Understanding Host-Microbiome Evolution through the Lens of Evolutionary Theory:

New Tricks for Old Dogs

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ABSTRACT

All plants and animals are host to a community of microorganisms, their microbiomes, that have crucial influences on the life history and performance of their hosts. Despite the importance of such host-microbiome relationships, relatively little is known about the role microbiomes play in mediating evolution of the host as well as entire host-microbe assemblages. This knowledge gap is partly due to the lack of theoretical frameworks that generate testable predictions on the evolutionary dynamics of host-microbiome systems. In this Perspective, we argue that the foundation for such frameworks exists in evolutionary theory. We highlight four examples of theoretical models - niche construction, indirect genetic effects, maternal effects and multilevel selection – that capture important aspects of host-microbiome evolution. We outline how each of these frameworks can provide key insights into the involved evolutionary dynamics, while also suggesting expansions of current theory to incorporate processes unique to host-microbe assemblages, for instance focusing on nuances in microbiome transmission and ecological microbial community dynamics. Expanding evolutionary theory to accommodate host-microbiome systems is key for a more integrative understanding of evolution, which is undoubtedly impacted by the association with microorganisms across the tree of life, guiding future empirical research on the function and evolution of these omnipresent interactions.

Introduction

All eukaryotic life has long-standing, intimate relationships with microorganisms. These host-associated microbial communities (including bacteria, archaea, viruses, protists, and fungi, together termed the microbiome) are crucial for host performance, affecting host traits related to metabolism[1], pathogen resistance[2], immune development[3], disease[4], and behavior[5], among many others. Beyond its fundamental interest, the potential applications of the microbiome vary widely, ranging from human health[6], to sustainable agriculture[7], conservation biology[8], and adaptation to climate change[9].

Yet, despite the clear relevance of host-associated microbiomes to host performance, relatively little is known about the causes and consequences of evolution in such host-microbe associations. Proposed almost two decades ago, the hologenome theory of evolution posits that the holobiont (i.e., the host and all its associated microbes) functions as a single, integrated evolutionary unit upon which selection acts[10]. Here, the hologenome refers to all

host genes together with the genes of all host-associated microbes. Since the introduction of this theory, various perspectives[11–19] have stimulated research on this, as it has turned out to be, controversial topic. Major challenges in considering hosts and their microbiomes as a single evolutionary unit are substantial variation in microbiome fidelity across generations (Box 1), and the multiple levels of selection and evolutionary interests possible in host-microbe associations[19].

An in-depth evaluation of these conflicting perspectives would greatly benefit from theoretical approaches[20]. Theory facilitates organization of observations, identifies generalities and gaps in our understanding, predicts future events, and provides guidance on the main questions and designs of empirical studies. Theory is especially useful for understanding processes that occur at temporal or spatial scales challenging to study, such as evolution. While previous studies developed theoretical models tailored to specific questions about host-microbe systems[21,22], the full breadth of well-established evolutionary theory has not been applied to understand the evolutionary dynamics and resulting consequences of host-microbe associations.

We propose to make use of the wealth of theoretical approaches in evolutionary biology to explore and dissect the evolution of host-microbiome interactions. We highlight four existing frameworks that address key characteristics of host-microbiome evolutionary dynamics. We discuss how we may borrow useful elements from each of these frameworks, while also highlighting fundamental differences between host-microbe evolutionary dynamics and existing frameworks, pinpointing features of host-microbiome evolution that require the development of new theoretical approaches. We point to important directions for future theoretical work, while emphasizing the importance of integrating theory and empirical work.

Box 1: Microbiome Inheritance

The fidelity of the microbiome (Figure B1) across host generations is the most critical factor that determines whether microbes share the same evolutionary interests as their hosts and thus may function as a single evolutionary unit. Several mechanisms could result in host-microbe associations exhibiting fidelity across host generations.

One process that could result in cross-generational host-microbiome fidelity is the vertical transmission of microbes from parents to offspring. Strict vertical transmission, akin to genetic inheritance, occurs through intracellular infection of germ cells, for example observed in aphid-*Buchnera*[23] and in carpenter ant-*Blochmannia*[24] systems. However, even in the absence of strict vertical transmission, 'intimate neighborhood transmission'[25] may result in the transmission from parents to offspring, for instance through the covering of eggs with microbes[26], through mode of delivery in humans[27], or through hosts shaping their microbial environment as a form of niche construction[28]. Further, vertical microbiome transmission goes beyond direct transmission from parents to offspring: living in proximity (e.g., sharing the same household with relatives) may promote microbiome fidelity[29]. Even in the absence of vertical transmission, host genotypes might directly influence the types of microbes that can establish in a particular host, shaping microbiome composition and increasing cross-generational fidelity[30]. Environmental transmission can also result in host-microbe fidelity across generations, whenever hosts faithfully acquire the same microbes from the environment every generation, as found in the Bobtail squid–*Vibrio*[31] and stinkbug-*Burkholderia* associations[32]. Whenever the environmental microbial pool responds to selection on hosts, environmental acquisition alone can lead to cross-generational microbiome fidelity, through 'collective inheritance'[33].

Despite all these different biological processes that may bolster microbiome fidelity, many host-associated microbes were proposed to lack cross-generational fidelity[19] and the exact degree of microbiome fidelity is often unknown for most host species. One way to quantify this relationship is to estimate the microbiome 'heritability' (Figure B1); the percent of microbiome variance (e.g., variance in relative abundance of a

microbial taxon across hosts in a population) attributable to host genotypic variance. Microbiome heritability has been estimated for only a limited number of plant and animal host species[34], suggesting low microbiome heritabilities in general, although some were on par with heritabilities of important host traits.

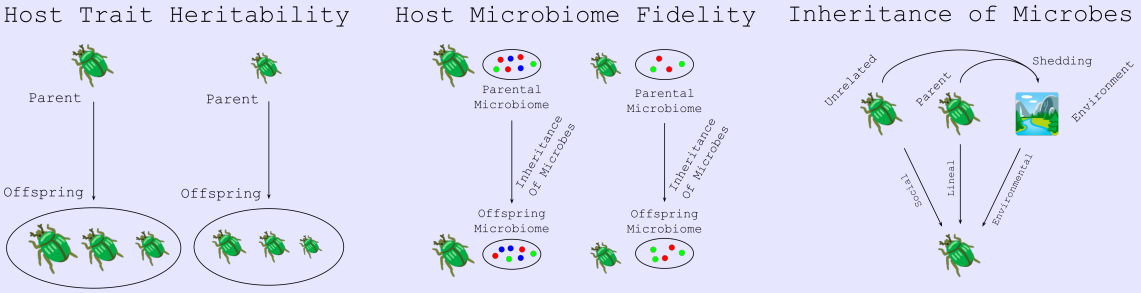

Figure B1: Components of microbially mediated inheritance. Heritability of host traits (left panel) measures the similarity of offspring traits to parental traits. Intergenerational microbiome fidelity (middle panel) is the similarity of microbiome compositions between host generations. Microbially mediated host trait heritability depends on microbiome fidelity, which in turn depends on the process of microbial inheritance (right panel).

Adapting Evolutionary Frameworks for Host-Microbiome Systems

A fundamental question is to what extent we need to develop new theory to describe host-microbiome evolution, and where we can draw on existing frameworks. Utilizing existing frameworks has the advantage of making the ideas, reasoning, and conclusions more accessible to researchers already familiar with such frameworks.

Host-microbiome systems are shaped by an array of diverse processes across many scales of biological organization, and it is unlikely that a single existing framework will capture them all. For example, metacommunity theory has been used to describe fundamental processes that influence the assembly of microbial communities, and this approach is relatively well established[35,36]. However, most such models ignore host-microbe feedbacks and host evolution[37]. In general, we lack an understanding of the consequences of natural selection on host-microbiome systems and the inheritance of selected (microbiome-mediated) variation in particular. In the coming sections, we explore how four evolutionary frameworks may help us understand such microbiome-mediated host adaptation over the timescale in which host microevolutionary dynamics occur (e.g., from a single to possibly thousands of host generations), each addressing different aspects of the evolution of host-microbiome associations (Figure 1): (1) Niche construction, (2) Indirect genetic effects, (3) Maternal effects, and (4) Multilevel selection.

Frameworks 1-3 focus on microbiome-mediated host evolution, considering host-associated microbiomes essentially as a form of non-genetic inheritance (NGI). NGI involves the transmission of other factors than the DNA (e.g., epigenetic patterns, cytoplasmic transmission, nutrient provisioning, and cultural inheritance), from parents (or other conspecifics) to offspring. Depending on how these non-genetic factors covary and interact with genetic, environmental and/or stochastic factors, NGI can manifest itself as, for instance, maternal effects[38], ecological inheritance[39] or indirect genetic effects[40]. There exists a large body of literature on the implications of NGI for plant and animal evolution[41]. Since various non-genetic inherited mechanisms share analogies with host-associated microbiomes, it provides a useful framing to think about microbiome-mediated host evolution, as we will discuss. As a fourth framework, we outline how we can use tools from multilevel selection and inclusive fitness theory to describe how composites of individuals respond to selection that jointly acts on various scales of biological organization, resulting in host-microbe coevolution.

For each framework, we briefly summarize the main concepts and discuss its merits and limitations for understanding host-microbiome evolution. We note these frameworks are not mutually exclusive, and each has a wide

variety of perspectives through which they may be viewed.

Niche Construction

The framework of niche construction is centered on the reciprocal dynamics of populations and their environment. Niche construction considers the indirect effects of organismal activity on their own or descendants' fitness through environmental modification, and it has been considered an evolutionary process in its own right[42]. There are two interpretations of niche construction, that may both apply to host-microbiome associations (Figure 1): A) environmental modification by organismal activity (which may or may not have evolutionary consequences) and B) an evolutionary process involving feedback between environmental change and organismal evolution.

Niche Construction as Environmental Modification

Niche construction as environmental modification by organismal activity without necessarily establishing an evolutionary process, applies to host-microbiome systems in at least two ways (Figure 1a). First, the microbiome of a host (such as microbiomes associated with the host's skin or gut) can be considered as a host's environment (Figure 1a-I). Host activity that results in microbe acquisition (such as through feeding, social behavior, or other means), and host immune responses that result in selection of microbes, provide mechanisms of niche construction.

Second, the microbiome of a host's immediate surroundings (e.g., microbial communities associated with different food sources, or with surfaces the host comes into contact with) can be considered as a host's environment. Niche construction then occurs when host activity alters the environmental microbiome composition, for instance by shedding microbes into their surroundings at a sufficient rate (Figure 1a-II), or by other activities including host-mediated structuring of the environment (e.g., nest building)[43], provision of nutrients (e.g., "priming" of soil microbes by plant roots)[44], and any kind of "farming" activity (e.g., the cultivation of fungi by insects)[45] (Figure 1a-III). These scenarios can alter either microbiome composition or microbial activity, and, through these changes in host habitat, may consequently affect host fitness (Figure 1a-IV). Such modifications can include increasing nutrient availability or suppressing pathogens, as has been observed to occur in soil surrounding plant roots[46,47].

Niche Construction as an Evolutionary Process

The interpretation of niche construction as an evolutionary process is more stringent, as it requires the inheritance of natural selection pressures (Figure 1b). This process, called ecological inheritance , requires that organismal activity shapes selection on genetic variation, and that these selection pressures are transmitted to subsequent generations[42]. Host-associated microbiomes can establish modes of ecological inheritance in at least two ways.

First, by mediating host trait expression, microbiomes can facilitate the inheritance of natural selection pressures on host genetic variation associated with that trait (Figure 1b-I) To illustrate this, consider a host trait z that is additively determined by a genetic component g and a microbiome component m such that z=g+m. This model of host trait architecture has previously been applied by[48]. Writing host fitness as a function of host trait, $W(z)$, selection on the host trait is defined as the covariance of fitness and phenotype, $\mathrm{Cov}(W,z)$. Then, setting $W_G(g)$ as the average of $W(z) = W(g+m)$ across m for fixed g (i.e., the marginal fitness of host genetic value g across variation of host microbiomes), and $W_M(m)$ as the marginal fitness of the microbiome component m, selection on host trait decomposes as follows:

$$\mathrm{Cov}(W,z) = \mathrm{Cov}(W_G,g) + \mathrm{Cov}(W_M,m). \tag{1}$$

This decomposition illustrates that selection at the level of host trait results in indirect selection at the levels of host genotype and host microbiome, and that these selection pressures are mediated by complementary components of host trait variation. In particular, because $W_G(g)$ is an average across microbiome variation, selection on host

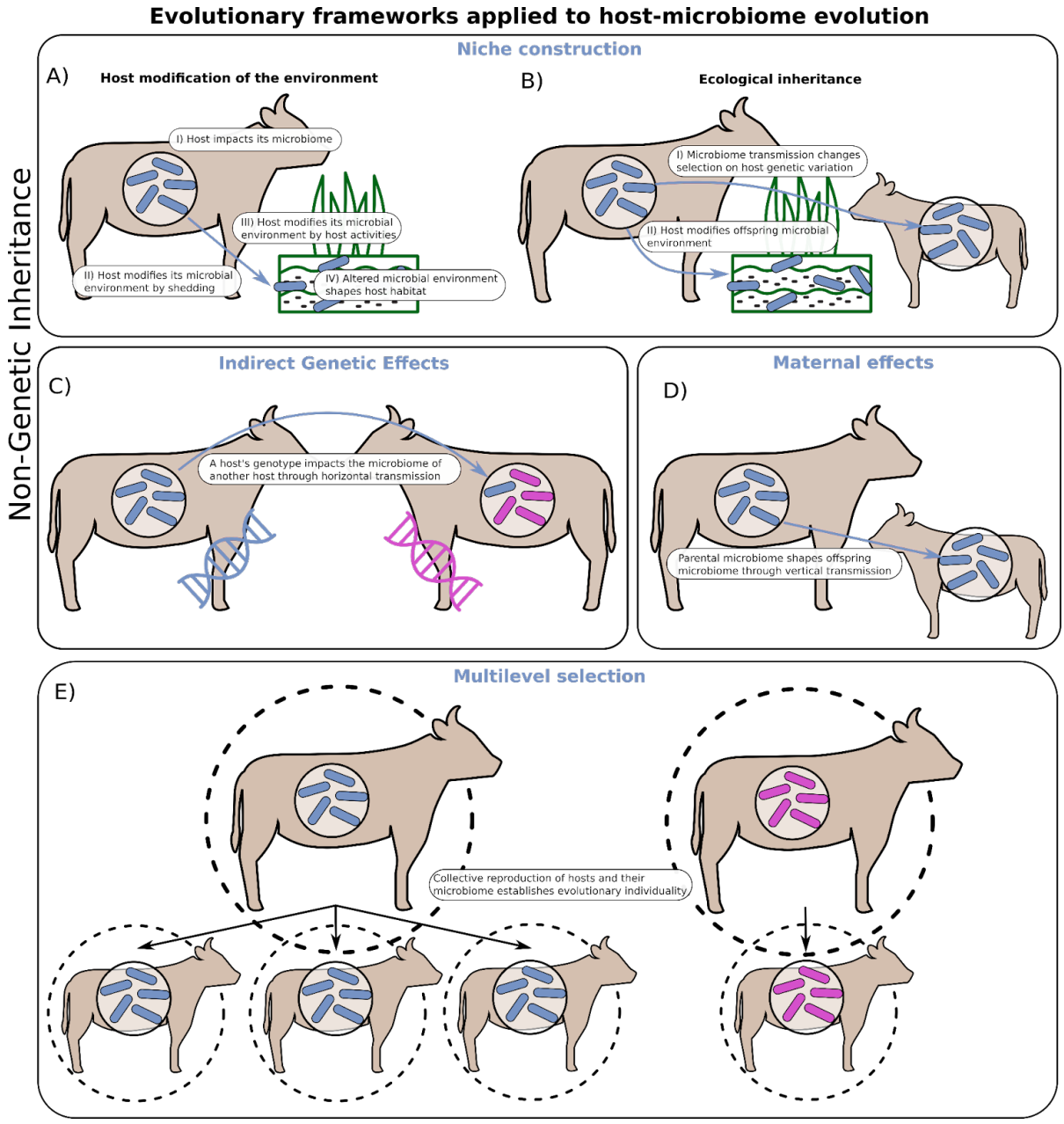

Figure 1. Graphical illustration of the discussed frameworks that exist in evolutionary biology and that address key characteristics of host-microbiome evolution. Note that these frameworks are not mutually-exclusive.

genotype ($\mathrm{Cov}(W_G, g)$), is a function of the distribution of host microbiome variation. Hence, in this case, the transmission of microbiome variation across host generations such that the distribution of microbiome variation in host parental generations resembles the distribution of microbiome variation in host offspring generations (see Box 1), establishes a mode of ecological inheritance.

Second, microbiomes can modify selection pressures on host genetic variation by altering the host environment (e.g., via host shedding), such as resource availability and habitat quality, (Figure 1b-II). These modified selection pressures can have long-term evolutionary consequences on host traits, such as immunological profiles, tissue structures, and physiological processes that influence specific microbial functions[14]. In this case, the focal host trait need not be mediated by the host microbiome, and instead could be purely genetically mediated. For the sake of clarity, in this paragraph we adopt this assumption, such that $z = g$. Summarizing the effect of the environmental microbiome on host fitness as m_E, we can include it as a parameter of the fitness function: $W(g|m_E)$. Then, the correlation of m_E between host generations maintained by host activity (such as shedding) results in the inheritance of selection pressures on host genetic variation, and therefore establishes a second mode of ecological inheritance.

Indirect Genetic Effects

Indirect genetic effects (IGE) are the influence of an individual's genotype on the phenotype of another (typically conspecific) individual[40]. Because IGEs contribute to the expression and inheritance of phenotypic variation, they have important evolutionary consequences. A major application of IGE is to understand the evolutionary consequences of social interactions in social insects[49–52].

Host-associated microbiomes establish IGE between host individuals when three conditions are met: 1) host genes determine microbiome composition, 2) microbiome composition is transmissible, and 3) microbiomes mediate a host trait. When these conditions are met, microbiome transmission (which may occur during social encounters) forms the mechanism for the genes of one host to influence the phenotype of another host (Figure 1c).

To illustrate this, consider microbiome composition as a host trait z_1 that is mediated by host genotype g_1 such that $z_1 = g_1 + e_1$, where e_1 is an environmental effect. Now consider another host trait that is mediated by host genes and microbiome composition

$$z_2 = g_2 + e_2 + z_1. \tag{2}$$

This is similar to the starting point taken by[53] to derive their model for interactions with nonreciprocal effects. As a consequence of microbiome transmission via social contact, we might take the same starting place and assume that each individual engages in a single interaction with another randomly chosen individual. Denote by z_1', g_1', e_1' the trait and trait components for the non-focal interacting individual. Suppose that the social interaction results in an exchange of microbes between the interacting partners, so that their microbiome composition traits become similar by some amount $0 \leq \psi \leq 1$. Writing z_1 as the microbiome composition of the focal individual after the interaction, we then have

$$z_1 = (1-\psi)z_1 + \psi z_1'. \tag{3}$$

Assuming the second trait z_2 is expressed after the exchange of microbes has occurred, it can then be written as

$$z_2 = g_2 + e_2 + z_1 = g_2 + e_2 + (1-\psi)(g_1 + e_1) + \psi(g_1' + e_1'). \tag{4}$$

The coefficient ψ , which measures microbial transmission via social contact, also quantifies an indirect genetic effect of the interacting partner's additive genetic value g_1' on the expression of the focal individual's trait value z_2.

The IGE framework has applications for understanding the dynamics of host-associated microbiomes, particularly for systems where social transmission of microbes between unrelated individuals plays an important role. Because the IGE framework considers interactions between arbitrary individuals, and only incorporates non-random interactions mediated by trait covariances, and not necessarily relatedness[40], it requires additional assumptions to apply to systems with substantial parent-offspring microbe transmission. To model this complementary scenario more directly, the related framework of maternal effects has greater utility.

Maternal Effects

A maternal effect is the influence of a parental phenotype on an offspring phenotype, controlling for genetic variation, mediated by parent-offspring interactions such as maternal care[54]. Host-associated microbiomes establish maternal effects between host parents and host offspring when a host trait is mediated by its microbiome, and part of the host's microbiome is inherited from direct parent-offspring transmission (see Box 1 and Figure 1d). Assume a host trait decomposes as

$$z = g + m, \tag{5}$$

where g is the additive host genetic effect, and m is the additive effect of host microbiome composition. To account for microbiome transmission directly from parents to offspring, suppose the offspring microbiome m' is given by

$$m' = \ell m + (1-\ell)\xi + \delta, \tag{6}$$

where ℓ is the proportion of the offspring microbiome inherited from its parent so that $(1-\ell)$ is the proportion acquired from the environment and unrelated hosts, ξ corresponds to the microbiome composition averaged across the environment and unrelated hosts, and δ is an ontogenetic differential of the microbiome that is independent of m. Using this simple analytical model, we can measure the microbiome's contribution to a maternal effect by quantifying maternal effects as the partial regression coefficient of offspring trait on maternal trait, holding genetic variation constant[38].

To measure the microbiome mediated maternal effect in the above model, we write the variance of the trait z as P, M the component of P explained by microbiome variation (i.e., the variance of m), and ω the maternal effect. The maternal effect can then be expressed as

$$\omega = \mathrm{Cov}_{g,g'}(z, z')/P = \mathrm{Cov}_{g,g'}(g + m, g' + m')/P = \mathrm{Cov}(m, \ell m)/P = \ell M/P, \tag{7}$$

where the subscript $_{g,g'}$ is a reminder that we are holding genetic variation constant in both the parent and offspring. This demonstrates that host-associated microbiomes can be modeled as maternal characters, but the application is limited to the analysis of microbiome inheritance resulting from strict parent-offspring transmission.

Multilevel Selection

This last framework applies to microbe-host associations in which microbiome-mediated traits are heritable and subject to natural selection. Heritable variation in both host and microbe fitness is essential for the host-microbe system to be an evolutionary individual that responds to natural selection (Box 1). In other words, Lewontin's conditions[55] must be met. Establishing host-microbe evolutionary individuality requires the collective reproduction of hosts and microbes, either through vertical microbe transmission or through horizontal transmission mechanisms that link host-microbe genomes and fitnesses[56]. Given these restrictive conditions, most host-microbe associations are not considered evolutionary individuals (we note that terms such as demibiont have been coined to describe

associations that exhibit less than perfect collective reproduction)[57].

The host-microbe systems with collective reproduction can experience natural selection as individuals, as kin, and as groups of unrelated organisms[58], all explicitly captured by multilevel selection (MLS) models Multilevel selection 1 (MLS1) models deal with selection among kin or relatives. For instance, populations of (nearly) clonal host-associated microbes experience inclusive fitness if their activities ensure transmission of their relatives to new host generations. Groups of individuals (e.g., hosts with all their microbes) operating as a collective are modeled by multilevel selection 2 (MLS2). Recently, multilevel selection 3 (MLS3) was proposed, merging MLS1 and MLS2 to consider the joint influence of microbe-inclusive fitness and group selection on emerging host-microbe trait evolution[33]. Multilevel selection models have been successful in describing the major evolutionary transitions in individuality that resulted in endosymbiont-derived organelles, multicellularity, and the germline[59–62].

By testing different MLS models, we can ascertain whether individual, kin, or group selection, or a combination, is the predominant force in the evolution of emergent host-microbe phenotypes. As for MLS1, because individual microbes are subdivided into groups among hosts, their selection coefficient can be split into two components: selection within-hosts and selection among-hosts[63]. For a population of individuals (i.e., microbes) to experience selection that can be modeled with MLS1, the relatedness between individuals (r) and the indirect fitness benefit from their interaction (b) must exceed the cost to individual fitness (c), expressed as $r > c/b$[64–66]. However, this equation, known as Hamilton's rule, is only valid for close relatives experiencing strong additive selection, not capturing more complicated models of selection[67].

Instead, a quantitative genetic model of direct and indirect fitness effects allows for simultaneous consideration of MLS1 and MLS2. Here, phenotype P of individual i (P_i), interpreted as either the host or the microbe, can be written as[68]:

$$P_i = A_{D,i} + E_{D,i} + \sum_{j \neq i}^{n} A_{s,j} + \sum_{j \neq j}^{n} E_{s,j}, \tag{8}$$

where $A_{D,i}$ is the direct heritable impact of individual i on its own phenotype, whereas $A_{S,i}$ is its indirect heritable impact of other host or microbe associates in the community on the focal individual. $E_{D,i}$ is the direct environmental impact on individual i, and $E_{s,j}$ is the environmental impact on the indirect effects of individual i on the community associates.

At the population level, the selection for individual i (C_i) can be expressed to depend both on focal phenotype P_i and on all other phenotypes in the group[68]:

$$C_i = P_i + g \sum_{j \neq i}^{n} P_j. \tag{9}$$

Here, g is the degree to which group selection acts (when $g = 0$, selection acts on individuals only; when $g = 1$, selection acts on the total group-level phenotype). This approach allows us to connect levels of selection occurring simultaneously across distinct scales of biological organization. In particular, this framework can be adapted for the study of diverse microbe-host systems by considering selection on phenotypes expressed by the host, the microbes, and the joint actions of the host and their associated microbes. The associative phenotypes that feedback indirectly on these focal individuals can be experienced by the host, the microbes, or the host and their associated microbes by varying the degree of relatedness among associates when modeling the group's response to selection. More than two levels of organization can be considered by generalizing equation (9)[68], allowing for structured populations of host-microbe groups and within-host microbe groups. Future work is needed to simultaneously model individual-level and emergent group-level phenotypes.

Discussion

Limitations of Existing Frameworks

Each of the discussed pre-existing frameworks is useful for understanding specific cases of host-microbiome evolution. At the same time, some fundamental properties of host-microbiome systems necessitate expanding these frameworks. Niche construction has clear applications for understanding the relationship between host and environmental microbiomes, and consequential selection of host-microbiome associations. Modification of the social environment via microbiome transmission may be considered a form of niche construction. While niche construction does not focus on nuances in microbiome transmission, the frameworks of indirect genetic effects (IGE) and maternal effects (ME) are particularly useful for understanding the evolutionary consequences of such social and parent-offspring transmission, respectively. Combining IGE and ME could account for mixed transmission modes, consisting of social and parent-offspring transmission. However, IGE and ME treat the consequences of microbiome transmission as fixed effects, limiting their ability to incorporate microbiome community dynamics, host immune response, and variation of transmission other than what is explained by trait covariances. Hence, further expansions are needed to incorporate specific biological details relevant for understanding host-microbiome dynamics.

Multilevel selection is useful as an overarching framework for understanding selection on complex host-microbiome assemblages, but this approach has important limitations as well. The evolutionary mechanisms that enable evolutionary transitions in individuality to occur are still under debate and models are in development. For example, it is still under debate whether MLS1 and MLS2 are inequivalent because the Price equation has supported their equivalency since the 1970s[69–71]. Further, while some group-level phenotypes may have relevance at the individual level, not all will. For example, metabolic complementation between aphids and their Buchnera endosymbionts for amino acid synthesis is selected for in the host-microbe assemblage, but not in the individual organisms, because the individual aphid and Buchnera genomes lack genes to complete the pathway.

Opportunities for Developing Novel Frameworks

Beyond the four frameworks discussed here, host-microbiome systems provide a number of exciting opportunities for extending and developing theoretical approaches to describe features that are not sufficiently captured by our focal frameworks. For example, microbiome composition varies over the course of a host's life[72,73]. Here, theory on ontogenetic changes in maternal and genetic contributions to host phenotypic variation[74] may provide useful insights to microbiome changes during host development and its implications for responses to selection. For instance, a maternal signal in microbiome composition that diminishes with host age[75] could be captured by a negative relationship between host age and the contribution of maternal effects. Further, host microbiome composition is shaped by fluctuating microbial abundances resulting in within-host ecological interactions, but such interactions are ignored in the non-genetic inheritance and group selection frameworks that we discussed.

These frameworks can be extended to account for such ecological details by integrating models of microbial community dynamics into host trait architecture. These biotic interactions are even further complicated by the existence of multiple trophic levels within a microbiome community (e.g., interactions of bacteria with phages or predatory bacteria)[76–78]. Microbes can also show context-dependence in their contributions to host fitness, where they act as mutualists in one environment, while as pathogens in another[79–82]. Theory on fluctuating selection[83] could be used to assess host-microbiome evolution in such a case.

Additionally, there are many opportunities to expand theory of multilevel selection. For example, stochastic simulation of multilevel selection processes could enable the development of new MLS models and theories to pinpoint the conditions required for cooperation among microbes and hosts to evolve. Spatial structure shapes the formation of groups that can respond to selection pressures[63,70,84,85], emphasizing the need to incorporate environmental parameters in MLS models. Genetic models for mapping trait selection onto the complex genetic

basis for that trait[86] could be used to map group-level phenotypic selection onto individual genotypes. Incorporating genetic parameters into MLS models will enable the use of genome-wide datasets. Further, the impact of host versus symbiont population size and generation time on the rates of co-evolution should be considered[33,87].

Lastly, it may be useful to consider microbiome mediated host traits as a form of phenotypic plasticity. However, the framework of phenotypic plasticity typically considers a single global environmental factor driving the plastic response of a population, and one that is not transmissible. Moreover, microbiome-mediated plasticity can act at different levels and time scales[88]. For example, a new environmental challenge can be accommodated fastest by ecological changes in microbiome community composition, followed by evolutionary genetic changes in single microbial lineages. Such microbiome plasticity can further selectively favor hosts that either select the beneficial microbes from the environment or ensure their vertical transmission, as a kind of microbiome-mediated Baldwin effect[88]. Hence, application of the phenotypic plasticity framework to microbiome mediated traits would need to be extended to account for environmental factors taking values unique to each host individual, and possibly transmissible between hosts.

The Need for "Empirically Friendly" Theory

We feel that it is important to recognize that existing theoretical frameworks were often developed with biological systems in mind other than host-microbiome systems. Not only has this resulted in frameworks that lack key aspects of the biology of host-microbiome systems (as we discuss in the previous section), but it has also limited the application of these frameworks to host-microbiome systems in the laboratory and the field. To make these frameworks maximally useful, it is important that the validity of the underlying assumptions of these frameworks is determined empirically. It is also crucial that these frameworks are constructed in a way that makes their predictions empirically testable, given the technical limitations of empirical microbiome research. For example, for many host-microbiome systems, empiricists are limited to surveying relative abundance or presence/absence of microbial taxa, and for theory to be maximally useful it must generate predictions for these microbiome attributes. Tailoring theory in this way will likely require direct collaborations between theoretical and empirical microbiome scientists, to enable an iterative refinement of theory with information from actual host-microbiome systems. This requires suitable host systems, such as the water flea *Daphnia* (Box 2), the nematode *Caenorhabditis elegans*[89,90], the zebrafish *Danio rerio*[91], or insect-*Wolbachia* associations[92] as examples.

Box 2: Empirical studies of the theoretical frameworks using the water flea host system as an example

The water flea *Daphnia* (Figure B2), a freshwater crustacean, is a model organism in many biological fields, such as ecotoxicology[93], epidemiology[94], and evo-evolutionary dynamics[95], and is investigated in different settings, ranging from controlled laboratory experiments, to mesocosms, to natural field observations. *Daphnia* are also increasingly being used to study host-microbiome interactions[96]. Previous studies have revealed various aspects of the *Daphnia*-microbiome system that make this system uniquely promising to parameterize and test theoretical frameworks on the evolution of host-microbiome interactions.

First, while gut-associated microbial communities in *Daphnia* are relatively simple with a few core members, these communities are clearly distinct from their surrounding aquatic microbial communities[97], suggesting a role of selective processes at play. Second, *Daphnia* microbiomes are impacted both by the environmental conditions (e.g., temperature[98]) and by host genotype[99]. Third, the microbiome of *Daphnia* is related to host fitness: associations between microbiome composition and various life history traits have been found[100,101], and microbiome-mediated plasticity may help adjust hosts to their environment[102]. Finally, both horizontal and vertical transmission shape *Daphnia* microbiome composition[103,104].

Practically, *Daphnia* are easy to culture in the lab, and clonal lineages can be established from hatching sexually produced resting eggs (which remain viable in the sediment for decades). Under favorable conditions, asexual reproduction can be ensured, enabling a high amount of control on genotypic variation. Further, due to their fast life-cycle, it is straightforward to perform experimental evolution on populations that can easily consist of a few hundreds individuals. Lastly, using *Daphnia* as a host system enables causal inferences on the role of the microbiome for host fitness, both by rearing germ-free hosts[101] and by microbiome transplants[105].

Altogether, this suggests a relatively straightforward integration of empirical data with evolutionary theory, in order to understand host-microbiome evolution. For example, *Daphnia*'s asexual reproduction facilitates the quantification of parent-offspring microbiome transmission as a maternal character, as the contribution of host genetics is known to be constant across generations. Also, *Daphnia* are primary consumers and a keystone freshwater species, and have been shown to mediate their surrounding aquatic microbial communities by grazing[28]. This is a clear example of niche construction as an environmental modification (Figure 1a), but may also establish a mode of ecological inheritance whenever the modified environment shapes selection on *Daphnia* genetic variation (Figure 1b).

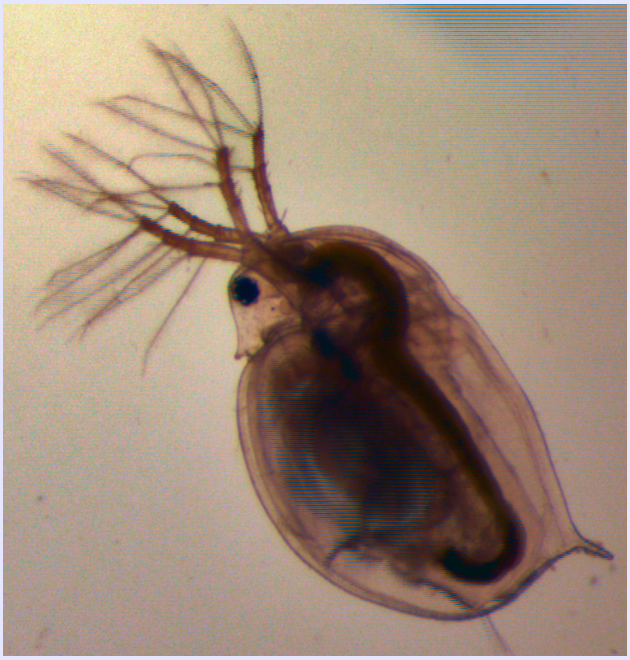

Figure B2: Photo of the water flea *Daphnia*. Photo credit: Dr. Marjolein Bruijning.

Conclusion

In this perspective, we presented four frameworks developed in the fields of evolutionary biology that help to generate new insights into host-microbiome evolution. In order to capture the biological diversity of such host-microbe systems and produce empirically testable predictions, these frameworks require thoughtful expansion and in some cases the development of novel theory, in close collaboration with empirical microbiome scientists. We envision that the initial result will be a mosaic of theoretical frameworks, each tuned to the set of processes considered and questions asked, with the initial goal of clarifying concepts. Such a mosaic could eventually lead to the identification of general principles underlying the interactions between microbes and their animal and plant hosts, greatly expanding our understanding of the evolutionary consequences of the host-microbe associations omnipresent across the tree of life.

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