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Review

A mechanistic framework for complex microbe-host symbioses

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Virtually all multicellular organisms on Earth live in symbiotic associations with complex microbial communities: the microbiome. This ancient relationship is of fundamental importance for both the host and the microbiome. Recently, the analyses of numerous microbiomes have revealed an incredible diversity and complexity of symbionts, with different mechanisms identified as potential drivers of this diversity. However, the interplay of ecological and evolutionary forces generating these complex associations is still poorly understood. Here we explore and summarise the suite of ecological and evolutionary mechanisms identified as relevant to different aspects of microbiome complexity and diversity. We argue that microbiome assembly is a dynamic product of ecology and evolution at various spatio-temporal scales. We propose a theoretical framework to classify mechanisms and build mechanistic host-microbiome models to link them to empirical patterns. We develop a cohesive foundation for the theoretical understanding of the combined effects of ecology and evolution on the assembly of complex symbioses.

Complex symbioses: a shared history of ecology and evolution

Complex symbioses encompassing **microbiomes** (see Glossary) and their multicellular hosts are a ubiquitous and essential aspect of life since the emergence of multicellularity [1]. Microbiomes act as 'multifunctional organs' for hosts by providing essential metabolic functions and engaging in a multitude of roles crucial for development, protection, health, nutrition, and more. The hosts, in turn, offer an entire ecosystem for the microbes, providing resources, habitats, and means of transportation [2]. In addition to being vital to the biology and ecology of individual hosts, the microbiome is a fundamental component of a host's entire evolutionary history [3]. Host and microbial species can shape and integrate each other in a coevolutionary process to such an extent that they can potentially become a single evolutionary unit [4]. In addition, microbiome composition can change through the acquisition or loss of community members, which can provide functional flexibility to the symbiosis (e.g., to allow for temporary adaptation to an environmental change) [5]. Consequently, to describe and understand the evolution and function of all multicellular life, it is essential to understand the nature of complex host-microbiome associations.

Describing the elements of a complex microbiome's function and composition involves uncovering the mechanisms underlying their emergence and maintenance. This challenge requires an understanding of the dynamical interplay between the ecology and evolution of both hosts and microbes [6]. The **complexity** of these communities is made from intricate causal links and feedback loops operating across spatial scales, from single microbes to host communities, and existing across several temporal scales, from a microbe's lifespan to an entire evolutionary history [7–9]. Thus, to understand complex symbioses, and their origins, it is necessary to consider the joint dynamical influences of a combined set of ecological and evolutionary mechanisms that operate across multiple scales [10].

Highlights

As in all complex ecosystems, multispecies symbiotic associations are shaped by ecological and evolutionary forces acting at several temporal, spatial, and organisational scales.

Microbiome assembly inside plant and animal hosts is shaped by, and in turn shapes, the traits of both microbes and hosts.

Theoretical frameworks combining ecological and evolutionary mechanisms are essential to provide a better understanding of the assembly of complex symbiotic microbial communities.

The generation of testable predictions from theory relies on the identification of key mechanisms playing a fundamental role on the questions and patterns addressed. In microbiome research this amounts to processes giving rise to their complex organisation.

Methods for matching empirical patterns to model outcomes through model selection and data analysis can reveal potential sets of mechanisms and conditions capable of generating observed patterns of organisation in complex microbiomes.

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Advances in DNA sequencing technologies have generated large amounts of information on the diversity and composition of the microbial world [11,12]. These advances should go hand in hand with the development of theory to build a mechanistic understanding of the processes generating the organisational patterns observed in microbial communities [9,13]. A first step towards this understanding is a comprehensive description of microbiome **assembly** mechanisms organised under a coherent framework. Once these mechanisms have been identified, such a framework can be extended to provide pattern-generating **dynamic models** and a basis for data analysis that would allow researchers to explain observed patterns through a mechanistic lens. Last, comparing outputs from different models can help in testing competing hypotheses.

In this review, we propose a conceptual unifying framework to incorporate ecological and evolutionary mechanisms of host-microbiome assembly into mathematical models. Our goal is to allow for a formal quantitative examination of their role in the assembly of complex symbioses. This framework is grounded in previous ecological theory aimed at understanding biodiversity across scales. It incorporates biological mechanisms as model elements, combining (i) the complex temporal ecological dynamics of microbes and resources mediated by hosts, (ii) the microbial community assembly process via speciation, dispersal, and invasions, (iii) the demographic dynamics of host communities, and (iv) the evolution of host and microbe traits through time. Additionally, we discuss the use and selection of models to generate empirical patterns and test specific hypotheses behind the emergence of these patterns.

Classifying mechanisms of host-microbiome assembly

Previous research on host-associated microbial communities has highlighted the need to move beyond descriptions of observed patterns of microbiome organisation and tackle the challenge of unveiling the specific ecological and evolutionary mechanisms underlying their assembly and composition [14–16]. Building towards this goal, recent studies have focused on developing a better understanding of different sets of mechanisms playing a role on specifics aspects of microbiome organisation. Adair and Douglas [16] provide a comprehensive discussion of ecological mechanisms (both deterministic and stochastic) behind the assembly of host-associated microbiomes by microbe colonisers from the external environment. Their focus is exclusively on ecological processes. Kohl [14] focuses on identifying mechanisms driving the pattern of phylosymbiosis observed in host-associated microbial communities, providing a theoretical conceptualisation of the shared evolutionary history between host and microbiome in terms of selection, drift, dispersal, and diversification. Culp and Goodman [15] provide an in-depth review of the specific mechanism of microbial cross-feeding and its role on the ecology and evolution driving microbiome composition. As useful as these (and other) previous efforts are at organising our knowledge on the mechanisms of microbiome assembly, in order to structure a unifying framework of complex symbioses it is desirable to first provide a comprehensive synthesis of both the ecological and evolutionary mechanisms of host-microbiome assembly. The focus is on a seamless integration into a theoretical modelling framework of microbiome assembly. Thus, as a first step towards developing a mechanistic framework for complex microbe-host symbioses, we present a systematic classification of the ecological and evolutionary mechanisms of host-microbiome assembly identified in previous empirical and experimental studies (Table 1).

We classify these mechanisms into different categories reflecting the separation between ecological and evolutionary processes. We further divide ecological processes into host- and microbe-related as a natural way of thinking about the processes concerning each of these distinct types of organisms involved in the symbioses. On the one hand, it allows for the grouping of ecological mechanisms comprising the dynamical states that generate interactions, reproduction, dispersal and death of individual microbes and hosts. On the other hand, it groups together evolutionary

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Table 1. Summary of mechanisms involved in microbiome assembly [17–20,22–27,29–31,33,35–66]

Mechanism[a]	Description	Refs
Priority effects	Changes in composition due to historical contingencies and the order in which microbes are able to colonize and grow within the host	[18–20,35]
Dispersal and horizontal transmission	Exchange of microbes across space and between hosts and environments, impacting their local and regional abundance and access to different types of environments and hosts, including neutral dispersal processes	[36–42]
Microbe–microbe interactions	Existence and strength of interactions between microbes, such as mutualism, competition, commensalism/amensalism, predation, cross-feeding, or higher-order interactions	[17–20,27,43–45]
Chemotaxis and attachment	Microbial mechanisms of mobility and attachment within the host environment, including navigation patterns and biofilm formation	[20,39,46]
Specificity of resource use	Range and efficiency of utilization and production/excretion of different resource types by microbes	[45,47]
Interaction with host	Capacity of microbes to evade host selection and to promote changes, benefits (host defence, nutrition, etc.) or harm to their host environment, with relationships ranging from mutualistic symbioses to commensalism and parasitism	[20,22–24,29,37,44, 48–54]
Dormancy	Capacity of microbes to stay dormant, improving survival and avoiding extinction, with subsequent activation in response to better conditions in the local environment	NA[b]
Host environment	Physical and chemical properties of the environment inhabited by the hosts. Perturbations and patterns of variations of this environment, and the presence of certain conditions ultimately enable or disrupt the presence of microbe types	[22,31,33,36,38,41,42,48, 49,53–59]
Host properties	Physical and chemical properties of the environment within the host, including space-availability within host and compartmentalization of host body	[20,29,39,40,47,57,60,61]
Host selection and enrichment	Mechanisms employed by the hosts to filter and differentially protect and attack microbes, resulting in a selective pressure upon their microbiomes and enrichment of favoured microbes. For example, the action of an immune system results in a mechanism of this type	[18,22–24,26,27,29–31, 33,36–38,40,41,47,52–54, 56,58–62]
Host life-history traits	Mechanisms related to properties of the host's life, such as age, habits, reproduction, and physiology, impacting their own survival and impacting their microbiome	[18,25–27,37,39,40,53,60, 63–66]
Substrate availability	Within-host presence and distribution of compounds used by the microbes for nutrition	[24,45,50,59,60,67]
Invasion	Invasion of the microbiome by external disrupting (e.g., pathogens), neutral, or beneficial organisms	[38,49,59,67]
Genetic evolution	Evolution of the genomic blueprint of hosts and microbes, determining phylogenetic relationships and what is functionally available, and subject to mutations	[20,23,30,33,44,47,48,51, 53,55,60–62,66]
Functional evolution	Evolution of traits following adaptation by functional niche occupation, irrespective of phylogenetic differences	[25,29,31,35,41,46–48,51, 53,55,56,58,65,68]
Lateral gene transfer	Evolution by direct exchange of genetic material between microbial individuals	[51,64]
Fast microbial evolution	Fast evolution of microbes, faster than host evolution and potentially happening during the lifetime of a single host	[29,46]
Vertical transmission	Transmission of microbes from parents to offspring at birth	[17,37,68]
Neutral/drift processes	Randomly determined variation of availability, traits and/or parameters of hosts and microbes	[19,36–38,41,42,66,68]

[a] Key:
🟥 Microbe-related ecological mechanisms.
🟦 Host-related ecological mechanisms.
🟩 Evolutionary mechanisms.

[b] No recent papers explicitly considering dormancy were found during our literature review. However, it is often mentioned as a potentially relevant mechanism of microbiome assembly.

mechanisms driving the change in species characteristics and the emergence of innovation over the course of many reproductive and colonisation events through time. Since the two types of objects being modelled via these processes are the hosts and the microbes, each ecological mechanism is defined as relating to either host or microbes.

Microbe-related ecological mechanisms

These mechanisms encompass microbial traits and functions that are relevant to their interactions with other microbes and the host environment (Table 1). For example, temporal patterns of succession and different stages of microbiome composition are shaped by mechanisms of microbe-microbe interactions, microbial function, and priority effects [17,18]. Functional trait-based relationships and competition for common resources between microbes within hosts can cause continuous turnover and patterns of change in microbiome composition associated to different

Glossary

Assembly: the process of building a community by the sequential addition of new organismal types, following a set of established assembly rules.

Complexity: as used in this article, the system-level unpredictability and intricate diversity of behaviours arising from high-dimensional (i.e., comprising many variables) and nonlinear interactive dynamics of numerous individual components. It is a feature applied to both models and systems in nature.

Dynamic model: a mathematical description of a system as a time-varying state that depends on multiple mechanisms acting together, usually in a nonlinear manner.

Metacommunity: a set of local ecological communities that are connected in space and allow for linking local and regional dynamics. Here, a set of hosts each with its own microbiome (the local community) connected via exchange of microbes.

Microbiome: the community of microbes in symbiosis with a host, together with the internal environment of the host accessed by the microbes.

Ordinary differential equation (ODE): a mathematical equation that can specify the total rate of change of an independent variable as a function of the variable itself and other variables. ODEs are commonly used to implement dynamic models in networks and other scientific applications. In community ecology, they constitute useful models to connect mechanisms to trajectories in population dynamics.

stages of host development [19,20]. Incorporating microbe-related ecological mechanisms into modelling frameworks should focus on defining the relevant features of microbial taxa (e.g., taxonomic versus functional), how they relate to each other and the host, their traits and distribution. This information should then be used to define their explicit interactions (including interaction types) with other microbes and the hosts.

Host-related ecological mechanisms

These mechanisms derive from the biology and ecology of hosts, encompassing both their bodies as the environmental setting for the microbiome and the dynamic changes and patterns influencing this environment over time (Table 1). Patterns of microbiome richness, abundance (i.e., microbial density), and complexity are strongly influenced by mechanisms of host selection and host's life-traits [21,22]. Mechanisms of host selection are diverse and can shape their microbiome in different ways. Hosts can, for example, alter microbial densities directly through genetic interactions [23] or control microbiome composition through substrate availability determined by the host's physiological state [24]. Composition of the microbiome is also strongly influenced by aspects of host behaviour, such as diet [25,26], which can explain substantial variations in alpha- and beta-diversity of microbiomes across several vertebrate clades [27]. The incorporation of host-related ecological mechanisms into modelling frameworks involves formal definitions of the host, translated as model parameters and conditions of the environment in which the microbial community exists.

Evolutionary mechanisms

These mechanisms concern the maintenance and change of information within communities as they experience different conditions across space and time (Table 1). This information is encoded in the genes that make up the species and can affect the outcome of assembly. Patterns of cophylogeny and co-diversification emerge as a consequence of a shared history of hosts and microbes through the action of evolutionary mechanisms [28–31]. Homogeneous coevolution can produce convergence of microbiomes in individuals of a single host species that live in geographically distinct locations [32] or different host species that share the same diet [25]. By contrast, genetic differences across individuals of the same host species living in different environments can drive a divergence of microbiome composition in response to adaptations to different environmental conditions [33]. The unique nature of microbial evolution, being faster than host evolution and capable of lateral gene transfer, is an additional source of complexity in host-microbe associations. Host-microbe interactions can potentially evolve to change between being mutualistic, commensal, and parasitic [34]. Incorporating evolutionary mechanisms into modelling frameworks involves changing model parameters governing species traits over time, with the corresponding filtering of resulting phenotypes via selection.

Towards a mechanistic framework of complex symbioses

Coevolutionary dynamics between interacting species commonly occur at large geographical scales when distinct, geographically divided, populations generate a diversity of local adaptations of species interactions across the landscape [67]. Microbial communities living symbiotically inside multicellular organisms can be viewed in a similar context, existing both within and across hosts. Host-associated microbiomes adapt to the local environmental conditions provided by individual hosts while experiencing a constant exchange of microbes with the wider environment and other hosts. In the long run, both specific microbial taxa and microbial consortia containing a few species may coevolve with their hosts, enabling the emergence of interdependence between host and microbes. This host-microbe coevolution via microbial exchange and local adaptations is realised through the interplay between various ecological and evolutionary processes.

Defining the mechanisms comprising this eco-evolutionary picture requires theory capable of merging the local scale of the microbiome in a single host individual with the geographic scale of host communities harbouring a network of microbiomes [68]. The ecological theory of **metacommunities** is useful for investigating patterns and mechanisms that connect spatial scales in ecosystems [69,70]. Under this framework, complex communities of interacting species make up local patches, which are in turn connected at larger spatial scales by processes of movement, dispersal, invasion, or colonisation. Looking at host-microbiome associations through this lens, we can represent individual hosts as patches harbouring local communities of interacting microbial populations. At a larger (i.e., regional) spatial scale, patches are then connected via direct host-host interactions or indirectly through the external environment, forming a metacommunity of connected patches. In this way, mechanisms of community assembly operating at different spatial scales can be summarised into a coherent unifying framework and analysed in combination [71]. Here, considering the mechanisms summarised in Table 1, we attempt to describe the specific concepts underlying this framework and how they relate to each other. The ultimate goal is to allow a better understanding of the evolutionary emergence of diversity and ecological composition of complex symbiotic communities (Figure 1).

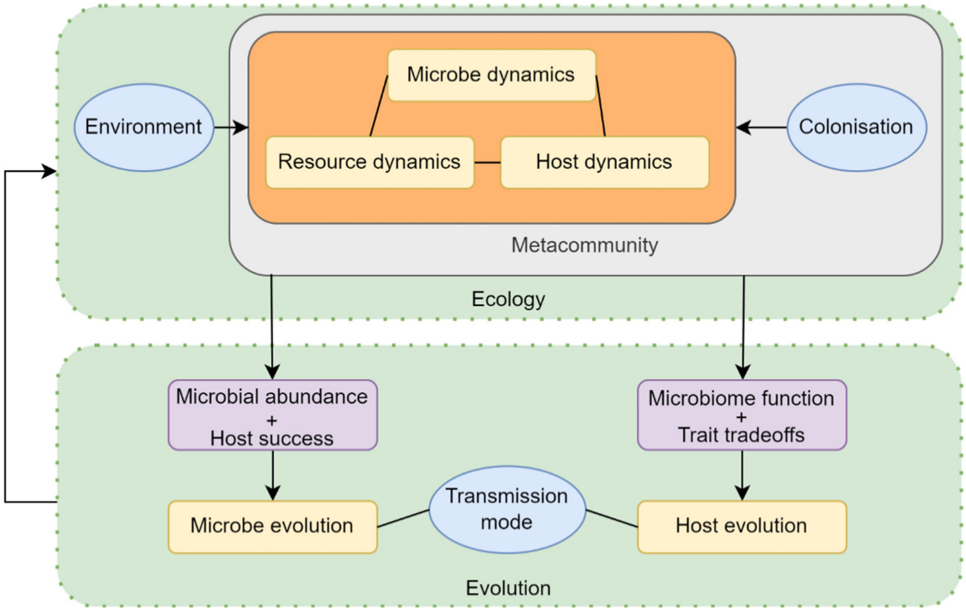

Figure 1. Conceptual framework incorporating the different components driving the assembly and composition of complex microbe–host symbioses. Ecological trajectories of microbiome assembly emerge from the interplay between host, resource, and microbe dynamics. The behaviour of the system is influenced by the properties of the environment and colonisation of local microbial communities inside hosts by external organisms. Overall, the ecology of the system is organised as a metacommunity of hosts (i.e., local communities) connected via the exchange of microbes. The metacommunity evolves via the joint adaptation of hosts and microbes linked by modes of microbial transmission. Microbial evolution is driven by the distribution of ecologically determined microbial abundances inside hosts, which ultimately determine the fitness of microbial types, and the success of the hosts. However, host evolution is determined by trade-offs between different host traits (e.g., their ability to import microbes from the environment versus their ability to sustain stable complex microbial communities) and the functions provided to the host by the microbiome. The evolutionary outcomes feed back into ecological processes with modified trait values that influence microbial and host dynamics. In the figure, microbe/resource/host dynamics and microbe/host evolution (light-yellow squares) are the main components of the system, containing the state variables that are focal to the analysis. Colonisation, environment, and transmission (blue ovals) are auxiliary elements influencing the main components, included in the system only through their interaction with them. Purple squares represent drivers of evolution, in the form of functions and conditions obtained as output from the ecological process.

Incorporating mechanisms into models of host-microbiome assembly

Different models of host-microbiome assembly have been proposed, focusing on specific aspects of the whole eco-evolutionary process, mainly addressing mechanisms of microbe transmission. The most common approach is to use pattern-generating models to link mechanisms to observed or predicted patterns (see the section 'Linking pattern to process'). Zeng and Rodrigo [72] developed an agent-based model to show that microbial transmission across hosts and environmental conditions have a strong influence on microbiome dynamics even under scenarios of neutral selection. Along the same lines, Zapién-Campos *et al*. [73] showed that a neutral model of microbial transmission can reproduce the level of inheritance necessary to drive the assembly and maintenance of microbe distribution in developing hosts. As identified in Table 1, neutral dispersal processes have emerged as important drivers of microbiome assembly.

From an evolutionary perspective, Roughgarden [74] has recently developed mathematical theory for the assembly of the host-associated microbiome. This theory has revealed that microbial transmission alongside hologenome evolution based on collective inheritance of microbes, including host selection and microbial function, are enough to generate selection at the holobiont level emerging from simple host-microbe interactions [74]. Furthermore, microbial vertical transmission from parent to offspring has been incorporated into modelling frameworks to demonstrate its relevance for heritability and the maintenance of selection at the host level [75], especially when directly linked to reproductive fitness of the host [76]. Expanding on these findings from the perspective of the microbe, Bansept *et al*. [77] incorporated microbial life stages into models of host-microbe selection to demonstrate their importance in creating adaptations observed in real microbial types. Taken together, evidence from recent modelling efforts corroborate the importance of many ecological and evolutionary mechanisms identified in Table 1 for host-microbiome assembly.

A common issue across existing models such as those described earlier is the simplistic view of the mechanisms involved in the dynamical complexity of host-microbiome associations, incorporating only one or a handful of them. In particular, the interdependence emerging from the plural multi-interactive nature of microbe-microbe and microbe-resource association networks, in turn mediated by host properties, is lacking. Dynamical interactions between microbial types are generally not considered in models of transmission and selection in host-microbe associations. While Angell and Rudi [78] modelled outcomes based on microbe-resource interactions to address microbiome composition in early development, the interactions and populations were only modelled as simple rule-based game theory models. Similarly, Coyte *et al*. [79] and Qian and Akçay [80] investigated the ecological assembly of communities with complex network models of interspecific interactions, and showed how the nature of these interactions can strongly determine the composition, stability, and feasibility of a large community. However, these models do not incorporate host-microbiome mechanisms and are purely ecological.

Current theories for host-microbiome assembly lack the tools to address the compound effects of the multiple mechanisms and conditions underlying the complexity and development of these communities. The challenge is to build an integrated mathematical framework to model the interdependence of transmission, selection, and host-microbiome interactive mechanisms with the dynamic ecological complexity of microbe and resource interaction networks. Here, we propose a conceptual description of the different elements and relations of a modelling theory capable of incorporating all identified mechanisms into a single coherent dynamical setting.

A holistic framework of complex host-microbe symbioses

The main components of a modelling theory for complex host-microbiome associations can be organised in a diagram emphasising how they connect to form an eco-evolutionary loop

(Figure 1). The basic dynamical unit is formed by the joint system of microbes-host-resources interactions, which is influenced by external environmental factors and by colonising microbial types. The elements are organised in a metacommunity structure, with microbe-resource networks inside a host community. This whole ecological scenario determines the distinct evolutionary trajectories of hosts and microbes, which potentially results in a coevolutionary process. Ecology defines microbial abundances and the reproductive success of hosts, thus providing the selective pressure for microbial evolution. Hosts success is determined by the trade-offs arising from their evolving traits and by the functions and effects of the microbiome on host fitness, thus shaping host evolution. An important factor mediating the evolution and coevolution of the host-microbe association is the mode of transmission and acquisition of microbes, which determines the variability in the heredity of microbiomes and if a microbe is endemic to a host. Closing the feedback loop, evolution happening across many generations then determines host and microbe traits that impact their abundances and success in the ecological dynamics during each generation.

We consider a dynamical community theory with the state of populations determined by their abundances, which are modelled by mechanistic rules of change. These rules are encoded as terms in **ordinary differential equations** (**ODEs**) representing particular mechanisms of microbiome assembly. The choice of ODEs is motivated by the conceptual characterisation of models as dynamical systems [81]. We consider the microbiome inside a host as a network in which the nodes are the different microbial types (e.g., species or any relevant group classification) and the edges between nodes represent interactions between microbes. Associated to each node in the network is a state variable describing the abundance of that specific microbial type. Network dynamics, representing the temporal dynamics of the population abundances of nodes, are governed by the set of ODEs modelling the rules of change of the population dynamics [92]. The states of the model focus on the abundances of each microbial population, with each microbiome represented as a community harboured by a single host individual.

Under this framework, ecological assembly (via the introduction of new hosts and microbes through reproduction or invasion) occurs concurrently with the ongoing network dynamics. Later, we propose ways in which the mechanisms identified in Table 1 can be incorporated into a general modelling framework with these features (Figure 1).

Microbe-related ecological mechanisms

Species abundances within local communities are determined by local interactions with the environment and other species, as well as the ability of the species to persist in and colonise a given host. As such, microbial dispersal and dormancy can drive microbe dynamics by directly increasing or decreasing abundances, including the appearance of new types from an external environment in the process of colonisation (Box 1). Additionally, horizontal transmission of microbes between hosts and dispersal across different environments is determined by the links between different microbiomes in the metacommunity (Box 1). Direct microbe-microbe interactions (e.g., competition, mutualism) also contribute to microbe dynamics, incorporating the frequency of interactions and being intrinsically proportional to the abundances of microbe types (intrinsically meaning that the proportionality emerges from the dynamics, but additional mechanisms driving interaction frequency could change the resulting functional structure). Microbe abundances and microbiome composition are driven by the frequency of interactions, which is a function of species traits, thus modelling mechanisms of microbe mobility, like chemotaxis, or trait-based interaction intensity.

The diversity of interaction types influencing microbe dynamics results in a set of different functional structures that together are responsible for complexity in the dynamical outcomes of persistence and abundance distributions of microbe types. Microbe types consume and produce resources from the environment. The numerous possibilities of resource-consumption-production profiles shape the resource dynamics and microbe dynamics in different ways (Box 1). The frequency of microbe-resource interactions is intrinsically proportional to microbe and resource abundances, which directly drives abundance distributions of both resources and microbes (with microbes feeding on resources and then being able to reproduce, or microbes dying with a lack of resources). Cross-feeding interactions, another important mechanism of microbial community assembly, are a consequence of the relationship between microbes and resources.

Box 1. Ecological state

Microbe dynamics

The variable defining the state of populations of microbe types in the microbiome is the microbial abundance. A rule of change (given by, e.g., a set of ODEs) determines how the abundances of each type vary with time in terms of interactions among microbes, and interactions with resources and the environment. The frequency of interactions is proportional to the abundances of microbes and resources and is a function of environmentally defined parameters and rates. Direct interactions between microbial types form a complex network of associations (Figure IA). The effects and conditions promoted by the host add sources of variation and control of microbial abundances, impacting and driving the dynamical state of the microbiome. Intraspecific demographic processes of microbes occur in terms of reproduction, death, and competition terms (e.g., logistic equation). Microbial reproduction and growth are directly shaped by resource availability and host selection.

Resource dynamics

Resources are consumed and produced by microbes. The environment inside the host can also provide resources to the different microbes. Thus, the abundance of resources available to the microbiome impact and are impacted by individual microbes. Their dynamics are interdependent in a complex microbe–resource bipartite network (Figure IB). In the same way as with microbes, a rule of change (ODE) based on these interactions and conditions determines the trajectories of resource abundances.

Host dynamics

Host individuals, their traits and development, can change as a function of time, but their birth–death dynamics happens across generations, with host populations changing as driven by their reproductive fitness. How successful each host becomes in a generation will depend on its traits and its microbiome, linked by the functions the host needs to survive. A fitness function computes all reproductive costs and benefits resulting from a host's strategies and the functions provided by their microbiome. Interactions with microbes can affect the host's fitness either positively or negatively, depending on whether mutualistic, commensal, or parasitic relations are established. The state of a host and their birth–death dynamics occur interdependently with the complex resource-microbe joint dynamics (Figure IC).

Environment

System dynamics are coupled to the external environment, which provides an additional source of parameters and conditions driving the ecological state. The environment provides selective forces such as the effects of host predators or fluctuations in food and weather. It also determines physical conditions that affect rates and the intensity of interactions, such as temperature, pH, and abiotic substances (Figure ID).

Colonisation

The assembly of the microbiome is shaped by the continuous process of colonisation, in which microbe types are added to the system (Figure IE). Apart from diversification by mutation, new microbe types are added to the microbiome network as colonisers from a regional pool. The complex nature of the dynamics means that the introduction of a new type could result in different types of disturbance to the microbiome; for example, exacerbated niche competition and extinction cascades. Local colonisation can also be enabled by dispersal between hosts, creating thus the metacommunity context.

Metacommunity

The model setting in which microbes and hosts coexist is organised as a metacommunity: a collection of local communities (i.e., hosts), each one containing a complex microbe network (the microbiome) and connected to others in a spatial network (Figure IF). By being connected, hosts can influence each other and exchange microbes and resources. This configuration reflects the path through which mechanisms acting at several scales are connected and determine host and microbiome dynamics. For example, a connection between hosts through dispersal can influence the abundance of microbes and the balance of interactions in their microbiome which, in turn, influence the health and survival of those hosts.

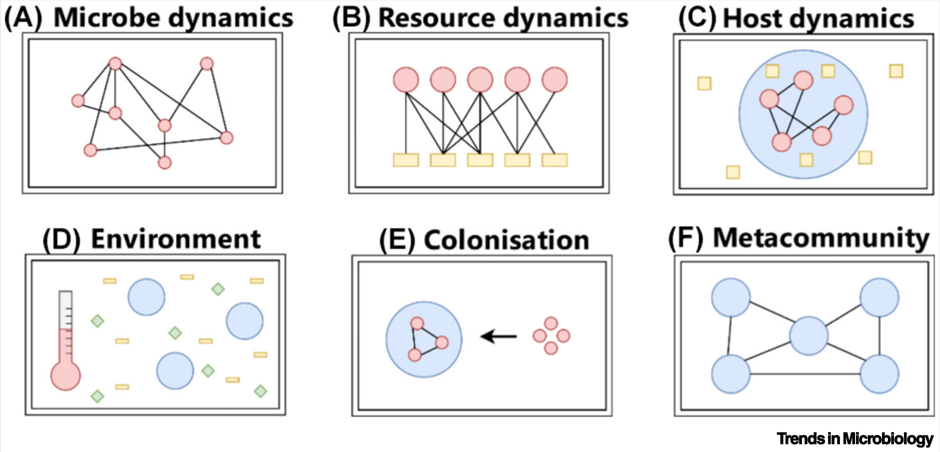

Figure I. Ecological components of a mechanistic framework for complex microbe–host symbioses.

Important determinants of the outcome of complex community assembly are the priority effects provided by an early colonisation and fast growth due to large resource availability and weak competition [82,83]. Priority effects relate to the importance of the order in which microbial types are sequentially added to an ecological community. This addition can be due to either dispersal events (as mentioned earlier) or a combination of ecological and evolutionary processes, including speciation, and especially as an outcome from the modes of microbe transmission (Box 2).

Processes such as attachment to, and defence against, hosts can impact microbial birth and death rates, their reproductive fitness, thus influencing the microbe dynamics (Box 1). The collective task of forming a biofilm for attachment to the host could potentially involve specialised mutualistic interactions. These microbe-host interactions can thus have an impact on host reproduction and death, ultimately influencing host fitness and host dynamics (Box 1). Alternatively, host health and reproduction can also be triggered by microbe-driven processes, such as nutritional levels increased by microbial activity, which in turn drives microbe abundances.

Host-related ecological mechanisms

Abundances of specific microbial types can be enriched by interactions with their hosts, and microbial reproduction is influenced by host traits or local environmental conditions within the host (Box 1). In this way, ecological phenomena known to drive biodiversity patterns, such as habitat filtering, can emerge. Hosts can influence microbes in a myriad of ways through their traits, modulating microbial dynamics via their influence on microbial flux, reproduction, death, interactions, transmission, and resource dynamics. Substrate availability within the host modulates the flux of resources, as a link between host and microbe dynamics established through resource dynamics.

Host behaviour can emerge as interactions between linked host individuals that possibly impact host parameters or events such as reproduction and death. Invasions to the microbiome, for example by host infection, drive microbial dynamics by introducing external populations that can interact with resident microbes and alter the outcome of community assembly and affect host health and survival, as a host-mediated colonisation.

The abiotic properties of the host's external environment (e.g., temperature, pH, salinity) can directly influence host reproduction and death, but also be considered as factors in other host-

Box 2. Host and microbe evolution

Evolution

Evolution includes trait adaptive changes and speciation by mutation across multiple generations. Therefore, ecology comprises the trajectory of the system within one generation, while evolution comprises the cumulative, sometimes directional, change of the system across multiple generations. Traits and species are defined by information encoded in the genetic material. As generations pass, genes mutate and change phenotypical outcomes in terms of variations in rates, parameters, and species interactions. Evolutionary changes are driven by selective pressures acting at the level of ecological dynamics, through differential death and reproduction (Figure IA).

Microbe evolution

Microbial abundance and the success of the host together define the reproductive success of microbe types. A microbe that is allowed to grow inside a successful host will increase its presence in future generations, and the functions promoting this scenario will be selected. Microbes generally evolve faster than hosts, with changes happening in every generation and even within a generation. A main feature of microbial evolution is the development and change of ecological interactions held by microbe types (Figure IB).

Host evolution

The reproductive success of hosts is the result of specific configurations of traits with trade-offs defining reproductive advantages and costs together with the specific functionality of the microbiome. These factors mediate the host's survival, health, and energy generation, and are selected accordingly. Hosts evolve more slowly than microbes, with functional mutations and diversification of species happening only after several generations. Evolutionary change in hosts shapes their internal environment, which is experienced by the microbiome (Figure IC).

Transmission mode

An important evolutionary connection between a host and its microbiome is the way in which hosts acquire microbes. The relative importance of vertical and horizontal transmission, and environmental dispersal of microbes, determine how close the evolutionary trajectories of hosts and microbes are. Together with host development, transmission modes also determine the paths of assembly of the microbiome inside each host individual. Transmission of microbes changes their abundances in the initial state of a host generation and throughout the generation time (Figure ID).

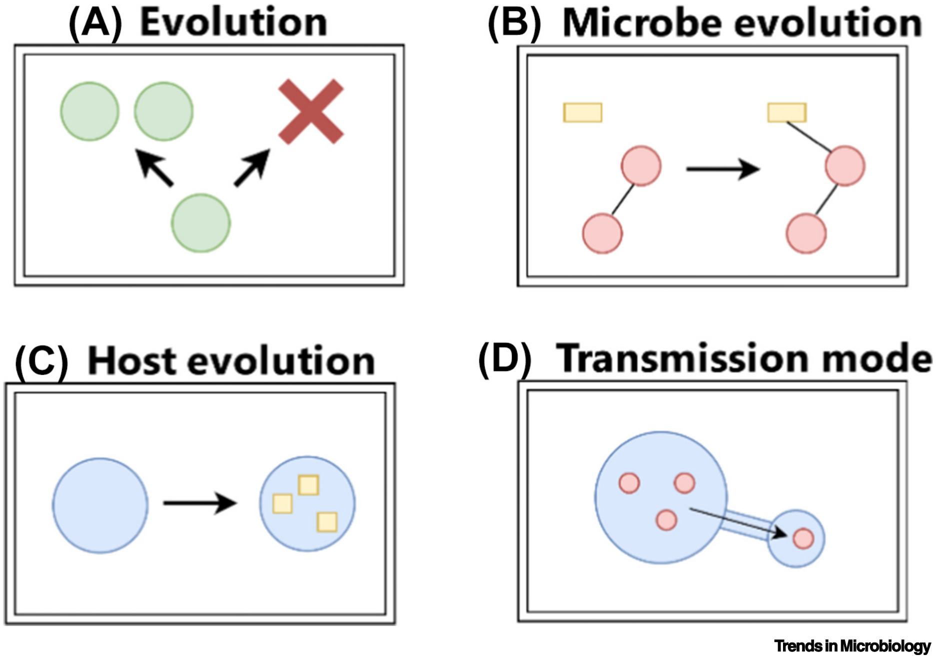

Figure I. Evolutionary components of a mechanistic framework for complex microbe–host symbioses.

related mechanisms, such as properties of the host body. For example, host temperature and pH are parameters with given optimal ranges for different microbe types thus generating a rich landscape of reproduction and death rates for microbes, thus influencing microbe dynamics. Environmental changes are encoded in two ways: by directly having parameters depend on a time variable (embedded in the general dynamics), where they can seasonally cycle, or by introducing punctuated external disturbance events that abruptly change abundances and parameter values. The life history traits and behaviour of the host, such as age, development, or detailed reproductive dynamics, act as additional steps and events subdividing host dynamics into stages, or effects that change over time according to specified rules, influencing host development, reproduction, and death. For example, host age can be sectioned in different stages with different environmental specifications, or reproduction can be sexual and require a combination of host's traits to define demographic rates.

Evolutionary mechanisms

Selection acts through the definition of explicit fitness functions summarising the adaptive advantages and costs of diverse traits and conditions for different individuals, a process in which traits confer an advantage at the cost of moving away from other capabilities, thus always posing a trade-off (Box 2). This context can provide the grounds for the emergence of adaptive dynamics [84]. Whenever deterministic selective pressures are not present, neutral and drift processes can result in patterns that evolve and establish themselves by chance. This can happen as a consequence of small population sizes, random rules, and stochastic dynamics. Evolution is also embedded in the process of assembly, with new types arising by mutation and speciation. Genetic evolution requires the definition of abstract constructs representing genomes within individual hosts and microbe types. They function as encoders of host and microbe traits corresponding to parameter values in the modelling framework. As individuals reproduce (both microbes and hosts), the genetic composition can change, thus altering traits values. Lateral gene transfer between microbes is an additional layer of variation in microbial evolution, where genetic combinations happen as part of the microbial dynamics, shifting existing types to new ones, at faster timescales.

Functional evolution might produce the convergence of phylogenetically distant types towards the same functional types. In these cases, the focus is not on modelling genetic composition, but on evolving traits associated to specific functions [85]. Trait values are assumed to vary directly, either randomly or through adaptive dynamics, to allow functions to evolve. The faster scale of microbial evolution can be adjusted by controlling how frequently microbial types are generated in relation to different types of host individuals. Evolution can also impact the set of microbes to be vertically transmitted during host reproduction, which in turn is essential to the coevolution of hosts and their microbiome (Box 2).

Linking pattern to process

The modelling framework presented in the previous section ('Towards a mechanistic framework of complex symbioses') can be used in two main ways to investigate the mechanisms behind the emergence of empirical patterns in complex symbiotic systems [81]. Simple models can first be created to simulate broad patterns and produce mechanistic insights, helping to develop the theory and inform a further, focused data collection. An example of this is the investigation of the mechanisms necessary to generate a specific single pattern such as, for example, co-diversification patterns between host species and microbial types. Another approach is to design complex models with the aim of formulating specific hypotheses and producing direct connections with data (e.g., via statistical testing of observed vs modelled patterns). This approach could involve creating a detailed model incorporating several mechanisms, for example, abundance data collected in an extensively studied environment. The model's structure is then statistically validated to the extent that it is capable of incorporating empirically measured parameter values while at the same time exhibiting a good fit to the data, replicating a diverse array of patterns.

The specifics of the choice of mechanisms and the design of experiments to empirically measure model parameters depend on the target systems and patterns. Feedback between models for pattern generation and models for statistical analysis with empirical observations allows us to break down the challenge of model-driven data analysis into simpler tasks. This, in turn, enables insights into the interplay between theory and experiments. The repeated iteration of these steps builds up to comprehensive mechanistic theories to better understand empirical patterns.

Box 3. Mechanism selection and pattern-generation: the example of the sponge microbiome

Sponges (Porifera) are an ideal system to study the coevolution of complex symbioses. They are considered one of the most ancient extant metazoans and have had intimate relationships with their microbiome for hundreds of millions of years. Many eco-evolutionary patterns have been described for these symbioses, including that sponge microbiomes encompass a wide range of richness, but have a high correlation of microbiome composition with host species [21]. Sponges can also be generally separated based on their microbiomes into two types: one characterised by low microbial abundance (LMA), and another characterised by high microbial abundance (HMA). Among many mechanisms thought to define HMA and LMA sponges, we focus on two ecological ones: water pumping rate ('Host properties' in Table 1 in the main text) and host selection on microbes ('Host selection/enrichment' in Table 1 in the main text). HMA sponges have, in general, lower rates of water pumping and a more effective selection and enrichment of desired microbes [29,31]. Thus, as an example of a simple hypothesis to find the essential mechanisms underlying the HMA–LMA abundance pattern, we construct a model to investigate whether a divergence of microbial abundance can be explained just by these two ecological mechanisms. This is a relatively simple model, which assumes independence of microbial types (i.e., microbes do not interact) and is purely ecological. However, it clearly illustrates how mechanism selection and pattern generation work in our proposed framework.

In this model, we assume a pool of microbes in the water column, each defined by three random numbers:

(i) D_i: the abundance (i.e., density) of the i-th microbe type in the water.
(ii) ω_i: a positive natural growth rate of the i-th microbe type.
(iii) t_i: a microbial trait describing the value of microbe *i* to its host, from less to more capable of assisting in host survival.

Each host (i.e., sponge) pumps microbes through its body and cultivates those microbes that best contribute to supporting its health and fitness. Thus, two host parameters characterise HMA and LMA sponges:

(i) ϵ_h: the pumping rate of host h.
(ii) δ_h: the selection strength of host h, denoting its capacity to enrich microbes according to their trait.

Representing the abundance/density of each microbe type inside each host x_{ih} (see Box 1 in the main text), we can write a simple equation for host-mediated microbe dynamics:

$$\frac{dx_{ih}}{dt} = x_{ih}\omega_i\delta_h^{t_i} + \epsilon_h(D_i - x_{ih}) - \gamma x_{ih}^2 \qquad [I]$$

Where:

(i) $\omega_i\delta_h^{t_i}$ is the growth rate of microbe *i*. Microbes are enriched to a higher growth rate according to δ_h driven by trait t_i.
(ii) $\epsilon_h(D_i - x_{ih})$ is the flux of microbes resulting from the balance of the influx of water microbes and efflux of internal microbes, pumped with rate ϵ_h.
(iii) γ represents the self-regulation of microbe populations.

A typical HMA host would be defined with small pumping rate and large selection strength, while an LMA host would be the opposite. Their total microbial abundance can be calculated from the microbe dynamics at equilibrium.

If such a model can reproduce the HMA–LMA abundance pattern (Figure I), this would suggest that the focus of mechanism selection is on water pumping rates and microbial enrichment. Further, this model would constitute a basis to investigate other patterns relating to HMA and LMA sponges. If this model is unable to reproduce the pattern, then it tells us that the underlying reason involves another mechanistic setting. In this example, the pattern is reproduced only if both mechanisms are present together.

A computer code implementation of this model and a tutorial on how to use it is available in the supplemental information online and also at: https://github.com/computational-ecology-lab/sponge-microbiome-abundances.

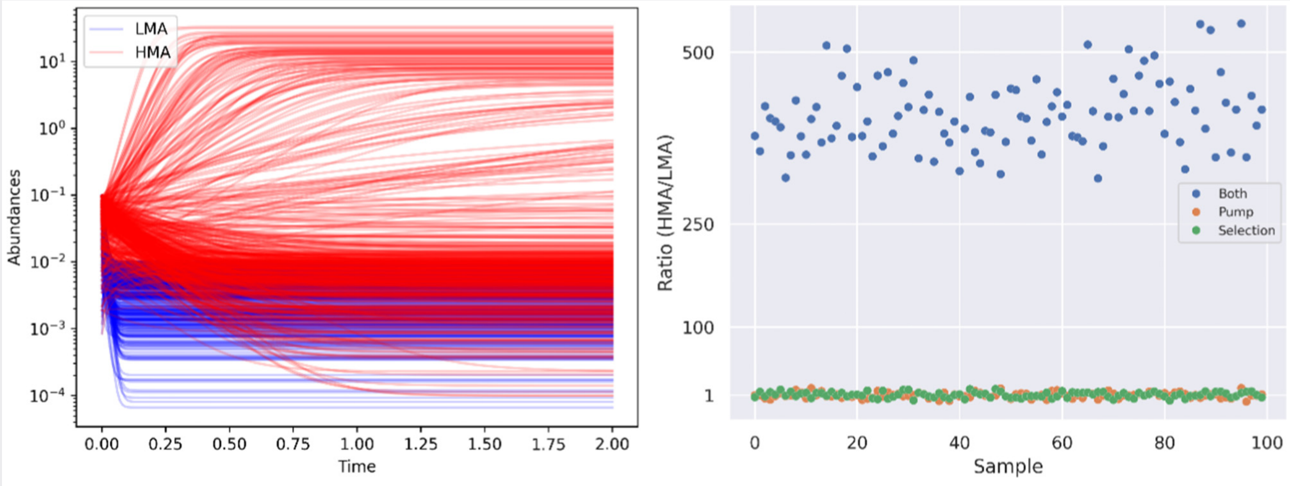

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Figure I. The emergence of the high microbial abundance (HMA)–low microbial abundance (LMA) pattern requires differences in both host-trait mechanisms. A set of 100 samples is simulated with the model described in this box for 500 microbial types. Left: abundances/densities of each microbe type for HMA and LMA sponges in a simulation of the dynamics through time until equilibrium of a single sample. The temporal scale (*x*-axis) reflects the scales of parameter values. Right: ratio of abundances for each sample for three models: one in which both water pumping rates ($_h$) and host selection (δ_h) differ between HMA and LMA hosts (both, blue dots), the second one in which only water pumping rates differ (pump, orange dots), and a final version in which only host selection differs across host types (selection, green dots).

Pattern generation

The particular system or empirical pattern chosen for investigation constrains the set of candidate mechanisms thought to produce the pattern. Many different mechanisms can be sufficient to generate a specific data pattern. The key in the modelling process is, however, to identify the minimal set of mechanisms needed to generate a given pattern, and to develop explanations for the action of mechanisms underlying it (i.e., how can a particular set of mechanisms generate the pattern?). Modelling can help us explore these questions as we test and control model conditions until we are able to predict an observed pattern. This is achieved by selecting mechanisms and by moving across different regions of a parameter space (i.e., changing sets of parameters, especially their orders of magnitude), in an interplay between preparing models and observing their results. There are many examples of this broad category of models in the microbiology literature, which focus on the mechanistic conditions necessary to generate a pattern instead of producing a precise statistical fit [73,77,86–88], and Box 3 discusses an example of this procedure. Once we have a good understanding of the elements necessary to reproduce a given pattern, measurable variables and experimental arrangements can be chosen to statistically test specific hypotheses.

Statistical test

The task of using models to communicate with data and statistically test hypotheses involves two steps. First, the process of model selection provides a method to choose a model (and hypotheses) among a set of informed possibilities. A model selection method commonly used with dynamical models is the calculation of metrics such as the Bayes factor or its approximations, the Akaike or Bayes Information Criteria (AIC or BIC) [89,90]. These are criteria that rank models by how much they can explain the variation in data and by their simplicity (e.g., requiring less parameters). Once a model is chosen, the process of model determination, or data fitting, is used to estimate parameters, or the point in parameter space, that are better adjusted to reproduce observations. An example of a good method of estimation for dynamical models is the Bayesian Markov chain Monte Carlo (MCMC) set of algorithms [91,92].

Concluding remarks and future perspectives

Theory is needed for bridging hypothesised biological mechanisms and empirical patterns. Ecological theory provides tools to combine ecological and evolutionary mechanisms acting at several scales in interactive evolving populations. We propose a unified and principled language for models aimed at understanding the origin of complex symbioses, achieved by classifying eco-evolutionary mechanisms and organising them in a metacommunity framework. This allows for an effective understanding of their complexity and diversity from fundamental components. With this theoretical framework as a guiding tool, future research can focus on the design of robust experiments to build detailed models for hypothesis-testing and data fit. We have shown how model development can be used to better understand different aspects of the organisation of these complex ecosystems. A promising avenue for future research enabled by this framework is the identification of advantageous evolutionary strategies developed by these systems to generate long-lasting associations between multicellular organisms and microbes (see Outstanding questions). Our review of mechanisms has also highlighted that an important challenge for future research is to increase focus on the empirical quantification of microbe-related mechanisms [2], such as, for example, those related to microbial dormancy and the evolution of microbial functions (Table 1, and see Outstanding questions). Similarly, an important selection mechanism for hosts, with a potentially intricate dynamical structure, is the action of the host's immune system. Precisely describing this type of selection is a good example of combining complex dynamical features and an eco-evolutionary process (see Outstanding questions). Finally, we highlight two broad avenues of theoretical research that would benefit from the proposed framework: (i) the modelling of diverse ensembles of mechanisms, encompassing different plausible biological scenarios, involved in the mapping between process and pattern to better understand specific biological systems, and (ii) the study of general patterns observed across multiple biological systems that might have similar underlying mechanisms as causes, in a sense acting as laws of complex symbioses (see Outstanding questions).

Outstanding questions

How do we collect data specifically for a given selection of mechanisms, with the goal to fit empirical patterns to model outputs? What are the experimental challenges and how can we inform the process of data collection?

Using the proposed theoretical framework, how can we define and characterise the emergence of core microbiomes observed in host species (e.g., sponges in ancient coevolution with their microbes)?

To what extent can specialised microbial evolutionary mechanisms, such as lateral gene transfer and faster evolution, influence the coevolution of microbes and hosts?

How important are understudied mechanisms, such as microbial dormancy, in the assembly of complex symbioses?

Are there any universal principles governing the coevolutionary process across host species, irrespective of idiosyncratic systems' characteristics?

Can we predict the sensitivity of the microbiome to perturbations in the host environment, such as rising temperatures, by adopting a theoretical approach?

How can we investigate the relationship between the microbiome and the host's immune system as a particular implementation of host selection and host life-history trait mechanisms?

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Declaration of interests

No interests are declared.

Supplemental information

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