[9]. This raises a number of discordances relative to theory developed for eukaryotic systems. For example, succession is frequently invoked in microbiome research to describe processes

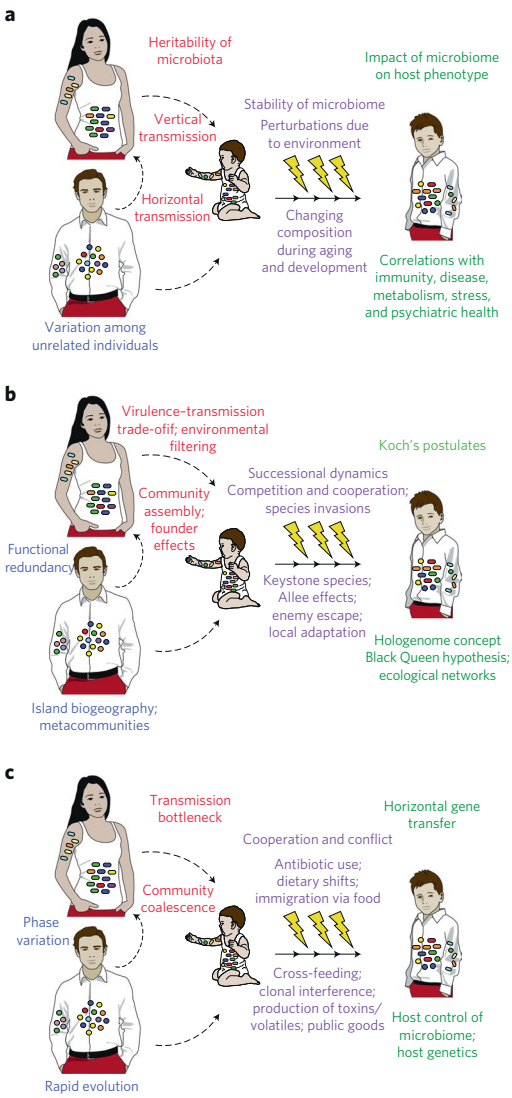

Fig. 2 | Evolutionary and ecological principles influencing microbiome establishment, stability, and transmission among generations. a, The observed patterns in microbiome variability (with similar or different species present on different individuals; blue text) must emerge from transmission of microbes (that is, either horizontally, from unrelated individuals or the environment, or vertically, from related individuals; red text), and will be shaped by the microbiome's stability (affected by perturbations associated with the environment and from features of the host such as aging or changes in diet; purple text) and may impact on host phenotype (obesity or disease susceptibility, for example; green text). **b**, The ecological and evolutionary theories and approaches that have or could be used to shed insight on these observations are shown, ranging from the virulence transmission trade-off from disease ecology (species that grow to higher within-host densities may have higher transmission probabilities) to the notion of environmental filtering (species can only colonize areas that meet required environmental conditions) and metapopulation theory; the variety of theories that tackle drivers of community stability (local adaptation and so on; see the main text and glossary in Box 1) to theories tackling emergent properties of the host–microbiome coevolution (for example, the Black Queen hypothesis). **c**, The characteristics of host-associated microbial communities that make them unique relative to either eukaryotic communities or, in some cases, free-living microbial communities are shown. These characteristics might therefore limit the direct application of existing conceptual frameworks including rapid evolution, the potential for whole communities to suddenly interact (community coalescence), the unique types of disturbances (such as dietary changes), interactions between species (cross-feeding) and more, see main text.

that occur during infant development[10–12], after disturbance events such as a course of antibiotics[13], routine tooth-cleaning[14], or following the arrival of a pathogen such as *Vibrio cholerae*[15]. However, short generation times and small genomes make de novo mutation, which is broadly ignored for eukaryotic systems, a potentially important source of variation during colonization and succession in the microbiome. Experimental transplantation of microbiota from various sources into gnotobiotic mice uncovered rapid adaptation in response to the host environment, especially for more 'foreign' microbiota, such as those from soil, microbial mats, or termite guts, relative to mouse cecal or human faecal microbiota[16]. This demonstrates that the habitat in which a microbe is found cannot always predict ecological succession, but also leads to an important question of whether and when resident microbiota will evolve to fill empty niches more rapidly than colonization by pre-adapted species can occur. For example, work from the lung microbiomes of cystic fibrosis patients after lung transplantation shows rapid adaptation of *Pseudomonas* after recolonization from the sinuses, including the evolution of increased biofilm formation and swimming motility[9]. Such swift adaptation underscores how rapidly microbiota can respond to host-mediated selection.

Whether rapid microbial adaptation will define patterns of local microbiome diversity may in part depend on how the speed of adaptation scales relative to rates of immigration, which in turn depends on microbial species' dispersal capacity and the body site being colonized. Evidence from the lung microbiome has been used to support limitation of microbial dispersal, as isolation distance from source communities (oral and nasal microbiome communities) is found to significantly shape microbiome taxonomic diversity[17]. While this pattern accords with island biogeography theory, where colonization is key and de novo mutation plays a relatively minor role in shaping diversity, local adaptation might still be an important driver of diversity if taxonomic diversity only weakly reflects functional diversity, such that focusing only on taxonomic diversity might miss in situ adaptation.

The rapid turnover of genes and/or species within microbiomes also complicates the question of how we tackle the classic question of species' coexistence mechanisms[18]. Classical theory developed for eukaryotic (and probably less dynamic) communities predicts that to coexist, species must not directly compete, and are likely to use primarily non-overlapping resources[19]. One path to coexistence is community-wide character displacement, whereby locally coexisting species are less functionally similar to each other than species drawn randomly from a larger regional pool, because species with overlapping niches (reflected by overlapping characters) have been locally competitively excluded. But do we expect to observe this in the microbiome? There is some evidence to suggest so; for example, the likelihood of establishment of an orally administered probiotic, *Bifidobacterium longum*, was found to be lower in individuals whose resident microbiome already included a *B. longum* strain[20]. However, if microbiome communities are in a constant state of flux as a result of fast and overlapping timescales (see above), competitive exclusion may not have time to play out. Furthermore, even if the species composition of the community is not swiftly changing, evidence from the human microbiome suggests that transcriptional downregulation of certain genes in the presence of another species might alter competition and allow for niche segregation at the transcriptional level[21]. Although rapid modification of competitive characteristics could functionally resemble character displacement, this outcome would not be observable from metagenomics or community composition data, complicating interpretation using standard tools.

The converse of character displacement, functional redundancy — where multiple bacterial species perform the same function — seems widespread in the microbiome[22]. For example, metabolic network models applied to two gut microbiome datasets revealed

Box 1 | Glossary

Allee effect. A positive density dependence, reducing the fitness of small populations; for example where low numbers result in a shortage of mates or cooperative defense strategies are more efficient at higher numbers.
Black Queen hypothesis. This describes the idea that stable, positive interactions among microbes can lead to a loss of genes/function to reduce redundancy.
Density dependence. The number (or density) of individuals in a population alters the survival or reproduction of a focal individual, typically as a result of resource limitation.
Ecosystem engineer. A species that alters the abiotic environment for other species (often resulting from niche construction).
Enemy release hypothesis. Immigrant species are thought to be able migrate away from their antagonists (particularly parasites or predators) to realize a fitness benefit.
Frequency dependence. The success of a particular species (or strain) depends on its frequency relative to other species (or strains).
Historical contingency. Ecological and evolutionary outcomes are thought to be constrained by historical events, including past environmental conditions, the order of species arrival, population dynamics, and potentiating mutations.
Holobiont concept. An evolutionary idea, in which the biological entity on which selection acts is the host together with its associated microorganisms (and therefore the genomes of both host and symbionts).
Horizontal (or lateral) gene transfer. The movement of genes between genomes in a manner other than by descent. For bacteria, this can occur via transformation (the uptake of DNA from the environment), transduction (the transfer of DNA through bacteriophage transmission), or conjugation (the transfer of DNA via cell-to-cell contact).
Horizontal transmission. The movement of a symbiont (a bacterium or virus, for example) between individual hosts that are not parent and child.
Island biogeography theory. The species diversity on an island is thought to be jointly determined by the rate of colonization and the rate of extinction.
Metapopulation theory. This theory describes the persistence and internal dynamics of a population that comprises spatially separated sub-populations.
Neutral theory. All species are considered to be similar in their competitive ability, dispersal and fitness. The dynamics of species diversity are defined by the probabilities of species loss (extinction, emigration) and gain (immigration, speciation) and are independent from species identity.
Niche overlap. The degree of shared resources among species (also referred to as functional redundancy). The characteristics of the niche and niche overlap will shape the degree to which earlier-arriving species can exclude species that share requirements for that resource (niche-pre-emption); and the degree to which species can modify the niches of others (niche modification).
Priority effect. The impact that a species has on community assembly after its arrival (note that this is a form of historical contingency).
Succession. The ordered sequence of species' establishment that arises following a disturbance.
Vertical transmission. The acquisition of a symbiont by offspring from their parent.

that co-occurrence of competing species within individual hosts was common, even after controlling for phylogenetic relatedness[23], and co-occurrence within body sites of the human microbiome was found to be more common among closely related microbiota[24]. Similarly, analysis of co-occurrence networks from both free-living and human-associated microbial communities found that phylogenetic distance, genome similarity, and functional association among microbes were the strongest predictors of their coexistence[25]. Of course, predicting the importance and outcome of competition within communities also requires understanding of the spatial scale of interactions[26]; something that is often elusive in microbiome systems.

If microbiome community dynamics are governed by dispersal (or mutation) limitation and stochastic extinctions rather than competitive differences, one might then argue that the neutral theory applies. The evidence so far is mixed. Analysis of the zebrafish gut microbiome suggests that the neutral theory provides a relatively good description of these communities early in life, but one that performs less well as the zebrafish develops[27]. The composition of the healthy human lung microbiome is also best explained by the neutral model; in contrast, the diseased lung microbiome showed clear signatures of adaptation to this specific environment[28]. Evidence against neutrality is also stacking up: analysis of phylogenetic diversity across a broad array of microbial communities, including gut and skin microbiota, indicates deviations from neutral expectations[29]; a result echoed by a recent analysis of human microbiome communities from 18 body sites across 242 individuals, where less than 1% satisfied the neutral theory model[30]. Similarly, studies of reproducibility in observed patterns of microbiome establishment, such as the dynamics of the mouse cecum microbiota after antibiotics use[31] and analyses of time-series data on microbial abundance in domesticated vertebrates[32], as well as microbiota co-occurrence data from the developing infant gut microbiome[10], all support non-neutral processes. Together, these data suggest that deterministic processes (that is, mechanisms with predictable outcomes, such as competitive interactions with a clear dominant species, or mutualistic ones with a positive impact on both species growth) are important in shaping microbiome assembly and composition, but the nuance of how these processes operate in the face of shifting timescales and when/why the neutral theory can be appropriately applied in many cases are important questions for further work.

Beyond adaptation to competitors, adaptations involved in interactions with predators[33] and parasitic phages[34,35] are also likely to be important in colonization of and success within the microbiome. Phages, in particular, are likely to shape bacterial colonization success, and the ratio of phages to bacterial cells has been found to be higher on mucosal surfaces, important access points for invading pathogens, than across other eukaryotic host environments[34]. Moreover, analysis of the co-abundance of gene groups from human gut microbiome samples found a negative relationship between bacterial persistence in the gut and the presence of associated phages[36]. Classical theory suggests that colonists might have an increased chance of establishment precisely because they have left behind an antagonist, as described in the enemy release hypothesis, but no such evidence yet exists for microbiota and their phages or predators. Again, fast and overlapping timescales may be important here: the speed at which phage-mediated selection can alter bacterial traits that influence both competition[37] and interactions with the host[38] can further blur the line between ecological and evolutionary

timescales (see above). In contrast to the typical role of parasites in the community ecology of eukaryotes, phages of the microbiota can rapidly recombine to achieve altered host ranges[39], seem more likely to be shared across diverse species given the commonality of many cell surface receptors and shared resistance mechanisms, and may move between being beneficial (prophage) and antagonistic (lytic phage), as revealed by data on the interactions between salivary phages and the oral microbiome[40].

A final challenge to embedding microbiome systems within relevant timescales to generate theoretical predictions is that many microbiome species also considerably alter their environment. For example, the shifting infant microbiome has been associated with the presence of species that reduce the oxygen gradient[11], altering the potential of establishment by other species, and during succession following tooth-cleaning in dental plaques, the presence of species that create structural supports are necessary to allow colonization of others[26]. Although the concept of ecosystem engineering is well-established in ecological theory[41], the focus has been primarily on impacts on the abiotic environment. For the microbiome, the speed at which ecosystem engineering occurs in and interacts with the biotic environment, including the host and other microorganisms, may well be unique. While such feedbacks between ecological interactions and evolutionary processes can be placed within the existing framework of eco-evolutionary dynamics, as has been suggested for symbiont-mediated evolution of host defense[42], the further complexities of timescales outlined here and coevolutionary interactions need to be carefully considered.

In concert with the development of new mathematical models[43], experimental (co)evolution studies are likely to be a core direction for determining the relative importance of neutral versus deterministic processes, de novo mutation versus species/strain sorting, colonization versus adaptive radiation, and competition versus predation in shaping microbiome communities. With sufficient data, we can reframe existing models accordingly and move more into a systems biology approach[44], which has already made important contributions to characterizing external (for example, diet) modulatory factors that shape successional networks[45].

A question of identity

Another major challenge in developing a predictive science for the microbiome has stemmed from the difficulty of identifying the players involved, either by taxonomy, phylogeny, or function. Even when these empirical challenges are overcome, as is beginning to happen with new bioinformatical and -omic approaches, conceptual and epistemological challenges arise around the question of identity in the microbiome. Processes from horizontal gene transfer (HGT) through to rapid convergent evolution and shared prophages and plasmids can blur the line between phylogenetic and phenotypic distance. The question of identity is further plagued by the seemingly high frequency of mutualisms within the microbiome, production of public goods, and other positive dependencies among microbiota — all of which decouple function from single identities. As such, the question of how to most meaningfully characterize and compare microbiome communities requires revisiting some of the key theoretical concepts underlying community ecology and ecosystem function.

The movement of genes among genomes via HGT, often mediated by phage or plasmid transfer, can blur many features of microbial identity and community composition, including the predictability of successional dynamics of species, as function and species identity can become decoupled[46]. The occurrence of HGT shows some consistency — for example, it seems to occur more frequently within the human microbiome than with unassociated microbial species[47], and seems to be driven by shared ecology (body site) rather than phylogenetic distance among species[48] — but much remains unknown. This uncertainty raises particular challenges where the outcome of species interactions depends on functional traits such as antibiotic production[8] or adhesion[49] (that is, when dynamics are not neutral). In eukaryotic systems, the strength of competitive or cooperative interactions among species can sometimes be inferred based on their degree of phylogenetic relatedness[50] as this maps onto functional similarity. By contrast, the potential for HGT among unrelated bacteria[48] makes the relationship between phenotypic distance and phylogenetic distance far from clear cut. Current gold standard analyses, such as UniFrac scores to examine community dissimilarity[51] or PICRUSt analysis to predict function from 16S sequence (rather than whole genome sequence data)[52], which rely in part on phylogeny and species identities, are likely to be less informative than their counterparts as applied to eukaryotic communities. The difficulty in predicting microbiome function from taxonomic composition is illustrated by a recent study on the early life succession of gut microbes, in which microbiota composition was found not to mirror functionality (that is, higher species diversity did not relate to wider functional breadth)[12].

The frequently reported disconnect between function and species identity is further complicated by another distinctive feature of microbiomes relative to eukaryotic species (although see ref. [53] for excellent counter examples): tightly-associated bacterial species are likely to rapidly lose genes that are functionally redundant in the presence of other community members. Potential explanations for this phenomenon include relaxed selection, genetic drift, or even positive selection, as elegantly described by the Black Queen hypothesis[54]. The combination of rapid loss of redundant genes/traits in microbial communities and rapid gain of genes through HGT make shifting the focus towards the genes making up the microbiome, and away from organisms, a potentially powerful approach (Fig. 1b; see also refs [4,46]) but raises considerable challenge in bringing current ecological and evolutionary theory to the microbiome.

In non-microbiome systems, simple principles have been successfully used to map environmental drivers (such as temperature and precipitation) to major biomes (tropical forests, savannahs, or tundras, for example) across the globe. The complex species/function mapping in the microbiome, combined with the difficulty in measuring environmental/physical variables within the host, makes this type of study hard to replicate across microbiome systems. Promising analyses comparing 'healthy' subjects to those diagnosed with particular diseases or syndromes, such as irritable bowel syndrome[45] or cystic fibrosis[1], or after antibiotic treatment[55], have led to some non-intuitive results. For example, the (simplistic) expectation that diversity should be associated with health is challenged by evidence indicating that increased vaginal diversity, also linked to changes in pH, may in fact be a marker for pregnancy complications[56]; and that highly diverse gut community enterotypes can show an increase in harmful byproducts of proteolytic pathways[57]. Moving away from taxonomic diversity towards functional diversity may be particularly informative in describing environmental drivers of the microbiome, as well as useful in identifying 'dysbiosis,' the microbiome composition associated with a diseased state.

Rapid gain/loss of genes is not the only complexity in considering the question of identity in microbiome dynamics. In classical ecological theory, stable long-term coexistence typically requires 'stabilizing mechanisms' that allow species to recover when rare — that is, frequency or density dependent interactions among species[18,58]. Beyond the clear issues in identifying whose density or frequency is relevant in terms of function or identity, intense mutualisms seem to flourish within the microbiome, with a range of cooperative practices such as production of public goods (for example, siderophores for sequestering free iron from the environment to make it available to surrounding cells[58]), cross-feeding (where one species depends on the products of another for nutrients), and bacterial cell-to-cell communication via quorum sensing (which allows bacterial cells

to gather information about local densities and adjust their own responses accordingly, maximizing the efficiency and benefit of social behaviors[59]; a process for which there no parallel in eukaryotic systems). All of these practices will affect densities/frequencies of microbial species, but it is unclear if and when they contribute to stable coexistence[8]. Furthermore, in eukaryotic systems density dependence generally results in negative effects on fitness, but the processes described above are overwhelmingly likely to result in positive effects of density on fitness. This is analogous to an 'Allee effect' in eukaryotic biology, expected to erode rather than promote diversity, such that one species or strain cannot establish within a location unless there are sufficient numbers of either itself or its interacting species[60]. Adding this coordination and positive interdependence to processes such as ecosystem engineering results in potentially highly directional trajectories of ecology and evolution that are probably very sensitive to initial conditions and thus may be very hard to predict using classic theory.

Blurry heritability

One of the more intriguing aspects of microbiomes is the degree to which these communities are heritable, that is, shared among generations of related hosts, as a highly heritable microbiome could result in co-selection acting on the microbiome and host together as a unit (the holobiont concept[61]). Tantalizing evidence for such co-selection in human microbiomes comes from two recent studies: first, a human twin study demonstrating a link between particular heritable microbiota and certain single nucleotide polymorphisms (SNPs) in host genes[62]; and second, a cohort study across family groups that found a third of faecal bacterial taxa to be heritable, and again predictably related to SNPs across the host genome[63]. Predicting how selection will act on hosts, microbiota, and their interaction over time requires quantifying such heritability, which in microbiome systems may be driven by vertical transmission (from parent to offspring) of microbiota (noting that we use this term more broadly than the classical definition, which describes transmission of microbes through gametes or embryos), a strong effect of host genetics on microbial colonization, and/or a shared parent and offspring environment. Teasing apart these mechanisms is difficult, but good headway has been made: for example through comparative metagenomics across generations[64], comparisons of monozygotic and dyzogotic twins[65], and experimental manipulations in non-human model systems (Supplementary Table 1).

What do we expect for evolution and coevolution of the host and microbiome in the context of heritability? Although there has been surprisingly little work on this question so far, there are good theoretical foundations to draw on. In disease ecology, quantifying the relative rates of vertical transmission versus horizontal transmission (among unrelated individuals) is key to predicting the evolutionary outcome of host–microbe interactions. Vertical transmission is predicted to most readily maintain mutualistic interactions between hosts and their symbionts, as symbiont reproduction is necessarily coupled with host reproduction, and therefore any increase in host fitness will also increase symbiont fitness[66]. Conversely horizontal transmission can select for more virulent pathogens because increased transmission success is often correlated with within-host reproduction, which itself is typically associated with increased harm to the host[66]. Theoretical advances based around these ideas must be paired with empirical understanding of microbiota transmission, as there are still many important unknowns, including how spore forming bacteria and fungi might colonize and recolonize sites differently than non-spore formers. Indeed, recent human microbiome studies have uncovered a large number of spore-forming species[67], with clear relevance for understanding the outcome of transmission and potentially persistence or extinction within the metapopulation of hosts. Overall, shifting the focus from the individual host to the population of hosts, metapopulation theory has the potential to explain persistence or extinction of particular species within the broader microbiome niche[9,68]. This theory accounts for the fact that while each host can be considered a population, dispersal between hosts may link microbiome communities[9]. However, in this case there is also a need to determine how current metapopulation dynamics can be scaled up to the metacommunity level[69].

Evidence for vertical transmission of the microbiome is accumulating across systems, including humans — where potential mechanisms include a placental microbiome[70] (but see ref. [71]), transfer through umbilical cord blood[72], transmission over the course of vaginal delivery[73] (including at the strain level[64]), and through ingestion of breast milk and skin-to-mouth contact[74] — but parent-to-offspring transmission seems to be highly variable across microbial taxa and body sites, and the drivers of this variability remain unexplained. Whether or not particular microbiota are stably transmitted across generations is key to predicting whether host–microbiome associations will persist and diverge over similar timescales to host divergence and speciation. In human populations, recent evidence suggests that although some strains show stable vertical transmission over evolutionary time[75], they are likely to be in the minority. Horizontal transmission among unrelated humans, on the other hand, is observed in studies of cohabitation[76] and direct contact[77]; and rapid adaptation to the host environment within a single host generation is likely to be important for many microbiota[9,16].

From a purely ecological perspective, the lack of heritability across many taxa and microbiome sites is not surprising given evidence that environmental conditions, especially during infancy, can shape microbiome formation[55]. Comparison across two large cohort studies uncovered several correlates of adult gut microbiome composition that included medication, blood parameters, health status, diet, and lifestyle, suggesting that perturbations throughout life drive among-individual variation and can obscure signatures of heritability[78]. Many of these environmental drivers reflect relatively recent changes in human evolutionary history. As most are associated with reducing microbiome diversity, this suggests the worrying possibility of irreversible change and/or loss of diversity of the global human microbiome pool[68], supported by evidence of higher microbiome diversity in uncontacted Amerindians[79] and of reduced human microbiome diversity relative to our nearest ancestors[80]. Understanding the complex role of heritability in host–microbiome coevolution will require titrating the relative importance of vertical versus horizontal transmission and micro- versus macro-evolutionary processes[81]. The accumulation of further empirical data will be key, but the development of novel theoretical tools and/or deployment of existing theory, with a careful eye on the underlying assumptions and timescales, will also be required.

One often-ignored but critical aspect of vertical transmission, and with little parallel in theory developed for eukaryotic systems, is whether the microbiome is transmitted as a 'whole,' whereby coevolutionary interactions among microbes can be preserved over multiple host generations, or whether mature microbiomes are formed after the initial colonization of only a small subsample of the maternal microbiota. Even where subsampling is occurring, the resulting adult microbiome might still retain strong similarities across individuals if priority effects are acting. The identity of the earliest arriving species or strains can shape the direction of community development via niche pre-emption, or niche modification[82], as can sequential dependencies, where each subsequent trophic level's successful establishment requires a previous level[60]. However, the theory underlying these concepts[60,82] is rooted in the functional features of the sequence of arrivals (such as the trophic level or metabolic profile), which may be divorced from taxonomic identity in the microbiome (see above), requiring careful consideration of the scale of the analysis. Microbiomes might further be shaped through the coalescence of multiple microbial communities (for example, through sampling of multiple maternal microbiome sites, or the paternal or social acquisition of microbiota),

Box 2 | Open questions in microbiome research and promising approaches to resolve them

How much of our microbiome is transmitted, inherited, or acquired?

- Characterization of the potential for paternal microbiome transmission via investigation of microbial species in seminal fluid (understudied relative to maternal microbiomes).
- Twin studies[62] to titrate the role of genetics, vertical transmission and acquisition in early life in shaping microbiome diversity.
- Temporal sampling to characterize when and potentially how new microbes are acquired; via cohort studies[12], for example (Supplementary Box 2).
- Community coalescence approaches[83] to determine what follows contact and mixing of two different microbiomes (via direct contact[77] or faecal microbiome transplants, for example) to understand microbial species acquisition in the context of existing communities.

How do current cultural practices and environmental factors influence microbiota transmission, acquisition, and function?

- Application of disease ecology theory on virulence/transmission trade-offs to understand which aspects of human interactions or broader environmental contexts might favour increased within-host growth rates and/or transmission.
- Experimental manipulation in model systems to directly quantify effects, such as how diet or drug use change the microbiome.
- Comparative microbiome studies across populations[57] and lifestyle factors[45] to characterize patterns in natural systems and uncover potential drivers.
- Examining macroevolutionary patterns[81] by comparing microbiomes across related species to identify co-divergence and co-speciation of hosts and particular microbiota lineages.

What shapes stability and resilience of the microbiome?

- Development of keystone or hub species approach[44] through network analyses to delineate those species with the greatest effects on the rest of the community.
- Evaluation of the importance of cooperation versus conflict[8]; via simulation studies grounded in known metabolic properties, for example.
- Exploring the role of rare species in the face of environmental perturbation, by detection of extreme changes in abundance under environmental change and detection/characterization of spore-forming strains, among other methods.
- Long-term cohort sampling before, during, and after intervention[55], such as antibiotic use, to identify changes in abundance and/or function.
- Identification of tipping points[96] via characterization of species with bistable patterns of abundance, for example, to shed light on the degree to which alternative stable states of communities (rather than a continuum) are to be expected.

How does microbial species diversity relate to microbiome function/ health?

- Measuring functional redundancy (niche overlap[12,46]) to characterize the degree to which species coexistence depends on niche separation and how compositional change influences functional diversity.
- Study of synthetic microbial communities in model systems[3] (Supplementary Table 1) to directly relate microbiome species composition to a focal health outcome.
- Comparing functional relatedness to phylogenetic relatedness[46] to evaluate the degree to which related species are expected to have similar function and/or compete versus coexist within the microbiome.
- Randomized control trials where the impact of specific microbiome-related interventions (such as probiotics and faecal transplantations) are rigorously tested for their effects on human health.

Is there such a thing as a general 'dysbiosis'?

- Incorporating host genetic diversity and environmental variation into models[31,44] that capture microbiome function of relevance to human health.
- Shifting the focus from average individuals to outliers (as has been successfully done in linking host genetics to particular diseases, for example).
- Adapting Koch's postulates to link disease with particular microbial communities[97].

Where does the holobiont begin and end?

- Characterizing transient members of the microbiota (as opposed to more 'permanent' or 'core' members) that are likely to experience co-selection with the host.
- Measuring the effects of microbial predators and bacteriophages (and the greater 'virome') that are often neglected, but are suspected to play a role in immune defence, for example.
- Examining the impact of the eukaryome on both the microbiome and host.

How does the scale at which we describe the microbiome influence our interpretation?

- Evaluating the sensitivity of conclusions to groupings that are based on OTUs/ecotypes/oligotypes[98].
- Characterization of the diversity at the strain level, including more in-depth culture collections to avoid calling very different entities by the same names, thus weakening inference — for example, pathogenic versus non-pathogenic strains of the same OTU for health outcomes.
- Combining -omics approaches to move beyond composition towards function in an attempt to bypass issues of species/ strain grouping.

How do non-bacterial microbiome communities impact host health and interact with the bacterial microbiome?

- Community profiling of the mycobiome, using the pan-fungal internal transcribed spacer 1 (ITS1) locus, for example.
- Characterization of single-celled microbial eukaryotes, including both bacterial predators and competitors, in the microbiome[99].
- Incorporation of the candidate phylaradiation group of ultrasmall bacteria[100].

thus potentially restructuring species interaction networks and enabling horizontal gene transfer among microbes from different host environments[83]. There is no clear analogy of these processes from eukaryotic systems, barring very dramatic events such as connection across the Bering Strait, and correspondingly little theory.

The issue of individual versus co-transmission of microbial strains/species is particularly important in light of the known interdependence among species listed above (see 'A question of identity'). Incomplete vertical transmission (that is, of only a small proportion of the community) could lead to a domino effect, whereby the loss of one species leads to subsequent loss of all those depending on it. Losses of the species or strains that have the highest number of links within the food web network of community interactions should have the greatest effects on overall diversity[84]. Indeed, if community composition is shaped by particular keystone species, as has been demonstrated in the human gut[85], the loss or gain of these

species at initial colonization could substantially alter the entire community and erase signatures of vertical transmission or heritability. Alternatively, self-organization might play a major role in determining microbiome communities, so that similarities among individuals may be merely incidental. These open questions are pivotal to predicting the impact of maternal microbiota on infant microbiome development and to managing infant health[10,11], but also to understanding the co-evolutionary potential among hosts and their microbiomes.

Host control

Microbial communities in general both shape and are shaped by the environment in which they live, and this is not at odds with what is observed for many eukaryotic communities. For those communities living inside hosts, however, there is a unique further layer of complexity: feedbacks between the host environment and the microbes inhabiting it can lead to rapid and ongoing dynamics. It is well documented that host genetics influence microbiome acquisition[62] and persistence[86]. Numerous immune genes, including *NOD2* and *IL-23R*, are known to be central in controlling the composition of the microbiome, and work from the Hutterites (a population that live and eat communally, minimizing variation due to environmental exposures) identified eight bacterial taxa that were associated with single SNPs in the host genome (including a variant near *PLD1*, a gene previously associated with body mass index and correlated to the genus *Akkermansia*[86]). Importantly, there is also evidence that the host can modify its epithelial secretions to 'culture' certain species within the microbiome[49]. For example, although the production of mucus across body sites has long been known to influence (and be influenced by) the microbiome, recent evidence suggests the possibility of a direct role of salivary mucins in altering bacterial coexistence[87], and therefore a role for host production of mucins in shaping microbiome diversity. As dietary fibre has also recently been linked to the proliferation of mucus-degrading bacteria in the gut[88], this suggests a complex interaction between host diet and mucus production in shaping bacterial competition.

Given that microbiome composition can affect host functioning and health (direct evidence for microbiome-mediated traits in model systems are summarized in Supplementary Table 1), selection should favour those associations that have the most positive effects on host fitness. Mechanisms such as the production of antimicrobial peptides by cells in specialized epithelial lineages that 'segregate' the microbiota from the host[89], or transfer of complex oligosaccharides in breast milk that are digestible only by the infant gastrointestinal microbiota and that interfere with pathogen adhesion[90] are increasingly well-documented. However, this evolutionary dynamic cannot be considered from the side of the host alone — microbiota also rapidly respond to such selection. For example, several human microbiota seem to have developed resistance to high levels of inflammation-associated antimicrobial peptides (for example, via lipopolysaccharide modification in the phylum Bacteroidetes[91], a necessary adaptation for persisting within hosts). Overall, the result is a co-evolutionary process, operating on profoundly different timescales (since hosts have far longer generation times than species within their microbiome), and in the context of complex community interactions and ecosystem engineering within the microbiome, all of which compound many of the challenges for ecological and evolutionary theory outlined in the sections above.

From the point of view of classical ecological and evolutionary theory, a further and unique challenge is that, for many species, the core nexus of the interaction will be the host immune system. The demands of recognizing a highly dynamic and changing diversity of pathogens has led to the evolution of adaptive immunity, a system that in some sense matches evolution itself. Broadly, random receptor variation is generated, followed by amplification of effectors with receptors that best match pathogens. Clearly, the nuances of identifying friend from foe are fantastically complicated in the context of the microbiome. It is unsurprising, therefore, that the colonization of microbiota during early life is thought to be particularly important in 'training' the host immune system, as neonatal immune cells learn to tolerate commensal microbiota[92]. There are key parallels here with theories linked to community succession (above), and historical contingency[82], but again, with complexities of timescales, identity, and the uniquely diverse function/species identity relationships that seem to characterize microbiomes across hosts within species.

We are increasingly realizing that the immune system is just one player in the complex coordinated network of signalling and regulation between the host and microbiome. Recently, it has been shown that murine epithelial cells secrete large quantities of microRNAs (small non-coding RNA molecules that regulate RNA silencing and post-transcriptional regulation of gene expression), which act directly on the microbiota by entering bacterial cells to regulate gene transcripts[93], and modulate community composition — a unique cross-species interaction. Understanding the contribution of these host factors, as well as the indirect interaction between the host and bacteriophages[34], to microbiota composition during different life stages and diseases will be key for developing personalized diagnostic and treatment options, including dietary and bacterial interventions. However, the road from identifying mechanisms to predicting evolutionary trajectories has proven challenging, and the incorporation of bottom-up versus top-down approaches[22] with the development of system-specific models that explicitly incorporate the host environment, will be necessary to fully unravel the complexities of the microbiome.

Conclusions

As in eukaryotic systems, the core principles of ecology and evolutionary biology provide a powerful toolkit for making sense of microbiome dynamics. However, for microbiomes, these core principles are filtered through unique ecological and evolutionary processes, ranging from horizontal gene transfer to host control. As a result, moving beyond correlative to predictive statements in microbiome research requires new angles and the creative framing of questions, as well as solid empirical foundations (Box 2). Progress is likely to stem from both explicit theoretical exploration of processes that have so far been neglected (such as coevolution in the context of heritability) and highly targeted simple experimental manipulations (for example, the removal or addition of specific species across contexts tied to specific theoretical predictions such as varying environmental drivers; Supplementary Table 2). Interpretation of the large datasets being produced will also benefit from more integrated systems biology approaches that incorporate suites of important processes and build on the diversity of results coming from new -omic techniques.

More specifically, our ability to translate existing theory and develop novel theory will depend on: (i) our ability to further unravel the complex network of interactions within the microbiome, including the role of phages both as shared parasites and potential gene pools [94]; (ii) better resolution of the temporal and spatial dynamics within the microbiome, including biochemical gradients within the host environment[95] and physical and chemical perturbations; and (iii) a larger knowledge base surrounding microbial function, which could be achieved through improved culturing techniques[67], and the systematic discovery and manipulation (through CRISPR–Cas genome editing, for example) of genes encoding proteins with unknown function. Overall, the rate of discovery will be as affected by the speed at which new theoretical tools and frameworks are developed as it will be by technological and bioinformatical advances. It is important that

we avoid 'reinventing the wheel' by ignoring existing theory, but also do not blindly apply theory without understanding the important nuances of host-associated microbiota; finding the right balance will require collaboration and concerted efforts across lab groups and fields.

Received: 8 September 2016; Accepted: 7 September 2017;
Published online: 16 October 2017

References

1. Magalhães, A. P., Azevedo, N. F., Pereira, M. O. & Lopes, S. P. The cystic fibrosis microbiome in an ecological perspective and its impact in antibiotic therapy. *Appl. Microbiol. Biotech.* **100**, 1163–1181 (2016).
2. Vatanen, T. et al. Variation in microbiome LPS immunogenicity contributes to autoimmunity in humans. *Cell* **165**, 842–853 (2016).
3. Blanton, L. V. et al. Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children. *Science* **351**, aad3311 (2016).
4. Vandenkoornhuyse, P., Quaiser, A., Duhamel, M., Le Van, A. & Dufresne, A. The importance of the microbiome of the plant holobiont. *New Phytol.* **206**, 1196–1206 (2015).
5. Yarza, P. et al. Uniting the classification of cultured and uncultured bacteria and archaea using 16S rRNA gene sequences. *Nat. Rev. Microbiol.* **12**, 635–645 (2014).
6. Jones, M. B. et al. Library preparation methodology can influence genomic and functional predictions in human microbiome research. *Proc. Natl Acad. Sci. USA* **112**, 14024–14029 (2015).
7. Costello, E. K., Stagaman, K., Dethlefsen, L., Bohannan, B. J. & Relman, D. A. The application of ecological theory toward an understanding of the human microbiome. *Science* **336**, 1255–1262 (2012).
8. Coyte, K. Z., Schluter, J. & Foster, K. R. The ecology of the microbiome: networks, competition, and stability. *Science* **350**, 663–666 (2015).
9. Beaume, M. et al. Rapid adaptation drives invasion of airway donor microbiota by *Pseudomonas* after lung transplantation. *Sci. Rep.* **7**, 40309 (2017).
10. Koenig, J. E. et al. Succession of microbial consortia in the developing infant gut microbiome. *Proc. Natl Acad. Sci. USA* **108**, 4578–4585 (2011).
11. Matamoros, S., Gras-Leguen, C., Le Vacon, F. & Potel, G. & de La Cochetiere, M.-F. Development of intestinal microbiota in infants and its impact on health. *Trends MicroBiol.* **21**, 167–173 (2013).
12. Vallès, Y. et al. Microbial succession in the gut: directional trends of taxonomic and functional change in a birth cohort of Spanish infants. *PLoS Genet.* **10**, e1004406 (2014).
13. Langdon, A., Crook, N. & Dantas, G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Gen. Med.* **8**, 39 (2016).
14. Stahringer, S. S. et al. Nurture trumps nature in a longitudinal survey of salivary bacterial communities in twins from early adolescence to early adulthood. *Gen. Res.* **22**, 2146–2152 (2012).
15. David, L. A. et al. Gut microbial succession follows acute secretory diarrhea in humans. *mBio* **6**, e00381–e00315 (2015).
16. Seedorf, H. et al. Bacteria from diverse habitats colonize and compete in the mouse gut. *Cell* **159**, 253–266 (2014).
17. Whiteson, K. L. et al. The upper respiratory tract as a microbial source for pulmonary infections in cystic fibrosis. Parallels from island biogeography. *Am. J. Respir. Crit. Care Med.* **189**, 1309–1315 (2014).
18. Chesson, P. Mechanisms of maintenance of species diversity. *Ann. Rev. Ecol. Syst.* **31**, 343–366 (2000).
19. Hutchinson, G. E. Homage to Santa Rosalia or why are there so many kinds of animals? *Am. Nat.* **93**, 145–159 (1959).
20. Maldonado-Gómez, M. X. et al. Stable engraftment of *Bifidobacterium longum* AH1206 in the human gut depends on individualized features of the resident microbiome. *Cell Host Microb.* **20**, 515–526 (2016).
21. Plichta, D. R. et al. Transcriptional interactions suggest niche segregation among microorganisms in the human gut. *Nat. Microbiol.* **1**, 16152 (2016).
22. Moya, A. & Ferrer, M. Functional redundancy-induced stability of gut microbiota subjected to disturbance. *Trends Microbiol.* **24**, 402–413 (2016).
23. Levy, R. & Borenstein, E. Metabolic modeling of species interaction in the human microbiome elucidates community-level assembly rules. *Proc. Natl Acad. Sci. USA* **110**, 12804–12809 (2013).
24. Faust, K. & Raes, J. Microbial interactions: from networks to models. *Nat. Rev. Microbiol.* **10**, 538–550 (2012).
25. Kamneva, O. K. Genome composition and phylogeny of microbes predict their co-occurrence in the environment. *PLoS Comput. Biol.* **13**, e1005366 (2017).
26. Welch, J. L. M., Rossetti, B. J., Rieken, C. W., Dewhirst, F. E. & Borisy, G. G. Biogeography of a human oral microbiome at the micron scale. *Proc. Natl Acad. Sci. USA* **113**, E791–E800 (2016).
27. Burns, A. R. et al. Contribution of neutral processes to the assembly of gut microbial communities in the zebrafish over host development. *ISME J.* **10**, 655–664 (2015).
28. Venkataraman, A. et al. Application of a neutral community model to assess structuring of the human lung microbiome. *mBio* **6**, e02284–e02214 (2015).
29. O'Dwyer, J. P., Kembel, S. W. & Sharpton, T. J. Backbones of evolutionary history test biodiversity theory for microbes. *Proc. Natl Acad. Sci. USA* **112**, 8356–8361 (2015).
30. Li, L. & Ma, Z. S. Testing the neutral theory of biodiversity with human microbiome datasets. *Sci. Rep.* **6**, 31448 (2016).
31. Stein, R. R. et al. Ecological modeling from time-series inference: insight into dynamics and stability of intestinal microbiota. *PLoS Comput. Biol.* **9**, e1003388 (2013).
32. Jeraldo, P. et al. Quantification of the relative roles of niche and neutral processes in structuring gastrointestinal microbiomes. *Proc. Natl Acad. Sci. USA* **109**, 9692–9698 (2012).
33. Welsh, R. M. et al. Bacterial predation in a marine host-associated microbiome. *ISME J.* **10**, 1540–1544 (2015).
34. Barr, J. J. et al. Bacteriophage adhering to mucus provide a non-host-derived immunity. *Proc. Natl Acad. Sci. USA* **110**, 10771–10776 (2013).
35. Koskella, B. Phage-mediated selection on microbiota of a long-lived host. *Curr. Biol.* **23**, 1256–1260 (2013).
36. Reyes, A., Wu, M., McNulty, N. P., Rohwer, F. L. & Gordon, J. I. Gnotobiotic mouse model of phage–bacterial host dynamics in the human gut. *Proc. Natl Acad. Sci. USA* **110**, 20236–20241 (2013).
37. Seed, K. D. et al. Evolutionary consequences of intra-patient phage predation on microbial populations. *eLife* **3**, e03497 (2014).
38. Meaden, S., Paszkiewicz, K. & Koskella, B. The cost of phage resistance in a plant pathogenic bacterium is context-dependent. *Evolution* **69**, 1321–1328 (2015).
39. Lin, T.-Y. et al. A T3 and T7 recombinant phage acquires efficient adsorption and a broader host range. *PLoS ONE* **7**, e30954 (2012).
40. Pride, D. T. et al. Evidence of a robust resident bacteriophage population revealed through analysis of the human salivary virome. *ISME J.* **6**, 915–926 (2012).
41. Hastings, A. et al. Ecosystem engineering in space and time. *Ecol. Lett.* **10**, 153–164 (2007).
42. Smith, A. H. et al. Patterns, causes and consequences of defensive microbiome dynamics across multiple scales. *Mol. Ecol.* **24**, 1135–1149 (2015).
43. Widder, S. et al. Challenges in microbial ecology: building predictive understanding of community function and dynamics. *ISME J.* **10**, 2557–2568 (2016).
44. Agler, M. et al. Microbial hub taxa link host and abiotic factors to plant microbiome variation. *PLoS Biol.* **14**, e1002352 (2016).
45. Greenblum, S., Turnbaugh, P. J. & Borenstein, E. Metagenomic systems biology of the human gut microbiome reveals topological shifts associated with obesity and inflammatory bowel disease. *Proc. Natl Acad. Sci. USA* **109**, 594–599 (2012).
46. Burke, C., Steinberg, P., Rusch, D., Kjelleberg, S. & Thomas, T. Bacterial community assembly based on functional genes rather than species. *Proc. Natl Acad. Sci. USA* **108**, 14288–14293 (2011).
47. Liu, L. et al. The human microbiome: a hot spot of microbial horizontal gene transfer. *Genomics* **100**, 265–270 (2012).
48. Smillie, C. S. et al. Ecology drives a global network of gene exchange connecting the human microbiome. *Nature* **480**, 241–244 (2011).
49. Schluter, J., Nadell, C. D., Bassler, B. L. & Foster, K. R. Adhesion as a weapon in microbial competition. *ISME J.* **9**, 139–149 (2015).
50. Anacker, B. L. & Strauss, S. Y. Ecological similarity is related to phylogenetic distance between species in a cross-niche field transplant experiment. *Ecology* **97**, 1807–1818 (2016).
51. Lozupone, C. & Knight, R. UniFrac: a new phylogenetic method for comparing microbial communities. *Appl. Environ. Microbiol.* **71**, 8228–8235 (2005).
52. Langille, M. G. et al. Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences. *Nat. Biotech.* **31**, 814–821 (2013).
53. Ellers, J., Toby Kiers, E., Currie, C. R., McDonald, B. R. & Visser, B. Ecological interactions drive evolutionary loss of traits. *Ecol. Lett.* **15**, 1071–1082 (2012).
54. Morris, J. J., Lenski, R. E. & Zinser, E. R. The Black Queen hypothesis: evolution of dependencies through adaptive gene loss. *mBio* **3**, e00036–12 (2012).
55. Rashid, M.-U. et al. Determining the long-term effect of antibiotic administration on the human normal intestinal microbiota using culture and pyrosequencing methods. *Clin. Infect. Dis.* **60**, S77–S84 (2015).

56. MacIntyre, D. A. et al. The vaginal microbiome during pregnancy and the postpartum period in a European population. *Sci. Rep.* **5**, 8988 (2015).
57. Vieira-Silva, S. et al. Species–function relationships shape ecological properties of the human gut microbiome. *Nat. Microbiol.* **1**, 16088 (2016).
58. Ross-Gillespie, A., Gardner, A., West, S. A. & Griffin, A. S. Frequency dependence and cooperation: theory and a test with bacteria. *Am. Nat.* **170**, 331–342 (2007).
59. Darch, S. E., West, S. A., Winzer, K. & Diggle, S. P. Density-dependent fitness benefits in quorum-sensing bacterial populations. *Proc. Natl Acad. Sci. USA* **109**, 8259–8263 (2012).
60. Holt, R. D., Lawton, J. H., Polis, G. A. & Martinez, N. D. Trophic rank and the species–area relationship. *Ecology* **80**, 1495–1504 (1999).
61. Zilber-Rosenberg, I. & Rosenberg, E. Role of microorganisms in the evolution of animals and plants: the hologenome theory of evolution. *FEMS Microbiol. Rev.* **32**, 723–735 (2008).
62. Goodrich, J. K. et al. Genetic determinants of the gut microbiome in UK twins. *Cell Host Microb.* **19**, 731–743 (2016).
63. Turpin, W. et al. Association of host genome with intestinal microbial composition in a large healthy cohort. *Nat. Genet.* **48**, 1413–1417 (2016).
64. Milani, C. et al. Exploring vertical transmission of bifidobacteria from mother to child. *Appl. Environ. Microbiol.* **81**, 7078–7087 (2015).
65. Goodrich, J. K. et al. Human genetics shape the gut microbiome. *Cell* **159**, 789–799 (2014).
66. Ewald, P. W. Transmission modes and evolution of the parasitism–mutualism continuum. *Ann. NY Acad. Sci.* **503**, 295–306 (1987).
67. Browne, H. P. et al. Culturing of 'unculturable' human microbiota reveals novel taxa and extensive sporulation. *Nature* **533**, 543–546 (2016).
68. Blaser, M. J. & Falkow, S. What are the consequences of the disappearing human microbiota? *Nat. Rev. Microbiol.* **7**, 887–894 (2009).
69. Leibold, M. A. et al. The metacommunity concept: a framework for multi-scale community ecology. *Ecol. Lett.* **7**, 601–613 (2004).
70. Aagaard, K. et al. The placenta harbors a unique microbiome. *Sci. Transl. Med.* **6**, 237ra265 (2014).
71. Perez-Muñoz, M. E., Arrieta, M.-C., Ramer-Tait, A. E. & Walter, J. A critical assessment of the "sterile womb" and "in utero colonization" hypotheses: implications for research on the pioneer infant microbiome. *Microbiome* **5**, 48 (2017).
72. Jiménez, E. et al. Isolation of commensal bacteria from umbilical cord blood of healthy neonates born by cesarean section. *Curr. Microbiol.* **51**, 270–274 (2005).
73. Dominguez-Bello, M. G. et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc. Natl Acad. Sci USA* **107**, 11971–11975 (2010).
74. Albesharat, R., Ehrmann, M. A., Korakli, M., Yazaji, S. & Vogel, R. F. Phenotypic and genotypic analyses of lactic acid bacteria in local fermented food, breast milk and faeces of mothers and their babies. *Syst. Appl. Microbiol.* **34**, 148–155 (2011).
75. Moeller, A. H. et al. Cospeciation of gut microbiota with hominids. *Science* **353**, 380–382 (2016).
76. Song, S. J. et al. Cohabiting family members share microbiota with one another and with their dogs. *eLife* **2**, e00458 (2013).
77. Meadow, J. F., Bateman, A. C., Herkert, K. M., O'Connor, T. K. & Green, J. L. Significant changes in the skin microbiome mediated by the sport of roller derby. *PeerJ* **1**, e53 (2013).
78. Falony, G. et al. Population-level analysis of gut microbiome variation. *Science* **352**, 560–564 (2016).
79. Clemente, J. C. et al. The microbiome of uncontacted Amerindians. *Sci. Adv.* **1**, e1500183 (2015).
80. Moeller, A. H. et al. Rapid changes in the gut microbiome during human evolution. *Proc. Natl Acad. Sci. USA* **111**, 16431–16435 (2014).
81. Groussin, M. et al. Unraveling the processes shaping mammalian gut microbiomes over evolutionary time. *Nat. Commun.* **8**, 14319 (2017).
82. Fukami, T. Historical contingency in community assembly: integrating niches, species pools, and priority effects. *Ann. Rev. Ecol. Evol. Syst.* **46**, 1–23 (2015).
83. Rillig, M. C. et al. Interchange of entire communities: microbial community coalescence. *Trends Ecol. Evol.* **30**, 470–476 (2015).
84. Dunne, J. A., Williams, R. J. & Martinez, N. D. Network structure and biodiversity loss in food webs: robustness increases with connectance. *Ecol. Lett.* **5**, 558–567 (2002).
85. Fisher, C. K. & Mehta, P. Identifying keystone species in the human gut microbiome from metagenomic timeseries using sparse linear regression. *PLoS ONE* **9**, e102451 (2014).
86. Davenport, E. R. et al. Genome-wide association studies of the human gut microbiota. *PLoS ONE* **10**, e0140301 (2015).
87. Frenkel, E. S. & Ribbeck, K. Salivary mucins promote the coexistence of competing oral bacterial species. *ISME J.* **11**, 1286–1290 (2017).
88. Desai, M. S. et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell* **167**, 1339–1353.e21 (2016).
89. Vaishnava, S. et al. The antibacterial lectin RegIIIγ promotes the spatial segregation of microbiota and host in the intestine. *Science* **334**, 255–258 (2011).
90. Zivkovic, A. M., German, J. B., Lebrilla, C. B. & Mills, D. A. Human milk glycobiome and its impact on the infant gastrointestinal microbiota. *Proc. Natl Acad. Sci. USA* **108**, 4653–4658 (2011).
91. Cullen, T. et al. Antimicrobial peptide resistance mediates resilience of prominent gut commensals during inflammation. *Science* **347**, 170–175 (2015).
92. Gensollen, T., Iyer, S. S., Kasper, D. L. & Blumberg, R. S. How colonization by microbiota in early life shapes the immune system. *Science* **352**, 539–544 (2016).
93. Liu, S. et al. The host shapes the gut microbiota via fecal microRNA. *Cell Host Microb.* **19**, 32–43 (2016).
94. Modi, S. R., Lee, H. H., Spina, C. S. & Collins, J. J. Antibiotic treatment expands the resistance reservoir and ecological network of the phage metagenome. *Nature* **499**, 219–222 (2013).
95. Muñoz-Tamayo, R. et al. Kinetic modelling of lactate utilization and butyrate production by key human colonic bacterial species. *FEMS Microbiol. Ecol.* **76**, 615–624 (2011).
96. Lahti, L., Salojärvi, J., Salonen, A., Scheffer, M. & de Vos, W. M. Tipping elements in the human intestinal ecosystem. *Nat. Commun.* **5**, 4344 (2014).
97. Byrd, A. L. & Segre, J. A. Adapting Koch's postulates. *Science* **351**, 224–226 (2016).
98. Eren, A. M. et al. A single genus in the gut microbiome reflects host preference and specificity. *ISME J.* **9**, 90–100 (2015).
99. Scanlan, P. D., Knight, R., Song, S. J., Ackermann, G. & Cotter, P. D. Prevalence and genetic diversity of *Blastocystis* in family units living in the United States. *Infect. Genet. Evol.* **45**, 95–97 (2016).
100. Baker, J. L., Bor, B., Agnello, M., Shi, W. & He, X. Ecology of the oral microbiome: beyond bacteria. *Trends Microbiol.* **25**, 362–374 (2017).

Acknowledgements

We thank the RAPIDD program of the Science & Technology Directorate, Department of Homeland Security and the Fogarty International Center, National Institutes of Health and Wellcome Trust for funding the workshop from which this manuscript emerged, and all workshop participants (M. Blaser; S. Brown; A. Buckling; S. Chen; D. Churamani; M. Claesson; W. Cookson; M. Cox; K. Coyte; J. Curtis; K. Davies; R. De Weirdt; J. Dore; S. D. Ehrlich; M. Ferguson; H. Flint; K. Foster; B. Grenfell; N. Ilott; A. Johnson; A. Kuspa; R. La Ragione; T. Lawley; S. Levin; J. M. Welch; K. Moses; J. Parkhill; P Rainey; J. Segre; D. Spratt; C. Steves; Z. Takats; C. Tropini; M. Tunney; A. Wallace; A. Watson; D. Weinkove; C. Weller; P. Wilmes; N. Wingreen; J. Xavier); as well as organizers, D. Cannon and A. Cave, for further discussion of the manuscript.

Author contributions

B.K., L.J.H. and C.J.E.M. all contributed to the formation of ideas and writing of this manuscript.

Competing interests

The authors declare no competing financial interests.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41559-017-0340-2.

Reprints and permissions information is available at www.nature.com/reprints.

Correspondence and requests for materials should be addressed to B.K.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.