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Forum

Theory of host-microbe symbioses: Challenges and opportunities

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Growing insight into microbial symbioses highlights the need to model these systems mathematically. We discuss three areas requiring theoretical advancement: nested ecology within a host or holobiont, holobiont population dynamics, and symbiont-mediated speciation. Developing the proposed frameworks will bridge theory and empirical findings, accelerating our understanding of host-microbe symbioses.

A holistic approach to studying hosts and their microorganisms

Microbes shape the biological world around us, and their interplay with hosts drives evolution and ecology in a multitude of systems, ranging from terrestrial to aquatic. Eco-evolutionary processes between hosts and their microbiomes can intertwine, leading to dynamic feedbacks that impact each other's physiology and fitness. In this context, we refer to a host and its associated microbes as a *holobiont*[1] (Figure 1A). An exemplar system is reef-building corals, one of the most well-studied holobionts, in which the coral host and the myriad of microorganisms that reside in and on its surface—such as photosynthetic microalgae (e.g., Family *Symbiodiniaceae*), bacteria, fungi, and viruses—are all integral parts of a dynamic living system[2] (Figure 1A). Another notable example of a holobiont is the human host and its gut microbiome, which consists of hundreds of species and can shift in composition and evolve over the course of the host's lifetime.[3] Such changes can affect the digestion, behavior, stress levels, and immune responses of the host. Likewise, the host can alter its microbiome through food choice, travel, genetic influences, immune responses, etc. These and other examples suggest that symbiotic interactions pervade the tree of life.[3]

Despite the recognized importance, there is limited mechanistic understanding and theoretical foundation for holobiont systems in natural and laboratory settings. This gap stems from the recent recognition of microorganisms as key drivers of host ecology, trait variation, and evolution, advancing a shift from individualistic to collectivistic views of life's hierarchical structures and processes. Mathematical models include a level of clarity that verbal descriptions lack, making them a powerful tool for advancing holobiont theory. Modeling such collective systems, however, poses new theoretical challenges, particularly as host-symbiont relationships blend the scopes of ecology and evolution, which have historically been examined separately.

Classic evolutionary models, largely based on parent-to-offspring transmission of nuclear genes, inadequately capture the dynamics of symbiont-encoded host traits that can be acquired or lost within a host's lifetime. Moreover, symbiont abundance within a host can fluctuate due to selection, mutation, competition with other symbionts, and host interactions. Advancing our understanding of host-symbiont dynamics requires developing an eco-evolutionary theory that integrates multiple levels of organized diversity, from genes to communities, and accounts for interdependent modes of selection. Here, we identify and discuss

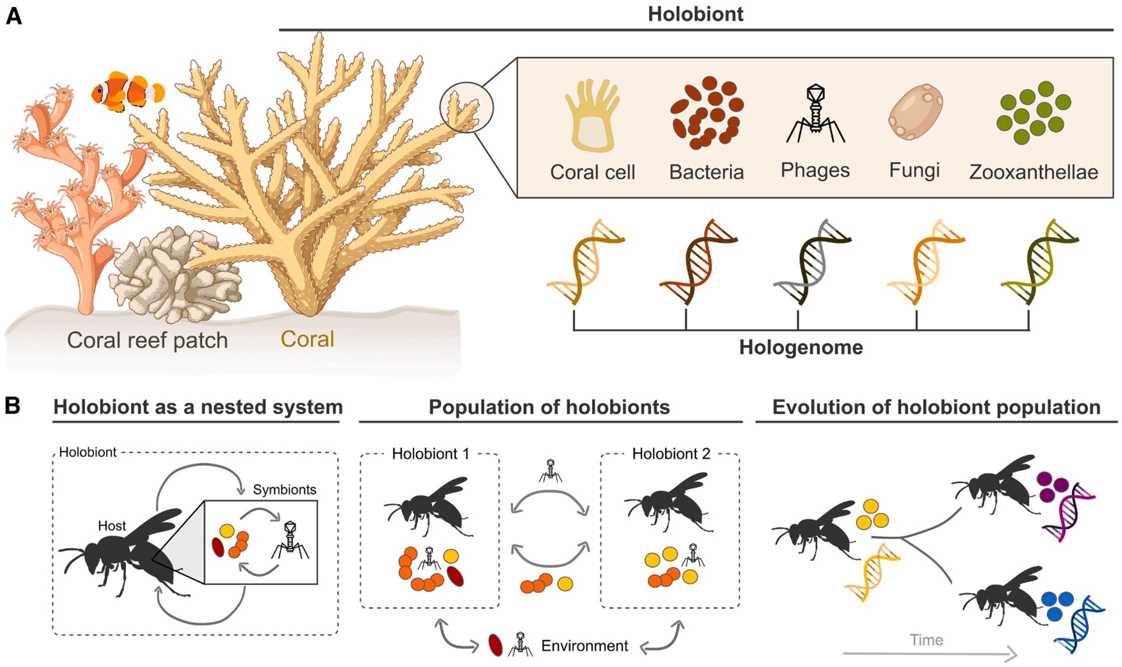

Figure 1. The holobiont as a dynamic living system

(A) Overview of the reef-building coral holobiont, composed of the host and its associated symbiotic microorganisms that, combined, define the holobiont. The combined genetic material of the host and its associated microorganisms defines the hologenome.

(B) Three major areas of current challenges and future opportunities for improvement in modeling host-symbiont systems. Figure partially created with BioRender.com.

research areas for theoreticians and empiricists to jointly develop a comprehensive theory of holobiont ecology and evolution.

Opportunities and challenges in modeling host-microbial systems

Current challenges in host-symbiont modeling can be divided into three major complementary areas of research that warrant theoretical investigation. These three areas, illustrated in Figure 1B, are the characterization and modeling of the following: (1) a single holobiont as a nested system of the host and its microbial symbionts (e.g., microbes and phages); (2) populations of holobionts (e.g., multiple host species and their associated symbionts, which can be vertically or horizontally transmitted among hosts); and (3) the evolutionary consequences of host-microbe interactions (e.g., divergence of holobiont populations and symbiont-driven host speciation).

Area 1: Individual hosts as nested systems

First and foremost, theory for holobiont biology must account for the nested structure of microbes and viruses within their hosts. In the coral holobiont, an example of a nested system, the coral's health is intertwined with its ability to retain a community of symbiotic algae and bacteria.[2] This symbiotic relationship is then fine-tuned by viruses, which can infect both bacteria and the dinoflagellates and modulate their prevalence and abundance in the host[2] (Figure 1A). Thus, coral holobionts constitute an archetype of a nested system of interactions prevalent throughout nature. Each element's dynamics must be accounted for in theoretical models to embody a holistic perspective that accounts for interactions across the symbiotic multitudes.

A set of models increasingly used for microbial communities are consumer-resource models. In these models, the structure of the microbial community emerges from the availability of resources and interactions between microbes, such as competition for nutrients. However, consumer-resource models typically do not capture the feedback dynamics between a host and its microbes. Many chemostat models assume a constant inflow of nutrients to the microbes, while in a nested context, the resources supplied by the host can fluctuate in response to factors such as diet or health status. These fluctuations, in turn, can be influenced by the microbiome or virome (e.g., Trevelline and Kohl[4]). Extending consumer-resource models to incorporate these reciprocal fluctuations can provide important insights into alternative mechanisms for community resilience. For example, a more diverse microbial community may affect host-derived resource availability, thereby changing microbial community dynamics and stability. Likewise, competition-colonization models of symbiotic bacteria with dynamic hosts may reveal feedback between host and symbiotic traits that lead to stable long-term equilibria.

As nested systems extend beyond the host and its microbes, the inclusion of a third layer of complexity (e.g., phages) will provide further insights into within-holobiont dynamics. Phages can interact with resident microbes either via lytic or lysogenic reproduction. In the former, the phage induces lysis of the microbial cell, while in the latter, the phage enters a longer-term symbiotic relationship with the bacterial cell, which can range from commensal to mutualistic. Relative abundances of lytic and lysogenic viruses can present non-trivial dynamics[5]; therefore, modeling their changes and how they relate to bacterial and host community dynamics is of particular interest to researchers studying tripartite host-microbe-virus interactions. For instance, lysogenic life histories are more common in holobiont systems, such as coral reefs or the mammalian gut, than in free-living environments. While the mechanism behind this trend remains unclear, mounting genomic evidence in reef corals points to a role for lysogenic phages in aiding the metabolic capabilities of coral symbiotic bacteria, such as assisting in sulfur cycling and photosynthesis.[6] Advancements in our theoretical understanding of nested host-bacteria-phage systems have the potential to shed light on the balance between mutualistic and competitive interactions implicated by viruses, microbes, and their hosts. Modeling a single holobiont encompassing all of these components is a key step in extending these frameworks to holobiont populations, as explored in the following section.

Area 2: Dynamics of holobiont populations

Overcoming the challenges associated with the mathematical modeling of a single holobiont represents a vital stepping stone to modeling populations of holobionts. Hosts are not isolated systems; rather, they are embedded in a larger ecological context that can influence the composition, functional capability, and stability of the host's microbial symbionts. Members of the microbiome can be horizontally transferred between holobionts depending on the duration, frequency, and structure of the social interactions between two hosts.[7] In addition, transmission can happen between hosts of different species, e.g., through predation, a shared environment, or exposure to fecal material.

Microbial flow potentially affects the fitness of any symbiotic partner. Such effects can confer improved digestion of certain nutrients, increase resilience against environmental stress or pathogenic infection, or facilitate host adaptation or acclimation to a new environment.[8] Combined, these factors can mediate the dispersal, competition, and coexistence of host populations.[8] Thus, holobiont population dynamics are determined by the ecological interactions occurring in and among the "micro" scale (i.e., between symbionts within a host and between symbionts and their host) and the "macro" scale (i.e., between hosts and between a host and the environment).

Metacommunity theory considers processes occurring at both local and broader scales, ranging from population dynamics within a patch (i.e., a certain habitat or geographical area) to species dispersal across different patches. In the context of holobionts, hosts can be seen as habitat patches for dispersing microbial symbionts,[9] where dispersal between patches is influenced by host social structure and the network of ecological interactions. Extending current metacommunity frameworks, such as island biogeography theory that links biodiversity to habitat size and isolation, will be crucial for developing theoretical expectations of holobiont population dynamics. Such extensions would include incorporating microbial transmission between hosts and their environment, as well as between hosts themselves. Additionally, extensions may consider how feedback between hosts and their microbes affects the suitability of hosts as habitats, ultimately shaping how hosts interact and are spatially distributed.

Previous theories that include intraspecific variation among host populations may also be leveraged to address this challenge. For example, some epidemiological models explicitly consider the transmission of multiple, co-infecting pathogenic strains between hosts. Implementing this class of models for host-microbe dynamics requires characterizing the type of transmitted microbes, which can range from pathogenic to commensal to mutualistic. In addition, changes in host fitness may result not only through the transmission of a specific microbial taxon but also through emergent properties of the whole microbiome. For instance, host-microbiome diversity and stability, which can be related to the degree of similarity of microbiomes among groups of interacting hosts, may elicit non-trivial physiological and immune responses.[7] Thus, understanding microbial transmission dynamics in light of host social structure will be essential to fully understanding microbiome composition in holobiont populations.

As holobionts consist of multitudes of species, the number of potential interactions and associated parameters increases faster than exponentially. Multiple options exist for simplifying microbial communities, including dimensionality reduction techniques and grouping organisms by their traits through allometrically scaled networks. Machine learning can also aid in reducing the dimensionality of systems by identifying modes of selection from trait distributions, or functional or co-occurring groups in a community of interest (e.g., San Soucie[10]). These computational tools can be used for model testing and prediction of holobiont dynamics and extended to include more granularity as we become able to measure the influence of individual symbiont groups empirically. By adopting mathematical structures and notation that work well in very high-dimensional spaces, such as tensors, we can systematically bookkeep the many players and parameters, forming a first step toward handling holobiont biology in its full complexity.

Methodological improvements in holobiont population dynamics will benefit, among others, researchers studying microbial ecology and host-microbiome dynamics from a population perspective, taking into account the host social structure (e.g., corals in a reef, distinct packs of wolves, or human villages). This new set of models would help decipher the relative importance of within-versus between-patch processes and the impact of host population dispersal on the microbiome, with implications for conservation ecology. For example, modeling the host network (e.g., the number and frequency of interactions between hosts) and the distribution of microbes within a host population will enhance our understanding of which host population structures are most resilient against environmental perturbations, such as climate change, soil pollution, habitat fragmentation, or biological invasion. Ultimately, this could inform the development of conservation measures aimed at protecting both host populations and their associated microbial communities. By gaining a deeper mechanistic understanding of these systems, key factors driving biodiversity loss can be identified, supporting efforts to prevent population loss and facilitate rehabilitation.

Area 3: Microbiome divergence and holobiont speciation

The complexities of holobiont population dynamics that we have discussed can have significant repercussions on host evolutionary trajectories. In herbivorous insects, for example, families with obligate, nutritional symbionts have 19-fold more species than families without obligate symbionts, suggesting symbioses drive significant diversification rates of holobionts.[11] In particular, multiple lines of evidence specify that symbionts can drive host speciation through various mechanisms spanning impacts on host reproductive success to host behavior and ecological interactions. In arthropod populations, for example, *Wolbachia* bacteria can cause postmating reproductive isolation via paternal-effect lethality that leads to hybrid death.[11] Holobiont breakdown in hybrids can also result in host-microbiome dysregulation, which is responsible for hybrid mortality. The acquisition of new dietary niches in various hosts and behavioral differences between holobiont populations with different microbiomes establish other premating mechanisms that also contribute to reproductive isolation.[11]

To assess the relative importance of symbiont-associated speciation, we need models that consider the eco-evolutionary diversification of the hologenome, defined as the total set of microbial and host nuclear genes[1] (Figure 1A). Changes in the hologenome will be simultaneously shaped by selection occurring at the level of individual hosts, individual microbes, and the entire holobiont. Quantifying the relative influence of selection at each level could help us understand how the functional integration between the host and the microbiome forms.[12] One possibility is that selection on the holobiont is mediated by interactions between members of the hologenome. Another possibility is that each member of the symbiosis is imposing selective pressures on the other simultaneously. This perspective suggests that adaptive assembly, whereby the host limits membership in the microbiome to those microbes that benefit it, can result in an integrated consortium of a host and its microbes.

In building models of holobiont evolution, researchers are confronted with addressing the complexity of disparate timescales. Indeed, genetic changes and microbially mediated phenotypic plasticity can both affect host evolution along different but overlapping time scales, where plastic responses may be shorter than a host generation time and span across multiple generations.[13] Additionally, large population sizes of symbionts with short generation time create the potential for rapid evolution.[13] Other systems with both fast and slow processes of interest have been modeled with a separation of timescales approach, wherein some dynamics are assumed to equilibrate immediately relative to others. This is a key component of adaptive dynamics, wherein a population of residents is assumed to reach a steady state after each new mutation arises. These timescale separation techniques are useful but fail to capture the effect of transient population sizes on evolutionary outcomes. Additionally, the interdependence of fast and slow processes may lead to multiple possible equilibria, creating ambiguity in the analysis.[14] A more robust approach could be to simulate evolutionary dynamics at a temporal resolution that can capture microbial ecology. If this is unfeasible, fast dynamics can be represented by including auxiliary state variables,[14] or new approaches may need to be adopted to model holobiont evolution in ways that are both realistic and useful.

The incorporation of a continuum of host-symbiont interactions—spanning parasitism to mutual benefit—into multilevel selection models could also offer broader insights into the emergence and evolutionary dynamics of symbiotic partnerships. Traditional mathematical models have often explained mutualism persistence through tight coordination between host and microbial reproductive cycles. However, emerging or facultative symbiotic associations often lack such synchrony and may instead adopt antagonistic strategies. Examples include resource overexploitation (sometimes lethally damaging their hosts), actively leaving hosts to adopt a free lifestyle, or recolonizing new hosts. In this sense, separately considering the benefits and costs of an interaction, allows us to explore a broader diversity of mechanisms driving host-symbiont evolutionary dynamics.[15] These interactions can be mathematically characterized using nonlinear functional forms that go beyond classical Lotka-Voltera equations.[15]

Understanding how host-associated microbiomes can generate speciation and, more broadly, variation in host traits over one or more generations remains an active area of research for theoretical and empirical studies. Due to this influence of microbes on host diversity, the theory of holobiont speciation has the potential to inform conservation and restoration efforts across a wide range of systems.

Conclusions

The study of microbial symbioses represents a rapidly growing field of research. However, our ability to model these systems mathematically is often hindered by their biological complexity. Here, we underscore the need for mathematical frameworks that more accurately represent the linked dynamics of microbial symbionts and their hosts and the implications of this interdependence across biological scales. We present the limitations of current frameworks on modeling nested host-microbe systems, multi-host communities, and the long-term evolutionary dynamics of these systems. Advancements in these areas will lead to an improved mechanistic understanding of these systems, with critical implications for the preservation, modulation, and restoration of complex holobiont communities. This set of theoretical frameworks, integrated with empirical microbiology, stands to blossom into a new subfield that accounts for the complexity of biological systems, leverages a holistic philosophy, and embraces, but is not limited to, a holobiont-centered perspective.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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