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Opinion

Microbiomes as Metacommunities: Understanding Host-Associated Microbes through Metacommunity Ecology

Elizabeth Theresa Miller,[1,*] Richard Svanbäck,[2] and Brendan J.M. Bohannan[1]

Interest in host-associated microbiomes has skyrocketed recently, yet our ability to explain microbiome variation has remained stubbornly low. Considering scales of interaction beyond the level of the individual host could lead to new insights. Metacommunity theory has many of the tools necessary for modeling multiscale processes and has been successfully applied to host microbiomes. However, the biotic nature of the host requires an expansion of theory to incorporate feedback between the habitat patch (host) and their local (microbial) community. This feedback can have unexpected effects, is predicted to be common, and can arise through a variety of mechanisms, including developmental, ecological, and evolutionary processes. We propose a new way forward for both metacommunity theory and host microbiome research that incorporates this feedback.

Hosts and Their Microbiomes Are Ecological Systems

Humans and other animals are chimeric creatures, covered inside and out with microorganisms. These microbes are collectively known as an individual's **'microbiome'** (see Glossary). In the past decade it has become clear that the microbiomes associated with **hosts** can play a pivotal role in their host's health and well-being. The composition of the microbiome has been implicated in everything from obesity [1] to mood [2], making understanding the drivers of variation in microbiome composition increasingly important. Such variation across individuals can be high; for example a recent study of the gut microbiomes of human twins found that no bacterial strains of relatively high abundance ($>0.5\%$ of the microbial community) were shared among all individuals [3]. Unfortunately, explaining the observed variation among individual microbiomes has been difficult. For example, a recent analysis of the human gut microbiome by Falony *et al*. compiled 503 possible host factors across nearly 4000 individuals, and explained at most only 16.4% of the variation between individuals [4]. Even though this variation is ubiquitously present and known to correlate with health outcomes, as well as genetic and regional differences, the bulk of it remains stubbornly inscrutable.

We suggest that this lack of success stems in part from ignoring the fact that hosts and their microbiomes are ecological systems, multispecies assemblages structured by some combination of ecological interactions (among microbiome members and between microbes and their host), ecological drift, and **dispersal**. Although this is not a new idea, it has not played a major role historically in microbiome science. In part, this is due to the lack of a conceptual foundation for understanding microbiome variation. Ecological theory, in particular metacommunity theory, can provide this needed foundation, but for it to be maximally useful it will need to take into account the unique nature of the host–microbiome relationship.

Highlights

Identifying the causes of variation among host microbiomes is an important unanswered question in human biology, and it is essentially an ecological question.

Incorporating microbial transmission among hosts has the potential to increase our understanding of host microbiome variation.

Existing metacommunity theory provides a framework for including transmission and other scale-related issues in microbiome science.

Including behavioral, developmental, and evolutionary feedback between the host and the microbiome into metacommunity theory is likely necessary to fully understand microbiome variation.

The feedback between the hosts and other potential reservoirs of microbial species, such as the abiotic environment or hosts of other species, can alter metacommunity predictions.

[1]Institute of Ecology and Evolution, University of Oregon, Eugene, OR, USA
[2]Department of Ecology and Genetics, Uppsala University, Uppsala, Sweden

*Correspondence:
emiller8@uoregon.edu (E.T. Miller).

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Understanding Microbiomes Requires Incorporation of Multiple Scales

This lack of explicability is likely due to researchers generally considering the drivers of microbiome composition only at the scale of a single host. The Falony *et al.* [4] study mentioned above considered an exhaustive list of questions about individuals (e.g., age, weight, diet, and medication usage), but gathered little information regarding potential drivers at scales above the individual, such as the network of people the subjects interact with and their interaction frequency and duration. It is likely that the assembly and maintenance of host microbiomes is driven, at least in part, over much larger scales than the individual host. Another recent study of human microbiomes [5] found that whether subjects lived together or not was the strongest predictor of microbiome variance, consistent with the idea that **transmission** (among hosts and between hosts and their environment) could be an important driver of microbiome variation. This makes sense, given that humans (and all other animals) are born nearly sterile with minimal microbiomes that must develop through exposure to microbes from outside their bodies (e.g., other humans or the non-human environment), and throughout their lifetime they continuously come into contact with other potential sources of microbial colonists. Transmission could even occur between sites on the same host [6], although we focus specifically on transmission between hosts.

Metacommunity Theory Explicitly Considers Scale

Recently, several reviews have called for the use of ecological theory to guide the study of host microbiomes [7–11], with an emphasis on the ecology of microbiomes at a broader scale than just the individual host. The field of community ecology has long acknowledged the importance of broader scale processes to community composition (e.g., [12]), and most recently, metacommunity theory [13,14] has developed a robust set of theories focused on the interplay of ecological processes across spatial scales and levels of biological organization [15]. Metacommunity theory posits that the dynamics within any local group of interacting species (a community) are governed both by processes that occur within the community (such as resource competition or abiotic factors such as temperature) and by the process of dispersal which links communities together. The relative strengths of dispersal and within-community dynamics create different patterns of diversity and species composition [13,16–18]. The key insight is that local observations might not be indicative of local processes.

Metacommunity theory has already been successfully applied to host microbiomes, but there are important aspects of host–microbiome systems that require new innovations in metacommunity theory. We review below the ways in which metacommunity ecology has already advanced the study of microbiomes, and then make the case for the need for key modifications to existing theory. Specifically, we propose feedback loops that account for the biotic nature of the host, and the addition of a separate yet dynamic **species pool**.

Recent Applications of Metacommunity Theory to Host Microbiomes

Niche versus Neutral Assembly

One useful application of metacommunity theory is to understand the processes that shape the composition of host microbiomes. For example, researchers have asked under what conditions local dynamics (especially selection by the host) outweigh transmission (neutral dynamics) in explaining variation in host microbiomes [19]. In one study, researchers showed that during the course of zebrafish development the composition of the intestinal microbiome changes from one that is well fit by a neutral model to one that is not [20]. This could indicate that selection by the host on the microbiome increases as the fish develops. Researchers have also found that in healthy humans the lung microbiome was best described by a neutral model, but in individuals

with cystic fibrosis it was not [21], suggesting that the disease state increases selection for specific members of the microbiome.

The Effect of Social Connections

Another promising route has been to look directly at the role of transmission between hosts in shaping the composition of the microbiome. Transmission can be studied directly or through proxies such as social network structure. Theoretical studies have shown that dispersal between hosts can increase the stability of mutualistic relationships in host–microbiome systems [22]. Field studies in wild mammals have shown that the social connectivity of the host can alter both the composition and the traits of the microbiome, consistent with metacommunity theory [23,24]. Similar results have been found in zebrafish, where co-housing resulted in microbiomes enriched for genes likely involved in dispersal (e.g., chemotaxis and flagellar assembly genes) compared with the microbiomes of fish raised in isolation [25]. There is even evidence that host phenotypes can be transmitted between hosts along with the microbiome. In one such study, lean mice co-housed with obese mice gained weight without extra food [26].

Modifying Metacommunity Theory for Microbiomes

The relative novelty of applying ecological principles to microbiomes leaves ample room for existing theory to make meaningful contributions, especially with regards to host social structure and microbial transmission. However, there are some aspects of host systems that require new theoretical innovations [11]. Because the general assumption of metacommunity theory is that communities are distributed among abiotic environmental **'patches'**, the biotic and responsive nature of the host-as-patch requires some special accommodation (Box 1). In particular, including feedback at various temporal and spatial scales might be necessary to fully capture the dynamics of microbiome metacommunities (Figure 1). In addition, the questions answered by metacommunity theory will need to expand to include a focus on the properties of the host, such as fitness and development, as we seek to understand these systems as a whole. Although these issues are particularly pressing in microbiome systems, they are not entirely absent in non-host ecological systems. Feedback between biotic resources and consumers in a spatial context is certainly possible [27], and the possibility of selection at the ecosystem level [28] is an idea that has long been of interest to ecologists. Incorporating microbiomes into general metacommunity theory could therefore prove useful for general ecology as well.

Feedback and Dynamic Patches

To successfully model host–microbial systems, metacommunity theory must explicitly incorporate the idea of feedback between the host and the microbial community as well as between the hosts and the species pool (Figure 1, Box 2). Generally, in metacommunity studies, the characteristics of the patch are considered to be immutable (although see [29]), preventing feedback between the resident community and the patch. Although feedback loops are not a new idea in ecology, they have rarely been discussed in the context of metacommunity theory. In the case of host-associated microbiomes, the discussion cannot be avoided [30]. There is growing evidence that the microbiome affects the condition of the host across multiple time-scales, through behavioral changes [31], development [2], and evolution [32,33]. At the same time, we are discovering many ways in which the host can manipulate the composition of the microbial community; numerous examples of hosts manipulating their microbiome have been documented, ranging from host sanctioning of non-cooperating rhizobia in plants [34] to host feeding of beneficial microbes in animals [35]. This combination of effects makes feedback likely, and can lead to complex trajectories of microbiome assembly. Processes of behavior, development, and evolution might be unique to biotic patches, but change is not. Expanding metacommunity theory to account for dynamic processes between the community and the

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Box 1. Questions, Variables, and Systems

Expanding the Scope of Questions

Traditionally, metacommunity ecology has been focused on the effects of multiscale processes on community composition and assembly. The properties of the patch are certainly considered, but usually only inasmuch as they influence community properties. For host–microbiome systems, however, the questions we ask must span the microbial community, the host, and the properties that result from their interactions. The stability and composition of the microbiome is still of interest, but now the properties of the host, like fitness, might be equally interesting, as are the properties of the entire system (i.e., phenotypes that result from the interaction of microbiome and host). Certainly, where medical applications are concerned, the well-being of the host is paramount, but anytime the patch is a changing and developing entity, the drivers of that change and development will be of interest.

New Variables

Expanding the scope of metacommunity questions, as detailed above, requires inclusion of a dynamic patch variable to model the condition, quality, or resource level of the host. In addition, biotic hosts are likely to change their transmission network through time. Both host state and dispersal network must be modeled as dynamic. Box 2 gives a framework for how this could be done. From this starting point, it becomes relatively straightforward to consider the effects of feedback on the development or evolution of the host, and to consider ecosystem-level effects (in Box 2, the host state becomes a model output). The benefits of this approach are not confined to host-associated microbiomes. This could be an effective way to model land use change or ecosystem function in a diverse range of ecological systems.
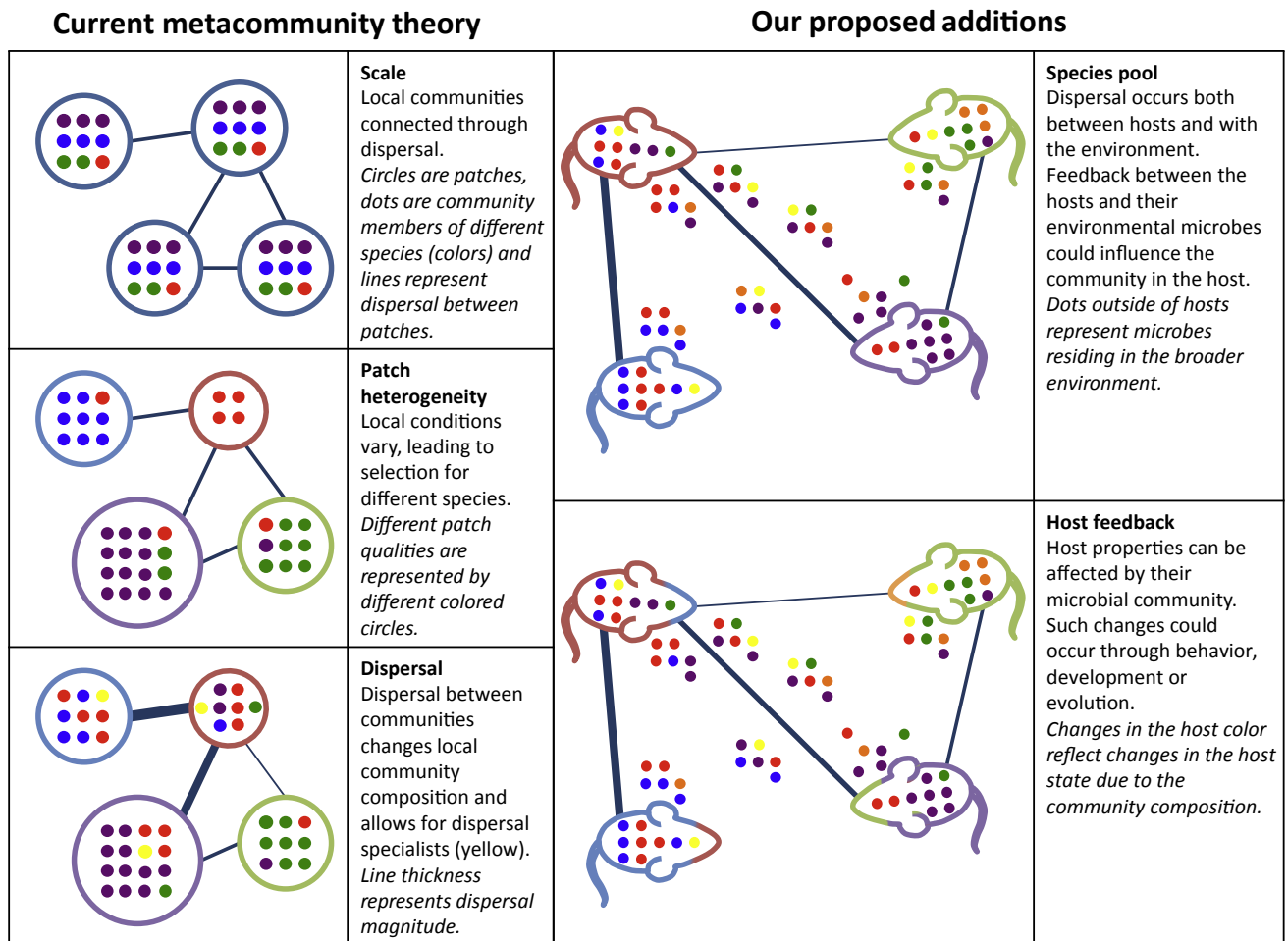
New Model Systems

Microbial microcosms have been useful to metacommunity research [28,29]; host–microbiome systems are a natural and convenient extension of that work. Zebrafish and mice (two popular model systems) have extensive host genetic information and tools, their commensal bacteria are rapidly being characterized, and their experimental tractability makes possible large sample sizes [30]. Host genetic tools enable manipulation of aspects of feedback (i.e., immune system function), and intra-host transmission can be manipulated either passively through housing or actively through addition of bacteria to food or directly into individual hosts [31]. Microbial genetic tools such as reporters and switches can help to identify the relative importance of within- versus between-patch processes [32]. These systems are also exciting because they allow the possibility of experimental evolution of the microbiome [33].

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patch will improve our understanding, not just of host-associated microbiomes, but also of ecology as a whole.

Behavior

Animal host behavior (including diet and habitat choice) can influence microbiome composition by altering host characteristics (the host 'environment' that the microbes experience [36–38]), as well as transmission of microbes between hosts and with the environment. The microbiome in turn can influence the behavior of the host [31], creating the potential for feedback loops. For example, foraging behavior has been shown to affect the microbiome of both three-spined sticklebacks (*Gasterosteus aculeatus*) and European perch (*Perca fluviatilis*) [39], either through transmission of microbial colonists on the food [40], or through changing the nature of host selection by changing the habitat provided by the host (e.g., gut substrate) [41]. Behavior can also alter microbial transmission through effects on social group size, the likelihood of encountering another individual, and grooming behavior. For example, Tung *et al.* [42] found that closely interacting baboon hosts had microbiomes with fewer transmission-related traits (such as spore formation and oxygen tolerance), presumably because host behavior made such traits unnecessary for microbiome membership. The quantitative and qualitative effects of behavior on transmission between hosts may affect metacommunity coexistence processes, such as a competition–colonization trade-off in a patch dynamic system. Conversely, resident microbes can influence host behavior through mechanisms such as mate choice [43], activity levels [44], and diet [45], complicating predictions about species-sorting mechanisms.

Current metacommunity theory

Scale
Local communities connected through dispersal.
Circles are patches, dots are community members of different species (colors) and lines represent dispersal between patches.

Patch heterogeneity
Local conditions vary, leading to selection for different species.
Different patch qualities are represented by different colored circles.

Dispersal
Dispersal between communities changes local community composition and allows for dispersal specialists (yellow).
Line thickness represents dispersal magnitude.

Our proposed additions

Species pool
Dispersal occurs both between hosts and with the environment. Feedback between the hosts and their environmental microbes could influence the community in the host.
Dots outside of hosts represent microbes residing in the broader environment.

Host feedback
Host properties can be affected by their microbial community. Such changes could occur through behavior, development or evolution.
Changes in the host color reflect changes in the host state due to the community composition.

Trends in Ecology & Evolution

Figure 1. Extensions of Metacommunity Theory to Accommodate Host–Microbiome Systems. Current metacommunity theory envisions patches as abiotic entities, which can exhibit heterogeneity through time and space, possibly causing selection to favor different species in different patches. Dispersal moves species between patches, allowing species to be found in patches where they might not otherwise survive and allowing for the coexistence of species that might not be found in any of the patches without dispersal. Our proposed additions incorporate feedback between the patches and the species pool and feedback between the patches and the microbial community. We explicitly model the dynamics in the species pool (microbes not residing in a host patch) since it is well documented that microbes that live and grow in the surrounding environment are common microbiome members, essentially making the species pool an additional, non-host patch. We also advocate considering the feedback between hosts and their resident microbiota. Because the microbiome can affect the host in a number of different ways (behavior, development, and evolution) ignoring two-way effects could result in fundamental misunderstanding of host–microbiome biology.

Development

There is growing evidence that the microbiome can alter the development of the host (e.g., gut [46], pancreas [47], and immune system [48]), changing the selective environment within a host as it ages. This process is not dissimilar from the idea of alternative stable states or ecosystem engineers. Theoretical research on macro-ecological systems indicates that alternative stable states are unlikely in metacommunities unless there is a large amount of abiotic variation between patches [49], but feedback between the host and the microbiome has the potential to create substantial variability. Feedback loops can create non-linear dynamics, leading to unexpected and divergent outcomes. Feedback between the community and the environment has been associated with founder effects [50] and alternative stable states [51]. Host–

Box 2. Updating the Metacommunity Model

In Box 1, we advocate for incorporating new variables into metacommunity models. Here we give a set of scaffolding equations to help organize the new variables and relationships. These equations are meant as symbolic, organizational tools, not as rigorous mathematical expressions. The variables, as discussed in Box 1, denote key entities, while the functions that link these variables are placeholders for specific functional forms (linear, non-linear, etc.) to be chosen by the researcher or determined through experimentation.

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\begin{aligned}
H &\approx f(H^*, C) \\
C &\approx g\left(H, E, \sum C_i\right) \\
E &\approx h\left(E^*, \sum C_i\right)
\end{aligned}
\qquad [\text{I}]
$$

Variables: we introduce a dynamic variable, H, which indicates the realized state of the host patch. H is affected by the immutable qualities of the host (H^*), such as genetics, and the composition of its microbial community (C). In turn, C is affected by H, the composition of the species pool in the broader environment (E), and the composition of all the other microbial communities in the population of hosts ($\sum C_i$). E is influenced by processes that occur outside of the metacommunity (E^*), and transmission from $\sum C_i$.

The functions: the functional forms f, g, and h are placeholders for the hard empirical work of determining the functional relationships between these variables. Transmission between hosts and between hosts and the environment will be crucial parameters, and may be modeled as variable in time and between hosts.

Implementation

We foresee two main tactics for incorporating our proposed changes for host–microbiome data: tweak existing metacommunity tools to incorporate feedback or draw inspiration from fields that already incorporate feedback and add metacommunity structure.

Tweaking Existing Tools

One option is to alter current metacommunity simulation software such as MCSim [16] to have a dynamic environmental variable for each patch. Instead of being set at the beginning of the simulation, each time-step of the model could update the patch environment depending on the patch state. Likewise, following the metacommunity coexistence model of Fournier *et al*. [60], one could treat the patch characteristic parameter e_x as dependent on the composition of the microbiome rather than fixed.

Drawing New Inspiration

If a researcher is interested in looking at the effect of social connections or other transmission networks, epidemiological tools such as EpiModel [61] allow dynamic network structure and could be modified to include multiple species instead of a single disease. Another option would be to employ techniques from co-evolutionary models that already take feedback into account. Spatial co-evolutionary models, such as the geographic mosaic theory [54] or other spatial co-evolution models [62], could be modified by increasing the number of species, varying the evolutionary rates of the players, and allowing positive as well as negative interactions.

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microbiome systems, with their multitude of feedback loops, may therefore be more likely to exhibit founder effects and alternative stable states than other systems. Development could also affect the transmission rates of microbes between hosts. Early-life transmission from the parents to the offspring can give way to transmission between mates as an organism ages. Time-variability of transmission would require metacommunity researchers to take into account past transmission states, especially in light of founder effects discussed above.

Evolution

While not as instantaneous as changes in development, host–microbial systems can form long-term associations over evolutionary time, where changes in the microbiome have been associated with speciation events due to hybrid lethality [33,52] or behavioral changes [53]. This co-evolutionary process between host and microbiome creates a situation not addressed in traditional metacommunity theory: the host has its own fitness imperative and it can be linked

with that of the microbiome. Although the topic of co-evolution across space has received some considerable attention [54], the patch itself is usually not one of the evolving entities. Some work has been done with co-evolution of hosts and parasites through space [55], but complex commensal communities have rarely been considered. Co-evolution between host and the microbiome is likely to increase the importance of species sorting relative to dispersal and other community assembly processes.

A Separate and Dynamic Species Pool

The concept of a species pool is common in community ecology. It is often used as shorthand for all possible colonists into a system or to describe the total possible diversity. In these cases species flow from the pool to the community and not the other way around [56]. Alternatively, the species pool is sometimes conceived as the total diversity represented in the system (i.e., gamma diversity). It is the sum of all the species in all of the patches in the system (e.g., [57]). We propose that host–microbiome systems reside between these two extremes. Evidence from studies of how microbiomes influence [58] and are influenced by [59] the environment imply that feedback with the species pool is critical to understanding microbiome composition. The species pool can, in effect, act as an additional patch with its own set of selective forces, potentially independent of the host patches. The characteristics of this environmental patch can have large effects on the microbes that disperse to and between patches and can often provide initial colonists after birth or following a disturbance event. For example, if the environmental patch is particularly selective, its effects on the community of colonists to the host patches could override selection by the host.

Testing Theory Requires Multiscale Data

Collecting multi-scale data is crucial to applying metacommunity theory to microbiomes, but it is nontrivial even in traditional ecology [63]. To interpret microbiome data in the context of metacommunity theory one must have information regarding dispersal between patches. Dispersal is notoriously difficult to quantify directly, but easier-to-measure proxies can suffice. If the hosts are relatively sessile, such as plants, or confined to a fixed territory, data on spatial distribution can provide information regarding the relative rates of dispersal. For example, the distance between plant rhizospheres or even between people and population centers might be useful proxies for transmission between microbiomes. For social hosts, information regarding membership in family or social groups or time spent in proximity can be a useful substitute for social information [23,42]. For aquatic hosts, information about watersheds or water flow could provide clues regarding how microbes could be transmitted.

One way of incorporating these data into statistical analyses of microbiome composition is to include a spatial co-variation term into a model, or to include a covariate for social group membership. For example, in a study seeking to understand the composition of nectar microbial communities, Belisle *et al.* [64] constructed a pair-wise spatial distance matrix for their patches and found that these spatial effects were the main drivers of microbial community composition. Plant ecologists have utilized this sort of spatial analysis to understand plant community composition [65]. Both of these types of data assume that transmission is straightforward and that it is equal for all species in a community; further study will reveal when this assumption is adequate.

Instead of using spatial or behavioral proxies, one could also attempt to infer transmission through methods such as source tracking [66], a Bayesian statistical method developed to understand the source of contaminates in microbial samples. Source tracking has been used to investigate the colonization by environmental microbes of infants born by C-section [67], and

contributions of the maternal oral and gut microbiome to placental microbial colonization [68]. It is important in such an analysis to know the potential dispersal sources. For example, when sampling for the commensal gut microbial communities one would also need to know the microbial communities associated with the food source as well as microbial communities from the surrounding environment (water, soil, sediment, etc.). Model organisms are ideal for these studies because they allow control of habitat and diet. Metacommunity models, specifically neutral models, can also be used for source identification, even in nonmodel organisms. In a study of the human lung, neutral models were used to pinpoint the most likely human source of lung bacteria [21].

Mutualism between the Fields of Metacommunity Ecology and Host Microbiomes

Medical research and microbiology have traditionally been whole campus quads apart from ecology and evolution. The application of ecological theory to host–microbiome communities is an opportunity for two fields that rarely intersect to benefit each other.

For microbiology and medical science, understanding the impact of microbiomes on human health is a pressing issue. Previous attempts at understanding compositional differences in microbiomes, one of the first steps in understanding microbiome function, have been stymied by low explanatory power of host variables. The incorporation of a sound conceptual basis for the importance of transmission between hosts could help to alleviate this problem (see Outstanding Questions). Furthermore, metacommunity theory and the resulting understanding of the effects of transmission could help medical researchers develop therapies to transmit desired microbiomes between individuals or through populations. In much the same way that understanding the transmission of diseases has enabled epidemiologists to better combat the spread of pathogens, understanding the transmission of health might allow us to encourage the spread of beneficial bacteria [69].

Box 3. New Hypotheses

Founder Effects and Alternative Stable States

One line of inquiry might be to look at the effects of feedback on the occurrence of founder effects and alternative stable states. Small differences in initial colonization could lead to changes in the development of the host and magnify differences between hosts through time. This might be one answer for the unexplained variation between the observed human microbiomes.

Co-evolution

Another interesting avenue would be to look at co-evolution between the host and its microbiome. It might be that the fitness of the host imposes a different level of selection on the microbiome, altering our expectations for the composition of the microbiome. A given species might proliferate in the microbiome, not because it is a good competitor or disperser, but because it increases its host's fitness, increasing its lifespan and offspring, and therefore increasing the ability of that species to persist in the metacommunity. This could be another mechanism of coexistence unexplored in metacommunity theory. An extension of this is that the feedback between the microbiome and behavior might contribute to sympatric speciation by influencing mate choice or habitat choice in the host, which in turn influence host microbiome.

Feedback with the Environment

The feedback between the host and the environment could also supply interesting hypotheses. Could environments where the host has a large effect on the species pool (built environments, nests, experimental housing conditions) change the expected metacommunity dynamics relative to systems where the host has a relatively small effect on the species pool (rivers with high flow, complex and well mixed communities)?

Ecology and evolution, however, have long been interested in the ways that processes translate across scales and across levels of biological organization. The realization that some of our theoretical expectations might not hold across all temporal [70] or spatial scales [71] has prompted calls for a new understanding of how scale interacts with ecological processes [72,73]. Host–microbiome systems are tiered ecosystems, with interactions between members who are experiencing life on very different scales. Investigation into how these systems work will give us insight into how ecology functions across scales of time, space, and even biological organization (Box 3). Methodologically, this is a fairly tractable system, especially when working with established model organisms such as mice or zebrafish. These organisms offer levels of replication and control often difficult to come by in ecology, while at the same time allowing for meaningful complexity and a connection to host fitness.

Concluding Remarks

The question of scale is one that has often been resisted by microbiologists; it is yet another complication to add to an already dazzling array of players and influences. Ecology has struggled through this problem and emerged with a set of theoretical approaches that enable the incorporation of multiple scales of focus. However, ecology has yet to comprehensively incorporate the possibility of dynamic feedback between communities and their environments, whether they are plant or animal hosts or even abiotic patches. This presents an opportunity for ecological theory and microbiology to mutually enrich each other through the incorporation of scale and feedback into a single conceptual framework. The implications of such a synthesis for human health are undeniable, as are the opportunities for expanding ecological understanding.

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Outstanding Questions

How does the size and nature of social groups contribute to the composition of the microbiome?

Is transmission of microbes generally host-to-host or through an environmental intermediary?

How does the living environment (nests, buildings, water) contribute to the composition and function of the microbiome?

Are directly transmitted microbes more host-specific than those that are acquired indirectly from the species pool?

Are directly transmitted microbes more mutualistic with the host than those acquired indirectly from the species pool?

How does the life history of the host (frequency of turnover, age structure) contribute to the composition of the microbiome?

How do the predictions of the metacommunity theory archetypes change with addition of feedback between the host and the microbial community?

How do we expect co-evolution to shape the traits of the microbiome?

How does the structure and composition of the microbiome affect the health and fitness of the host?

How does the stability of the host's diet (diet switching) contribute to the composition of the microbiome?

Are disturbed microbiomes (either by antibiotics, host stress factors, etc.) easier to colonize than undisturbed microbiomes, and under what conditions do they return to their original community composition?

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