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Calling for a systems approach in microbiome research and innovation

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Microbiomes are all around us in natural and cultivated ecosystems, for example, soils, plants, animals and our own body. Microbiomes are essential players of biotechnological applications, and their functions drive human, animal, plant and environmental health. The rapidly developing microbiome research landscape was studied by a global mapping excercise and bibliometric analysis. Although microbiome research is performed in many different science fields, using similar concepts within and across fields, microbiomes are mostly investigated one ecosystem at-a-time. In order to fully understand microbiome impacts and leverage microbial functions, research needs to adopt a systems approach connecting microbiomes and research initiatives in divergent fields to create understanding on how microbiomes can be modulated for desirable functions as a basis of sustainable, circular bioeconomy.

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Introduction

Microbiomes are defined as characteristic microbial communities, which include prokaryotes, fungi, protozoa, other micro-eukaryotes and viruses, that occupy well-defined habitats [1••]. The term microbiome is broader than other terms, for example, microbial communities, microbial population, microbiota or microbial flora, as microbiome refers to both its composition (the microorganisms involved) and its functions (their members' activities and interactions with the host/environment), which contribute to ecosystem functions [1••]. As microbiomes occur in a broad range of natural and cultivated ecosystems, such as humans, plants, soils, sediments and livestock animals [2••,3], they are crucial for the development of new, sustainable applications in the bioeconomy ranging from industrial biotechnology, agri-tech applications to re-use of waste [4]. Microbiomes have been identified as a key priority research area for the food system transformation [2••,3,5,6] because of their potential to improve human and environmental health, protect crops and restore soils [7]. Microbiome applications, such as biofertilizers, biocontrol agents and pre- and probiotic food supplements, are expected to provide valuable contributions to combat major societal challenges, such as zero hunger, reversing biodiversity loss and mitigating climate change [2••,8,9].

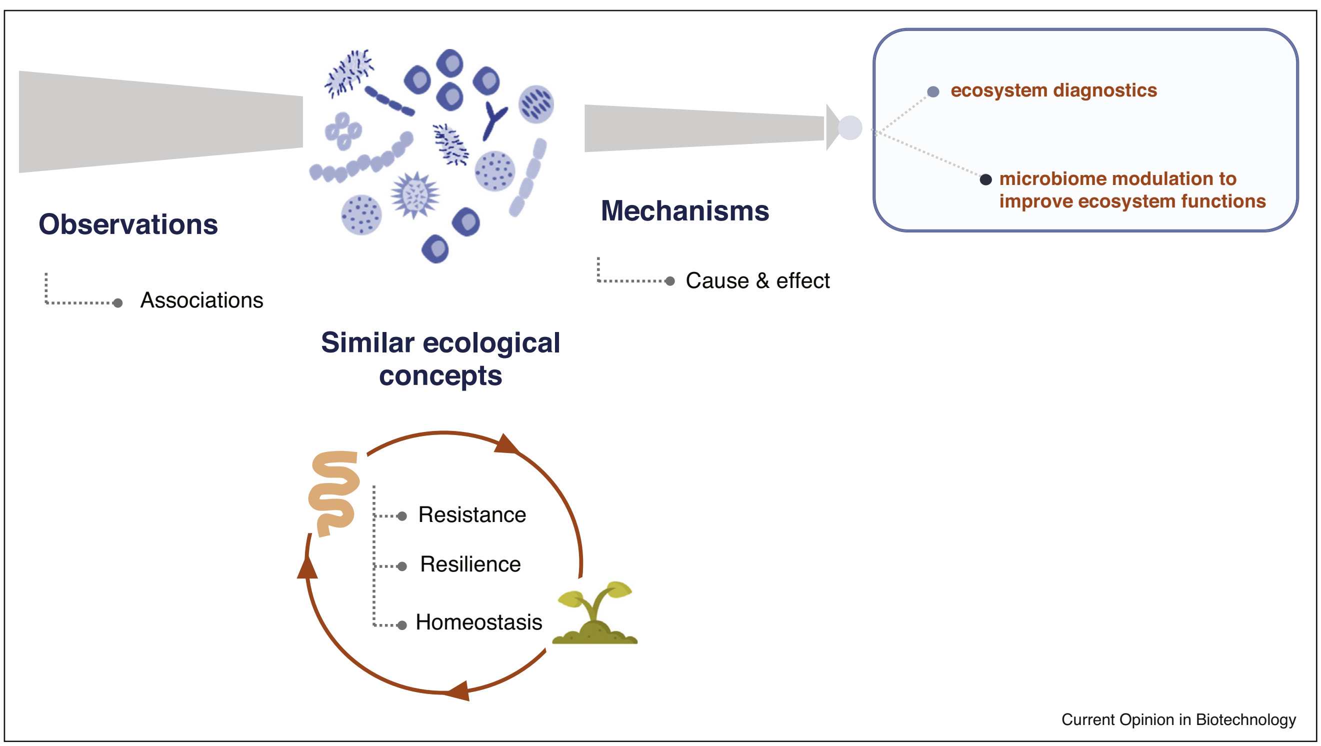
Microbiological research has already been performed for centuries [10]. However, the importance of microbial interactions for microbial community dynamics and microbiome functions has been recognised only recently [1••]. Microbiome research has developed into a major field, with 78 122 publications in the period 1990–2019 (Web of Science; keywords 'microbiome*', 'microbial communit*') with >13 500 publications in 2019 alone. Beyond research, microbiome-based applications are expected to be important contributors to the global economy. For example, the human microbiome market is expected to increase by 58% in 2027 compared with 2019 [11], and microbials in agriculture are expected to reach a global market value of >11 billion USD by 2025 (https://www.marketsandmarkets.com/Market-Reports/agricultural-microbial-market-15455593.html).

Although microbiome research is booming and recognised as an important driver for future applications, many microbiome research projects are descriptive [12,13•], rather than exploring causality and mechanistic aspects important for knowledge-based modulation of microbiomes (Figure 1). In this review paper, we will discuss routes on how we can benefit from the huge potential of microbiome research to drive bio-innovations. Thereto, we first describe the current state of microbiome research. Then, we discuss the similarities and differences of microbiome research performed in different fields. We further discuss the benefits of a systems approach, and conclude by discussing the framework conditions needed to further boost microbiome-based bio-innovations.

Current state of microbiome research

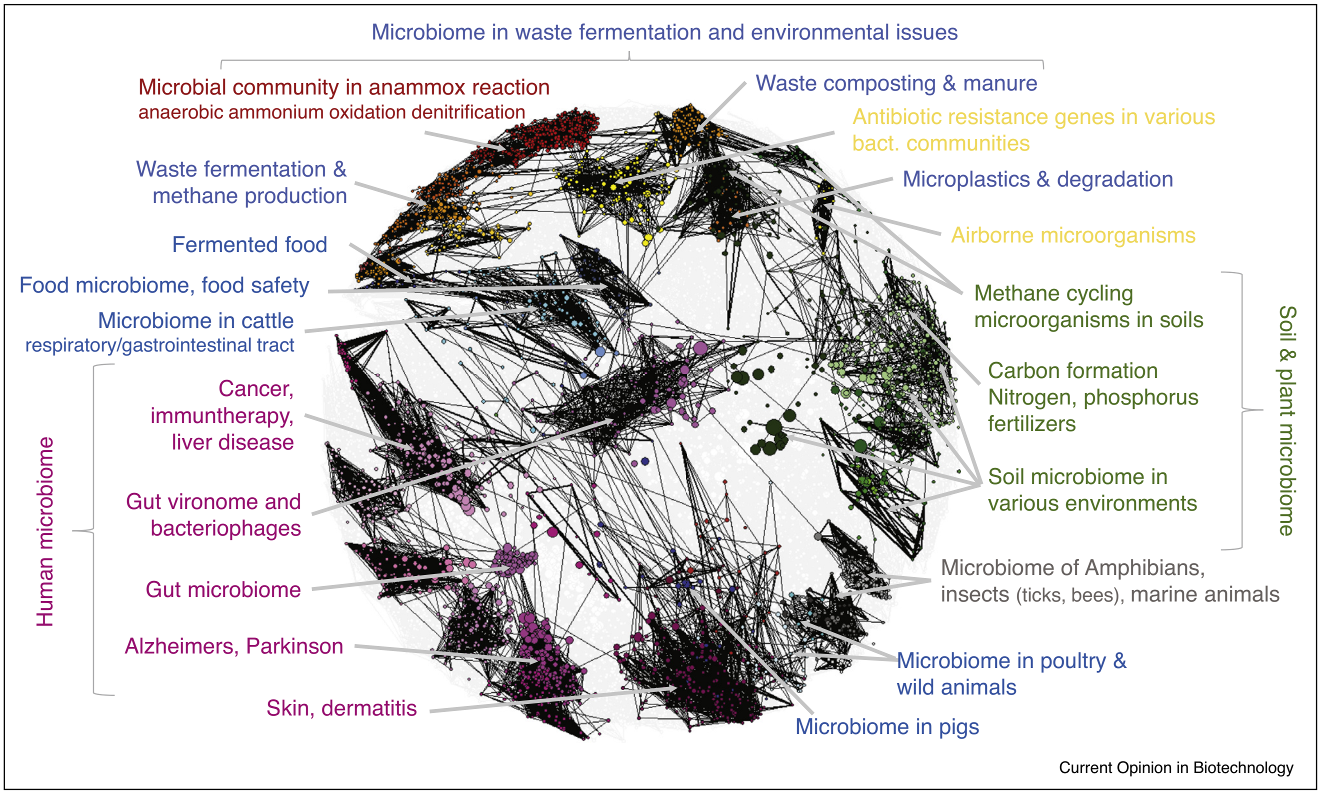
The current state of microbiome research was established through bibliometric analysis and a mapping exercise collecting relevant research and innovation activities (see supplement for methods). Both methods revealed that the leap that microbiome research has taken over the past years is truly breath-taking. Microbiomes are an integral component of many science fields, such as medical, veterinary or environmental sciences (Figures 2 and 3; Figure S1). Most publications and research projects, however, address human microbiomes, and particularly gut microbiomes (Figures 2 and 3). The second biggest thematic cluster comprises publications on soil and plant microorganisms (Figure 2) and research projects on microbiomes in the environment (mostly soil) and in primary production systems (mostly agriculture) (Figure 3).

Figure 1



Schematic overview of major pillars of microbiome research applied to different ecosystems. Studies performing observations, describe the diversity of microorganisms in a given environment. Studies exploring mechanisms, stimulate question-driven research that test specific hypotheses. This will give insight into the cause and effects of a certain biodiversity. There are several ecological concepts studied within experiments that are similar in ecosystems, such as resistance and resilience against disturbance of the ecosystem (for example, drought to soil microbiome, or antibiotics addition to gut microbiomes). Tools for ecosystem diagnostics or microbiome modulation to improve ecosystem functions can only be properly performed if the mechanisms are understood.

Figure 2



Bibliometric analysis. A network of interlinkages between the knowledge bases of publications was created using the BibMonTechTool [55]. Each colour represents a thematic group of publications as identified research topics are summarized thematically in the figure. The closer topics are the more references they share and thus draw on a similar knowledge base. The larger the node, the more publications are connected to the reference it represents. Each line represents connections between the nodes by being listed in different publications concurrently, for better visibility only 1% of all connecting lines are shown. Web of Science was accessed on 24.02.2020 with keywords microbiome* OR 'microbial communit*' and article, review, meeting abstracts or proceedings papers published in the years 2017 to the beginning of 2020 were selected.

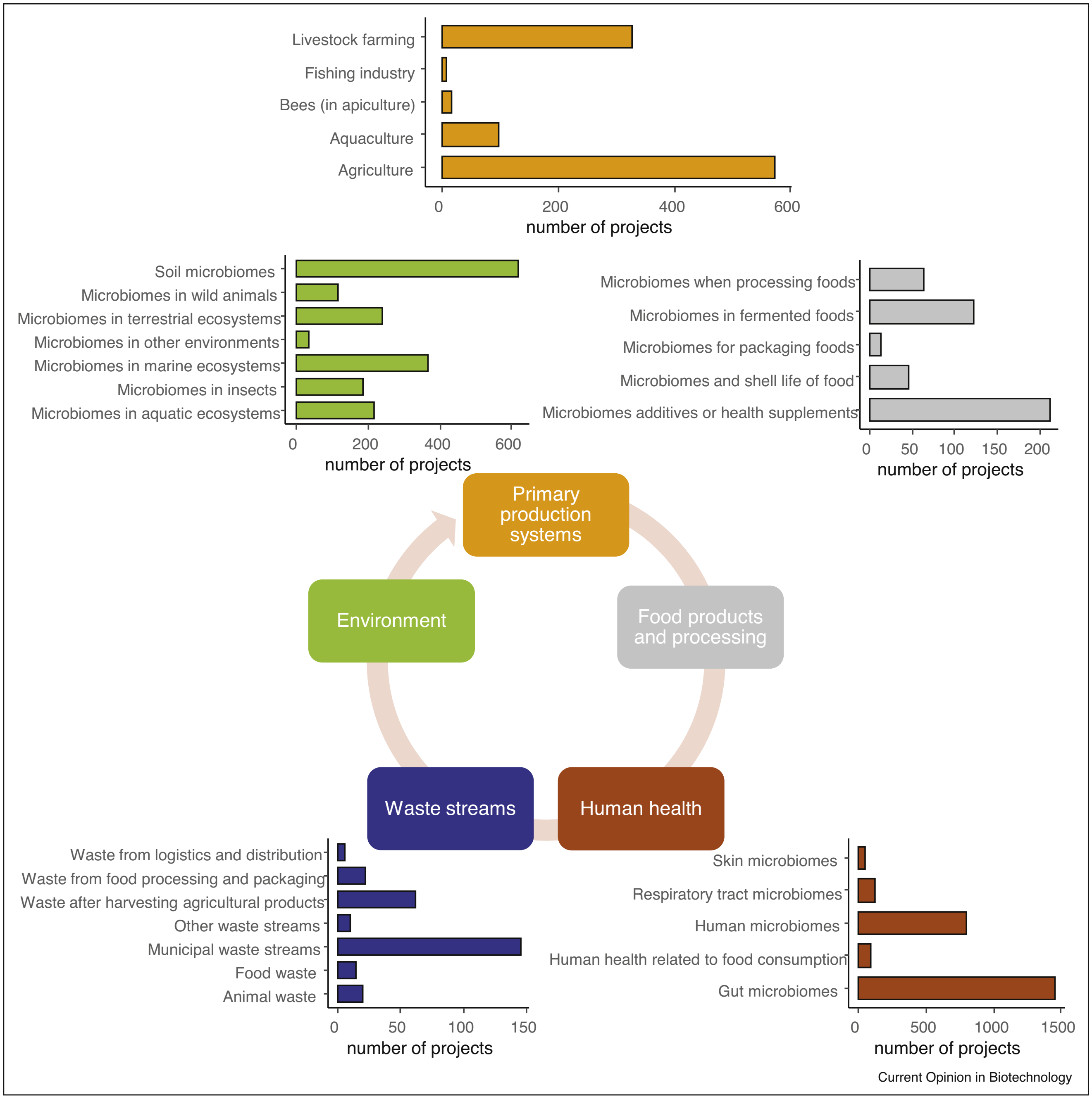
The nearer topics appear in the publication network, the more common knowledge they share and the closer the research is thematically connected (Figure 2). However, less than 0.01% of the 78 122 publications used a holistic approach connecting different ecosystems. Similarly, 91% of research projects study microbiomes within one ecosystem. Reasons for this fragmentation may be found in the following circumstances: (i) that the majority of projects has a budget of <250 kEuro, often supporting one early career scientist (Figure S2); (ii) many past projects focussed on describing microorganisms within the studied ecosystem [12,13•]; (iii) decentralization of research organization (see supplement); and (iv) microbiomes being sparsly addressing in research strategies published before 2020 (Figure S3).

To overcome the fragmentation of microbiome research within science fields, we argue that a concerted action towards integrated research on connections of different ecosystems is needed to combat many societal challenges [2••,8,9] and move towards a circular food system and economy [7]. In the following, we discuss current limitations and opportunities for the establishment of such holistic approaches in microbiome research.

Microbiome research in different fields uses similar concepts

Different science fields employ similar ecological concepts to study microbiomes, but knowledge is at different stages of development (Figure 1). For example, indigenous microbiota often prevents or outcompetes colonization of introduced microorganisms (including pathogens) [14,15]. A well-studied example concerns soil disease suppression where antagonistic microbiomes prevent proliferation of soil-borne pathogens in consistent monocropping systems [16]. Knowledge on microbiomes involved can be translated into practical applications, such as synthetic endophyte communities to suppress the fungal root pathogen of sugar beet [17]. Similarly, colonization resistance against gut pathogens is enhanced via infection-induced remodelling of host metabolism (for example, bile acid metabolism) that in turn triggers

Figure 3



Target areas per subcategory of research projects collected from 25 countries and supranational initiatives. The projects can be involved in more than one subcategory (see supplement for detailed information about the mapping exercise).

microbiome functions promoting resistance to infection [18••]. Furthermore, resilience concepts are likely similar across fields. For instance, antibiotic treatment affects gut microbiomes [19]. By identifying keystone species associated with a recovered state [19], potential microbiome applications could be developed that spur gut microbiome recovery. Similarly, compositional and functional features of soil microbiomes are affected by drought [20]. Although crops grown in soil with a history of drought experience less severe drought damage [21], microorganisms associated with this response have not yet been applied in agricultural products. Resident microbiomes may also be modulated via mixtures of microorganisms and elements of their associated environment [22,23], as exemplified by soil transplantations [24] or fecal transplants [25].

In addition to shared concepts, microbiome research uses similar tools [see for recent reviews: Refs. 26•,27] that to date, however, largely focused on bacterial composition [1••]. Following a systems approach, microbiome research should address compositional and functional features of all prokaryotic, eukaryotic and viral members to provide holistic understanding of microbiome functioning as well as how changes in these features affect ecosystem functioning. Furthermore, ecosystems can differ extensively, because different fractions of microorgansisms are present, for example, regarding the metabolically active fraction of microbiomes or the fraction of transient versus resident microorganisms. At a given time point, only ca. 5% of soil microbiomes are considered metabolically active and important for function [28] whereas the active microbiome may be close to 100% in upper parts of the gut. Further, the upper parts of the gut consists mainly of transient microbiomes that are ingested via food-or-feed associated microbiomes [29]. Although, the fraction of transient-over-resident microorganisms is likely much lower in soils, plants or lower gut, transient microorganisms can affect microbiome–host interactions or induce shifts in the resident microbiome [30] that potentially affect ecosystem functioning.

Microbiomes in different ecosystems are connected

Although microbiomes are often studied one ecosystem at-a-time, they are connected to other ecosystems and may affect microbiomes therein, as recognised by the One Health and eco-Holobiont concepts [31,32]. For example, soil microbiomes influence microbiomes associated with plant tissue and raw products [33,34], which is also reflected in the microbiome publication network (Figure 2). In turn, food products with different microbiome characteristics or microbiome-derived metabolites may influence the gut microbiome and its symbiosis with the host [35]. However, this link is not well established in literature and points towards unexplored opportunities for domain-spanning microbiome research (Figure 2). Another route for microbial dispersal is via aerosols [36], which may result in colonization of other environments, as shown by detectable traces of soil microbiomes in human gut microbiomes [37]. After introduction to another ecosystem, microorganisms can become abundant via a phased process of colonization, establishement and growth [38]. Microorganisms that become abundant in many ecosystems, such as *Enterobacteriaceae*, have strategies to cope with a wide range of environmental conditions [39], ranging from low pH in the stomach, high nutrient concentrations in the gut, fluctuating environmental conditions (temperature, osmotic pressures, (an) oxic conditions), to low carbon resources in soil. Also, the acquisition or loss of a low-abundant microbial keystone species in one ecosystem could impact its performance and dynamics in another system, improving health or causing disease [40••,41].

Towards a systems approach

Understanding how microbiomes affect interactions between ecosystems is essential for a circular and sustainable food production. This needs a holistic approach to realize the full potential of the impact that microbiome innovation could have to address health, environmental issues and related economic problems and opportunities. A holistic approach comprises: (1) understanding how the modulation of microbiomes affects both microbiome composition and function as well as functioning of the ecosystem and microbiome–host-interactions; and (2) how these changes in one ecosystem affect changes and features in connected ecosystems. For circularity of waste streams, connections of microbiomes between ecosystems are essential and a holistic approach is needed. For example, agricultural waste streams are often decomposed to compost. The addition of microbial biocontrol agents to compost improves the suppression of crop diseases [42] and may affect the resident microbiomes in the rhizosphere [43]. However, little is known how these added microorganisms influence microbiomes in the phyllosphere, the food produced and gut microbiome. Further, anaerobic bacteria in waste-water can accumulate phosphorous [44], representing a promising basis for soil-improving products. A holistic approach is also needed for the development of plant protection products based on 'beneficial' micoorganisms (also known as probiotics) that combat pests and diseases without the use of chemical pesticides [26•,45], as these microorganisms may affect microbiomes in other connecting ecosystems. All elements and activities that relate to sustainable food production, their consequences for environmental and human health as well as corresponding waste-streams are considered in a systems approach [6], where microbiomes play crucial roles [46]. For example, microbiome modulations along the food system chain that increase the microbiome diversity of the environment, may have positive health benefits for humans [47]. As such, a systems approach is needed to create an understanding on how microbiomes can be intentionally manipulated for desirable functions and how and to what extent this manipulation propagates into other, connected, ecosystems. Further integration of ecological concepts with new technologies, new detection methods, Artificial Intelligence and new linkages with data sciences will be essential for microbiome research [48].

Framework conditions

In parallel with the need to improve fundamental, biological understanding of microbiomes using a systems approach, several framework conditions need to be improved to support further exploitation of microbiome-based innovations.

Research and Innovation (R&I) strategies should direct future research towards concerted actions addressing microbiomes. Projects should be stimulated to use a systems approach and to work inter-disciplinarily and trans-disciplinarily to understand the role of microbiomes in different ecosystems and assess how microbiomes are inter-connected. Clustering of complementary research projects can build comprehensive approaches that address microbiomes to provide a basis for novel innovations, such as the H2020 Innovation Actions CIRCLES (https://circlesproject.eu/), HoloFood (https://www.holofood.eu/), MASTER (https://www.master-h2020.eu/) and SIMBA (https://simbaproject.eu/). The MicrobiomeSupport project (https://www.microbiomesupport.eu/) is currently developing a strategic R&I agenda that may be used for stronger connections and collaborations through targeted calls on microbiomes under the Horizon Europe programme [46].

A reason that microbiomes are still not addressed explicitely in many R&I strategies may be lack of technical competence as well as awareness of their benefits and potential applications [46,49•]. Therefore, policymakers, regulators, farmers, citizens and other stakeholders should be informed and educated that microbiomes are everywhere and have numerous highly important functions. This spans from primary school children to curricula that build competences in scientific and professional communities. Further dialogue with stakeholders is highly needed to improve aceptance of microbiome applications [50]. The establishment of an international Microbiome Network can support knowledge exchange, dialogue and cooperation among key actors and would fosters co-creation among stakeholders to find innovative solutions to pressing challenges [46].

Deployment of microbiome knowledge and products faces regulatory issues. Numerous new microbiome-based innovations that could contribute to improving public, animal and environmental health are *de facto* kept in waiting for years due to lengthy regulation procedures [51]. Challenges include defining the scientific criteria to substantiate potential health impacts [52], with clear roadmaps for testing not only single members of a microbial consortium but also the microbial consortium as a whole [53]. As such, appropriate regulatory frameworks need to be developed for safe, yet swift implementation of microbiome applications in health, food and environment.

Conclusions

Microbiome research has developed into an exciting scientific area as an integral part of many science fields, including agriculture, human health, livestock farming and environmental protection. Until today, however, research continues to be performed one ecosystem at-a-time, leading to fragmention of the microbiome research landscape. Such fragmentation shadows new biological concepts to be discovered: patterns in microbiome interaction, diversity of functions and roles may not be seen. This may prevent discovering the full, intriguing complexity of microbiomes. In turn, segregated microbiome science fields base their research on similar concepts, questions and tools, however, more knowledge is needed to explore the extent of concepts and ensure that findings can be transferred between ecosystems. Also, microbiomes within one ecosystem are connected to other ecosystems, as shown from the spread of emerging pathogens and antibiotic resistance genes between environments [54]. Future research needs to assess the impact of microbiome modifications in one ecosystem on microbiomes and ecosystem functioning in connecting ecosystems. As such, the time is right for a systems approach that connects research between scientific fields to create understanding on how microbiomes can be modulated for desirable functions.

Several conditions are needed to spur microbiome R&I. These include targeted R&I agendas for microbiome research that connect ecosystems, co-creation processes for developing novel applications, education and information for raising awareness and microbiome literacy, appropiate regulatory frameworks, and an international network of stakeholders and scientists. This will enable the development of microbiome-inspired biotechnology applications and product innovations, which will make full benefit of microbiome functions and leverage circular economy to move towards sustainable and resilient systems.

Conflict of interest statement

Nothing declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.copbio.2021.08.003.

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