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Potential of microbiome-based solutions for agrifood systems

Few microbiome-based solutions for agricultural productivity, food processing and human nutrition have been successfully commercialized. A systems-based approach that considers the ecology of microbial communities may help finetune extant tools to increase their reliability while promoting innovation and greater adoption.

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ost-associated microbiomes are central to food production systems and human nutrition and health. Harnessing the microbiome may help increase food and nutrient security, enhance public health, mitigate climate change and reduce land degradation^{1,2}. Although several microbiome solutions are currently under development or commercialized in the agrifood, animal nutrition, biotechnology, diagnostics, pharmaceutical and health sectors³, fewer products than expected have been successfully commercialized beyond food processing, and fewer still have achieved wider adoption by farming, animal husbandry and other end-user communities. This creates concerns about the translatability of microbiome research to practical applications⁴. Inconsistent efficiency and reliability of microbiome solutions are major constraints for their commercialization and further development, and demands urgent attention.

Plant- and animal-associated microbiomes are probable targets for the development of novel agricultural solutions due to the intimate associations with their hosts, which can modulate host health and productivity⁵, and due to growing demands for increased production intensity (for example, hydroponic systems) and sustainability. Emerging diagnostic technologies can gather information about microbiomes as indicators of host health or productivity to predict outbreaks of crop diseases, select appropriate crop or animal genetic varieties, and to improve the efficacy of agronomic practices. In contrast, therapeutic technologies actively modify the host metabolism and the microbiome towards a desirable conformation to optimize host health or productivity while also ensuring the long-term stability of the microbiome and

its functions. In agriculture, biofertilizers that enrich the soil with bioavailable nutrients and biopesticides can reduce the use of synthetic chemicals that negatively impact the environment, food quality and human health, while maintaining productivity². In animal production systems, microbiome therapeutics may reduce the need for antibiotic use and human pathogen loads linked to zoonotic diseases⁶, directly contributing towards public health.

Despite vast differences in host genetics, physiology and ecology, novel insights suggest that universal eco-evolutionary processes control the assembly of host microbiomes (for example, through host selection, microbial competence and interactions, host immune responses and environmental conditions7) and determine the success of microbiome-based solutions, but are not sufficiently integrated into their development. We argue that addressing these knowledge gaps using ecological and evolutionary frameworks and employing systems-based approaches can improve the efficiency and success of host-associated microbiome-based solutions across food production systems.

Cataloguing a vast microbial diversity

Development of microbiome-based solutions depends firstly on characterizing microbiomes. US and European funding agencies have invested more than US\$1 billion and \notin 1.4 billion in microbiome-related research, respectively^{1,8}, and much of this initial work generated massive microbiome inventories that now provide empirical baselines for future research. Global catalogues of human⁸, animal⁹ and crop⁵ microbiomes can now be leveraged as references for future applied research. Available inventories have revealed extensive variation in the composition of microbiomes among hosts, reflecting host genetics, metabolism and the environment¹⁰, as well as host behaviour. A refined understanding of these sources of variation will probably improve the resolution of diagnostic tools.

With computational developments, the ability to analyse these growing datasets has advanced. Machine learning, a branch of artificial intelligence and computer science, allows the analysis of such complex data and may aid in the identification of individual microbes or consortia as indicators of host health or candidates for intervention in the near future¹¹. Nevertheless, the use of machine learning for precision diagnostics is in its infancy, and future research is necessary for the use of microbiome-based solutions in advanced diagnostics and to transition these findings into therapeutic technologies¹². Innovation in the coming decade will probably be fuelled by novel insights generated from investments in data collection and analysis¹.

Microbiome-based solutions and applied science

A deeper understanding of the microbiome has fostered the development of technologies that add, remove or stimulate targeted portions of the microbiome, or that combine these strategies (Fig. 1). Probiotics introduce a set of microbes, often as dietary (animal) or seed or soil (plant) supplements, to a native microbiome to bolster host productivity and health. Probiotics in agricultural systems (that is, microbial inoculants) have been in use for more than a century and include, among others, nitrogen-fixing and phosphorus-solubilizing microbes that supplement plants with nutrients or protect against other abiotic (for example, drought) or biotic (that is, pathogen) stressors¹³. However, inconsistent

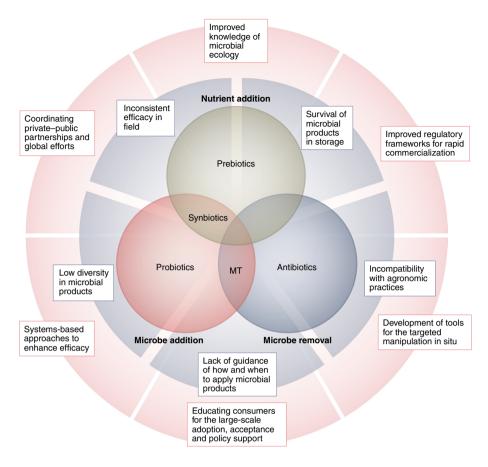


Fig. 1 An updated toolset for managing the microbiome as an ecological system. Emerging microbiome solutions aim to manage microbiomes by focusing on the ecology of their members. Microbe-removal strategies take advantage of the limited ecological tolerance of target bacteria, while nutrient addition strategies focus on their ecological preferences. Microbe-addition strategies must consider the ability of the introduced microbe to reach the target tissue and compete with resident bacteria. Increasingly, research is showing the improved success of combined strategies. The orange ring includes current barriers to the widescale adoption and development of microbiome solutions. The red ring includes suggestions to remove or ease these barriers.

outcomes driven by a lack of phylogenetic diversity of products, inconsistent survival in the formulation, and competition with indigenous soil and plant microbiomes have precluded the widescale adoption of these technologies. New research in this area seeks to improve success rates in product performance and further replace conventional pesticides, herbicides and fertilizers with microbial interventions to improve plant yields while considering the environment and host–microbiome interactions, in line with United Nations recommendations².

As the link between dietary fibre intake, the gut microbiome and host health has strengthened, so has the emphasis on diet as a means of improving the microbiome¹². Prebiotics (substrates that stimulate the growth of specific members of the native microbiome¹⁴) can be easily produced and administered industrially as feed supplements. In poultry, prebiotic dietary supplements (for example, inulin, fructo-oligosaccharides and galacto-oligosaccharides) can stimulate the growth of beneficial resident gut microbes, regulating the host's immune responses, improving gut function and preventing colonization by pathogenic bacteria^{6,15}. Combining probiotics and prebiotics (synbiotics) can enhance the success of probiotic bacteria¹⁴ (Fig. 1). As maintaining microbial strains or communities is extremely labour intensive, expensive and in some cases not feasible, postbiotics (preparations of inactivated microbes or components that have beneficial effects on the host, reviewed in ref. 14) have emerged as a viable alternative for industrial development. Postbiotics are effective in minuscule quantities and can therefore be

easily produced, transported, stored and applied to food production systems (for example, along with fertilizers, seed dressing or irrigation, or as feed additives).

Microbiome interventions historically focused on the untargeted removal of a portion of the microbiome (for example, with antibiotics including fungicides) regardless of their pathogenicity, but a deeper understanding of host-microbiome feedbacks highlighted the dangers of broad-spectrum antibiotic usage to humans and food production systems alike¹⁶, and this remains a formidable challenge. New approaches such as CRISPR-based technologies may be used to selectively kill pathogenic microbes or control gene expression in the microbiome, or to introduce novel genes into the microbiome that can be expressed as biochemical products;17 however, ethical concerns about such technologies persist.

Microbiome transplants (MTs) combine antibiotic usage and microbe additions to transplant a desirable community to an unhealthy host, and can improve host productivity and health. In animals, antibiotic treatment prior to faecal MT reduces the number of resident bacteria, increases the availability of nutrients and reduces competition against the transplanted microbes¹⁸. However, uncertainties around successful colonization and functional expression within introduced microbiomes remain high.

Ecology for microbiome-based solutions

Expansion of microbiome-based solutions for transformative impacts on food production systems requires a paradigm shift in our approach to develop, test, validate and use these tools. Key to this shift are research frameworks that consider target microbiomes as dynamic, responsive, interactive and evolving ecological entities (Fig. 2).

Microbes interact with their environment, their host and one another in ways that have been described in the ecological literature for several decades. The microbiome is affected by host properties, such as immune response, aging, genetic makeup and, in the case of animal hosts, behaviour, as well as by the ecological preferences of the community members (that is, competitive ability, nutrient preferences) and their ability to synthesize molecules that foster synergistic (as is the case with nitrate-oxidizing bacteria) or antagonistic (as is the case with bacteriocins) interactions with other microbes, and to withstand interventions. The microbiomes of young hosts follow patterns of primary succession similar to

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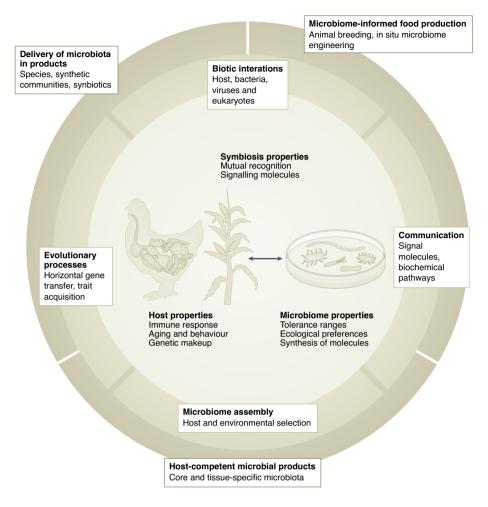


Fig. 2 | **Critical knowledge gaps hinder our ability to consistently predict and manage the outcomes of microbial interventions.** These knowledge gaps (inner circle) include biotic interactions between hosts and microbiomes, and between different compartments of the microbiome (for example, bacterial-fungal, bacterial-protist interactions); the ecological processes that govern microbiome assembly (for example, host and environmental filtering); evolutionary processes (for example, the role of horizontal gene transfer in microbiome functioning); and the modes of communication between microbes and between host and microbiome. These knowledge gaps must be systematically addressed to improve and further develop microbiome solutions (outer circle). In the future, developing products from more diverse groups of microbes (for example, most crop-related current products come from *Rhizobium, Bacillus, Streptomyces* and *Trichoderma*) may result in more consistent outcomes, while synthetic communities and synbiotics can potentially provide improved efficiencies. This can be further enhanced by selecting microbial products from core microbiomes (microbes that consistently colonize hosts), improving the probability of success of the introduced microbes. Finally, considering microbiomes into extant practices (for example, in situ microbiome engineering and microbiome-assisted breeding) can increase the yields of food production systems.

those observed in other young communities. Following birth or germination of the host, the microbiome becomes more diverse (for example, in pigs¹⁹), and continues to shift with the development and aging of the host, becoming increasingly specialized over time. While it has been known for nearly half a century that host-associated microbiomes are most susceptible to interventions in early life²⁰, new insights suggest that introduced microbes also face stronger competition to successfully establish in more diverse and specialized communities²¹. In this light, the appeal of combined therapeutic approaches, which introduce microbes as well as the resources they need to establish, is expected to grow. Nevertheless, the difficulty of studying microbial interactions in natural communities in situ remains a major hurdle in this area, largely due to the difficulty of sampling these microbiomes without disturbing the host. A better understanding of the factors shaping the development of host microbiomes and colonization by introduced microbiota is essential to identify the optimal time windows for interventions, reduce their frequency, and accelerate their adoption¹⁹. This will require the design and execution of long-term studies to determine temporal dynamics of the host microbiome, as well as the link between the microbiome and the host's metabolism as it develops.

The colonization by introduced microbes (in probiotics or MT) is constrained by the host and its immune system, which actively select the resident microbiota for specific tissues (for example, from the soil to plant tissues¹⁰), directly modulating the success of introduced taxa. The use of microbes from the core microbiome (which consistently colonize a particular host species), or from site- or tissue-specific communities, can lead to more effective probiotic treatments by improving the colonization, adaptation and proliferation of beneficial members of the microbiome and the restoration of normal microflora, especially after antibiotic use¹⁸ (Fig. 2). This effectiveness can be further enhanced by applying ecological (for example, biotic interactions, host filtering) and evolutionary (trait acquisition, mutations) frameworks. Such approaches will help identify biochemical, microbial and molecular tools for in situ microbiome engineering, which is expected to revolutionize microbiome-based solutions¹⁰. Deepening our understanding of the ecological preferences of members of the microbiome will help to determine how therapeutics affect niche availability in the community (for example, by increasing nutrients with prebiotics or by killing native microbes (Fig. 1)), develop a predictive understanding of microbiome responses to management, and improve success rates.

Ecology can inform the development of microbiome solutions. For example, assembly theory suggests that microbial communities are determined by four key processes: selection (by the environment, the host or other microbes), dispersal of microbes into the microbiome, diversification through evolution, and random processes. This framework can inform the selection of probiotic microbes that can successfully establish in target tissues, predict the range of environmental conditions or hosts for which a particular therapeutic might be effective, and explain the increased success of MT in disturbed microbiomes. Following therapeutic treatments, ecological theories can help to evaluate and predict their functional consequences. For example, keystone taxa are expected to disproportionately contribute to community functions.

Shifting to systems-based and ecology-focused approaches to management will require long-term vision, continuous investment in research and training, and sustained policy support. For diagnostics, the continued monitoring of microbiome development in long-term cohort studies or field experiments may serve to identify biomarkers of disease in the short term, and to generate predictive risk-assessment models in the long term. For probiotics, large trials will be necessary to evaluate the effectiveness of interventions given the variability and context dependency of microbiomes (for example, in microbiome-based restoration interventions²²). Shifting from experimental microbiome manipulations in vitro to manipulations in situ will leverage the native microbiota, which will likely improve the efficacy of treatments and lower their cost.

Key knowledge gaps must be filled, including the potential role of non-bacterial solutions (viruses, protists and invertebrates), and the role of interacting communities in determining the success of extant bacterial technologies. A lack of fundamental research into their ecology precludes the development of applications for all three groups^{10,13}. Novel concepts may be necessary to describe ecological phenomena that have not been observed in macro-ecosystems. For example, microbial community coalescence describes the encounter of entire microbiomes, their exchange and the composition and functioning of the resulting community²³, and may be particularly relevant to microbiome therapeutics, where novel communities are deliberately introduced into existing microbiomes (for example, in animal and plant MT). At the same time, it is also essential to develop microbiome literacy programs to match the public's growing excitement and inform consumer choices¹. Simultaneously, policy engagement will ensure rapid commercialization (for example, regulatory streamlining) of microbiome products.

Conclusion

Microbiome-based solutions have altered the research landscape on key global challenges. Microbiome research has stimulated a more nuanced view of microbes, from seeing the host and its microbiome as a unit, to acknowledging the importance of biotic interactions on host health and performance. Research continues to develop new products to improve animal health¹⁵ and farm productivity¹³, and to reveal novel targets for microbiome-based solutions. However, key bottlenecks to wider adoption of the products, such as inconsistent outcomes in farms and the logistic requirements of manufacturing and use of microbiome-based solutions, require prioritization. The next decade will probably see substantial growth in both targets for interventions and strategies for management. For successful outcomes, we argue that goals set for microbiome-based solutions should consider host-associated microbiomes as complex and dynamic ecological systems and integrate ecology and systems-based approaches into the innovation pipeline, from conception to commercialization.

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Author contributions

B.K.S. conceived the idea in consultation with N.E. and S.J., and led the discussion which was attended by all authors. S.J. and B.K.S. wrote the manuscript and all contributed to refine it.

Competing interests

The authors declare no competing interests.

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