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Road MAPs to engineer host microbiomes

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Microbiomes contribute directly or indirectly to host health and fitness. Thus far, investigations into these emergent traits, referred to here as microbiome-associated phenotypes (MAPs), have been primarily qualitative and taxonomy-driven rather than quantitative and trait-based. We present the MAPs-first approach, a theoretical and experimental roadmap that involves quantitative profiling of MAPs across genetically variable hosts and subsequent identification of the underlying mechanisms. We outline strategies for developing ‘modular microbiomes’ — synthetic microbial consortia that are engineered in concert with the host genotype to confer different but mutually compatible MAPs to a single host or host population. By integrating host and microbial traits, these strategies will facilitate targeted engineering of microbiomes to the benefit of agriculture, human/animal health and biotechnology.

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Introduction

Interspecies interactions may affect an organism’s fitness across a wide range of ecological and environmental conditions [1]. In particular, mounting interest into the relationship between host organisms and their microbiomes has been fueled by the discovery that microbes contribute in shaping the phenotype of their hosts [2,3,4^{••}]. Although the microbiomes of eukaryotic hosts differ taxonomically, there are striking cross-kingdom similarities in the underlying mechanisms by which they affect their hosts’ phenotypes [5,6]. For plants, the seed, root and shoot-

associated microbiomes may generate a broad range of emergent traits including growth [7], root architecture [8], time of flowering [9], drought resilience [10], disease suppression [11], and nutrient acquisition [12]. Furthermore, these *microbiome-associated phenotypes* (MAPs) have a genetic basis [13,14,15[•]], providing means for natural and artificial selection. Indeed, engineering MAPs is expected to have a pervasive impact in biotechnology, contributing to fields such as personalized medicine [16], and as a harbinger of the next Green Revolution [17]. Essential to this approach is that microbial communities and their hosts should not be seen nor engineered in isolation; rather, host phenotypic features are dependent on the interplay between host genotype, abiotic conditions and microbiome composition and functions.

A large number of studies have provided insight into the taxonomic and functional basis of MAPs through amplicon sequencing, isolation and phenotypic screening, and through shotgun ‘omics approaches [18–24]. Nonetheless, widespread practical adoption of this fundamental knowledge is still being deferred until the complexity of these multivariate interactions can be integrated into effective, consistent and cost-effective strategies to engineer microbiomes. To navigate this large parameter space, we propose a top-down, bottom-up approach, encompassing both a mathematical and experimental basis to quantitatively assess the potential and ecological context of MAPs (top down), thereby affording targeted analyses to identify the functional basis of MAPs at the molecular and (bio)chemical level in both host and microbes (bottom up). Within this context, we introduce the concept of the ‘modular microbiome’, microbial consortia that are engineered in concert with the host genotype to confer different but mutually compatible MAPs to a single host or host population. We discuss how experimentally altering microbiome compositions may facilitate strategies that increase the persistence and functionality of augmented native microbiomes, which remains a major bottleneck in microbiome engineering [25]. While, throughout our review, we draw primarily upon examples from plant-microbe interactions, we note the broad applicability of our engineering principles for microbiomes of other hosts, including the design of microbial consortia for the human gut.

MAPs first

A seminal guiding principal to navigate plant microbiome engineering is ‘going back to the roots’ to re-instate microbial associations on or in plant roots that may have been lost during the domestication process [26^{••},27,28] or

during breeding for disease resistance [29]. This search for ‘missing plant microbes’ is similar to investigations into the human microbiome of pre-agricultural societies and isolated tribes [30,31]. However, the ecological consequences of plant domestication and breeding on crop microbiomes are not fully understood, nor should they be considered unequivocally detrimental [29]. In fact, the relative importance of the microbiome for plant growth, development and/or health has not been experimentally investigated for most crop species. Therefore, systematic quantification of the most significant MAPs across wild and domesticated hosts should precede mechanistic examinations (Figure 1). In the following subsection, we propose a mathematical and experimental framework which forms the backbone of a ‘MAPs-first approach’ (Figure 1): this involves profiling the variation in MAPs across genetically variable hosts followed by the identification of the key mechanisms and selection of the microbial consortia that confer a particular MAP. This then forms the basis for mechanistically informed strategies toward the design of synthetic microbial communities in tight conjunction with host breeding (i.e. for plants and livestock), aimed at combining multiple desired MAPs (e. g., disease suppression, drought resilience) while minimizing losses due to functional trade-offs between them. In light of the increasing understanding of the relationships between hosts and their microbiomes, the term ‘holobiont’ has emerged as a convenient lexicon when referring to the host and microbiome as an integrated unit [32,33*,34]. Here we adopt this terminology, while recognizing the inherent limitations of using a single term to define relationships between host and microbe of varying intimacy [34–37].

A mathematical basis of MAPs

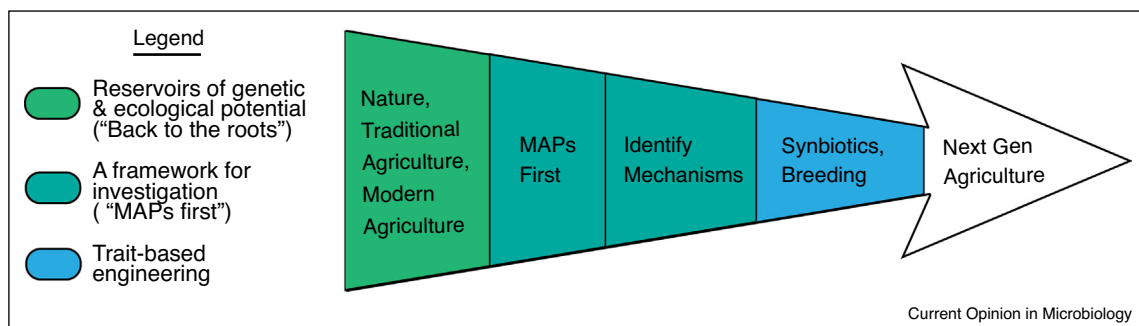
To quantify the contribution of the microbiome to the holobiont’s fitness in a context-dependent manner, Kopac

and Klassen (2016) introduced two equations. In Equation (1), N_{holo} is the realized niche of the holobiont, N_{apo} is the realized niche of the host under germ-free conditions (i.e. in absence of the microbiome), and A represents the cumulative microbiome effect on N_{apo} . In other words, the fitness of the holobiont (N_{holo}) may be represented as the sum of the fitness of a germ-free host (N_{apo}), plus the influence the associated microbiome (A) has on host fitness (Figure 2a).

To quantify the impacts of changes in holobiont fitness (ΔN_{holo}) as a result of an altered microbiome (ΔA), Equation (2) was also introduced [38**]. Equation 2 is especially powerful when comparing the impacts of altered microbiomes on germ-free hosts ($\Delta N_{apo} = 0$) [1]. However, to compare two holobionts differing only by their microbiome (i.e., with identical host genotypes), Equation 2 must be further expanded by solving a system of linear equations through subtraction, which results in dropping ΔN_{apo} from the equation. In other words, when all other variables are held constant, the difference in the change in fitness between two holobionts can be attributed to differences between their microbiomes (Equation (3), Figure 2b).

Microbiomes are not static; they change through time and are not necessarily stable between host generations or individuals. To address this, Equation 3 reveals two additional functional parameters that may be empirically derived, the holobiont recruitment rate (α_{holo}), the rate at which a maximum A (i.e., cumulative microbiome effect on the host) is reached in time, and holobiont fitness stability (σ_{holo}^2), the variation of A between individuals or generations (Equations (4) and (5), and Figure 2c). We note that the recruitment and stability of fitness are functional parameters, which do not require the inheritance of specific members of a microbiome across time.

Figure 1



A road map for engineering MAPs. Natural ecosystems, as well as traditional and modern agricultural systems, serve as reservoirs of genetic and ecological potential that may be mined for identifying MAPs. An analogous approach may be taken to identify these reservoirs for engineering microbiomes of other eukaryotes, such as understanding non-westernized, non-agricultural human microbiomes. This large parameter space represents a challenge to navigate. Consequently, we propose a ‘MAPs first’ approach, in which MAPs are systematically screened and quantified to identify instances (e.g. plant, microbe, environmental combinations) in which MAPs provide the largest fitness advantage. In this manner, empirical experimental work will guide investigations into the mechanisms that drive MAPs, which in turn, will be instrumental in guiding plant breeding programs and microbiome engineering.

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