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STUDENT AWARDEE PAPER

Gut Microbiome as a Mediator of Stress Resilience: A Reactive Scope Model Framework

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Synopsis Stress resilience is defined as the ability to rebound to a homeostatic state after exposure to a perturbation. Organisms modulate various physiological mediators to respond to unpredictable changes in their environment. The gut microbiome is a key example of a physiological mediator that coordinates a myriad of host functions including counteracting stressors. Here, we highlight the gut microbiome as a mediator of host stress resilience in the framework of the reactive scope model. The reactive scope model integrates physiological mediators with unpredictable environmental changes to predict how animals respond to stressors. We provide examples of how the gut microbiome responds to stressors within the four ranges of the reactive scope model (i.e., predictive homeostasis, reactive homeostasis, homeostatic overload, and homeostatic failure). We identify measurable metrics of the gut microbiome that could be used to infer the degree to which the host is experiencing chronic stress, including microbial diversity, flexibility, and gene richness. The goal of this perspective piece is to highlight the underutilized potential of measuring the gut microbiome as a mediator of stress resilience in wild animal hosts.

Introduction

All organisms seek to maintain homeostasis for critical systems, a stable internal state that resists deviations from a set point when acted upon by external forces (Wingfield et al. 1995; Williams 1966). Individuals with the ability to return to a previous homeostatic state or establish a new state after significant perturbations exhibit increased stress resilience (Wingfield 2013; Crespi et al. 2021). Researchers can begin to quantify challenge-induced changes in homeostatic state by measuring physiological systems that comprise the stress response (Gormally and Romero 2020). Stress responses to ecological challenges are often mediated by physiological processes, such as activation of the hypothalamic–pituitary–adrenal (HPA) axis, which can respond to internal and external cues. The HPA axis releases glucocorticoids, which act as central hormonal regulators of the vertebrate stress response. At baseline levels, glucocorticoids regulate energy metabolism, but at high levels, they orchestrate widespread phenotypic adjustments that influence the ability of individuals to cope with and recover from stressors (Sapolsky et al. 2000).

Though the hormonal stress response has received much attention, individual differences in stress resilience may be influenced by other physiological mediators. Other components of the physiological response to challenges, and therefore, potential contributors to stress resilience, include cytokines (Hodes et al. 2014), telomere attrition (Haussmann and Marchetto 2010), DNA damage (Gormally et al. 2019), microRNAs (Chen et al. 2015), and heart rate variability (Thayer et al. 2012; Gaidica and Dantzer 2020), among others. The gut microbiome is another physiological system that may serve as a mediator of individual variation in stress resilience. The gut microbiome encompasses the microorganisms including bacteria, archaea, and fungi, and the wide array of microbe-produced molecules including structural elements (e.g., proteins, lipids, nucleic acids, and so on) and metabolites (e.g., signaling molecules, toxins, and so on) that are structured by the environmental conditions of the gut tract (Whipps et al. 1988;

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Berg et al. 2020). Gut microbiota refer to the community of living microorganisms residing in the gut tract. The gut microbiome plays key functional roles for the host, including immune system training (Gensollen et al. 2016), digestion of complex dietary items (Zhu et al. 2011), and pathogen colonization resistance (Kamada et al. 2013). However, the potential for the gut microbiome to impact host stress resilience has only recently been explored in the context of its relationship with the HPA axis via the microbiota–gut–brain axis (reviewed in Cussotto et al. (2018)).

Evidence has accumulated supporting the idea that the relationship between the gut microbiome and the HPA axis can be bidirectional, whereby altered glucocorticoid levels can affect gut microbiome composition and altered gut microbiome composition can modulate HPA axis function. Correlational studies have reported a negative relationship between glucocorticoid levels and microbial diversity (Levin et al. 2016; Stothart et al. 2016; Petrullo et al. 2022). Experimentally elevating glucocorticoids can causally affect gut microbial diversity and composition, although the effect of these changes on metrics of diversity and community composition vary. Corticosterone elevation can increase gut microbial diversity (MacLeod et al. 2022) or result in the underrepresentation of certain microbial taxa (Noguera et al. 2018). Sterile germ-free mice exhibit increased glucocorticoid levels and anxiety-like behavior (Bercik et al. 2012; Luczynski et al. 2016). Postnatal exposure to gut microbiota regulates the development of the stress response, suggesting that the presence of a gut microbiome is necessary for development of the HPA axis (Sudo et al. 2004); however, probiotic administration later in development did not rescue HPA axis function. Thus, there is clear evidence of the importance of the gut microbiome in the development of the HPA axis, but microbial community composition later in life may also affect the regulation of the HPA axis.

Beyond its connection with other physiological systems such as the HPA axis, the gut microbiome has seldom been considered a standalone effector of host stress resilience in vertebrates (Sommer et al. 2017; Dogra et al. 2020). The gut microbiome is both shaped by the environment and has myriad effects on host phenotype; therefore, it could serve as a mediator of plastic responses to stressful external stimuli (Soen 2014). When referring to the gut microbiome as a mediator of stress resilience, this could imply that the gut microbiome impacts organismal-level stress resilience directly, or indirectly through its effects on other elements of the stress response including the HPA axis. Microbiota-mediated physiological functions of the host that neutralize potential perturbations to host homeostasis including toxin degradation (i.e., neutralization of a toxin that could lead to disruption of host homeostasis) and cellulolytic activity (i.e., hydrolyzation of cellulose that could cause nutritional stress in herbivores that cannot naturally degrade cellulose) are examples of direct effects of the gut microbiome on organismal-level stress resilience. The gut microbiome of hibernating ground squirrels contributes to protein homeostasis by recycling nitrogen via ureolysis during hibernation (Regan et al. 2022).

In this perspective piece, we focus on indirect effects of the gut microbiome on host stress resilience because there is more existing experimental support for them, but we expect that the integration of direct effects with this framework will be a fruitful area for future investigation. We suggest that because of the role of the microbiome in mediating diverse elements of the stress response: (1) measurements of the gut microbiome could be used to assess the degree to which the host is experiencing chronic stress (e.g., Pannoni et al. 2022), and (2) the current state of the host's microbiome could be used to predict resilience to future challenges. Identifying which aspects of the gut microbiome influence the maintenance of host homeostasis through environmental change will be crucial for understanding the causes of individual variation in host stress resilience and fitness.

Here, we introduce the gut microbiome as a mediator of stress resilience within the framework of the reactive scope model. The reactive scope model, originally proposed by Romero et al. (2009), develops a framework for how physiological mediators allow animals to respond to stressors associated with unpredictable environmental changes. First, we explore the gut microbiome as a physiological mediator of host homeostasis within the four ranges of the reactive scope model including predictive homeostasis, reactive homeostasis, homeostatic overload, and homeostatic failure (Romero et al. 2009). Second, we identify which metrics of the gut microbiome could be used as measures of microbial resilience including microbial diversity, flexibility, and gene richness. Though numerous invertebrate taxa possess a microbiome, we will focus on the application of the gut microbiome in vertebrate hosts, paralleling other physiological systems applied to the reactive scope model. The goal of this perspective piece is to highlight the underexplored potential of measuring the gut microbiome as a mediator of stress resilience in wild animal models.

Summary of the reactive scope model

Physiologists have long struggled with how to define and conceptualize the stress response since it was first described by Selye (1946). Over 130 different hypotheses have been proposed to explain the stress response

Table 1 The gut microbiome as a physiological mediator of stress resilience within the framework of the reactive scope model (Romero et al. 2009). The four ranges include the predictive homeostasis range, reactive homeostasis range, homeostatic overload, and homeostatic failure. We present examples of gut microbiome shifts that correspond with how a physiological mediator would respond within each range of the reactive scope model.

Ranges of reactive scope model	Definition	Gut microbiome example
Predictive homeostasis	Levels of physiological mediator vary according to predictable life history changes	1) Aging/development 2) Seasonal changes in food availability or temperature 3) Hibernation 4) Migration
Reactive homeostasis	Levels of the physiological mediator necessary to maintain homeostasis following an unpredictable event that threatens homeostasis	1) Infection 2) Change in diet 3) Antibiotic usage
Homeostatic overload	Levels of physiological mediator where the mediator itself starts to cause damage	1) Overgrowth of toxigenic bacteria 2) Microbe-mediated immune system overactivation 3) Obesity
Homeostatic failure	Levels of physiological mediator are too low to maintain homeostasis	1) Loss of keystone gut microbiota 2) Captivity 3) Germ-free or antibiotic-depleted animals

and its tradeoffs (Harris 2020), but one of the most popular and comprehensive frameworks used by stress physiologists is the reactive scope model (Romero et al. 2009). The reactive scope model illustrates how an individual organism responds to acute stressors and when the physiological mechanisms underlying these responses can become pathological to the animal. The reactive scope model assumes that physiological mediators of the stress response exist in four distinct ranges that encompass levels of the mediator that sustain functions for normal daily activities (i.e., predictive homeostasis) and acute emergency conditions to survive unpredictable stressors (i.e., reactive homeostasis). The model also helps make predictions about when the physiological mediators will start to cause problems to the host, either at levels too low to sustain life (i.e., homeostatic failure) or so high that the organism enters a pathogenic state (i.e., homeostatic overload).

Each mediator changes in its levels or concentrations across the four ranges of the model depending on the frequency and intensity of perturbations. The predictive and reactive homeostasis ranges encompass the normal reactive scope of the organism depending on the specific physiological mediator. Organisms incur costs when physiological mediators enter the reactive homeostasis and homeostatic overload ranges too frequently or for an extended period of time. A variety of experiences (e.g., repeated stressors, social environment, reproductive state, and so on) can change the boundaries between the four ranges, limiting the reactive scope of the organism. Romero et al. (2009) uses the term wear-and-tear to describe the gradual decrease in the ability to counteract stressors and the narrowing of the normal reactive scope. Maintaining one physiological mediator in the reactive homeostasis range can also decrease the amount of investment the organism can give to upkeep of other physiological systems. For example, elevated glucocorticoids can lead to suppression of the immune system (Cain and Cidlowski 2017). Given that the gut microbiome can orchestrate its effects on the host through other physiological systems, investigations into how shifts in the gut microbiome may affect the normal reactive scope of other physiological systems are warranted.

There are key differences between the gut microbiome and other physiological mediators that make its application to the reactive scope model more complicated (see Table 1 in Romero et al. (2009) for a discussion of various other mediators). The gut microbiome comprises a community of living microorganisms rather than nonliving, molecular components of the host. Though the host exhibits environmental and genetic control over the gut microbiome (Bonder et al. 2016), microbe–microbe interactions provide a direct connection to the extensive literature on ecosystem resilience and community ecology (McDonald et al. 2020). Due to these complex interactions, the gut microbiome cannot be measured as a single continuous level or concentration that can be plotted on the y-axis of the reactive scope model except, in some cases, for specific metrics described below (see Metrics of a resilient gut microbiome). When mapping the gut microbiome onto the reactive scope model, the y-axis may depict an ordination (e.g., PC1 on a Principal Component Analysis) or n-dimensional distance from the population average. The gut microbiome could influence host stress resilience by changing the reactive scope of other physiological mediators (Fig. 1), the amount of time needed to recover the full reactive scope (Fig. 2), or the magnitude of other physiological responses mounted in response to a perturbation (Fig. 3). All three possibilities are non-mutually exclusive; gut microbiome dysbiosis could result in all three types of changes at the same time.

To our knowledge, the gut microbiome has yet to be applied to the reactive scope model framework. The incorporation of gut microbiome surveys into studies of wild animals has only recently occurred in the past two decades with the advent of affordable, high-throughput sequencing technologies. Using the gut microbiome as the physiological mediator in the model, we identify known stressors that cause shifts in the gut microbiome and give examples of how the gut microbiome responds across the four ranges of the reactive scope model (Table 1).

Stressors of the gut microbiome

A stressor is defined as an unpredictable and/or uncontrollable stimulus that challenges homeostasis (Levine and Ursin 1991). Both intrinsic and extrinsic factors can serve as stressors for the gut microbiome and control the differential distributions of microbial taxa and overall diversity of the community (Karl et al. 2018). Significant stressors that have been shown to alter the gut microbiome include infection (Li et al. 2019), shifts in diet (David et al. 2014; Sen et al. 2017; Arias-Jayo et al. 2018), social challenges (Archie and Tung 2015), antibiotic usage (Francino 2016; Strati et al. 2021), pollutants (Jin et al. 2017), and changes in temperature (He et al. 2019; Sepulveda and Moeller 2020) or inclement weather (Lau et al. 2019). The frequency and duration of individual stressors in addition to the compounding effects of multiple stressors occurring simultaneously or successively must also be taken into consideration when assessing the responses of the gut microbiome to stress.

An important distinction to make between the gut microbiome and other physiological mediators discussed in Romero et al. (2009) is the length of the response time of the mediator after a single acute stressor versus repeated stressors. Most of the physiological mediators applied to the reactive scope model—including heart rate, glucocorticoids, and cytokines—produce a measurable response to a single acute stressor within seconds to minutes. Due to the nature of the timescale over which changes are likely to occur to the gut microbiome, it may not be possible to detect measurable changes on such short timescales. Thus, it may be more relevant to consider how the gut microbiome changes in response to repeated or chronic stressors (e.g., multiday usage of antibiotics rather than a single dosage) and expand the response time of the y-axis to longer periods of time such as hours to days when applying it to the reactive scope model.

When the composition of the gut microbiome is disrupted or shifted from a former state by a stressor, the community undergoes dysbiosis (Carding et al. 2015). When applied to the reactive scope model, gut microbiome dysbiosis could change the magnitude of the stress response to the same stressor determining whether the organism reaches homeostatic overload. The upper threshold of the reactive homeostasis range decreases after each stressor as the dysbiotic gut microbiome loses the ability to cope with repeated stressors (i.e., wear-and-tear). Under normal conditions, a healthy gut microbiome would recover after each stressor; however, there is currently not a one size fits all definition of what constitutes a healthy gut microbiome due to high interindividual variability (Falony et al. 2016; Healey et al. 2017; MacLeod et al. 2022). Therefore, a dysbiotic microbial community can take on many forms. Studies on gut microbiome stability have shown that stressors produce stochastic changes in dispersion (i.e., distribution or spread of data). For example, fecal glucocorticoid metabolites are positively correlated with phylogenetic clustering/stochasticity in the gut microbiome of eastern gray squirrels (Stothart et al. 2019). The high degree of interindividual variability can be explained by the Anna Karenina hypothesis, which states that all healthy microbiomes are similar (though dependent on several factors such as host species, sex, life history stage, and so on), but each dysbiotic microbiome is unique to the individual host (Zaneveld et al. 2017). Researchers can begin to distinguish between these states by characterizing the gut microbiome of their study organism and/or population across life history stages in healthy individuals (i.e., uninjured and noninfected). Thus, we must keep our definition of a healthy gut microbiome flexible and assess natural intra- and interspecific variation in gut microbial communities when contextualizing the effects of stressors on the gut microbiome.

Gut microbiome in the predictive homeostasis range

The predictive homeostasis range consists of the normal circadian and seasonal range for the physiological mediator (Romero et al. 2009). The gut microbiome can undergo circadian changes over the course of a day, as demonstrated in wild meerkats that exhibit diurnal oscillations in gut bacterial load and composition (Risely et al. 2021). Seasonal variation in gut mi-

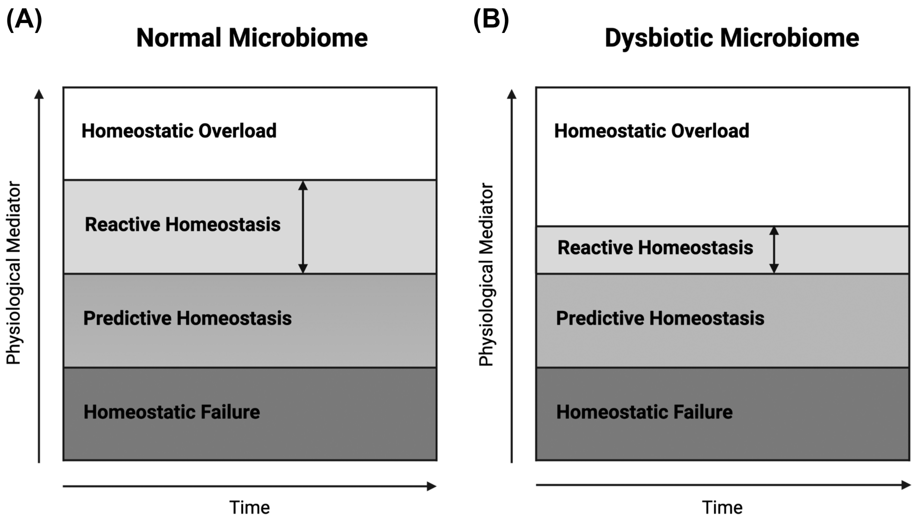

Fig. 1 Gut microbiome composition could influence stress resilience by changing the reactive scope of other physiological mediators. (**A**) The reactive scope of a physiological mediator of a host with a normal gut microbiome. (**B**) Gut microbiome dysbiosis could limit the normal reactive scope of other physiological mediators by narrowing the upper threshold of the reactive homeostasis range. Adapted from Romero et al. (2009). Created with BioRender.com.

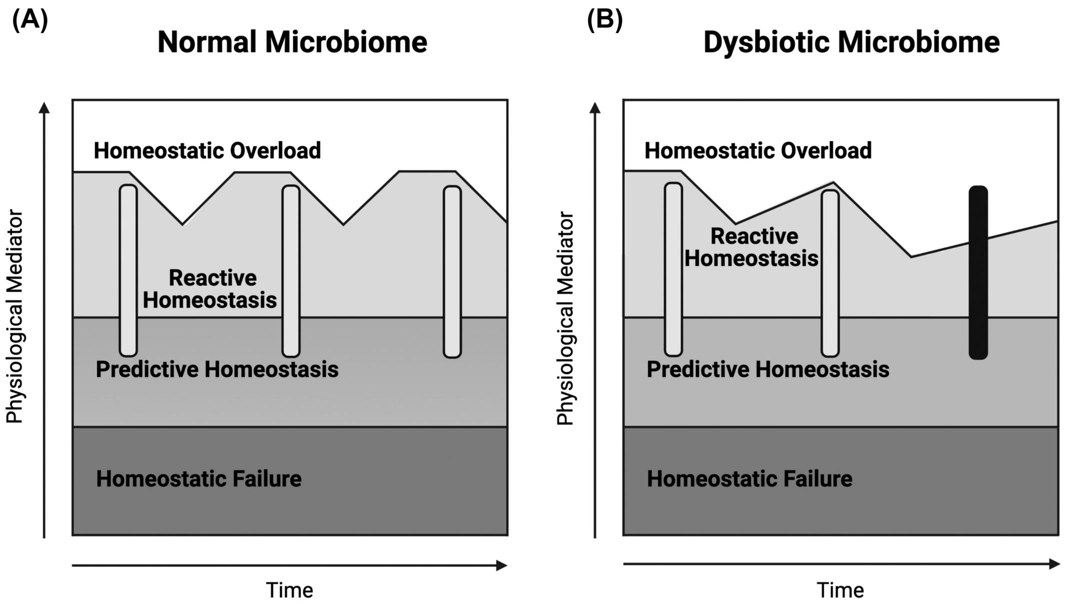

Fig. 2 Gut microbiome composition could influence stress resilience by changing the amount of time needed to recover the full reactive scope for other physiological mediators (i.e., wear-and-tear). (**A**) A physiological mediator in response to stressors of a host with a normal gut microbiome. Each colored bar represents a spike in a physiological mediator from the predictive homeostasis range into the reactive homeostasis range to maintain homeostasis in the face of a perturbation. All stressors are of equivalent strength but occur at different times. (**B**) A physiological mediator in response to stressors of a host with a dysbiotic gut microbiome. The upper threshold of the reactive homeostasis range decreases after each stressor as the dysbiotic gut microbiome loses the ability to cope with repeated stressors. Lighter colored bars denote mediator responses that stay within the reactive homeostasis range, and darker colored bars denote mediator responses that exceed the homeostatic overload threshold. Adapted from Romero et al. (2009). Created with BioRender.com.

crobial communities has been reported across a wide array of host taxa including fish (Dulski et al. 2020), amphibians (Huang and Liao 2021), reptiles (Ordorica et al. 2008), birds (Góngora et al. 2021), non-human mammals (Carey et al. 2013; Wu et al. 2017; Hu et al. 2018; Xiao et al. 2019; Baniel et al. 2021), and humans (Davenport et al. 2014; Smits et al. 2017). These seasonal changes in gut microbial communities are often driven by predictable shifts in environmental factors associated with each season such as food availability or tempera-

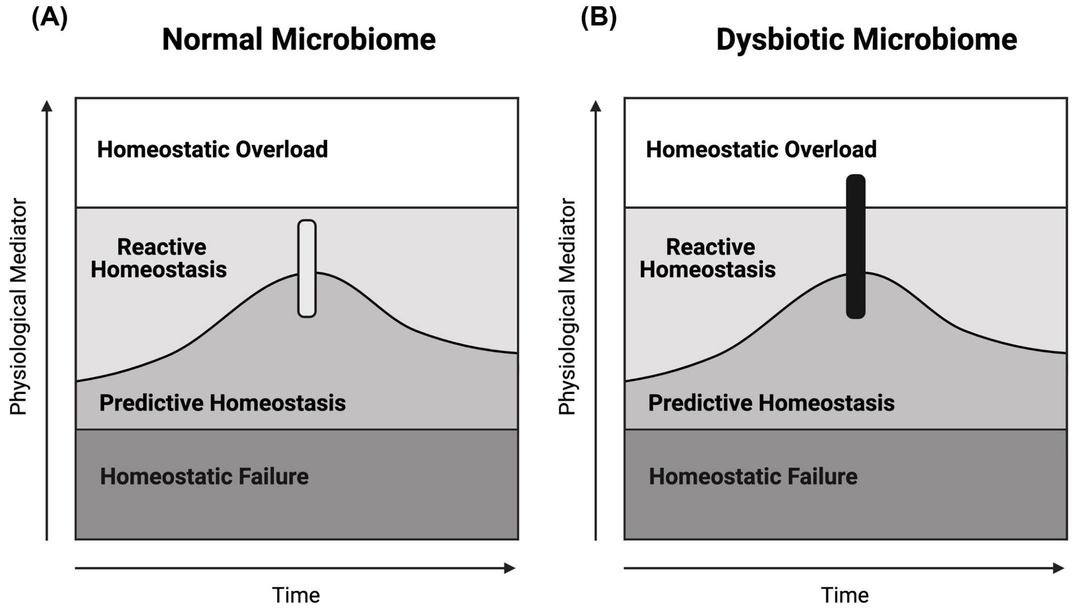

Fig. 3 Gut microbiome composition could influence stress resilience by changing the magnitude of other physiological responses mounted in response to a perturbation. (**A**) A physiological mediator in response to a stressor of a host with a normal gut microbiome. The predictive homeostasis range changes seasonally, depending on life history demands of the host. The lighter colored bar denotes a physiological mediator response that remains within the reactive homeostasis range. (**B**) A physiological mediator in response to a stressor of a host with a dysbiotic gut microbiome. The darker colored bar denotes a physiological mediator response that exceeds the homeostatic overload threshold. Adapted from Romero et al. (2009). Created with BioRender.com.

ture. For example, the abundances of particular microbial taxa are driven by dietary fluctuations between seasons with respect to produce availability in different human populations including the Hutterites (Davenport et al. 2014) and Hadza hunter–gatherers (Smits et al. 2017).

In addition to generalized seasonal transitions, extreme examples of predictable changes in host physiology that shift gut microbiota are hibernation and migration. Seasonal physiological changes associated with hibernation alter the gut microbial community structure and function across different mammalian species (Carey et al. 2013; Dill-McFarland et al. 2014, Dill-McFarland et al. 2016; Xiao et al. 2019). Brown bears double their fat stores during the summer for use during winter hibernation. Transplantation of the brown bear summer gut microbiota into germ-free mice promotes fat accumulation, suggesting that gut microbiota may contribute to host energy metabolism in preparation for hibernation (Sommer et al. 2016). Similar to physiological changes experienced before and during hibernation, migratory animals may undergo seasonal fluctuations in gut microbiome composition as they are exposed to disparate habitats and their metabolic needs change (Skeen et al. 2021). Migratory birds can lose up to 50% of their body mass during migration, requiring them to regain body stores quickly before completing another trip (Piersma et al. 1999). Recently migrated shorebirds possess significantly higher abundances of *Corynebacterium* in comparison to conspecific residents, suggesting this microbial genus may be involved in fat deposition during migration (Risely et al. 2018). Thus, the composition of the gut microbiome shifts in a predictable pattern in accordance with seasonal transitions experienced by the host.

The temporal scale of the reactive scope model can encompass longer time periods, beyond a single year. By extending the model's temporal scale, we can assess how gut microbial communities change at marked points of host development. For example, the human gut microbiome changes throughout development with timed host dietary transitions within the first 10 years of life (Derrien et al. 2019). The gut microbiome of human children experiences gradual specialization to deal with the diet substrates available during different stages of development. Infant microbiomes contain higher levels of *Bifidobacterium* species, which can break down human milk oligosaccharides (Bäckhed et al. 2015). However, the infant gut microbiome contains microbial species capable of breaking down plant-derived glycans, indicating that the microbial communities are metabolically ready for the introduction and metabolism of simple plant-derived foods associated with the introduction of solid foods (Koenig et al. 2011). The gut microbiome of human children reflects the dietary items of each developmental state (e.g., breastfeeding, transition to solid foods) but still maintains functional complexity in preparation for future dietary transitions.

Gut microbiome in the reactive homeostasis range

The reactive homeostasis range includes levels of the physiological mediator that are needed to counteract unpredictable changes in the environment (Romero et al. 2009). Though some vertebrate species harbor a higher degree of phylosymbiosis (i.e., microbial community relationships that recapitulate the phylogeny of their host) with their gut microbiota than others (Lim and Bordenstein 2020; Song et al. 2020), the gut microbiome of host species will naturally fluctuate within the boundaries of the predictive homeostasis range in response to circadian, seasonal, or circannual events. When the gut microbiome experiences an unpredictable stressor, it will shift into the reactive homeostasis range to counteract the stressor until the challenge ceases, allowing the mediator to return to its former levels within the predictive homeostasis range. Examples of unpredictable stressors that can shift the gut microbiome into the reactive homeostasis range include infections, rapid changes in diet, and antibiotic usage. As previously mentioned, the reactive scope model is largely focused on physiological mediators that show initial measurable responses to a stressor within minutes to hours; however, many of the transitions among the ranges of the reactive scope model can take much longer (i.e., days to weeks) for these mediators. When we refer to rapid responses of the gut microbiome to stressors, we assume that both the initial response to stressors and the subsequent transitions among the ranges of the reactive scope model are occurring over longer timescales such as days to weeks.

Infections occur when harmful microorganisms including bacteria, viruses, or fungi invade the host. When faced with an infection, the host initiates an inflammatory response that can alter the community structure of the gut microbiome. For example, several studies have shown an alteration of the gut microbiome in hospitalized patients infected with SARS-CoV-2 (Yamamoto et al. 2021). Similarly, infection by the monkey simian immunodeficiency virus destroys the previously stable gut microbiota in chimpanzees, resulting in broader changes in gut microbiota and the enrichment of potential pathogens (Moeller et al. 2013). After the acute infection is remedied, the gut microbiome must return to a stable state or risk fluctuating to levels outside of the normal reactive scope of the organism. For patients recovering from SARS-CoV-2, the gut microbiome typically rebalances its composition 6 months after the resolution of the infection (De Maio et al. 2021), providing evidence that the gut microbiome can return to a stable state post-infection.

Rapid changes in diet can also cause significant shifts in gut microbial communities, but eventually the gut microbiota stabilizes to fit the new dietary strategy (Leeming et al. 2019; Ang et al. 2020). For example, consumption of plant secondary compounds modifies gut microbial community composition in herbivorous woodrats, but past exposure to these plant secondary compounds affects how the gut microbiome, and therefore the host, responds to toxin consumption in comparison to naïve populations (Kohl and Dearing 2012). A drastic shift in diet can shift the community structure and metabolic pathways of the gut microbiome within a single day (Turnbaugh et al. 2009). Short-term consumption of diets composed entirely of animal or plant products alters gut microbial community structure and macronutrient intake of the hosts (David et al. 2014). An animal-based diet increases the abundance of bile-tolerant microorganisms and decreases the abundance of Firmicutes that metabolize dietary plant polysaccharides, reflecting trade-offs between carbohydrate and protein fermentation (David et al. 2014). The gut microbiomes of hosts on the animal-based diet reverted to their original structure 2 days after the diet ended (David et al. 2014), reflecting a transition from the reactive homeostasis range back to the predictive homeostasis range.

Antibiotic usage is another unpredictable stressor that albeit artificial can shift the microbiome toward a dysbiotic state (Ramirez et al. 2020). Antibiotic treatment reduces the overall diversity of the resident gut microbiome, which can cause shifts in metabolic profiles and a decrease in colonization resistance to enteropathogens (Maier et al. 2021). Early exposure to antibiotics can lead to pathogenesis, as demonstrated in a cohort study of infants with irritable bowel syndrome who received antibiotics in the first year of life (Kronman et al. 2012). However, the gut microbiome can usually recover to near-baseline composition after antibiotic usage depending on the age and disease state of the host (Palleja et al. 2018).

Organisms can return to the predictive homeostasis range after antibiotic perturbations because of the suite of antibiotic resistance genes present within their gut microbiomes. Through antibiotic-induced selection, bacteria have developed a range of processes to elude the effects of antibiotics including enzymatic pathways that degrade the antibiotic or addition of efflux pumps that remove the antibiotic from inside the cell membrane (Vega and Gore 2014). These antibiotic resistance genes help the gut microbiome withstand antibiotic perturbations, but can also lead to overgrowth of harmful enteropathogens that push the host into the homeostatic overload range. In comparison to the wide array of host taxa discussed in the predictive homeostasis range section, most of the work on how stressors could shift the gut microbiome into the reactive homeostasis range has been conducted on humans or domesticated laboratory rodents; thus, there is a strong need for more research on reactions of microbiomes in response to reactive homeostasis in non-human and non-domesticated animal models.

Gut microbiome in the homeostatic overload range

When a physiological mediator exceeds the upper threshold of the reactive scope, the animal enters a pathological state (Romero et al. 2009). The host can enter the homeostatic overload range when the level of the physiological mediator extends beyond the normal reactive scope of the organism or remains in the reactive homeostasis range for an extended period of time. As described above, resident gut microbiota provide a protective barrier against enteropathogens via competitive colonization resistance (Kamada et al. 2013). Depletion of gut microbiome diversity with antibiotics could send the host into the reactive homeostasis range by increasing susceptibility to enteropathogens. Open microbial niches within the gut can lead to overgrowth of enteropathogens such as *Clostridium difficile and Helicobacter pylori*, which at high counts can become toxigenic and send the host into the homeostatic overload range (Ianiro et al. 2020).

Overgrowth of *C. difficile* in the gut can cause diarrhea that leads to fatal colitis, a chronic digestive disease characterized by inflammation of the inner lining of the colon (Leffler and Lamont 2015). Overgrowth of *H. pylori* can lead to gastric and duodenal ulcers, intestinal metaplasia, and gastric cancer (Suerbaum and Michetti 2002). There is also potential for overgrowth of one enteropathogen to promote the overgrowth of another. Disease-inducing human isolates of Enterobacteriaceae and Bacteroidales spp. are capable of symbiotic cross-feeding, resulting in synergistic growth under malnourished conditions (Huus et al. 2021). Overgrowth of more than one species of enteropathogen may keep the host in the reactive homeostasis range for a longer period of time, causing overactivation of other physiological mediators such as the immune response that could also send the host into the homeostatic overload range.

The gut microbiome can also enter the homeostatic overload range without involving enteropathogens through its effects on other physiological mediators that induce pathological damage that is too severe to be immediately repaired. Alterations of gut microbial communities can cause immune system overactivation, leading to autoimmune disorders (Wu and Wu 2012). At homeostatic states, the gut microbiome provides a protective immune response through colonization resistance of pathogens (Kamada et al. 2013) and training of the adaptive immune system (Gensollen et al. 2016); however, shifts in gut microbial composition can cause an immune system-mediated pathological state.

Dysbiotic gut microbiomes are commonly observed in diseases involving inflammation in the gut, including inflammatory bowel disease (Gong et al. 2016). Increases in Gram-negative bacteria such as Bacteroidetes and Proteobacteria that contain lipopolysaccharides can shift immune cells such as macrophages toward a pro-inflammatory phenotype (Fujihara et al. 2003). Macrophages infiltrate tissues during inflammation and perform phagocytosis on foreign pathogens; however, a dysbiotic gut may leak microbiota-derived lipopolysaccharides into the bloodstream causing pro-inflammatory macrophages to destroy host cells (Wang et al. 2020). As another example, an increase in the ratio of Firmicutes to Bacteroidetes within the gut microbiome has been identified as a contributing factor to the pathophysiology of obesity. The gut microbiome of obese individuals may be more efficient at extracting energy from a given diet than the microbiota of lean individuals (Turnbaugh et al. 2006). Thus, shifts in the ratios of different bacterial phyla within the gut microbiome may lead to pathogenesis of other physiological mediators such as the immune system or lipid metabolism. Similar to gut microbiome responses of hosts within the reactive homeostasis range, the majority of studies on gut microbiome responses to homeostatic overload are found primarily in humans, necessitating a call for expansion of investigations on this topic in non-human systems, as well as in non-captive systems.

Gut microbiome in the homeostatic failure range

When a physiological mediator drops below the lower threshold of the reactive scope, the organism enters the homeostatic failure range (Romero et al. 2009). The terminal lack of a functional gut microbiome either due to an absence of any microbiota or a reduction in the abundance of certain taxa could cause the host to enter homeostatic failure. A single microbial species may provide a key physiological process that causes homeostatic failure when that microbe is eliminated, even if the rest of the microbial community is still intact. Keystone microbes are species that individually or in a group exert a considerable influence on microbiome structure and functioning irrespective of their abundance across space and time (Banerjee et al. 2018; reviewed in Tudela et al. (2021)). For example, interspecific cross-feeding of metabolites within the gut microbiome causes reliance on specific microbes that perform essential functions for other microbiota or the host itself. Following an antibiotic stressor, gut microbiota that can degrade complex dietary polysaccharides are keystone species for the recovery process of community diversity, as they promote the growth of other microbial species that feed from the broken-down components (Chng et al. 2020). Microbiota that produce butyrate, a short-chain fatty acid, are essential for maintaining intestinal integrity. Butyrate provides various functions for the host such as serving as an important energy source for colonocytes and inducing differentiation of T regulatory cells. Without butyrate-producing keystone microbiota, intestinal integrity and mucosal immune homeostasis would collapse (Furusawa et al. 2013).

Microbial extinctions within the human gut microbiome associated with a Westernized lifestyle also provide an example of homeostatic failure. Microbiota-accessible carbohydrates (MAC) acquired from dietary fiber impact the diversity and composition of the human gut microbiome, but they are notably reduced in the low fiber, high fat Western diet. Over several generations, mice fed a low-MAC diet significantly decrease gut microbial alpha diversity, which is not recoverable after the reintroduction of dietary MACs (Sonnenburg et al. 2016). Captive mammal gut microbiomes resemble those of Westernized humans due to dietary shifts, medical treatments, reduced contact with conspecifics, and variable environmental substrates that act as sources of microbial inoculates (McKenzie et al. 2017). Gut microbiotas of captive non-human primates display predictable, host species specific responses to captivity (Houtz et al. 2021), suggesting each host species experiences unique losses of host-associated microbiota and gains of human-associated microbiota. Given that the gut microbiome profoundly influences animal health, anthropogenically induced loss of key microbial taxa may disrupt vital functions such as nutrient acquisition that cause the host to undergo homeostatic failure.

Germ-free or sterile organisms present the ideal system to answer the question of what consequences hosts face when they do not harbor a gut microbiome. Germ-free organisms are raised in sterile isolators, which fully block exposure to microorganisms including bacteria, viruses, and eukaryotic microbes (Al-Asmakh and Zadjali 2015). Germ-free animal models exhibit physiological and morphological shortcomings in immune function, gut function, and nervous system activation in comparison to those with a resident gut microbiome. Germ-free mice exhibit weakened immune responses characterized by decreased expression of pathogen-recognizing toll-like receptors (Huhta et al. 2016), altered cytokine production (reviewed in Kennedy et al. (2018)), and smaller lymphoid tissues within the gut such as Peyer's patches (Pollard and Sharon 1970). However, colonization of germ-free organisms with host-associated gut microbiota rescues immune system function (Hapfelmeier et al. 2010).

The morphology and function of the host gut tract are also compromised in germ-free models. In germ-free mice, intestinal surface area and number of villi are reduced (Wichmann et al. 2013), resulting in insufficient digestion and nutrient absorption (Martinez-Guryn et al. 2018). Germ-free rodents have reduced production of short chain fatty acids (Høverstad and Midtvedt 1986) and essential vitamins such as vitamins K and B-6 (Gustafsson 1959; Sumi et al. 1977). Absence of a gut microbiome also decreases the integrity of the intestinal wall, which has the potential to leak bacterial components into the bloodstream that trigger the onset of low-grade inflammation (Sorini et al. 2019).

Finally, absence of a gut microbiome influences the degree to which the host can enact other physiological systems to counteract stressors. Germ-free mice exhibit impaired short-term recognition and working memory (Gareau et al. 2011), potentially making them less efficient at recognizing and averting external stressors. Acute restraint stress induces an exaggerated hormonal stress response in germ-free mice compared with controls, but HPA axis hyperactivity is completely normalized when juvenile germ-free mice are colonized with beneficial gut microbial taxa (Sudo et al. 2004). Though germ-free organisms present the ideal system to answer the question of what consequences hosts face when they do not harbor a gut microbiome, findings in germ-free models cannot be directly applied to free-living populations. The examples we provide above heavily rely on laboratory rodent or captive animal models. Homeostatic failure of the gut microbiome in wild animals is probably more explicitly related to the extinction or loss of genes in gut microbial populations (Sonnenburg et al. 2016).

In conclusion, we have provided examples of how the gut microbiome changes across the four ranges of the reactive scope model. We highlight a key caveat about differentiating between homeostatic overload and failure, whereby individual microbial taxa could exhibit overgrowth (i.e., homeostatic overload) or extinction (i.e., homeostatic failure), but at the community level these processes will often occur simultaneously. For example, we present overgrowth of enteropathogens (e.g., *C. difficile* and *H. pylori*) as an example of gut microbial homeostatic overload; however, loss of keystone microbial taxa, which we use as an example of gut microbial homeostatic failure, often sets the stage for overgrowth of opportunistic pathogens. The reactive scope model is ideally designed for physiological mediators that vary linearly along a single axis, but the gut microbiome varies along a combination of axes especially when considering beta diversity. Therefore, a failure state of the gut microbiome within the framework of the reactive scope model could involve a combination of overgrowth and extinctions in natural settings. Despite this discrepancy between the gut microbiome and other physiological mediators, and given the overwhelming evidence connecting the gut microbiome and host stress resilience, it is essential to identify metrics of the gut microbiome that could be measured on a single axis by researchers to quantify microbiome resilience.

Metrics of a resilient gut microbiome

Resilience, the ability to rebound to a homeostatic state after exposure to a perturbation, is an intrinsic property of ecological communities; therefore, the composition and diversity of the gut microbiome determines the resilience potential of the microbial community itself. Other reviews provide thorough discussions of the ecological processes that determine gut microbial diversity and composition including dispersal, diversification, drift, and selection (Nemergut et al. 2013; Sommer et al. 2017). Much research on resilience of the gut microbiome has focused on its link to human health and strategies for intervention such as fecal transplants (Dogra et al. 2020) or identifying broad patterns of responses to environmental stressors (Rocca et al. 2019). In addition to measuring the gut microbiome to help diagnose when animals are currently experiencing chronic stress or transitioning among homeostatic states, it may be possible to predict the resilience of an individual's gut microbiome to future stressors, and thus theoretically, the resilience of the host. While we do not, yet, have a full perspective on what constitutes a resilient gut microbiome, we present some possible metrics that may indicate a greater resilience of microbial communities to future perturbations.

Alpha diversity

Studies on the benefits of the gut microbiome to host health often refer to alpha diversity of the microbial community (reviewed by Heiman and Greenway (2016)), the distribution of species abundances in a given sample or individual. Diversity can be broken down into richness and evenness. Richness refers to the number of unique species and effectively measures presence/absence (e.g., Chao1), whereas evenness refers to the relative abundances of species within a community (e.g., Shannon and Simpson). Additionally, one can consider phylogenetic alpha diversity, which incorporates information from phylogenetic relationships between species in a community. For example, Faith's phylogenetic diversity is calculated as the sum of branch length of all species in a community. At present it is unclear whether one metric is more informative than others in the context of measuring resilience of the gut microbiome. Calculating alpha diversity metrics that inform all three factors (i.e., richness, evenness, and phylogenetic relatedness) may uncover patterns that warrant further investigation (Berg et al. 2020).

Low microbial alpha diversity may be a sign of a dysbiotic community with weakened resilience. Low microbial diversity has been observed in human patients with diseases such as inflammatory bowel disease (Gong et al. 2016), psoriatic arthritis (Scher et al. 2015), type 1 diabetes (Zhou et al. 2020), and obesity (Stanislawski et al. 2019). A community with increased species richness or phylogenetic diversity may be more resilient against perturbations such as antibiotics because related microbial species with similar functions can compensate or replace the functional niche originally filled by the eliminated taxa (Raymond et al. 2016). For example, gut microbiomes with increased richness become more stable in response to a dietary fiber challenge (Tap et al. 2015).

It may be intuitive to assume high alpha diversity always translates into improved host health (Heiman and Greenway 2016), but it often depends on what host trait is in question. There are multiple examples of communities of low alpha diversity which are stable or beneficial for the host, and conversely, other communities are more diverse in their pathogenic state (Shade 2017). Experimentally reducing diversity of the gut microbiome through antibiotic administration has been shown to improve host growth (Kohl et al. 2018; Potti et al. 2002). Reducing the number of gut microbial inhabitants also decreases competition between the host and gut microbiota for nutritional resources, allowing hosts to divert energy toward their own growth. The direction of the relationship between host health and gut microbiome diversity may be dependent on species, life history stage, or population. We caution against the sole use of alpha diversity as a proxy for gut microbial community stability or resilience without an intraspecific and interspecific comparative context. Additionally, when measuring alpha diversity, multiple axes (i.e., richness, evenness, and phylogenetic relatedness) should be considered when making connections between microbial diversity and host health metrics.

Flexibility

In addition to overall alpha diversity, the ability to adapt and flexibly respond to changing environmental conditions may also be a measurable metric of a resilient gut microbiome. Traditionally, phenotypic plasticity of a vertebrate host has been defined as the ability of a single genotype to produce different phenotypes in response to environmental stimuli. Emerging evidence supports the existence of an extended hologenome in vertebrates, the sum of their own genomes and the combined genomes of their microbial inhabitants, and the environment that contributes to plasticity of host phenotype (Bordenstein and Theis 2015; Maebe et al. 2021). Microbial flexibility is defined as the ability to dynamically restructure the gut microbial community in the face of environmental change (Sommer et al. 2017). Microbiome flexibility could be measured as change in diversity of composition in relation to the baseline from the pre-disturbance state or relative to magnitude of perturbation, quantifying how well the system has returned to its pre-perturbation state or how much it has recovered from the impact of perturbation.

We will explore the concept of microbial flexibility through the lens of generalist versus specialist microbiota. In classical ecology, habitats with frequent perturbations favor generalists (i.e., taxa with broad-resource utilization) over specialists (i.e., taxa with narrow-resource utilization; Robinson and Strauss 2020). The gut environment naturally varies in pH, oxygen saturation, and enzymatic profile along its length. Shifts in host diet can also influence what nutrients are supplied to the gut microbiota. These continual changes in environmental conditions and/or resource availability may drive cyclic growth and extinction events for specialist microbial taxa. Generalist microbiota are able to maintain more stable populations given that they are more adaptable to environmental change (Sriswasdi et al. 2017).

Generalist microbial taxa can alternate between energy sources, carbon sources, and oxygen requirements (Chen et al. 2021). Bacterial species utilize a wide spectrum of electron donors (e.g., organic carbon, sulfide, and hydrogen; Falkowski et al. 2008), oxidants (e.g., oxygen, nitrite, fumarate, sulfur, and fermentation; Gyuraszova et al. 2017), and carbon sources (e.g., heterotrophy and autotrophy; Wang et al. 2019). It is assumed that microbial taxa with increased metabolic flexibility such as facultative anaerobes are more resilient to perturbations in the gut environment (Chen et al. 2021). From the holobiont perspective (Bordenstein and Theis 2015; Maebe et al. 2021), low microbial flexibility may limit the phenotypic plasticity of the host in response to environmental cues. Thus, high microbial flexibility presumably promotes adaptation of the holobiont to environmental changes.

Similar to microbial alpha diversity, increased microbial flexibility does not always equate to increased host fitness or resilience. As discussed above, microbial flexibility is adaptive for the host if it is responding to an environmental challenge; however, if a certain gut microbial composition makes the host well-matched to its environment, then microbial flexibility or mutability might be maladaptive for the host (Alberdi et al. 2016). Therefore, we urge researchers to consider the role of microbial flexibility in the context of environmental variables and how the host responses to its environment with different gut microbial compositions.

Gene richness

Beyond the taxonomic membership of the gut microbiome, one could argue that the community-level biochemical functions and metabolic interaction patterns are more important for host fitness than the taxa responsible for them (Doolittle and Booth 2017). In other words, researchers should focus more on the song of the holobiont (i.e., functional pathways) rather than the singers (i.e., the taxonomic identities of the gut microbiota). One way to measure the functional capacity and subsequently, resilience of the gut microbiome is by measuring the richness of functional genes. Metagenomic approaches such as metagenome-assembled genomes provide a direct assessment of the full suite of functional genes of the microbiome, although the results are dependent on sequencing depth (Durazzi et al. 2021). Previous metagenomic sequencing approaches were limited by low sequencing depth (e.g., Illumina HiSeq only), which are unable to capture low abundance microbial genomes, but a combination of long-read sequencing approaches (e.g., HiSeq-PacBio hybrid) can cover repetitive and low-coverage regions, increasing metagenomic assembly contiguity (Jin et al. 2022). Regardless of the specific microbial taxa present, the overall diversity of genes and subsequent metabolic functions can be used as a measure of resiliency (Xu et al. 2014). Metagenomics could also be used to identify sources of dysbiosis by characterizing the presence or absence of a functional gene that provides a key metabolic pathway.

One of the main ways that the gut microbiome may acquire novel functional genes is from horizontal gene transfer among community members or the environment. Quantifying metrics that consider gene function over taxonomic identity may be preferred as a significant proportion of microbiota are horizontally acquired from environmental reservoirs that may be different for each host generation. In some cases, gut microbiota of offspring may be taxonomically identical to those of the previous generation; however, in other cases, newly acquired microbiota are not the same taxa as their predecessors but belong to the same functional guild (Burke et al. 2011). Thus, selection is most likely acting at the functional level rather than at the taxonomic level (Doolittle and Booth 2017), necessitating more work on how selection may act on functional microbial guilds to promote a resilient gut microbiome.

We will focus on examples of horizontal gene transfer in bacteria since it is most commonly studied in this kingdom, but horizontal gene transfer can also occur between other members of the gut microbiome including fungi, plants, and animals (Rancurel et al. 2017; Garcia-Vallvé et al. 2000). Horizontal gene transfer allows microbiota to acquire genes from distant species that are not in a parent-offspring relationship (Keeling and Palmer 2008). There are three main mechanisms through which microbiota can horizontally acquire novel DNA: conjugation, transduction, and transformation. Relying on cell-to-cell contact via conjugative pili, DNA can be pushed out of a donor cell and transported into a recipient cell during bacterial conjugation. During transduction, genetic material is introduced from a phage into bacterial genomes. Transformation involves the uptake of DNA from the environment (Price et al. 2019).

The gut is an ideal location for horizontal gene transfer-mediated adaptation to perturbations because the probability of horizontal gene transfer occurrence increases due to the proximal contact of donor–recipient genomes with each other (Adato et al. 2015). Though not all horizontally transferred genes are beneficial (Bliven and Maurelli 2016), they can provide a selective advantage to the host organism by increasing the genetic diversity and subsequently functional capacity of its microbial residents (Vogan and Higgs 2011). New functions acquired by mobile genetic elements within the gut microbiome include antibiotic resistance, digestion of complex carbohydrates, and toxin resistance.

Horizontal gene transfer can occur and acquire new functionality in the gut microbiome within a single individual (Zlitni et al. 2020). The most striking example of this can be found in human populations with industrialized lifestyles, which are associated with higher horizontal gene transfer rates. The functions of these horizontally transferred genes are also related to the level of host industrialization (Groussin et al. 2021). As urbanization increases around the world, measuring gene richness and rate of horizontal gene transfer within gut microbiomes may be a highly relevant proxy for how resilient the microbiome is against anthropogenic stressors.

Limitations and additional approaches

As described briefly above, a limitation of many linear metrics of the gut microbiome is that similar directional change can be caused by multiple underlying processes, which may be differentially related to resilience. For example, as the average alpha diversity of a community increases, beta diversity tends to increase as well, simply due to the fact that there are more axes across which communities can differ. Thus, as alpha diversity increases, the gut microbial community may also exhibit greater dispersion. This creates an inherent pitfall of universally interpreting high alpha diversity as increased resilience, as stressors produce stochastic changes in beta dispersion (i.e., distribution or spread of data) of gut microbiome communities. Eco-phylocomparative null modeling offers an alternative approach to parse deterministic versus stochastic change in the gut microbiome (Stegen et al. 2013). This approach quantitatively estimates the influence of ecological processes that drive community assembly such as drift, dispersal, and selection, while also using ecological patterns to characterize known and unknown abiotic variables that impose selection or result in low levels of dispersal. Ultimately, eco-phylocomparative null modeling may be a useful tool for drawing inferences on what constitutes a resilient gut microbiome that cannot be achieved by solely measuring alpha diversity.

We acknowledge the limitations of focusing on broad directional metrics such as alpha diversity, flexibility, and gene richness, but in some cases, these metrics provide measurable proxies that are likely to provide valuable information, and potentially to serve as indicators of microbial resilience. Additionally, we encourage researchers to explore context-dependence (i.e., in relation to other aspects of host phenotype and environment) to better understand the relationships between the gut microbiome and organismal-level stress resilience.

Conclusions and future directions

In recent years, it has become more feasible for researchers working in a wide variety of host taxa to measure the gut microbiome using high-throughput sequencing technologies enabling approaches such as 16S rRNA amplicon sequencing or shotgun metagenomic sequencing (Goodrich et al. 2014; Jovel et al. 2016; Gilbert et al. 2018). Amplicon-based sequencing of the 16S rRNA gene (i.e., a highly conserved and universal gene found in bacteria and archaea) is an affordable and reliable option for researchers interested in conducting gut microbiome surveys of their study organisms. We encourage future studies investigating mediators or biomarkers of host stress resilience to include the gut microbiome among the list of other measurable aspects of host phenotype. Microbe-mediated effects on the host are often context-dependent, highlighting the need to measure the full range of the host's phenotype. For example, glucocorticoid treatment decreases interindividual variation in microbial communities in nongravid female lizards, but this effect was not observed in late-gestation females (MacLeod et al. 2022). If researchers desire to identify dysbiosis, they must know what constitutes a healthy microbiome for their study organism according to whichever life history stage and/or sex is of interest. To control for this high interindividual variability, researchers should longitudinally sample the gut microbiomes of the same individuals throughout the course of the study if possible.

Though not all animals are dependent on a gut microbiome (Hammer et al. 2019), host-associated gut microbial communities are pervasive across animal taxa and influence a suite of phenotypic traits. While there is overwhelming evidence that the gut microbiome may be associated with aspects of stress resilience, there is still relatively little work in wild systems on its role as a mediator of organismal-level stress resilience, providing ample opportunities for future studies on the microbiota–gut–brain axis. Future studies should explore what characteristics indicate a resilient gut microbiome, and test when and how resilient gut microbiomes increase host resilience, especially in natural environments. We provide examples of how the gut microbiome varies throughout the four ranges of the reactive scope model (Romero et al. 2009), and identify measurable metrics including gut microbial alpha diversity, microbial flexibility, and gene richness that can be used as a proxy for the degree to which the host is experiencing chronic stressand potentially predict resilience to future stressors. In conclusion, we urge researchers across disciplines to include the gut microbiome as a mediator of host stress resilience and hope this perspective piece inspires more investigations into this topic.

Authors' contributions

J.L.H. conceptualized and wrote the original draft. C.C.T. and M.N.V. critically reviewed and revised the manuscript. All authors gave final approval for publication.

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Data availability

No new data were generated or analyzed in support of this perspective piece.

References

Adato O, Ninyo N, Gophna U, Snir S. 2015. Detecting horizontal gene transfer between closely related taxa. PLoS Comput Biol 11:e1004408.

Al-Asmakh M, Zadjali F. 2015. Use of germ-free animal models in microbiota-related research. J Microbiol Biotechnol 25:1583–8.

Alberdi A, Aizpurua O, Bohmann K, Zepeda-Mendoza ML, Gilbert MTP. 2016. Do vertebrate gut metagenomes confer rapid ecological adaptation? Trends Ecol Evol 31:689–99.

Ang QY, Alexander M, Newman JC, Tian Y, Cai J, Upadhyay V, Turnbaugh JA, Verdin E, Hall KD, Leibel RL et al. 2020. Ketogenic diets alter the gut microbiome resulting in decreased intestinal Th17 cells. Cell 181:1263–75.e16.

Archie EA, Tung J. 2015. Social behavior and the microbiome. Curr Opin Behav Sci 6:28–34.

Arias-Jayo N, Abecia L, Alonso-Sáez L, Ramirez–Garcia A, Rodriguez A, Pardo MA. 2018. High-fat diet consumption induces microbiota dysbiosis and intestinal inflammation in zebrafish. Microb Ecol 76:1089–101.

Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, Li Y, Xia Y, Xie H, Zhong H et al. 2015. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe 17:690–703.

Banerjee S, Schlaeppi K, van der Heijden MGA. 2018. Keystone taxa as drivers of microbiome structure and functioning. Nat Rev Microbiol 16:567–76.

Baniel A, Amato KR, Beehner JC, Bergman TJ, Mercer A, Perlman RF, Petrullo L, Reitsema L, Sams S, Lu A et al. 2021. Seasonal shifts in the gut microbiome indicate plastic responses to diet in wild geladas. Microbiome 9:1–20.

Bercik P, Collins SM, Verdu EF. 2012. Microbes and the gut-brain axis. Neurogastroenterol Motil 24:405–13.

Berg G, Rybakova D, Fischer D, Cernava T, Vergès MCC, Charles T, Chen X, Cocolin L, Eversole K, Corral GH et al. 2020. Microbiome definition re-visited: old concepts and new challenges. Microbiome 8:1–22.

Bliven KA, Maurelli AT. 2016. Evolution of bacterial pathogens within the human host. Microbiol Spectr 4:1–13.

Bonder MJ, Kurilshikov A, Tigchelaar EF, Mujagic Z, Imhann F, Vila AV, Deelen P, Vatanen T, Schirmer M, Smeekens SP et al. 2016. The effect of host genetics on the gut microbiome. Nat Genet 48:1407–12.

Bordenstein SR, Theis KR. 2015. Host biology in light of the microbiome: ten principles of holobionts and hologenomes. PLoS Biol 13:e1002226.

Burke C, Steinberg P, Rusch D, Kjelleberg S, Thomas T. 2011. Bacterial community assembly based on functional genes rather than species. Proc Natl Acad Sci 108:14288–93.

Cain DW, Cidlowski JA. 2017. Immune regulation by glucocorticoids. Nat Rev Immunol 17:233–47.

Carding S, Verbeke K, Vipond DT, Corfe BM, Owen LJ. 2015. Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis 26:26191.

Carey HV, Walters WA, Knight R. 2013. Seasonal restructuring of the ground squirrel gut microbiota over the annual hibernation cycle. Am J Physiol Regul Integr Comp Physiol 304:R33–42.

Chen RJ, Kelly G, Sengupta A, Heydendael W, Nicholas B, Beltrami S, Luz S, Peixoto L, Abel T, Bhatnagar S. 2015. MicroRNAs as biomarkers of resilience or vulnerability to stress. Neuroscience 305:36–48.

Chen YJ, Leung PM, Wood JL, Bay SK, Hugenholtz P, Kessler AJ, Shelley G, Waite DW, Franks AE, Cook PL et al. 2021. Metabolic flexibility allows bacterial habitat generalists to become dominant in a frequently disturbed ecosystem. ISME J 15:2986–3004.

Chng KR, Ghosh TS, Tan YH, Nandi T, Lee IR, Ng AHQ, Li C, Ravikrishnan A, Lim KM, Lye D et al. 2020. Metagenome-wide association analysis identifies microbial determinants of post-antibiotic ecological recovery in the gut. Nat Ecol Evol 4:1256–67.

Crespi E, Burnap R, Chen J, Das M, Gassman N, Rosa E, Simmons R, Wada H, Wang ZQ, Xiao J et al. 2022. Resolving the rules of robustness and resilience in biology across scales. Integr Comp Biol 61:2163–79.

Cussotto S, Sandhu KV, Dinan TG, Cryan JF. 2018. The neuroendocrinology of the microbiota–gut–brain axis: a behavioural perspective. Front Neuroendocrinol 51:80–101.

Davenport ER, Mizrahi-Man O, Michelini K, Barreiro LB, Ober C, Gilad Y. 2014. Seasonal variation in human gut microbiome composition. PLoS ONE 9:e90731.

David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA et al. 2014. Diet rapidly and reproducibly alters the human gut microbiome. Nature 505:559–63.

De Maio F, Ianiro G, Coppola G, Santopaolo F, Abbate V, Bianco DM, Del Zompo F, De Matteis G, Leo M, Nesci A et al. 2021. Improved gut microbiota features after the resolution of SARS-CoV-2 infection. Gut Pathog 13:1–4.

Derrien M, Alvarez AS, de Vos WM. 2019. The gut microbiota in the first decade of life. Trends Microbiol 27:997–1010.

Dill-McFarland KA, Neil KL, Zeng A, Sprenger RJ, Kurtz CC, Suen G, Carey HV. 2014. Hibernation alters the diversity and composition of mucosa-associated bacteria while enhancing antimicrobial defense in the gut of 13-lined ground squirrels. Mol Ecol 23:4658–69.

Dill-McFarland KA, Suen G, Carey HV. 2016. Bears arouse interest in microbiota's role in health. Trends Microbiol 24: 245–6.

Dogra SK, Doré J, Damak S. 2020. Gut microbiota resilience: definition link to health and strategies for intervention. Front Microbiol 11:2245.

Doolittle WF, Booth A. 2017. It's the song, not the singer: an exploration of holobiosis and evolutionary theory. Biol Philos 32:5–24.

Dulski T, Kozłowski K, Ciesielski S. 2020. Habitat and seasonality shape the structure of tench (*Tinca tinca* L.) gut microbiome. Sci Rep 10:1–11.

Durazzi F, Sala C, Castellani G, Manfreda G, Remondini D, De Cesare A. 2021. Comparison between 16S rRNA and shotgun sequencing data for the taxonomic characterization of the gut microbiota. Sci Rep 11:1–10.

Falkowski PG, Fenchel T, Delong EF. 2008. The microbial engines that drive earth's biogeochemical cycles. Science 320:1034–9.

Falony G, Joossens M, Vieira–Silva S, Wang J, Darzi Y, Faust K, Kurilshikov A, Bonder MJ, Valles-Colomer M, Vandeputte D et al. 2016. Population-level analysis of gut microbiome variation. Science 352:560–4.

Francino MP. 2016. Antibiotics and the human gut microbiome: dysbioses and accumulation of resistances. Front Microbiol 6:1543.

Fujihara M, Muroi M, Tanamoto KI, Suzuki T, Azuma H, Ikeda H. 2003. Molecular mechanisms of macrophage activation and deactivation by lipopolysaccharide: roles of the receptor complex. Pharmacol Ther 100:171–94.

Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T et al. 2013. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 504:446–50.

Gaidica M, Dantzer B. 2020. Quantifying the autonomic response to stressors - one way to expand the definition of stress in animals. Integr Comp Biol 60:113–25.10.1093/icb/icaa0090

Garcia-Vallvé S, Romeu A, Palau J. 2000. Horizontal gene transfer in bacterial and archaeal complete genomes. Genome Res 10:1719–25.

Gareau MG, Wine E, Rodrigues DM, Cho JH, Whary MT, Philpott DJ, MacQueen G, Sherman PM. 2011. Bacterial infection causes stress-induced memory dysfunction in mice. Gut 60:307–17.

Gensollen T, Iyer SS, Kasper DL, Blumberg RS. 2016. How colonization by microbiota in early life shapes the immune system. Science 352:539–44.

Gilbert JA, Jansson JK, Knight R. 2018. Earth microbiome project and global systems biology. MSystems 3:e00217–17.

Gong D, Gong X, Wang L, Yu X, Dong Q. 2016. Involvement of reduced microbial diversity in inflammatory bowel disease. Gastroenterol Res Pract 2016:695109.

Góngora E, Elliott KH, Whyte L. 2021. Gut microbiome is affected by inter–sexual and inter–seasonal variation in diet for thick-billed murres (*Uria lomviai*). Sci Rep 11:1–12.

Goodrich JK, Di Rienzi SC, Poole AC, Koren O, Walters WA, Caporaso JG, Knight R, Ley RE. 2014. Conducting a microbiome study. Cell 158:250–62.

Gormally BM, Fuller R, McVey M, Romero LM. 2019. DNA damage as an indicator of chronic stress: correlations with corticosterone and uric acid. Comp Biochem Physiol A Mol Integr Physiol 227:116–22.

Gormally BM, Romero LM. 2020. What are you actually measuring? A review of techniques that integrate the stress response on distinct time-scales. Funct Ecol 34:2030–44.

Groussin M, Poyet M, Sistiaga A, Kearney SM, Moniz K, Noel M, Hooker J, Gibbons SM, Segurel L, Froment A et al. 2021. Elevated rates of horizontal gene transfer in the industrialized human microbiome. Cell 184:2053–67.e18.

Gustafsson BE. 1959. Vitamin K deficiency in germfree rats. Ann NY Acad Sci 78:166–74.

Gyuraszova M, Kovalcikova A, Gardlik R. 2017. Association between oxidative status and the composition of intestinal microbiota along the gastrointestinal tract. Med Hypotheses 103:81–5.

Hammer TJ, Sanders JG, Fierer N. 2019. Not all animals need a microbiome. FEMS Microbiol Lett 366:fnz117.

Hapfelmeier S, Lawson MA, Slack E, Kirundi JK, Stoel M, Heikenwalder M, Cahenzli J, Velykoredko Y, Balmer ML, Endt K et al. 2010. Reversible microbial colonization of germ–free mice reveals the dynamics of IgA immune responses. Science 328:1705–9.

Harris BN. 2020. Stress hypothesis overload: 131 hypotheses exploring the role of stress in tradeoffs transitions and health. Gen Comp Endocrinol 288:113355.

Haussmann MF, Marchetto NM. 2010. Telomeres: linking stress and survival ecology and evolution. Curr Zool 56:714–27.

He J, He Y, Pan D, Cao J, Sun Y, Zeng X. 2019. Associations of gut microbiota with heat stress–induced changes of growth fat deposition intestinal morphology and antioxidant capacity in ducks. Front Microbiol 10:903.

Healey GR, Murphy R, Brough L, Butts CA, Coad J. 2017. Interindividual variability in gut microbiota and host response to dietary interventions. Nutr Rev 75:1059–80.

Heiman ML, Greenway FL. 2016. A healthy gastrointestinal microbiome is dependent on dietary diversity. Mol Metab 5:317–20.

Hodes GE, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, Bregman D, Rebusi N, Heshmati M, Aleyasin H, Warren BL et al. 2014. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. Proc Natl Acad Sci 111:16136–41.

Houtz JL, Sanders JG, Denice A, Moeller AH. 2021. Predictable and host-species specific humanization of the gut microbiota in captive primates. Mol Ecol 30:3677–87.

Høverstad T, Midtvedt T. 1986. Short-chain fatty acids in germfree mice and rats. J Nutr 116:1772–6.

Hu X, Liu G, Li Y, Wei Y, Lin S, Liu S, Zheng Y, Hu D. 2018. High-throughput analysis reveals seasonal variation of the gut microbiota composition within forest musk deer (*Moschus berezovskiiI*). Front Microbiol 9:1674.

Huang C, Liao W. 2021. Seasonal variation in gut microbiota related to diet in *Fejervarya limnocharis*. Animals 11:1393.

Huhta H, Helminen O, Kauppila JH, Salo T, Porvari K, Saarnio J, Lehenkari PP, Karttunen TJ. 2016. The expression of Toll-like receptors in normal human and murine gastrointestinal organs and the effect of microbiome and cancer. J Histochem Cytochem 64:470–82.

Huus KE, Hoang TT, Creus-Cuadros A, Cirstea M, Vogt SL, Knuff—anzen K, Sansonetti PJ, Vonaesch P, Finlay BB. 2021. Cross-feeding between intestinal pathobionts promotes their overgrowth during undernutrition. Nat Commun 12:1–14.

Ianiro G, Mullish BH, Kelly CR, Kassam Z, Kuijper EJ, Ng SC, Iqbal TH, Allegretti JR, Bibbò S, Sokol H et al. 2020. Reorganisation of faecal microbiota transplant services during the COVID-19 pandemic. Gut 69:1555–63.

Jin H, You L, Zhao F, Li S, Ma T, Kwok LY, Xu H, Sun Z. 2022. Hybrid, ultra-deep metagenomic sequencing enables genomic and functional characterization of low-abundance species in the human gut microbiome. Gut Microbes 14:2021790.

Jin Y, Wu S, Zeng Z, Fu Z. 2017. Effects of environmental pollutants on gut microbiota. Environ Pollut 222:1–9.

Jovel J, Patterson J, Wang W, Hotte N, O'Keefe S, Mitchel T, Perry T, Kao D, Mason AL, Madsen KL et al. 2016. Characterization of the gut microbiome using 16S or shotgun metagenomics. Front Microbiol 7:459.

Kamada N, Chen GY, Inohara N, Núñez G. 2013. Control of pathogens and pathobionts by the gut microbiota. Nat Immunol 14:685–90.

Karl JP, Hatch AM, Arcidiacono SM, Pearce SC, Pantoja-Feliciano IG, Doherty LA, Soares JW. 2018. Effects of psychological environmental and physical stressors on the gut microbiota. Front Microbiol 9:2013.

Keeling PJ, Palmer JD. 2008. Horizontal gene transfer in eukaryotic evolution. Nat Rev Genet 9:605–18.

Kennedy EA, King KY, Baldridge MT. 2018. Mouse microbiota models: comparing germ-free mice and antibiotics treatment as tools for modifying gut bacteria. Front Physiol 9:1534.

Koenig JE, Spor A, Scalfone N, Fricker AD, Stombaugh J, Knight R, Angenent LT, Ley RE. 2011. Succession of microbial consortia in the developing infant gut microbiome. Proc Natl Acad Sci 108:4578–85.

Kohl KD, Brun A, Bordenstein SR, Caviedes-Vidal E, Karasov WH. 2018. Gut microbes limit growth in house sparrow nestlings (*Passer domesticus*) but not through limitations in digestive capacity. Integr Zool 13:139–51.

Kohl KD, Dearing MD. 2012. Experience matters: prior exposure to plant toxins enhances diversity of gut microbes in herbivores. Ecol Lett 15:1008–15.

Kronman MP, Zaoutis TE, Haynes K, Feng R, Coffin SE. 2012. Antibiotic exposure and IBD development among children: a population–based cohort study. Pediatrics 130:e794–803.

Lau AS, Mitsuyama E, Odamaki T, Xiao JZ, Liong MT. 2019. El Niño altered gut microbiota of children: a new insight on weather–gut interactions and protective effects of probiotic. J Med Food 22:230–40.

Leeming ER, Johnson AJ, Spector TD, Le, Roy CI. 2019. Effect of diet on the gut microbiota: rethinking intervention duration. Nutrients 11:2862.

Leffler DA, Lamont JT. 2015. *Clostridium difficile* infection. N Engl J Med 372:1539–48.

Levin II, Zonana DM, Fosdick BK, Song SJ, Knight R, Safran R.J. 2016. Stress response gut microbial diversity and sexual signals correlate with social interactions. Biol Lett 12:20160352.

Levine S, Ursin H. 1991. What is stress?. In: Brown MR, Koob GF, Rivier C, editors. Stress –neurobiology and neuroendocrinology. New York (NY): Marcel Dekker. p. 2–21.

Li N, Ma WT, Pang M, Fan QL, Hua JL. 2019. The commensal microbiota and viral infection: a comprehensive review. Front Immunol 10:1551.

Lim SJ, Bordenstein SR. 2020. An introduction to phylosymbiosis. Proc R Soc B Biol Sci 287:20192900.

Luczynski P, McVey-Neufeld KA, Oriach CS, Clarke G, Dinan TG, Cryan JF. 2016. Growing up in a bubble: using germ-free animals to assess the influence of the gut microbiota on brain and behavior. Int J Neuropsychopharmacol 19: 213–9.

McDonald JE, Marchesi JR, Koskella B. 2020. Application of ecological and evolutionary theory to microbiome community dynamics across systems. Proc R Soc B Biol Sci 287:20202886.

McKenzie VJ, Song SJ, Delsuc F, Prest TL, Oliverio AM, Korpita TM, Alexiev A, Amato KR, Metcalf JL, Kowalewski M et al.

2017. The effects of captivity on the mammalian gut microbiome. Integr Comp Biol 57:690–704.10.1093/icb/icx090

MacLeod KJ, Kohl KD, Trevelline BK, Langkilde T. 2022. Context-dependent effects of glucocorticoids on the lizard gut microbiome. Mol Ecol 31:185–96.

Maebe K, Vereecken NJ, Piot N, Reverté S, Cejas D, Michez D, Vandamme P, Smagghe G. 2021. The holobiont as a key to the adaptation and conservation of wild bees in the anthropocene. Front Ecol Evol 9:849.

Maier L, Goemans CV, Wirbel J, Kuhn M, Eberl C, Pruteanu M, Müller P, Garcia-Santamarina S, Cacace E, Zhang B et al. 2021. Unravelling the collateral damage of antibiotics on gut bacteria. Nature 599:120–4.

Martinez-Guryn K, Hubert N, Frazier K, Urlass S, Musch MW, Ojeda P, Pierre JF, Miyoshi J, Sontag TJ, Cham CM et al. 2018. Small intestine microbiota regulate host digestive and absorptive adaptive responses to dietary lipids. Cell Host Microbe 23:458–469.e5.

Moeller AH, Shilts M, Li Y, Rudicell RS, Lonsdorf EV, Pusey AE, Wilson ML, Hahn BH, Ochman H. 2013. SIV-induced instability of the chimpanzee gut microbiome. Cell Host Microbe 14:340–5.

Nemergut DR, Schmidt SK, Fukami T, O'Neill SP, Bilinski TM, Stanish LF, Knelman JE, Darcy JL, Lynch RC, Wickey P et al. 2013. Patterns and processes of microbial community assembly. Microbiol Mol Biol Rev 77:342–56.

Noguera JC, Aira M, Pérez-Losada M, Domínguez J, Velando A. 2018. Glucocorticoids modulate gastrointestinal microbiome in a wild bird. R Soc Open Sci 5:171743.

Ordorica AM, Pough FH, Cate S, Deutch CE. 2008. Seasonal variations in microbial communities in the nasal passages of captive desert tortoises. J Ariz Nevada Acad Sci 40: 121–7.

Palleja A, Mikkelsen KH, Forslund SK, Kashani A, Allin KH, Nielsen T, Hansen TH, Liang S, Feng Q, Zhang C et al. 2018. Recovery of gut microbiota of healthy adults following antibiotic exposure. Nat Microbiol 3:1255–65.

Pannoni SB, Proffitt KM, Holben WE. 2022. Non-invasive monitoring of multiple wildlife health factors by fecal microbiome analysis. Ecol Evol 12:e8564.

Petrullo L, Ren T, Wu M, Boonstra R, Palme R, Boutin S, McAdam AG, Dantzer B. 2022. Glucocorticoids coordinate changes in gut microbiome composition in wild North American red squirrels. Sci Re0070 12:1–12.

Piersma T, Gudmundsson GA, Lilliendahl K. 1999. Rapid changes in the size of different functional organ and muscle groups during refueling in a long-distance migrating shorebird. Physiol Biochem Zool 72:405–15.

Pollard M, Sharon N. 1970. Responses of the peyer's patches in germ–free mice to antigenic stimulation. Infect Immun 2:96–100.

Potti J, Moreno J, Yorio P, Briones V, García-Borboroglu P, Villar S, Ballesteros C. 2002. Bacteria divert resources from growth for magellanic penguin chicks. Ecol Lett 5:709–14.

Price VJ, Mcbride SW, Hullahalli K, Chatterjee A, Duerkop BA, Palmer KL. 2019. Enterococcus faecalis CRISPR–Cas is a robust barrier to conjugative antibiotic resistance dissemination in the murine intestine. mSphere 4:e464–19.

Ramirez J, Guarner F, Bustos Fernandez L, Maruy A, Sdepanian VL, Cohen H. 2020. Antibiotics as major disruptors of gut microbiota. Front Cell Infect Microbiol 10:731.

Rancurel C, Legrand L, Danchin EG. 2017. Alienness: rapid detection of candidate horizontal gene transfers across the tree of life. Genes 8:248.

Raymond F, Ouameur AA, Déraspe M, Iqbal N, Gingras H, Dridi B, Leprohon P, Plante PL, Giroux R, Bérubé È et al. 2016. The initial state of the human gut microbiome determines its reshaping by antibiotics. ISME J 10:707–20.

Regan MD, Chiang E, Liu Y, Tonelli M, Verdoorn KM, Gugel SR, Suen G, Carey H, Assadi-Porter FM. 2022. Nitrogen recycling via gut symbionts increases in ground squirrels over the hibernation season. Science 375:460–3.

Risely A, Waite DW, Ujvari B, Hoye BJ, Klaassen M. 2018. Active migration is associated with specific and consistent changes to gut microbiota in Calidris shorebirds. J Anim Ecol 87:428–37.

Risely A, Wilhelm K, Clutton-Brock T, Manser MB, Sommer S. 2021. Diurnal oscillations in gut bacterial load and composition eclipse seasonal and lifetime dynamics in wild meerkats. Nat Commun 12:1–12.

Robinson ML, Strauss SY. 2020. Generalists are more specialized in low-resource habitats increasing stability of ecological network structure. Proc Natl Acad Sci 117:2043–8.

Rocca JD, Simonin M, Blaszczak JR, Ernakovich JG, Gibbons SM, Midani FS, Washburne AD. 2019. The microbiome stress project: toward a global meta-analysis of environmental stressors and their effects on microbial communities. Front Microbiol 9:3272.

Romero LM, Dickens MJ, Cyr NE. 2009. The reactive scope model - a new model integrating homeostasis allostasis and stress. Horm Behav 55:375–89.

Sapolsky R, Romero LM, Munck AU. 2000. How do glucocorticoids influence stress responses? Integrating permissive suppressive stimulatory and preparative actions. Endocr Rev 21:55–89.

Scher JU, Ubeda C, Artacho A, Attur M, Isaac S, Reddy SM, Marmon S, Neimann A, Brusca S, Patel T et al. 2015. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis resembling dysbiosis in inflammatory bowel disease. Arthritis Rheumatol 67:128–39.

Selye H. 1946. The general adaptation syndrome and the diseases of adaptation. J Clin Endocrinol Metabol 6:117–230.

Sen T, Cawthon CR, Ihde BT, Hajnal A, DiLorenzo PM, Claire B, Czaja K. 2017. Diet-driven microbiota dysbiosis is associated with vagal remodeling and obesity. Physiol Behav 173: 305–17.

Sepulveda J, Moeller AH. 2020. The effects of temperature on animal gut microbiomes. Front Microbiol 11:384.

Shade A. 2017. Diversity is the question, not the answer. ISME J 11:1–6.

Skeen HR, Cooper NW, Hackett SJ, Bates JM, Marra PP. 2021. Repeated sampling of individuals reveals impact of tropical and temperate habitats on microbiota of a migratory bird. Mol Ecol 30:5900–16.

Smits SA, Leach J, Sonnenburg ED, Gonzalez CG, Lichtman JS, Reid G, Knight R, Manjurano A, Changalucha J, Elias JE et al. 2017. Seasonal cycling in the gut microbiome of the Hadza hunter-gatherers of Tanzania. Science 357:802–6.

Soen Y. 2014. Environmental disruption of host-microbe coadaptation as a potential driving force in evolution. Front Genet 5:16

Sommer F, Anderson JM, Bharti R, Raes J, Rosenstiel P. 2017. The resilience of the intestinal microbiota influences health and disease. Nat Rev Microbiol 15:630–8.

Sommer F, Ståhlman M, Ilkayeva O, Arnemo JM, Kindberg J, Josefsson J, Newgard CB, Fröbert O, Bäckhed F. 2016. The gut microbiota modulates energy metabolism in the hibernating brown bear *Ursus arctos*. Cell Rep 14:1655–61.

Song SJ, Sanders JG, Delsuc F, Metcalf J, Amato K, Taylor MW, Mazel F, Lutz HL, Winker K, Graves GR et al. 2020. Comparative analyses of vertebrate gut microbiomes reveal convergence between birds and bats. MBio 11:e02901–19.

Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. 2016. Diet-induced extinctions in the gut microbiota compound over generations. Nature 529:212–5.

Sorini C, Cosorich I, Conte ML, De Giorgi L, Facciotti F, Lucianò R, Rocchi M, Ferrarese R, Sanvito F, Canducci F et al. 2019. Loss of gut barrier integrity triggers activation of islet-reactive T cells and autoimmune diabetes. Proc Natl Acad Sci 116:15140–9.

Sriswasdi S, Yang CC, Iwasaki W. 2017. Generalist species drive microbial dispersion and evolution. Nat Commun 8:1–8.

Stanislawski MA, Dabelea D, Lange LA, Wagner BD, Lozupone CA. 2019. Gut microbiota phenotypes of obesity. npj Biofilms Microbiomes 5:1–9.

Stegen JC, Lin X, Fredrickson JK, Chen X, Kennedy DW, Murray CJ, Rockhold ML, Konopka A. 2013. Quantifying community assembly processes and identifying features that impose them. ISME J 7:2069–79.

Stothart MR, Bobbie CB, Schulte-Hostedde AI, Boonstra R, Palme R, Mykytczuk NCS, Newman AEM. 2016. Stress and the microbiome: linking glucocorticoids to bacterial community dynamics in wild red squirrels. Biol Lett 12:20150875.

Stothart MR, Palme R, Newman AE. 2019. It's what's on the inside that counts: stress physiology and the bacterial microbiome of a wild urban mammal. Proc R Soc B Biol Sci 286:20192111.

Strati F, Pujolassos M, Burrello C, Giuffrè MR, Lattanzi G, Caprioli F, Troisi J, Facciotti F. 2021. Antibiotic–associated dysbiosis affects the ability of the gut microbiota to control intestinal inflammation upon fecal microbiota transplantation in experimental colitis models. Microbiome 9:1–15.

Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, Kubo C, Koga Y. 2004. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J Physiol 558:263–75.

Suerbaum S, Michetti P. 2002. *Helicobacter pylori* infection. N Engl J Med 347:1175–86.

Sumi Y, Miyakawa M, Kanzaki M, Kotake Y. 1977. Vitamin B-6 deficiency in germfree rats. J Nutr 107:1707.

Tap J, Furet JP, Bensaada M, Philippe C, Roth H, Rabot S, Lakhdari O, Lombard V, Henrissat B, Corthier G et al. 2015. Gut microbiota richness promotes its stability upon increased dietary fibre intake in healthy adults. Environ Microbiol 17:4954–64.

Thayer JF, Åhs F, Fredrikson M, Sollers JJ, Wager TD. 2012. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev 36:747–56.

Tudela H, Claus SP, Saleh M. 2021. Next generation microbiome research: identification of keystone species in the metabolic regulation of host-gut microbiota interplay. Front Cell Dev Biol 9:2321.

Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444:1027–31.

Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. 2009. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med 1:6ra14

Vega NM, Gore J. 2014. Collective antibiotic resistance: mechanisms and implications. Curr Opin Microbiol 21:28–34.

Vogan AA, Higgs PG. 2011. The advantages and disadvantages of horizontal gene transfer and the emergence of the first species. Biol Direct 6:1–14.

Wang J, Chen WD, Wang YD. 2020. The relationship between gut microbiota and inflammatory diseases: the role of macrophages. Front Microbiol 11:1065.

Wang X, Xia K, Yang X, Tang C. 2019. Growth strategy of microbes on mixed carbon sources. Nat Comm 10:1–7.

Whipps J, Lewis K, Cooke R. 1988. Mycoparasitism and plant disease control. In: Burge M, editor. Fungi in Biological Control Systems. Manchester: Manchester University Press. p. 161–87.

Wichmann A, Allahyar A, Greiner TU, Plovier H, Lundén GÖ, Larsson T, Drucker DJ, Delzenne NM, Cani PD, Bäckhed F. 2013. Microbial modulation of energy availability in the colon regulates intestinal transit. Cell Host Microbe 14: 582–90.

Williams GC. 1966. Natural selection, the cost of reproduction, and a refinement of Lack's principle. Am Nat 100:687–90.

Wingfield JC, Kubokawa K, Ishida K, Ishii S, Wada M. 1995. The adrenocortical response to stress in male bush warblers, *Cettia diphone*: a comparison of breeding populations in Honshu and Hokkaido, Japan. Zoolog Sci 12:615–21.

Wingfield JC. 2013. The comparative biology of environmental stress: behavioural endocrinology and variation in ability to cope with novel changing environments. Anim Behav 85:1127–33.

Wu HJ, Wu E. 2012. The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes 3:4–14.

Wu Q, Wang X, Ding Y, Hu Y, Nie Y, Wei W, Ma S, Yan L, Zhu L, Wei F. 2017. Seasonal variation in nutrient utilization shapes gut microbiome structure and function in wild giant pandas. Proc R Soc B Biol Sci 284:20170955.

Xiao G, Liu S, Xiao Y, Zhu Y, Zhao H, Li A, Li Z, Feng J. 2019. Seasonal changes in gut microbiota diversity and composition in the greater horseshoe bat. Front Microbiol 10:2247.

Xu Z, Malmer D, Langille MG, Way SF, Knight R. 2014. Which is more important for classifying microbial communities: who's there or what they can do?. ISME J 8:2357–9.

Yamamoto S, Saito M, Tamura A, Prawisuda D, Mizutani T, Yotsuyanagi H. 2021. The human microbiome and COVID–19: a systematic review. PLoS ONE 16:e0253293.

Zaneveld JR, McMinds R, Vega Thurber R. 2017. Stress and stability : applying the Anna Karenina principle to animal microbiomes. Nat Microbiol 2:1–8.

Zhou H, Sun L, Zhang S, Zhao X, Gang X, Wang G. 2020. Evaluating the causal role of gut microbiota in type 1 diabetes and its possible pathogenic mechanisms. Front Endocrinol 11:125.

Zhu L, Wu Q, Dai J, Zhang S, Wei F. 2011. Evidence of cellulose metabolism by the giant panda gut microbiome. Proc Natl Acad Sci 108:17714–9.

Zlitni S, Bishara A, Moss EL, Tkachenko E, Kang JB, Culver RN, Andermann TM, Weng Z, Wood C, Handy C et al. 2020. Strain-resolved microbiome sequencing reveals mobile elements that drive bacterial competition on a clinical timescale. Genome Med 12:1–17.