Hierarchical Eco-Evo Dynamics Mediated by the Gut Microbiome

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Abstract

The concept of eco-evolutionary (eco-evo) dynamics, stating that ecological and evolutionary processes occur at similar time scales and influence each other, has contributed to our understanding of responses of populations, communities, and ecosystems to environmental change. Phenotypes, central to these eco-evo processes, can be strongly impacted by the gut microbiome. The gut microbiome shapes eco-evo dynamics in the host community through its effects on the host phenotype. Complex eco-evo feedback loops between the gut microbiome and the host communities might thus be common. Bottom-up dynamics occur when eco-evo interactions shaping the gut microbiome affect host phenotypes with consequences at population, community and ecosystem-level. Top-down dynamics occur when eco-evo dynamics shaping the host community structure the gut microbiome.

Main text

The Need to Integrate Gut Microbiome Research and Eco-Evolutionary Dynamics

Our insight into the assembly and functionality of **microbiomes** (see Glossary) has increased in recent years. The microbiome affects nearly every aspect of the **host phenotype** [1–3], extends the genetic repertoire of the host and contributes to host plasticity [4,5]. Hosts can manipulate colonization of microbial communities, e.g., through bacterial quorum-sensing signals leading to phenotypic switches in the bacterial colonizers and the host [6,7]. Hosts can thus potentially select for specific microbes with large phenotypic effects to persist in novel environments [8] extending their adaptive capacities beyond their own genome [9].

Largely in parallel, the field of **eco-evolutionary (eco-evo) dynamics** has gained strong momentum following the observation that ecological and evolutionary processes can occur at similar time scales and therefore influence each other [10–12]. There is strong empirical evidence for evolutionary trait change impacting population, community and ecosystem features, with the field rapidly advancing through novel metrics to quantify the relative contribution of these processes in observed trait change [13], the integration of phenotypic plasticity in eco-evo dynamics [14], the inclusion of a multiple species perspective [12] and the extension of eco-evo dynamics to macro-ecological patterns [15].

Both the fields of microbiome research and eco-evo dynamics have considerably shaped our current understanding of ecology and evolution and contributed strongly to our capacity to understand and predict ecological responses to global change [16–18]. Here, we argue that there is a need to integrate them. The phenotype is central to the concept of eco-evo dynamics because it is the phenotype that evolves (based on genetic changes) and impacts ecological dynamics by changing responses to the environment, interactions with conspecifics and other species, or direct ecosystem processes. Phenotypic plasticity thus alters how eco-evo dynamics play out, as does microbiome-mediated plasticity.

Integrating host microbiomes and eco-evo dynamics goes beyond the straightforward assessment that microbiome-mediated trait change can influence eco-evo dynamics. It is likely that eco-evo dynamics at two scales – at the level of the microbiome within a single host individual and at the level of the host population and community – interact with each other. Eco-evo dynamics that act at the level of host communities [19] and free-living microbial communities [20] very likely affect microbiome assembly. Eco-evo dynamics impacting gut microbiome assembly might impact host phenotype and thus eco-evo dynamics in the host community. Conversely, eco-evo dynamics in the host population and community are expected to impact microbiome assembly of individual hosts, host populations and host communities.

Eco-Evolutionary Dynamics in the Microbiome

Evolution can profoundly impact community assembly [19]. While understudied, it is likely that evolution is an important determinant of community trajectories and functioning of host-associated microbiomes. Features of bacteria that favour the importance of rapid evolution in shaping microbiome assembly include their large population sizes, short generation times, rapid mutation rates, and the possibility to acquire traits through horizontal gene transfer [5].

Box 1 highlights three main selective agents that may drive evolution in microbiomes. We outline three pathways through which evolution of host-associated microbiota can impact microbiome composition and phenotype (Figure 1).

Evolution-Mediated Priority Effects. Community development is often influenced by **priority effects**, wherein the order and timing of species arrival determine community assembly trajectories [21,22]. Priority effects can have long-lasting consequences, particularly if species arrival history varies during the early stages of community development [23,24]. In the gut, the initial adhesion of early colonizers shapes the environment in a manner permissive for establishing a more diversified collection of bacterial species [23]. Additionally, primary bacterial colonists in the gut may alter the composition of metabolic end products, thereby determining which bacteria are likely to flourish [23]. Although often attributed to purely ecological mechanisms, priority effects can also be mediated by evolutionary adaptation of the early colonizers. In evolution-mediated priority effects, local genetic adaptation augments transient numerical priority effects, accelerating the initial rate of increase of the early colonists. This promotes their long-term dominance by equalizing or elevating their fitness relative to later-arriving taxa (Figure 1a) [25–27]. Evolution-mediated priority effects are an example of how rapid evolution can impact community assembly [19]. More specifically, the speed of evolutionary change of the primary colonist (i.e., the rate of adaptation) relative to the speed of arrival of later immigrants (i.e., the immigration rate) determines the scope for eco-evo dynamics [25].

Evolution of Cross-feeding Interactions Affects Community Assembly Trajectories. A key characteristic of microbial communities is cross-feeding of metabolites, whereby certain members in close physical proximity consume the metabolic waste products of each other [28]. The development of such complementary metabolic repertoires in the members of the gut microbiome leads to improved functional productivity and affects community assembly trajectories [29]. Metabolic models and experimental analyses revealed that nutrient context can influence bacterial interactions within the *C. elegans* microbiome and affect host fitness [30,31]. Metabolic features of microbial strains can also evolve in response to community context [32,33]. Through the evolution of molecular signaling between microbes and the host immune system, hosts provide a stable ecological niche to diverse commensal microbial communities. This provides access to a staggering variety of enzymatic reactions and novel bioactive molecules that surpass the host's metabolic capabilities (Figure 1b) [34]. Such metabolite driven host-microbiome assemblies can be subtle and might involve co-adaptation [35].

Evolutionary Community Rescue. Evolution also plays a role in allowing community persistence during environmental challenges, such as abrupt host diet alterations, oxygen depletion, or exposure to antibiotics and toxicants. Some bacterial taxa show evolutionary rescue whereby they acquire stress tolerance from standing genetic variation or de novo mutations [36]. This has the potential to protect other community members from extinction, thereby resulting in evolutionary community rescue (Figure 1c) [37]. This can occur by transferring tolerance genes through horizontal gene transfer or by indirectly providing an advantage to other species, for example by degrading an antibiotic in the environment.

Nevertheless, the opposite may also occur, wherein bacterial adaptation is constrained by interactions within communities [38].

Eco-Evolutionary Dynamics in the Host Community

The host individual is part of eco-evo interactions that shape populations, communities and ecosystems [11–13]. The potential for interactions between evolution and community assembly is large given the parallels in drivers of population and community assembly, and the interactions occurring between them [13]. The phenotype of individuals is central to the concept of eco-evo dynamics. Trait change in a population can be mediated by plasticity or evolution [14], where evolution involves both evolution of the mean trait value and evolution of plasticity [13]. Phenotypic plasticity may involve direct effects of environmental change but may also be mediated by the host microbiome [39], which can alter phenotypes at any life stage and thus also affect developmental trajectories. This direct link between microbiome-mediated changes in host phenotype and eco-evo dynamics at the host population level suggests much scope for interactions between eco-evo dynamics within the microbiome of host individuals and eco-evo dynamics in host populations, communities and ecosystems.

Microbiomes can influence host adaptive evolution when the characteristics and composition (diversity or presence of strains) of the microbiota (1) affect the host phenotype and provide a fitness benefit, and (2) are host genotype dependent [40]. Host genotypes harbouring a set of symbionts that provides them with fitness advantages will be more successful, and this can influence host evolutionary trajectories [41–43]. This also involves selection for host genotypes associated with a specific set of microbial genomes and can result in the evolution of host genes involved in the acquisition, control and tolerance of beneficial microbiota [39,44,45]. Reciprocal evolutionary change among the host and microbiota driven by natural selection can shape eco-coevolutionary dynamics [46,47].

Hierarchical Feedback Loops: from Gut Microbiome to Host and Vice Versa

The microbiome of the intestinal ecosystem is a community that resides within a host that also is part of its own community and ecosystem. Considering the intricate nature of this integrated system and the fact that microbiomes can change host phenotypes, there is much potential for **hierarchical eco-evo feedback loops** between the eco-evolutionary systems of the microbiome and that of the host community (Figure 2). This implies that ecological, evolutionary and eco-evo dynamics in microbiomes can impact ecological, evolutionary and eco-evo dynamics at the level of the host population, community and ecosystem they are embedded in, and vice versa.

Ecology and Evolution of the Gut Microbiome Influence Host Populations, Communities and Ecosystems. The **bottom-up eco-evo feedback loop**, where ecological and evolutionary dynamics in the gut microbiome affect host populations, communities and ecosystems critically depends on the capability of the microbiome to alter the host phenotype. The influence of the microbiome on host phenotype can be mediated by different mechanisms. Microbial digestion and nutrient provision directly affect host growth and development [48–50]. Microbiome-pathogen interactions can enhance host disease tolerance [51,52]. Detoxification mechanisms of the microbiome may confer protection to the host [39,53].

Symbiotic microbes can reduce or enhance tolerance to pesticides [54] improve desiccation resistance through cuticle biosynthesis and sclerotization and detoxify heavy metals in insects [55]. As such, individual symbionts or microbial communities can expand or constrain the abiotic niche space of their host and determine its adaptability to fluctuating environments [55]. The effect of microbiome-associated pheromones and kairomones has been shown to play a crucial role in shaping interactions within insect communities [56,57]. Antibiotic-treated fish have a reduced effect on induced antipredator morphology in their prey species *Daphnia* [58]. Microbiomes are also recognized as influencers of host-parasite dynamics by the production of chemical cues [59]. These microbiome-mediated changes in the host phenotype have the potential to strongly influence host ecology and evolution, eventually scaling up to host community dynamics and ecosystem functioning.

We know of no studies that directly investigated to what extent eco-evo dynamics in the microbiome (e.g., evolution-mediated microbiome assembly) affect host phenotype. Yet, the opportunity for such interactions is broad. Microbiomes are dynamic and this has important ecological consequences. For instance, howler monkey species can utilize a higher diversity of food resources through their microbiome, generally resulting in a broader geographical range [60]. In sea urchins, expression of morphological plasticity is associated with changes in microbiome composition [61]. These effects on host phenotype can translate to population, community and ecosystem impacts. Building on the example of Macke et al. [39] showing that the microbiome provides protection against cyanotoxins in *Daphnia* resulting in microbiome-mediated phenotypic plasticity of the host, it is conceivable that the acquisition of this tolerance trait, for instance through uptake of plasmids, can facilitate the continued persistence of *Daphnia* as a dominant grazer, which may influence eco-evo dynamics in pond food webs [39,62]. An intriguing case is where the gut microbiome induces speciation by contributing to reproductive isolation. Divergence of the gut microbiomes of wasps of the genus *Nasonia* caused speciation into two descendant species [63].

As the microbiome can modify host phenotypes, it can also alter the evolutionary response to selection. So, whereas the classical perspective in eco-evo dynamics assumes that the response to selection is shaped by predetermined genotype-to-phenotype links, incorporating the microbiome into this framework might alter the picture, for instance by weakening the genotype-to-phenotype link [61]. Because selection acts on the expressed phenotypes of individuals, microbiomes can influence the trajectory and pace of phenotypic evolution by altering the response to selection, amongst other by exerting a buffering effect on environmental change.

Eco-Evo Dynamics in the Host Community Influence Gut Microbiome Assembly. Thus far, there is no direct evidence of **top-down eco-evo feedback loops** where eco-evo dynamics within the host community influence gut microbiome assembly. Yet, there is evidence for host genotypes impacting microbiome composition [64]. It is thus conceivable that evolution within the host population will impact gut microbiome composition. Beyond the direct impact of host genotype on microbiome composition, possibly mediated by antimicrobial peptides [65], eco-evo dynamics within the host community can also impact microbiome assembly by evolution-mediated changes in diet, behaviour and habitat use, which can impact nutrient

availability to the microbiome as well as exposure to toxicants and free-living bacterial communities.

How to Study Eco-Evolutionary Dynamics Involving the Gut Microbiome

To quantify bottom-up eco-evo dynamics, one needs (i) to study and manipulate eco-evolutionary dynamics in microbiomes, (ii) assess their effect on host phenotypes, and (iii) quantify the effects of the observed divergence in host phenotypes on host population, community and ecosystem ecology. For the first phase, one needs to carry out manipulative experiments testing specific mechanisms of eco-evo dynamics in shaping microbiomes (see Figure 1). Using adaptation to a host genotype as an example, the experiment would involve allowing one or more microbiome members to adapt to different host genotypes and then quantify how this influences microbiome community composition when inoculated in the same or another host genotype. For the second phase of this research, one needs to quantify whether the resulting differences in microbiome composition influence host genotype. This can be done by using a common-garden approach in which one assesses trait values of traits of interest. In a third and final phase, one can then assess to what extent these differences in host phenotypes affect population, community or ecosystem features. This can be done using a common gardening approach commonly used in eco-evolutionary research [66]. In some cases, one may refer to earlier work showing these impacts in case one studies divergence in trait values for which such common gardening experiments have already been done.

Top-down hierarchical eco-evo dynamics are potentially slightly easier to study. If prior research demonstrate that specific host genotypes are selected by the environment or community context resulting in evolutionary trait change, then one can expediate the study by using these divergent genotypes. This allows for the quantification of how they contribute to differential trajectories of microbiome assembly. One then generates germ-free individuals of these genotypes and exposes them to standardized microbiome inocula (artificial mock communities or natural free-living communities) to then quantify community composition and other community features of the microbiomes that assemble in these host genotypes. Assessing the taxonomic composition of the resulting gut microbiomes can be done using 16S rRNA gene sequencing. Shotgun metagenomics allow to also assess the potential metabolic profile of the gut microbiome [67]. As amplicon sequencing methods do not account for active gene expression and cannot make the distinction between active members contributing to the observed ecosystem behaviour and members that are simply present [68], an integration of meta-transcriptomics, meta-proteomics and metabolomics may help elucidate functional pathways and track host-microbe interactions [69][70].

As evident from the previous paragraphs, the study of bottom-up and top-down hierarchical eco-evolutionary dynamics is complex and is dependent on many criteria. The choice of the model system is therefore critical. First, there is a need to generate “germ-free” individuals and work under controlled conditions without interference from resident microbiome communities. Second, model systems that allow easy manipulation and possess knowledge from earlier work on gut microbiome assembly and dependence on host genotype are important. Third, knowledge on how the microbiome can impact host phenotypes increases

the likelihood of informative experiments. Similarly, model systems that are strong ecological interactors in their natural environment are to be preferred, given their disproportionately large impact on the ecosystem. One obvious model system is the freshwater cladoceran, *Daphnia*, which meets these criteria and offers a unique opportunity to study eco-evo interactions. Yet, we see a broad range of potential model systems, such as snails, spider mites, honeybees, birds, and mice [71–75]. In *Daphnia*, a strong link between the microbiome and host phenotype has been observed [76–78], host genotype x microbiome interactions [39], where toxin resistance is dependent on the microbiome and the microbiome on host genotype. Such host genotype and microbiome-mediated trait change can influence community and ecosystem properties. For instance, larger body sizes attributed to a better adapted gut microbiome [50,76,79] can influence *Daphnia* feeding efficiency, resulting in stronger grazing pressure on phytoplankton populations [80]. These microbiome-mediated effects also alter *Daphnia's* competitive abilities, enabling them to outcompete smaller competitors and influence the composition and diversity of zooplankton communities.

Finally, research on hierarchical eco-evolutionary dynamics will profit strongly from an increased understanding of the complex interactions between the host genotype, microbiome composition and functional profile, and host phenotype. This can also be achieved *in silico,* using genome scale metabolic models, agent-based models and models based on microbial sequence read abundance [81–84] which allow for the incorporation of genomic, transcriptomic and metabolomic data in the construction of ordered metabolic pathways that capture intricate biochemical interactions underlying host-microbe and microbe-microbe interactions.

Concluding Remarks

Reciprocal eco-evolutionary interactions between hosts and their gut microbiome might be important. This is based on (i) the importance of traits in ecological and evolutionary dynamics, (ii) the impact of the microbiome in determining host traits, (iii) the importance of eco-evo feedbacks on community assembly, and (iv) the importance of host genotype on gut microbiome assembly. Combining these four elements suggests that complex eco-evo feedback loops between host and microbiome communities may be common and impact ecological and evolutionary trajectories in both microbiome and host communities. It is a special case of eco-evo dynamics that involves interactions with ecologically distinct groups of organisms. This might lead to intriguing dynamics in space and time, because microbial taxa and their hosts are expected to respond in diverse ways to environmental gradients and react at different resolutions in space and time. It is currently not known how important these interactions are and how they influence ecological patterns in space and time (see Outstanding Questions).

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XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX BOX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Box 1. Drivers of evolution in the microbiome. There are three main drivers of evolution in microbiota populations associated with hosts (Figure I). These selection factors impact both microbial evolution and species sorting (community composition). As they occur concurrently, they can influence each other [12].

Driver 1. Evolution Mediated by the Host. Microbiota adapt to the host immune system and the specific gut environment created by the host [85]. The rate and predictability of adaptive evolution of microbiota is influenced by the host immune system [86]. Moreover, gut microbiota show adaptation to the specific gut environment through mutations in genes involved in adhesion to host epithelial cells [87]. Adaptation to the host may occur through de novo mutations as well as through loss of redundant and expensive pathways that provide little or no adaptive value in the specific host environment [88].

***Driver 2. Evolution in Response to Microbial Interactions*.** A balance between cooperation and competition both within and between microbial species plays a key role in regulating evolutionary dynamics in the gut microbiome [89]. For instance, important traits such as antibiotic resistance can spread rapidly via plasmids [90], and microbiota might become dependent on secreted molecules produced by other members of the microbial community, and consequently lose the ability to produce these compounds themselves [91]. Moreover, interspecific competition over limited resources may drive evolution of toxin production to limit growth of competing strains [92].

Driver 3. Mechanisms of Evolution in Response to Environmental Stress

Environmental factors, such as dietary substances and external microbes may drive evolution of resident microbiota. Studies in mice demonstrated the adaptation of *Bacteroides sp.* and *E. coli* gut microbiota to degrade diet-specific polysaccharides [87,93]. A study on human inhabitants of Japan demonstrated the emergence of a porphyrin degrading enzyme in gut microbiota through horizontal gene transfer from a marine bacterial strain, associated with a diet on seaweed [94]. Microbiota can also evolve to protect animal hosts against infection by external pathogenic bacteria [51].

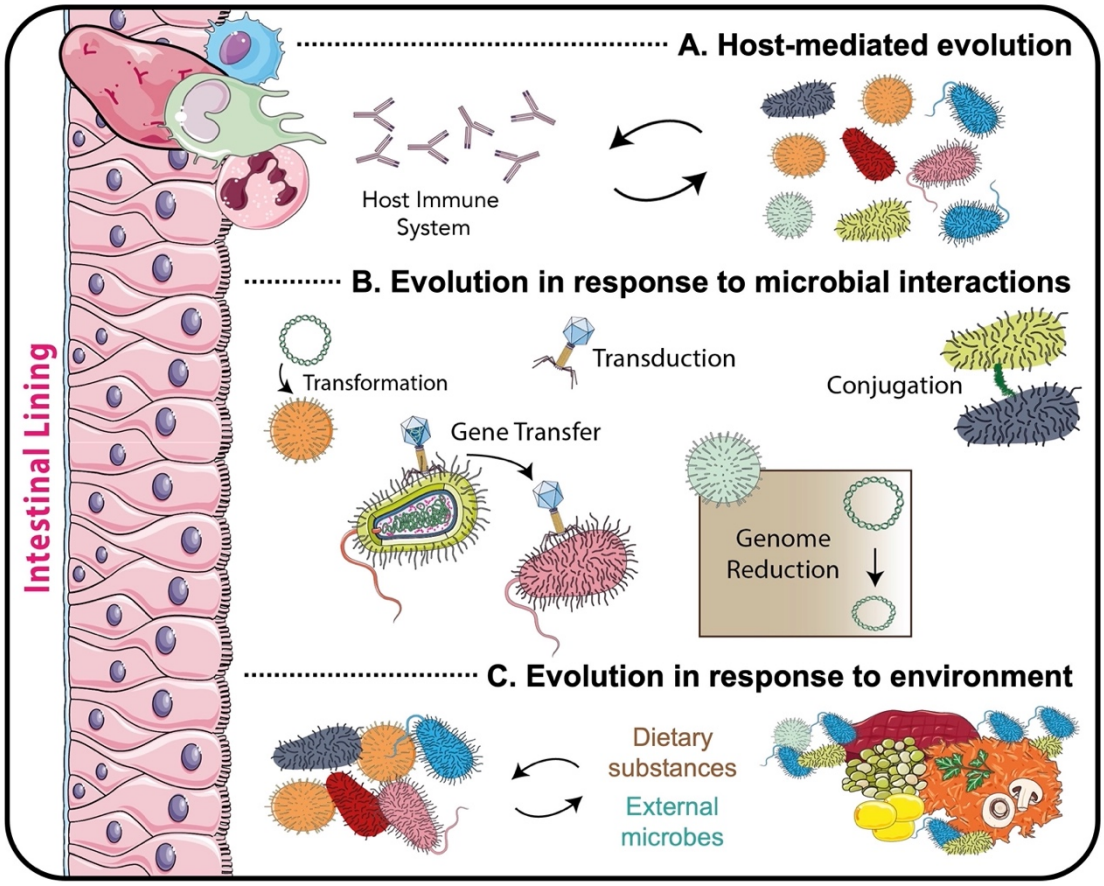

Figure I. Drivers of evolution in the gut microbiome. A: Evolution of gut microbiota in response to host immune system and gut environment. B: Evolution of gut microbiota in response to microbial interactions. C: Evolution of gut microbiota in response to environmental stressors.

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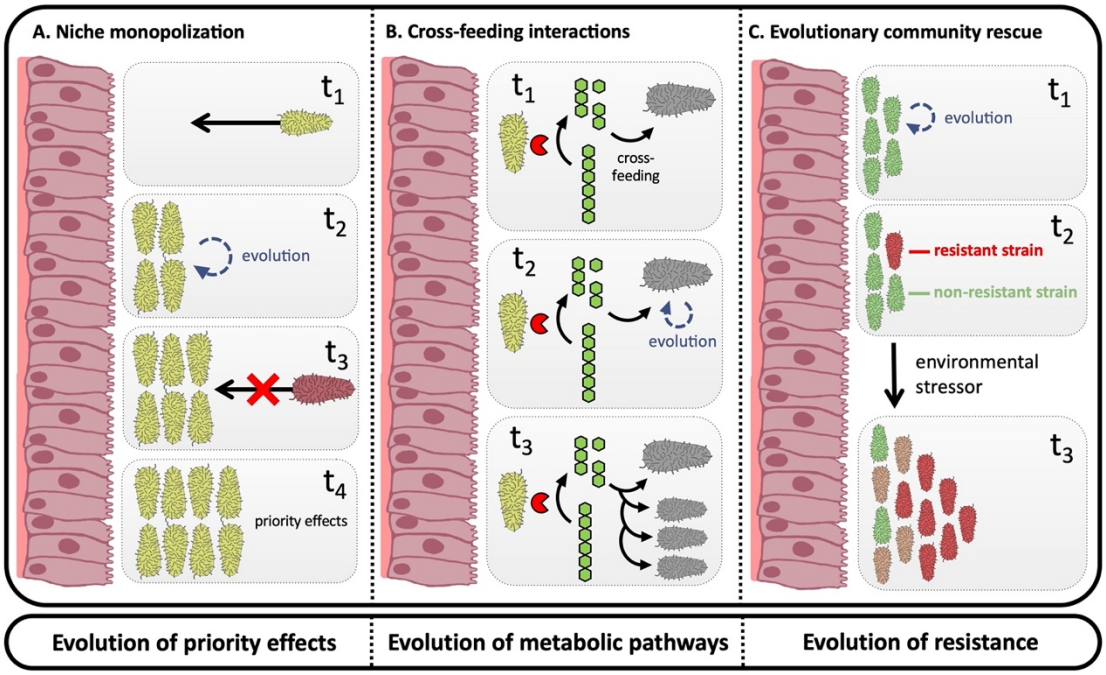

Figure 1. Eco-evolutionary dynamics in the gut microbiome. A: Niche monopolization: adaptation to the local gut conditions of early colonists can promote their long-term dominance creating or enhancing priority effects. B: Evolution of metabolic pathways and community assembly: genetic adaptation of bacteria to the trophic conditions provided by the microbial community can create alternative trajectories of community assembly. C: Evolutionary community rescue: when specific strains evolve resistance against an environmental stressor (e.g., antibiotics), then this may contribute to the rescue of the entire community by either directly transferring resistance genes to other strains (i.e., strains with acquired resistance - indicated in red), through recombination, or by protecting other strains by detoxification in the environment (strains that profit from this - indicated in orange).

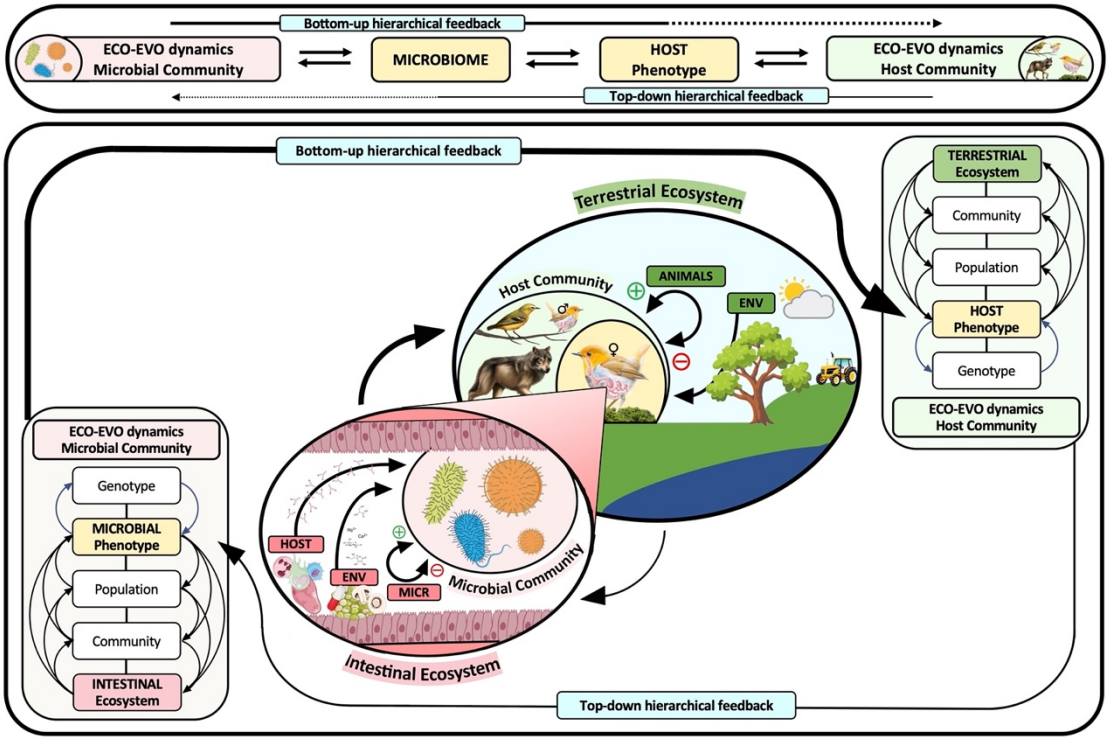

Figure 2. Hierarchical feedback loops between eco-evo dynamics in the gut microbiome and in the host community. The bottom-up feedback loop involves eco-evo dynamics in the gut microbial community shaping the functionality of the microbiome, which can feed back to the host phenotype and influence ecological and evolutionary dynamics in the host population and community. A top-down feedback loop involves eco-evo dynamics in the host community shaping the host phenotype, which in turn feeds back on the gut microbiome and the phenotype of individual microbial populations. ENV: environment. MICR: microbes.

Glossary

Bottom-up eco-evo feedback loop: effects of ecological, evolutionary and eco-evo dynamics at the level of the microbiome within a given host individual on host populations, communities and ecosystems.

Eco-evolutionary (eco-evo) dynamics: interactions between ecological and evolutionary processes caused by both ecological dynamics impacting evolution and evolutionary change in space and time affecting ecological processes and patterns.

Host: the organism on or in which the microbiome resides.

Hierarchical eco-evo feedback loop: hierarchical effects between ecological, evolutionary and eco-evo dynamics at the level of microbiome communities and at the level of host communities.

Microbiome: the consortium of microbes that live on or in a given host and their associated gene functions.

Priority effects: effects of species arrival order on population and community dynamics and structure.

Top-down eco-evo feedback loop: effects of ecological, evolutionary and eco-evo dynamics within host communities on the microbiome community of a given host individual.

Germ-free animals: also known as gnotobiotes; organisms that are devoid of all resident micro-organisms; usually achieved with the use of antibiotics, chemical agents or genetic modifications.