Review

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The demographic determinants of human microbiome health

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The human microbiome is a vast reservoir of microbial diversity and increasingly recognized to have a fundamental role in human health. In polymicrobial communities, the presence of one species can modulate the demography (i.e., growth and distribution) of other species. These demographic impacts generate feedbacks in multispecies interactions, which can be magnified in spatially structured populations (e.g., host-associated communities). Here, we argue that demographic feedbacks between species are central to microbiome development, shaping whether and how potential metabolic interactions come to be realized between expanding lineages of bacteria. Understanding how demographic feedbacks tune metabolic interactions and in turn shape microbiome structure and function is now a key challenge to our abilities to better manage microbiome health.

The human microbiome: an ecological network of metabolic interactions

The human body is home to an extraordinary diversity of microbes, which are increasingly suggested to have pivotal roles in human health. Human microbiome (see Glossary) sequencing projects have revealed intriguing correlations between specific patterns of microbial diversity and multiple aspects of host health, including autoimmune disorders [1,2], diabetes [3], obesity [4,5], and even psychiatric conditions [6]. The establishment of microbial causal roles (particularly in obesity) is gathering pace thanks to experimental manipulations of germ-free mice (e.g., [7]); however, the causal mechanisms frequently remain obscure.

A major challenge to unraveling the mechanisms of microbiome functioning is the need to combine molecular and ecological approaches to study the highly complex assemblies of billions of interconnected bacterial cells. Systems biological approaches are beginning to make important headway by building and analyzing complex computational models of metabolic interactions within microbial communities [8–10]; however, these approaches typically make strongly simplifying assumptions on the spatiotemporal dynamics of constituent species, reducing their population biology to a simple 'presence/absence' dichotomy. This simplification (shared by ecological approaches to microbial community assembly [11]) enables mapping of potential metabolic interactions among species, but fails to predict the extent to which any interaction will be realized. To address this issue, we propose a spatially explicit population dynamic framework of microbiome development, to understand when and how potential metabolic interactions come to be realized via demographic feedbacks (i.e., reciprocal impacts on growth and distribution) between expanding lineages of bacteria.

Metabolic interactions and demographic feedbacks within a minimal microbiome

To develop a complete mechanistic understanding of a microbial community, it is vital to understand how the presence of one species modulates the growth of each of the other species, and how these coupled demographies together shape the functional and spatial structuring or architecture of the community. Microbes constantly modify their environment through the secretion and excretion of both functional exoproducts [12,13] and metabolic by-products

Glossary

Competition: ecological interaction where all species are negatively affected by association due to, for example, consumption of shared and limiting resources.
Cross-feeding: act of using the extracellular metabolic by-products of other organisms for growth.
Demography: the study of population structure, emerging from patterns of births, deaths, migration, and development.
Demographic feedback: an interaction where one species influences the demographic processes (births, deaths, and movement) of another species, and vice versa.
Exo-product: molecule secreted extracellularly and usually costly to produce (e.g., exopolysaccharide or exoenzyme).
Exploitation: ecological interaction where one species benefits from association at the expense of the other species.
Individual-based models (IBMs): computational models tracking the dynamics of individual 'agents', often used to explore emergent properties of the population aggregate behavior.
Microbiome: the set of microorganisms sharing a particular habitat (e.g., the human lower intestine).
Mutualism: mutually beneficial ecological interaction between species.

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[14,15], setting the stage for complex interspecific interactions. Of particular interest are 'cross-feeding' interactions, where species use metabolic by-products of others as energy or nutrient resources. Some cross-feeding relationships are characterized as mutualistic (i.e., enhancing the growth rate of both species [14,16]); however, the exchange of metabolites can also promote exploitation where one species gains at the expense of another [17].

If we reduce the complexity of species interactions to a simple menu of discrete impacts on interacting species (positive +, negative –, or neutral 0), then for a two-species community there are six distinct patterns of potential ecological interaction [(0,0), (0,+), (0, –), (+,+), (+,–), and (–,–)]. However, there is a combinatorial explosion in potential ecological complexity with increasing community diversity [18]. Given the high dimensionality of interactions within the human microbiome, there is a pressing need to create tractable model systems, as a necessary step towards understanding more complex multispecies dynamics. Here, we suggest that, to understand more diverse and complex microbial communities (such as the human microbiome), we first need to develop a thorough mechanistic understanding of coupled metabolic and demographic dynamics in defined 'minimal' microbiomes.

Previous studies on defined two-species communities highlight that these are capable of considerable ecological complexity [19–22]. Recent theoretical work has suggested that a single mechanism of interspecific metabolic exchange between two species can generate a diverse array of ecological relationships, spanning mutualism, competition, and exploitation; and that such diversity can arise by simply changing the properties of the metabolite that is exchanged (Figure 1A) [19]. A relevant empirical example of this diversity of outcomes is the interaction between the human oral commensal bacterium *Streptococcus gordonii* (*Sg*) and the pathogenic oral bacterium *Aggregatibacter actinomycetemcomitans* (*Aa*). Co-culture experiments of *Sg* and *Aa* in well-mixed liquid cultures have highlighted that the *Sg–Aa* interaction (mediated by *Sg* metabolic by-products lactate and H_2O_2) can readily move between mutualism and competition, depending on environmental conditions (Figure 1B) [23]. In aerobic conditions, *Aa* consumes lactate and relieves *Sg* of H_2O_2 toxicity, generating a marginally mutualistic relationship. However, under anaerobic conditions, *Aa* cannot grow on lactate and, therefore, competitive interactions (mediated by shared consumption of glucose) dominate (Figure 1B). By contrast, when grown in a structured *in vivo* model infection system, *Aa* gains significantly from the association while *Sg* neither benefits nor is harmed [23]. A key question is whether this stronger benefit to *Aa* is due solely to the many biochemical differences between the *in vitro* and *in vivo* growth environment, or whether there is a significant contribution from the effect of growing in a spatially structured environment.

Demography matters in spatially structured communities

Empirical work on microbial cross-feeding has shown that spatial structure has an important role in shaping species interactions (e.g., [21,22,24–26]). From a modeling perspective, studying the role of metabolic interactions and demographic feedbacks in shaping the dynamics of spatially structured microbial communities is a challenging task, in part due to the computational challenge of studying mechanistically explicit models over space and time.

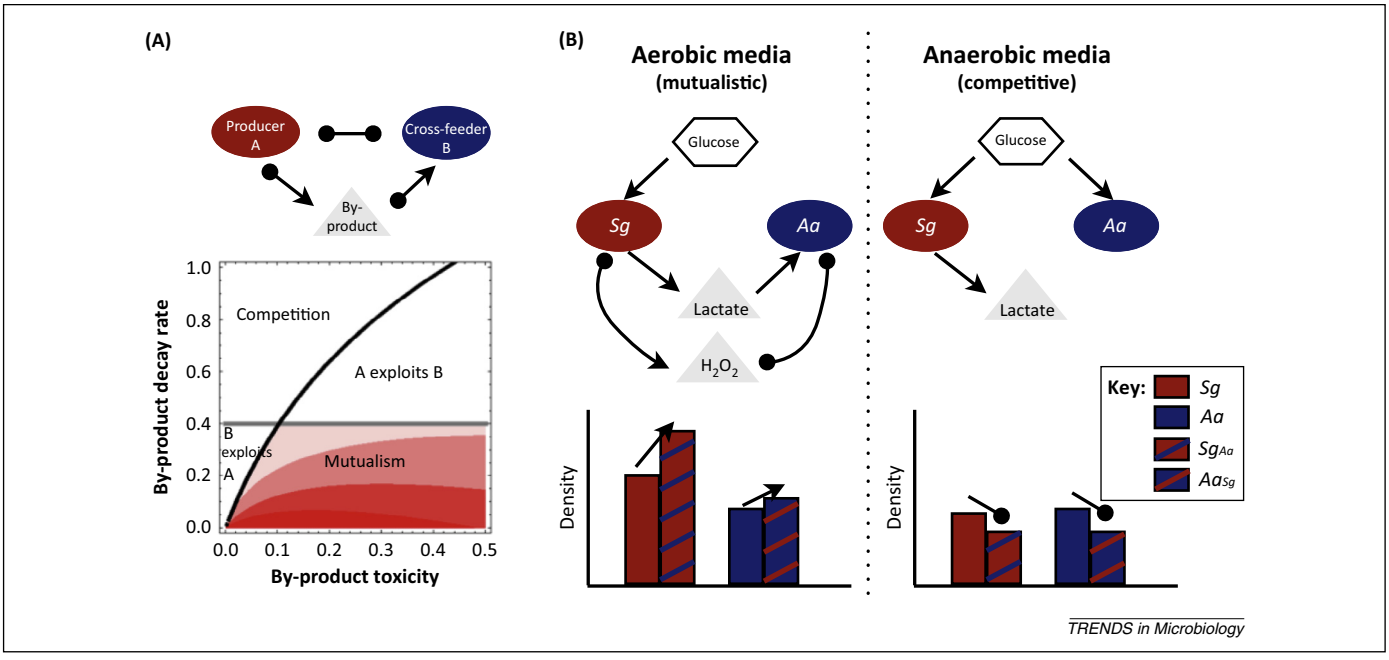

Figure 1. Metabolic interactions within a two-species community. **(A)** A single mechanism of metabolic exchange can generate diverse functional relationships in liquid (well-mixed) cultures. Mutualism: density of A in co-culture (A_B) is larger than when alone (A), and B in co-culture (B_A) is larger than when alone (i.e., A_B>A and B_A>B). Red shading indicates the strength of mutualism [$A_B + B_A - (A + B)$]. Competition: A_B<A and B_A< B. A exploits B: A_B>A and B_A<B. B exploits A: A_B<A and B_A>B. **(B)** S*treptococcus gordonii* (*Sg*) and *Aggregatibacter actinomycetemcomitans* (*Aa*) engage in multiple forms of metabolic interactions. Schematic model of *Sg–Aa* metabolic exchange under aerobic (left) and anaerobic (right) conditions [63]. Open arrows represent a positive effect, whereas oval arrows represent a negative effect upon the population or metabolite that they are pointing toward. *Sg* and *Aa* form mutualistic or competitive interactions in liquid culture that are dependent on oxygenation. Adapted, with permission, from [19] (A) and redrawn from [23] (B).