

## REVIEW

# The potential role of the gut microbiota in shaping host energetics and metabolic rate

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**Handling Editor:** Andy Fenton**Abstract**

1. It is increasingly recognized that symbiotic microbiota (especially those present in the gut) have important influences on the functioning of their host. Here, we review the interplay between this microbial community and the growth, metabolic rate and nutritional energy harvest of the host.
2. We show how recent developments in experimental and analytical methods have allowed much easier characterization of the nature, and increasingly the functioning, of the gut microbiota. Manipulation studies that remove or augment gut microorganisms or transfer them between hosts have allowed unprecedented insights into their impact. Whilst much of the information to date has come from studies of laboratory model organisms, recent studies have used a more diverse range of host species, including those living in natural conditions, revealing their ecological relevance.
3. The gut microbiota can provide the host with dietary nutrients that would be otherwise unobtainable, as well as allow the host flexibility in its capacity to cope with changing environments. The composition of the gut microbial community of a species can vary seasonally or when the host moves between environments (e.g. fresh and sea water in the case of migratory fish). It can also change with host diet choice, metabolic rate (or demands) and life stage. These changes in gut microbial community composition enable the host to live within different environments, adapt to seasonal changes in diet and maintain performance throughout its entire life history, highlighting the ecological relevance of the gut microbiota.
4. Whilst it is evident that gut microbes can underpin host metabolic plasticity, the causal nature of associations between particular microorganisms and host performance is not always clear unless a manipulative approach has been used. Many studies have focussed on a correlative approach by characterizing microbial community composition, but there is now a need for more experimental studies in both wild and laboratory-based environments, to reveal the true role of gut microbiota in influencing the functioning of their hosts, including its capacity to tolerate environmental change. We highlight areas where these would be particularly fruitful in the context of ecological energetics.

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## KEYWORDS

assimilation, bacteria, digestion, food, holobiont, microbiome, microorganism, nutrition

## 1 | INTRODUCTION

Whilst ecologists have appreciated the key role of energy flow in structuring ecological communities, and hence the importance of inter- and intraspecific variation in metabolic rate, there has been growing recognition of the fact that an animal's metabolism can be significantly influenced by the microbial communities in its gut. These communities, henceforth termed the gut 'microbiota' (see Box 1 for definitions), are fundamentally ecological in nature in that they interact with each other (competitively and symbiotically) and with the host upon which they reside (mutualistically and commensally), and are dependent on the biophysical environment that the host creates (Jandhyala et al., 2015; Tremaroli & Backhed, 2012). There are frequently differences in species composition and abundance between the microbial communities found at different locations on a single host, underpinned by variation in the micro-environments that the microbes encounter. For example, within the vertebrate gut, the dynamics of cell turnover, secretions and peristalsis all drive micro-variation in microbial community structure (Rolig et al., 2017). The complexity of the microbial community can also differ markedly between hosts, for example, the gut microbiota is simpler in *Drosophila* than within mammals (Erkosar et al., 2013). Significant microbial diversity also exists between the same intra-host niche among different individuals (Burns et al., 2016). Most observed interindividual diversity is as yet generally unexplained, though host genetics, diet, environment and

early exposure to microbes are each thought to have a role (Alberdi et al., 2016; Consortium, 2012; Navarrete et al., 2009; Tremaroli & Backhed, 2012; Zarkasi et al., 2016).

The gut microbiota is the most diverse and populous microbial assemblage on the host (Senghor et al., 2018) and is thought to interact with the host in a myriad of ways (Gajardo et al., 2016; Gomez & Balcazar, 2008). Microbial symbionts are thought to affect many aspects of the host's metabolism and physiology, and hence have direct relevance for ecological studies, since effects of the microbiota can have marked impacts on the host and the way in which it interacts with its environment. Microbes interact with the immune system (Mackos et al., 2017) and aid in the regulation of fat storage (Cani & Delzenne, 2009), but their most direct role is in supplying nutrients to the host via the digestion of components of the host's diet or the synthesis of amino acids (Carey et al., 2013; den Besten et al., 2013), so influencing its ability to compete for scarce resources. As such, the gut microbiota can influence the host's food assimilation efficiency, energy consumption and metabolic rate (collectively comprising its energetic phenotype). Through exploring the links between the gut microbiota and host lifestyle, genotype and environment, we discuss the impacts of the microbiota on host ecology. In so doing, we aim to highlight the need for future ecological research to focus not only on the host but also on the 'holobiont' (Bordenstein & Theis, 2015), which comprises the host and its associated microbiota.

Research on host-microbiota interactions has to date largely been focused on laboratory-based studies and model organisms, but clearly has broader relevance; for example, studies of hosts such as gorillas (Hicks et al., 2018) and house sparrows (Teyssier et al., 2018) have provided ecological insight into host-microbiota interactions specifically relevant to natural systems by assessing spatio-temporal effects on the host microbiota. In this review, we aim to highlight the multiple advantages of conducting such studies on wild animals, specifically in relation to the ecological understanding this might provide, including generating insights into how gut microbes can underpin host energetic plasticity in changing environments. This burgeoning research area is not without its complications however, and this review aims to identify many of the limitations involved with the exploration of ecological questions in the context of wild and laboratory-reared host-associated microbiota.

## BOX 1 Glossary of relevant terms

## Glossary

Axenic	An environment devoid of contaminating microorganisms
Gnotobiotic	An environment in which all microorganisms are absent, used to establish gnotobiotic (germ-free) animals
Holobiont	The combination of different species that form an ecological unit. In the context of the microbial ecology, the holobiont incorporates the host and its microbiota
Hologenome	The collective genomes of the holobiont. In the context of microbial ecology, the hologenome considers the genomic content of the host and its symbiotic microbes
Microbiota	Microorganisms found both within and on every multicellular species

## 2 | OLD AND NEW TOOLS FOR DETERMINING THE IMPACT OF MICROBIOTA ON HOST ENERGETICS

To make sense of so many recent advances, we first need to describe the 'toolkit' of approaches that are now available to researchers in this

**TABLE 1** An overview of current approaches to research the ecology and function of gut microbiota

Approach	Description	Use	Limitations	Reference
Next Generation Sequencing (NGS)	DNA sequencing using the concept of massively parallel sequencing, which describes the high-throughput and high speed of the technology	Identifies the diversity of microorganisms present via targeted (e.g. 16S rDNA) or non-targeted (e.g. shotgun metagenomics) approaches	Issues with reliability of library preparation (i.e. selectivity of primers) Provides information only on functional capacity, not function	Hovda, Lunestad, Fontanillas, and Rosnes (2007) and Kimura et al. (2020)
Meta-omics	Metagenomics, genome; metatranscriptomics, transcriptome; metaproteomics, proteome; and metabolomics, metabolome Following these -omics approaches, mass spectrometry (MS) and nuclear magnetic resonance (NMR) allow characterization of compounds/metabolites that microorganisms are producing	Used in combination to analyse the complex ecology of microbiota—characterizing communities but also providing detail on alpha and beta diversity and metabolic functions Metatranscriptomics are typically targeted at microbial mRNA to reveal community level gene expression MS and NMR allow metabolic profiles of a species or population of species to be assessed. Characterization of these metabolites (such as short-chain fatty acids and volatile fatty acids) can indicate function of the microbial species or population	Expensive Difficult to scale-up to population samples Transcriptomics are subject to contamination by ribosomal RNA Often highly sensitive to sample preparation	Ni and Tokuda (2013), Xie, Zhang, Zheng, and Jia (2013) and Rambold et al. (2019)
Reverse Transcription Quantitative PCR (RT-qPCR)	RNA is first reverse transcribed into complementary DNA, before this is then used as a template for qPCR. qPCR quantifies presence and abundance of this DNA	Quick and targeted quantitative measurement of microbial gene transcription (e.g. CAZenzymes, see text), allowing identification of which microbial genes are being expressed	Difficulties associated with RNA work Same PCR issues as found within library preparation for NGS	Bredon, Dittmer, Noël, Moumen, and Bouchon (2018), Gajardo et al. (2016), Olsvik, Vikeså, Lie, and Hevrøy (2013) and Smith and Osborn (2009)
Gnotobiotic manipulations	Complete removal of microbiota—the host is reared in an axenic environment	Can be used to examine physiology of the host in the absence of all specific microbial symbionts, thereby allowing identification of the role of the microbiota Facilitates testing of role of individual microbes or microbial communities in defining host phenotype Creating axenic hosts and environments can be challenging. Eggs of oviparous species can be sterilized by antiseptics and antibiotics. Germ-free viviparous species can currently only be achieved via aseptic caesarean or hysterectomy	Limited to sterile lab environments Costly to establish and maintain gnotobiotic lines Findings not always transferable to natural conditions	Marques, Ollevier, Verstraete, Sorgeloos, and Bossier (2006), Martin, Bermúdez-Humarán, and Langell (2016), Rawls, Samuel, and Gordon (2004), De Swaef, van den Broeck, Dierckens, and Decostere (2016) and Zhang et al. (2020)
Mono-associations	The host is inoculated with a single microbial taxon	Enables researchers to view the impact of a single microbial taxon on a (gnotobiotic) host	Limited to sterile lab environments Biologically unrealistic	Lee, Han, Kim, Jeon, and Hyun (2020), Morimoto, Simpson, and Ponton (2017)
Microbiota-transplants	A gnotobiotic host is inoculated with the microbiota of another individual	Enables researchers to view the impact of a full microbial community on the host Can be deployed xenobiotically (e.g. bear to mouse, human to mouse) in order to use sterile lab conditions Can be used to determine the extent to which the microbiota can influence the host phenome	Limited to laboratory environments Findings not always transferable to natural conditions	Chevalier et al. (2015), Crawford et al. (2009), Rawls, Mahowald, Ley, and Gordon (2006) and Sommer et al. (2016)

(Continues)

TABLE 1 (Continued)

Approach	Description	Use	Limitations	Reference
Antibiotics	Single strains or multiple varieties of antibiotics are administered to a host	Reveals how reduction of the microbiota can impact the host Can be deployed to specifically target sensitive classes of microbes Can be used to sterilize eggs of oviparous species Can be used in species in which gnotobiotic methods would not be feasible	Difficulties in repeatability as different antibiotics and dosages can have varying effects Some bacterial taxa are difficult to eliminate; higher antibiotic doses may have toxic effects on the host Problem of antibiotic resistance, especially in the field	Hu et al. (2013), Lin, Kang, Pann, and Liu (2015), Morgun et al. (2015), Raymann, Bobay, and Moran (2018) and De Swaef et al. (2016)

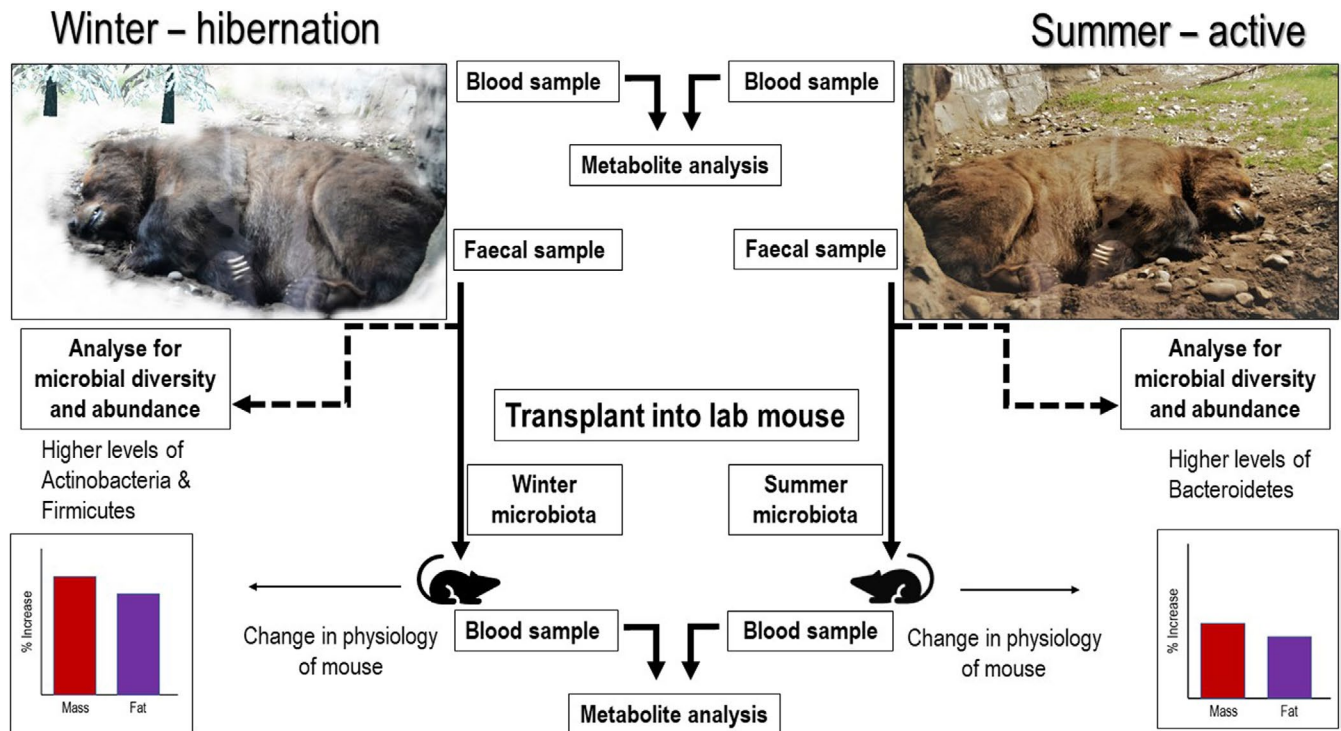
field. Characterization of the composition and function of the microbiota has classically relied on DNA and RNA sequencing techniques. Most commonly, high throughput sequencing of the 16S rRNA gene is used to identify the bacteria present within microbial communities (Table 1). However, research is gradually moving from simply measuring the diversity of bacteria present to determining microbial expression profiles, to delineate the functional basis of the host-microbiota relationship. Techniques such as reverse transcription quantitative PCR (RT-qPCR) can identify transcriptional responses in host species (Table 1), whilst various meta-omics approaches used in tandem with 16S rRNA sequencing can describe not only what bacteria are present, but the impact that their presence has on the host (Alberdi et al., 2016; Tremaroli & Backhed, 2012). Metabolomic approaches, for example, can identify metabolites produced by gut microbiota, especially volatile fatty acids (VFAs), short chain fatty acids (SCFAs), lactic acid and aromatic amino acids, so revealing how the microbiota can make specific nutrients available to the host or other members of the bacterial community (Le Gall et al., 2011; Mashego et al., 2007; Sridharan et al., 2014; Zheng et al., 2011).

A complication consistently encountered when studying host-microbiota relationships is disentangling cause from effect, since studies are often correlational. Progress has been made to overcome this limitation via the use of germ-free technologies, in which animals are reared in axenic environments, allowing the host to remain entirely devoid of microbes. Gnotobiotic, or germ-free, models have been successfully established in order to both determine how hosts perform in the absence of all microbes and to measure how this changes when the 'clean' animal is then seeded with selected microbial taxa (Table 1). Such studies have revealed various effects of gut microbiota on the host, including modulation of bone-mass density, fat storage and the immune system in mice (Tremaroli & Backhed, 2012) and regulation of fatty acid metabolism in zebrafish (Semova et al., 2012). In one such landmark study, transplantation of the gut microbiota from an obese host into a gnotobiotic recipient mouse led to an improved capacity for energy harvest and higher levels of fat deposition in comparison to when a host was colonized with a 'lean microbiota' (Turnbaugh et al., 2006). This early study highlighted

the link between gut microbiota and metabolism and showed that traits can be transmissible via microbiota transplants; another example is shown in Figure 1. Now, mono associations (in which a gnotobiotic host is the recipient of a single microbial taxon) and the transplantation of microbial communities between hosts (Table 1) have the potential to reveal the effect that the microbiota have on host phenomes.

It is difficult to render a host germ-free once it has already been colonized with microbes (i.e. once it is free-living), but antibiotics can be used to examine the impacts of a disrupted gut microbiota (Table 1), whereby antimicrobial compounds are used in ecological research as a tool to knock out groups of microbes in order to explore their function (Lin et al., 2015; Morgun et al., 2015; Raymann et al., 2018). Antimicrobial knock-out approaches have revealed, for example, the effects of the microbiota on host metabolism: the standard metabolic rate (SMR) of *Periplaneta americana* cockroaches was altered when the gut microbiota was disrupted by antibiotics (Ayayee et al., 2018). Unsurprisingly, antibiotic administration resulted in a reduction of bacterial load within the cockroach gut, but interestingly, this led to a decrease in host metabolic rates. Fine-scale effects on bacterial taxa remained unquantified, so these physiological effects could not be ascribed to specific microbes. However, other studies have shown antibiotics to cause changes in gut microbial community composition in mice (Yoon & Yoon, 2018) and honeybees (Raymann et al., 2018); the latter study showed that two key bacterial species of the bee gut responded differently to antibiotics, with *Gillamella apicola* experiencing a large reduction in genetic diversity, whilst *Snodgrassella alvi* remained largely unaffected. However, the use of antibiotics in ecological and microbiota research is not without its limitations (Table 1).

Whilst several of these promising new experimental approaches, such as gnotobiotic treatments followed by seeding with selected microbial communities, are now available, to date their use has been restricted to a small number of laboratory model organisms. These allow determination of the causal role of host-associated microbial communities, but field-based studies remain the best way of truly understanding host-microbiota relationships



**FIGURE 1** An illustration of how an experimental approach can be used to determine microbiome–host relationships in an ecological context. This single study utilized many of the methods discussed within this review. Researchers used 16S rRNA profiling of bear faeces and the caeca of colonized mice to assess diversity and abundance of the microbes present within the gut. Blood metabolites were also analysed and compared between hosts to examine metabolites relevant to metabolism. Transplantation of gut microbiota from a wild bear to gnotobiotic mice demonstrated that the seasonally dependent energetic phenotype was transmissible, as shown by the gut microbiota, blood metabolite profiles and the resulting physiological state of the new host being dependent on the season of transfer. This study highlights the range of ways a single study can examine the gut microbiota in relation to the host metabolic phenotype and combines lab and field-based approaches. Information taken from Sommer et al. (2016)

since they place host–microbe interactions in an ecological context (Figure 1). An example of this is the demonstration that the social environment of red-bellied lemurs *Eulemur rubriventer*—which can only be realized fully in groups of wild animals—plays a role in modifying their microbial community (Raulo et al., 2018). However, there remain significant logistical challenges to implementing some of these lab-derived approaches in the field (Table 1). As such, this review draws attention to the range of approaches being used to explore the host–microbiota relationship, which are allowing direct links to be found between host-associated microbial communities and host energetics.

### 3 | GUT MICROBIOTA NUTRITIONAL NICHES AND HOST NUTRITIONAL ENERGY HARVEST

Many host species consume diets for which they lack the endogenous enzymatic repertoire to fully exploit, and so depend on their gut microbiota to produce the key digestive enzymes. Obvious examples of this are termites and ruminants, which rely on microbial hydrolase enzymes to break down the cellulose in their plant-based diet into monosaccharides and oligosaccharides (Ni & Tokuda, 2013; Varel & Dehority, 1989).

These are then fermented by microbes such as saccharolytic bacteria to produce short chain fatty acids (den Besten et al., 2013). The cell walls of woody plants contain lignocellulose, a complex composed of lignin, cellulose and hemicellulose. Digestion of lignocellulose requires multiple carbohydrate-active enzymes (CAZymes), only some of which may be produced by the host (Bredon et al., 2018). For example, whilst mealworms *Tenebrio molitor* and woodlice have been found to produce degradation enzymes such as cellulases, they rely on their gut microbiota to produce the enzymes that break down compounds like lignin and phenols (Bredon et al., 2018; Genta et al., 2006). Similarly, termites symbiotically combine with their microbiota to produce the range of CAZymes needed to break down lignocellulose, producing metabolites which drive the termite's energy metabolism (Ni & Tokuda, 2013). The hindgut microbiota of higher termites also has a role in fixing, recycling and upgrading nitrogen, without which termite growth would be constrained (Brune & Dietrich, 2015). These examples highlight how the gut microbiota allows the host to exploit otherwise inaccessible niches.

An analogous phenomenon is also observed in some cetaceans (Sanders et al., 2015). Baleen whales (*Mysticeti*) require CAZymes to break down the large quantities of the polysaccharide chitin that they consume in the form of krill and other zooplankton. Sanders et al. (2015) found that the microbiome of baleen whales shares characteristics with those of both terrestrial carnivores and



herbivores, with an amino acid metabolism gene profile resembling that of a carnivore, but a gene profile associated with energy metabolism and lipid metabolism reflecting those of herbivores. Similarities of the cetacean gut microbiota to that of a fermentative herbivore are thought to aid release of chitin nutrients to the whales (Sanders et al., 2015).

The waste products of microbial metabolism, such as the acetate and butyrate produced by fermentative bacteria, can have significant effects on host metabolism since they are involved in the regulation of fatty acid, glucose and cholesterol metabolism, as well as being used by the host as an energy source (den Besten et al., 2013). For example, the symbiotic class Mollicutes was found to convert dietary citrate into acetate to fuel host metabolism in Panamanian fungus-growing leaf-cutter ants (Sapountzis et al., 2018). Short chain fatty acids such as acetate and butyrate provide much of the energy needed to sustain the high turnover rate of colonocytes and enterocytes (epithelial cells of the colon and cells of the intestinal lining, respectively) within the host gut, with oxidation of butyrate alone able to provide up to 70% of energy needed by colonocytes in rats (Roediger, 1982).

As well as impacting the nutritional niche of organisms by allowing them to digest complex and otherwise inaccessible biological polymers, the gut microbiota is also thought to play a role in the detoxification of dietary components, allowing the host to exploit a niche intolerable to most other species (Genta et al., 2006; Heys et al., 2019; Wienemann et al., 2011). One such example is that of the coffee berry borer *Hypothenemus hampei*, an insect pest of coffee. Caffeine is a known toxicant that has negative effects on insects, including impacting DNA repair and phosphodiesterase activity (Ceja-Navarro et al., 2015); nonetheless, the coffee berry borer completes its entire life cycle on the coffee plant. This is made possible due to caffeine degradation carried out by its gut microbiota. When the gut microbiota is incapacitated with antibiotics, the host loses its ability to degrade caffeine, but this is restored by reinfection with *Pseudomonas fulva*, known to produce an enzyme that causes demethylation of caffeine (Ceja-Navarro et al., 2015). A similar study in mealworms *Tenebrio molitor* compared germ-free larvae with conventionally reared individuals and found the gut microbiota had a role in detoxifying allelochemicals within *T. molitor*'s plant-based diet. Detoxification in this context was thought to be due to the microorganisms' ability to catabolize toxic plant glycosides and aglycones, with some bacterial species using aglycones as a carbon source (Genta et al., 2006). Similar relationships are seen in diverse host species: the caecal microbiota of the Western capercaillie *Tetrao urogallus* allows its host to survive on its potentially toxic resin-rich winter diet (Wienemann et al., 2011), whilst the unusual tolerance of sheep and goats to toxins in the ragwort *Jacobaea vulgaris* is thought to be due to the detoxification role of the rumen microbiota (Ratray & Craig, 2007). In allowing hosts to exploit otherwise indigestible or toxic dietary compounds, the gut microbiota thus permits hosts to expand their niche and to reduce interspecific competition by feeding on underutilized sources.

## 4 | STUDYING GUT MICROBIAL ENERGETICS IN THEIR ECOLOGICAL CONTEXT

As researchers strive to understand specific functional benefits of the microbiota, an advantage to studying holobiont dynamics in wild animals is the existence of pronounced variation in environmental conditions experienced by the hosts. This allows researchers to examine whether there is selection for microbial taxa that are more effective under different environmental conditions, which in turn allows the host to function across a broader range of environments. Of particular relevance is the influence of dietary composition, which can show pronounced seasonal changes that have a powerful influence on gut microbial communities (Hang et al., 2013). By way of example, seasonal changes in gut microbial community composition have been found in the giant panda *Ailuropoda melanoleuca* as its diet transitions from protein-rich bamboo shoots to bamboo leaves that are less rich with a higher cellulose content (Wu et al., 2017). The shift to the poorer quality diet is associated with the gut microbiome becoming less diverse, but more specialized on breaking down cellulose. The presence of cellulose-digesting bacteria in the gut of the panda also helps to explain how a carnivore can feed on plants (Wu et al., 2017; Xue et al., 2015).

Similar effects of diet on microbial community composition have been seen across a variety of species; often the consequences for the host are unknown, but there are some suggestive examples. In American bison *Bison bison*, an increased abundance of the Phylum Tenericutes, which metabolize simple sugars, is found when the diet is biased more towards plants lower in secondary metabolites (Bergmann et al., 2015). Human studies are informative: microbial community structure within the human gut differs between subjects consuming an animal-based diet compared to a plant-based diet, which has consequences for microbial gene expression and activity: animal-based diets result in greater activity of amino acid catabolism pathways whereas plant-based diets lead to an emphasis on biosynthesis pathways (David et al., 2013). Energy requirements in the Western capercaillie are met primarily by foraging on resinous coniferous needles during winter, reducing the diversity of the caecal bacterial community in comparison to when the birds have a more diverse diet (Wienemann et al., 2011). Interestingly though, greater differences in community composition exist between wild and captive individuals. Within captive capercaillie, there is an absence of certain fermentative bacterial species, such as those from the *Synegetistes* phylum. These species ferment carbohydrates to produce acetate, propionate and succinate, so contributing to succinate turnover and supplying energy to the host. Reduced fermentative capacity compromises detoxification activities within the gut, which is necessary to tolerate the birds' resin- and phenol-rich winter diet (Wienemann et al., 2011). The gut microbiota differences between wild and captive individuals could in part explain why reintroductions using captive-bred birds have thus far largely been unsuccessful (Wienemann et al., 2011).

Although the complex interplay between host diet and the gut microbiota has been examined in many contexts, reproducibility can

remain poor, so attempts to define the diet–host–microbiota relationship remain a challenge. Understanding can be further complicated due to variation in the ecology of bacterial species: Holmes et al. (2017) found that responses to dietary nitrogen levels were divergent between bacterial taxa, which had repercussions for host health. Specifically, the taxa positively responding to limited protein availability (endogenous nitrogen users), such as members of the Phylum Bacteroidetes, included species known to provide maintenance to intestinal barrier functions and immunoregulation within the murine host and promote good overall ‘cardiometabolic health’ (avoidance of cardiovascular disease). This was in contrast to the poorer cardiometabolic health phenotype seen in mice administered with a higher protein diet that favoured microbes that rely upon dietary nitrogen (Holmes et al., 2017). Other human and laboratory animal studies also indicate complex interactions between diet, gut microbiota and host metabolism and health (Ayayee et al., 2018; Cani & Delzenne, 2009; Musso et al., 2011), emphasizing the importance of taking into account the dietary factors impacting microbial community dynamics and assembly.

In addition to coping with changes in dietary composition, wild animals often have to withstand significant fluctuations in the quantity of food available, both directly due to seasonal changes and indirectly as a result of their life history: e.g. when they migrate, hibernate or otherwise become dormant, or show ontogenetic niche shifts. These periods, in which the energetic phenotype of the host changes, can reveal potential functional links between the energetics of the gut microbiota and that of the host. Short-term fasts can induce responses from the gut microbiota that benefit the host, for example, by increasing the supply of SCFAs through fermentation of glycans (Crawford et al., 2009). A more extreme fast is experienced by species that hibernate—although it is important to note that hibernation and fasting are not equivalent physiological states for endotherms. In contrast to fasting, hibernation is often characterized by the lowering of the core body temperature to  $<10^{\circ}\text{C}$ , producing a much reduced metabolism of around  $<4\%$  of the level seen in the active mammal (Carey et al., 2013). As a consequence, the gut microbiota may respond differently to the two situations: Syrian hamsters *Mesocricetus auratus* showed no reduction in total bacterial numbers or SCFA concentrations when entering hibernation, but showed significant decreases in both measures of microbial activity when involuntarily starved (Sonoyama et al., 2009), suggesting that the microbiota are more resilient to a predictable seasonal change in host energetic status than to an unexpected (and potentially more stressful) crash in food intake.

The diversity of the gut microbiota can nonetheless decrease during a period of hibernation, with an increase in the preponderance of bacteria that can live directly off the host (e.g. feeding off host mucins) and a loss of species that are reliant on host dietary compounds (Carey et al., 2013). Studies of the metabolomics of hibernating species have identified compounds produced by microbes that will affect host energetics during the period of hibernation. The shift in the composition of the gut microbiota in ground squirrels *Ictidomys tridecemlineatus* as they prepare for and enter torpor may

contribute to the build-up of fat stores and leads to an increase in the relative production of acetate, which can be used as an alternative to glucose for energy in certain organs (Carey et al., 2013). Hibernating and active ground squirrels differ in the levels of SCFAs known to play key roles in host energy metabolism (Carey et al., 2013). A direct effect of the microbiota on the physiology of a hibernating host, allowing it to conserve energy, was demonstrated by showing that the transfer of the ‘winter microbiota’ (i.e. that present within the gut during winter hibernation) of wild brown bears *Ursos arctos* into gnotobiotic mice had different effects on the mice than did the transfer of the ‘summer microbiota’ (Sommer et al., 2016; Figure 1). Moreover, metabolites in the blood of these mice correlated with those observed in the wild bears in the appropriate season, further demonstrating that the modulation of host energy metabolism was a direct result of the microbiota (Sommer et al., 2016). That a seasonal metabolic phenotype was in part transferable even between host species (Figure 1) provides dramatic empirical evidence that the microbiota can provide the means by which a host shows metabolic acclimation under different environmental conditions.

Some host species are adapted to prolonged period of fasting regardless of environmental conditions: Burmese pythons *Python molurus* experience extended periods of time without food before consuming an exceedingly large meal (sometimes exceeding 50% of their body weight; Costello et al., 2010). This host therefore offers a different insight into host–microbiota–metabolism interactions, due to the altered circumstances in which nutrient deprivation occurs. The snake undergoes large physiological and morphological changes when it feeds, including enteric hypertrophy, and experiences dramatic but short-term changes in its metabolic demands and energy flux (Costello et al., 2010). There are parallel changes in the python's gut microbiota: Costello et al. (2010) discovered that the gut microbiota of a fed python was characterized by a higher proportion of taxa associated with proteolytic activity, including an increase in Firmicutes, known to increase energy harvest in other animals.

## 5 | ADAPTABILITY, PLASTICITY AND HOST ENERGETICS

Flexibility in the microbial community composition or activity can potentially be beneficial to a host, since it can allow the host to respond to changing food availability or metabolic demands (Foster, 2017; Sommer et al., 2016); conversely, the benefit of a particular functional profile of microbes can vary in time and space (Risely et al., 2017; Sommer et al., 2016). The gut microbiota–host relationship can vary temporally in response to changes in environmental factors other than simply diet (Burns et al., 2016; Uren Webster et al., 2020). This should be most evident in animals that experience large environmental shifts over their lifetime. Thus, the transition from fresh to salt water in Atlantic salmon *Salmo salar* has been found to influence the number of microbial species present in different regions of the gut and the overall bacterial load (Llewellyn et al., 2015; Rudi et al., 2018). The microbiota

might be especially relevant at key developmental stages, as found for Wood frogs where disruption of the microbiota in early larval life was found to have legacy effects on development that lasted until after metamorphosis, long after the microbiome had recovered from the perturbation (Warne et al., 2019). This highlights the value of considering a host's lifecycle and changing energetic demands when elucidating the impact of the gut microbiota. As a further example, Gould et al. (2018) found the diversity of the gut microbiota of *Drosophila melanogaster* influenced the life history of the host, with interactions between the five major bacterial species commonly found in the fruit fly affecting the scheduling of reproduction. Germ-free flies had an increased lifespan, but a lower reproductive rate (Gould et al., 2018). The complexity of the host-microbial relationship is thus increased when considered in the host's ecological context, highlighting the dynamic nature of the association.

Longitudinal studies examining changes in energy demand benefit from being able to compare the gut microbiota within the same host under different conditions, but always have the confounding factor of time (or host age). This can be circumvented where host species exhibit intraspecific variation in energy demand at the same time point. Risely et al. (2017) simultaneously compared the gut microbiota of migratory *Calidris* spp. shorebirds to that of their non-migratory conspecific counterparts. Long-distance migration can represent physiological and morphological challenges for the host (such as the need to reduce body mass in order to reduce the costs of locomotion), often in association with high energy demands. Migrant individuals of two species were found to have a 30-fold higher abundance of the *Corynebacterium* genus in their guts in comparison to conspecific residents, though the remaining community structure remained broadly similar (Risely et al., 2017). The reason for this dramatic increase in the prevalence of *Corynebacterium* species in migrants is as yet unknown.

The dynamic nature of the microbiota-host relationship means that it can be difficult to determine the relative importance of the microbiota in determining the phenotype of the host. Recent work has begun to revolve around the holobiont and to incorporate the 'hologenome' concept, in which the evolutionary capacity of both the host and its associated microorganisms is considered together (Alberdi et al., 2016; Bordenstein & Theis, 2015). Within the field of ecology, consideration of the hologenome/holobiont allows researchers to, for instance, more properly evaluate the potential for phenotypic plasticity or adaptation in the face of changing environments.

If gut microbial plasticity is to enhance the host's utilization of its niche, the composition and activity of the microbiota must be capable of altering with changing environmental conditions, resulting in the provision of different services to the host (Alberdi et al., 2016). Studies that simply identify shifts in microbial community composition in response to environmental changes cannot identify the functional mechanism that underpins any such effect, but have nonetheless proved useful, for instance in showing how the microbiota changes over time within an individual as a result of

ontogenetic (Burns et al., 2016), dietary (Abid et al., 2013; Carmody et al., 2015) or other environmental changes (Candela et al., 2012). This longitudinal intraindividual variation in microbiota diversity can exceed interindividual variation, particularly when hosts have been exposed to similar environmental conditions (Rudi et al., 2018; Schmidt et al., 2015).

## 6 | FUTURE RESEARCH DIRECTIONS

As the focus moves to wild and non-model organisms and more importance is placed on the function rather than simply the characterization of the microbiota, the important questions in an ecological setting include: how stable is the gut microbial community across different life stages, environments or seasons? Does it truly offer phenotypic plasticity to the host? How much does it impact on host metabolism? And given this impact, how might modulating the microbiota affect the energy balance of the host? Answering these complex questions will require integration of knowledge from a variety of biological fields.

Many different techniques are being used to characterize the gut microbiota and untangle the complicated host-microbiota-physiology axis, with the ultimate aim of detecting causal rather than just correlational relationships, but not all can be combined with an ecological approach. Whilst gnotobiotic studies have allowed researchers to examine the physiological impact of mono-associations and specific community compositions of microbes (Lee et al., 2020; Marques et al., 2006; Rawls et al., 2004), they are restricted to sterile laboratory environments and usually involve a limited range of model organisms (Table 1). Antibiotics can be used to examine the effect of disrupting the gut microbiota (Gao et al., 2018; Lin et al., 2015; Raymann et al., 2018; Yoon & Yoon, 2018; Zhou et al., 2018), but studies to date have focussed on the impacts on either the host or on microbial community composition. Future studies would benefit from combining these two in order to deepen our understanding of the functional profile of specific taxa, but there may be too many ethical issues with the use of antibiotics to make this a commonly adopted approach in ecological studies.

A more promising technique to disrupt microbiome identity and/or function is to administer probiotic bacteria to the host. Probiotics are live bacteria chosen specifically for their potential beneficial effects on host health, including acting as antagonists against pathogenic bacteria as well as aiding the host immune system development and homeostasis (Abid et al., 2013; Ringø et al., 2007). Depending on the treatment chosen, probiotics have the capacity to alter microbial load and change community composition, and as a result impact the host's intestinal immunity (Abid et al., 2013) as well as its growth rate and survival (Bagheri et al., 2008). The complication lies in understanding which bacterial taxa should be targeted in such interventions. One option is to adopt the approach of Holmes et al. (2017) who recommend describing the composition of microbial communities by their requirements rather than by their function. By looking at responses to dietary interventions at the



community level, bacterial communities could be broadly targeted, as opposed to trying to predict the response of individual bacterial taxa. If this information is combined with the resulting impact on host energetic phenotype, the targets of probiotic intervention might then be identified. Consideration must also be given to the fact that the most beneficial functional profile in terms of host fitness will likely vary spatially, temporally and ontogenetically, reflecting the changing environment faced by the host.

Understanding the complexities of host-microbiota interactions remains at the forefront of gut microbiota research and to take this research further, a wide variety of studies will be necessary: mono-associations with just one microbial species can elucidate functions of specific bacterial taxa, wild-based studies can characterize how the prevalence of certain bacteria changes within the natural environment, whilst studies in a laboratory environment may inform the best dietary interventions. From an ecological perspective, increasing knowledge of spatial and temporal changes in the gut microbiota as a result of environmental change remains a priority. The seasonal, life-history and genetic diversity seen in nature necessitates a breadth of approaches in order to understand the impact of the gut microbiota on host metabolism under these different conditions. As yet, these approaches are in their infancy, but some studies are beginning to adopt a more integrative approach: a study of three species of small mammal that compared the effects of genetics versus environment on gut microbiota composition found environment to be of secondary importance in comparison to host genetic similarity. Specifically, the gut microbiota of mice, voles and shrews were more similar within species at different locations than between different species living in sympatry (Knowles et al., 2019). Since many gut microbiota-host associations are highly conserved (Erkosar et al., 2013; Rawls et al., 2004) and there is increasing emphasis on the concept of co-evolution (Chevalier et al., 2015), this idea could be integrated with such studies incorporating both inter- and intraspecific comparisons, in order to provide greater resolution.

It is clear that longitudinal studies in the wild would be most insightful, but sample size and repeatability often suffer, and studies to date have tended to be correlational and so cannot explicitly separate cause from effect. The growing assumption that the microbiota of the gut is both beneficial and essential needs to be continually challenged, since there is now evidence of species that have no such reliance on gut microbes and their associated services (Hammer et al., 2017), and colonization models suggest that many microbes do not appear to adapt to the host environment, simply passing through alongside food items (Heys et al., 2019). These colonization models, such as those proposed by Sloan and others (Burns et al., 2016; Sloan et al., 2006), can be useful in clearly identifying those microbial taxa that are responding to the host environment, and so narrowing the focus onto a subset of organisms that may have some functional role (positive or negative) on host fitness.

To further understand the relationship between host energetics and gut microbiota, characterization of the enteric bacteria must occur alongside robust phenotyping of the metabolic status of the host. This can be achieved via metabolite profile analysis of

host blood, urine and faeces (Xie et al., 2013), in combination with techniques providing a greater overview of host metabolic rate, such as respirometry. These top-down techniques will allow information on host energetics to complement quantification of bacterial community composition and their functional profiles, allowing greater understanding of the interface between microbial complement and host dynamics. Non-invasive metabolomic techniques will allow for longitudinal data collection, enabling researchers to examine how microbial community profile and host metabolic profile covary under a range of conditions.

## 7 | CONCLUSIONS

This review has highlighted the increasing number of studies now finding direct links between gut microbiota and host energetics. Given the plastic nature of both the host and microbe phenotypes, it is clear that the gut microbiota should be a key consideration of host adaptability in changing environmental conditions. Research should now move from broad characterization of community composition to elucidation of impacts on the host, in both laboratory- and field-based studies, to allow a broader understanding of the ecological perspectives of these dynamic relationships. This will require us to define the function of specific microbial taxa in an effort to reliably inform the ways in which gut microbiota impact host metabolism.

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## AUTHORS' CONTRIBUTIONS

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