6.03 Manipulation of Biodiversity to Steer and Optimize Microbial Community Function

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Glossary

Biorefinery Facility that combines the production of marketable bio-based chemicals and energy (typical of industrial biotechnology maximizing product yields) to the treatment and valorization of renewable carbon-based feedstocks (typical of environmental biotechnology minimizing by-product streams) using specialized microbial consortia.

Confined ecosystems Engineered, closed systems, such as bioreactors, that circumvent the physical, chemical and biological limiting factors of microbial-driven processes in highly controlled environments with sophisticated monitoring tools.

Consortium A co-existing group of two or more microbial populations that occur together in space and time (i.e., a microbial community). A defined and rationally-designed consortium obtained by the assembly of microbial populations and maintained under aseptic and axenic conditions is also called a synthetic microbial community (i.e., a gnotobiotic microbial community).

Engineered, open ecosystems Any open ecosystems built and managed by humans under non-aseptic conditions (e.g., activated sludge systems or anaerobic digesters).

***Ex situ, in vitro* manipulation** Control or change of biodiversity by human actions at a location different than the native environmental context in a laboratory-controlled environment (e.g., bioreactors). *Ex situ*, from the Latin, meaning out of place. *In vitro*, from the Latin, meaning within glass.

***Ex situ, in vivo* manipulation:** Control or change of biodiversity by human actions outside the laboratory at a location different than the native environment through maintenance of microorganisms under specific engineering parameters and operating conditions using real-time monitoring of process performance. *In vivo*, from the Latin, meaning within the living.

***In situ* manipulation** Control or change of biodiversity by human actions within the context of the native natural environment where microorganisms evolve (i.e., at the same place). *In situ*, from the Latin, meaning in the natural or original place (on site).

Microbial population A group or lineage of genetically related individuals of the same species in the same place at the same time. A microbial population maintained under aseptic conditions refers to a pure culture (i.e., a microbial isolate or a strain).

Natural ecosystems Any naturally-occurring ecosystem evolving without deliberate human actions.

Probiotics Microorganisms, in isolation or in consortia, that provide human or animal health benefits when consumed, or that enhance the growth and yield of the host plants, and may suppress diseases, when applied.

6.03.1 Introduction

Microbial diversity is a major determinant of the performance of multiple natural or industrial processes, such as nutrient cycling, microbiome-driven immunomodulation[1] or fermentation technologies to produce bread, wine or cheese.[2] In natural ecosystems, microbial communities play a key role in supporting the global ecosystem services or agricultural sustainability and are the drivers of ecosystem functioning and homeostasis. Microbial communities with different functional traits, sometimes unique, can now be characterized and controlled thanks to the advances of molecular microbiology and systems engineering. Therefore, microbiome-based technologies have become the cornerstones of the cradle-to-cradle concept, bioeconomy and biorefinery, and environmental protection and restoration policies. Microbial communities have a fundamental role not only in environmental and industrial biotechnology but also in plant and medical biotechnology. Plant-associated microbiomes ensure plant productivity and protection against pathogens.[3] Likewise, the human microbiome plays a starring role in human development, immunity and nutrition.[1]

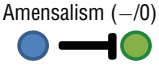
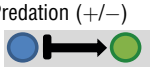
To get the full utilitarian value of microbial diversity for practical and technological applications, multiple strategies of microbial community manipulation have emerged as a function of the investigated habitats or environments (e.g., natural ecosystems or confined environments) and the target functions (general or specialized metabolic activities). For instance, manipulation of the diversity of naturally-occurring microbial communities will involve strategies to trigger (i) a selection pressure (i.e., a change in microbial community composition and structure due to deterministic fitness differences between community members under a specific environmental condition) and/or (ii) a propagule pressure (i.e., the number of microorganisms released into an ecosystem to which they are not autochthonous, such as during a soil bioaugmentation process using non-native biodegradative microorganisms). In *in situ*, *in vivo* manipulation strategies, agricultural practices, such as land use, crop residue management or tillage techniques, can have significant impacts on soil microbial communities by selecting and favoring specific autochthonous soil microorganisms and microbial life strategies.[4] On the other hand, microbial community composition and structure can be modulated following a bioaugmentation process to complement a missing catabolic competence in the native/autochthonous community, as demonstrated for the bioremediation of TCE-contaminated groundwater plume.

In *ex situ*, *in vivo* manipulation strategies, microbial communities are maintained outside their natural or original conditions in a location to which they are not native. For instance, *ex situ* bioremediation using excavation of contaminated soils or pumping of polluted groundwater is commonly used to manipulate the microbial community diversity and function to improve pollutant removal under controlled and appropriate physico-chemical conditions. In wastewater treatment plants, the incoming wastewater, with its associated microbial communities and chemical composition, is transported into engineered, open ecosystems for the selection and maintenance of robust and complex microbial communities. Specific functional guilds, such as nitrifying bacteria and methanogens, are mastered by the control of operational parameters and engineering design.

On the other side, *ex situ*, *in vitro* manipulation strategies select for microbial communities (enrichments) in specific bioreactors from environmental samples or rely on synthetic ecology with the construction of defined consortia. Artificial microbial diversity can be engineered *in vitro* through the rational design of synthetic microbial assemblages using a bottom-up approach starting from wild-type or mutant microbial strains selected for their desired functional traits. This strategy is promising for industrial bioprocesses and the production of structurally-complex chemicals that require simultaneous and cooperative anabolic pathways incompatible for single microbial strains grown in isolation.[5,6] In the past two decades, the applications and engineering of microbial consortia have therefore gained considerable traction[7] because they can circumvent the limitations related to the use of axenic cultures of individual strains (wild-type or genetically modified). For instance, the use of a single mutant strain for the heterologous production of complex molecules requiring multiple biosynthetic steps is hindered by the genetic instability and the high metabolic burden on the individual strain. In contrast, microbial consortia can perform more complex functions than microorganisms in isolation thanks to division of labor and synergistic interactions between community members (**Table 1**). They are characterized by a higher functional redundancy, stability and robustness and exhibit a wider enzymatic and metabolic portfolio for the biocatalysis of cascade reactions at higher efficiency than single taxa grown in isolation. Moreover, the use of artificial microbial communities can represent an attractive alternative in bioprocessing applications for their reduced complexity and higher controllability[8] compared to the use of complex and undefined microbial communities.

Different strategies have been developing to manipulate, control and optimize the microbial community activities in confined laboratory environments as well as in natural and engineered, open ecosystems. These strategies generate knowledge of fundamental nature and enable specific biotechnological applications. For instance, the necessity of sustainable and robust supply of bio-based energy and chemicals from renewable carbon-based feedstocks has led to the merging of industrial biotechnology, which maximizes titer, rate and yield (TRY) targets (historically in pure culture fermentation), and environmental biotechnology, which minimizes waste streams and optimizes stability and functional robustness through microbial diversity. This led to the development of biorefinery platforms and resource recovery that strongly rely on microbial resource management and guidance to strategies for biodiversity manipulation.[9,10] Here, we provide an overview of the rational and knowledge-based approaches to manipulate or modulate microbial communities and to assemble individual microbial populations into robust microbial consortia. In addition, some examples of applications of biodiversity engineering are presented, with their benefits and potentials, spanning from industrial and environmental to plant and medical biotechnology.

Table 1 Main interaction motifs that underpin the functions of microbial consortia ("+", positive effect; "−", negative effect; "0", no effect).

Interaction motif	*Nature of interaction*	*Examples of biotechnological application*	*Reference*
Commensalism (+/0) 	Unidirectional	Electricity production from cellulose biodegradation (*Clostridium cellulolyticum* degrades cellulose producing fermentation products, which are oxidized by the electrochemically-active *Geobacter sulfurreducens*).	[18]
Mutualism (+/+) 	Reciprocal	Lipid production using CO_2 and sunlight (Phototrophs provides a C-source to heterotrophs, which in turn produce lipids with antioxidant activities and promote phototroph survival by alleviating oxidative stress).	[25]
Neutralism (0/0) 	No Interaction	Consumption of glucose, xylose, and arabinose in the presence of the inhibitor acetate (A consortium with three *Escherichia coli* strains (ALS1370, ALS1371, ALS1391), each engineered to utilize only one sugar, and one acetate-consuming *E. coli* strain (ALS1392) can simultaneously degrade the sugars mixture).	[28]
Competition (−/−) 	Reciprocal	Use of probiotics to benefit plant health through competition with pathogens (*Pseudomonas* species reduce pathogen density in the rhizosphere community and decreases the disease incidence due to intensified resource competition).	[32]
Amensalism (−/0) 	Unidirectional	Inhibition of food spoilage and pathogenic bacteria in dairy products (*Lactococcus lactis* strains prevents the growth of *Listeria monocytogene* by producing antimicrobial compounds in fresh cheese manufacturing).	[34]
Predation (+/−) 	Reciprocal	Bacteriophages used as biocontrol to reduce the excessive proliferation of filamentous bacteria in activated sludge (Bacteriophages infect *Nocardioforms* to prevent foaming and viscous bulking).	[37]

Adapted from Großkopf and Soyer.[16]

6.03.2 Mastering Community-Level Properties and Microbial Interactions to Reach Functional Engineering Objectives

Microbial communities contain a huge number of genes and metabolic capabilities in comparison to monocultures. This biodiversity allows important community-level properties, such as the division of labor, through species interactions, and robustness.[7] Intra-species interactions and inter-species network interactions and metabolite trafficking govern the functioning of the whole community, shaping its structure, dynamics, resistance and resilience.[11] For example, community members can rely on each other through metabolite exchanges (e.g., release of metabolites by the marine cyanobacterium *Synechococcus elongatus*, used as a source of energy and carbon by heterotrophic bacteria[12]) or excreted growth factors (e.g., exchange of organic cofactors between vitamin B_{12}-producing microorganisms and corrinoid-auxotrophic *Dehalococcoides* sp.). Get insights into these community-level properties is essential to manipulate the microbial community toward a desired state or to design and construct *de novo* consortia performing novel tasks.[13] For example, increasing cooperative interactions between species can be the key to achieve a specific output, such as biodegradation of structurally-diverse pollutants (e.g., mixture of hydrocarbons) or complex anthropogenic compounds (e.g., the phenylurea herbicide linuron[14]). In a mangrove sediment-derived bacterial consortium, the interactions between *Mycobacterium* spp. with the other members, *Novosphingobium pentaromativorans* PY1, *Ochrobactrum* sp. PW1 and *Bacillus* sp. FW1, led to improved pyrene biodegradation thanks to the cooperation of metabolic activities for the removal of pyrene intermediates.[15]

Basal interaction patterns can be defined using binary interactions based on microbial species communication (intra- and inter-population) via their metabolic products and intercellular chemical signaling molecules (**Table 1**). From these interaction motifs, it is possible to understand higher order-level properties of consortia containing more than two populations.[16,17] Here, we report the main binary interaction motifs that underpin the functions of microbial consortia and their relevance in different biotechnological applications (**Table 1**).

A common interaction motif is commensalism, where one species derives benefits from the association, while the other partner is neither positively nor negatively affected, creating a beneficial relationship through, for example, a food chain pattern.[18] Another form of commensalism arises when one community member creates a suitable environment for another species as demonstrated in a synthetic co-culture composed of an O_2-consuming *Escherichia coli* strain that favors the exoelectrogenic activity of *Geobacter sulfurreducens* under hypoxic conditions.[19] Mutualism is a positive interaction motif where two species grow or perform better when living together than in isolation. Mutualistic interactions involve inter-species dependencies through metabolic cooperation (e.g., syntrophy defined here as an obligately mutualistic metabolism and thermodynamically interdependent lifestyle where the transformation of an organic substrate by a microorganism, such as a volatile fatty acid, occurs only when degradation end products, such as hydrogen, are consumed below a certain threshold concentration by another microbial strain[20]). The importance of cooperative interactions in communities has been demonstrated in numerous studies.[21–23] A well-known example of mutualism is the syntrophic relationship in the anaerobic digestion process between hydrogenotrophic methanogens and secondary, fatty acid-fermenting bacteria, with the former consuming the hydrogen produced during acetogenesis and maintaining its partial pressure low enough to ensure the activity of the latter.[24] Another application of microbial mutualistic interactions is the engineered relationship between phototrophs and heterotrophs for lipid production. Using CO_2 and sunlight, the phototroph provides organic carbon sources to heterotrophs, which in turn produces lipids with antioxidant activities and promotes phototroph survival by scavenging reactive oxygen species.[25]

In the presence of a neutral interaction motif, in which the two populations do not have any detrimental and beneficial interactions, ecological niche differentiation and partition of carbon and energy sources between community members can lead to an enhanced community-level function. Resource partitioning and complementarity effect play also a key role in all positive interactions, especially for the biodegradation of a mixture of pollutants or complex substrates involving multiple degradation pathways that could not likely be expressed and supported by a single microbial isolate.[15,26–29]

Another form of interaction, this time a negative one, is competition. Species compete with each other when they use the same finite resources (e.g., substrate, nutrient or electron acceptor). When competition for resources prevails in a microbial ecosystem, the community functioning is reduced.[30] Nevertheless, Coyte et al.[31] have recently shown that competition between the members of the gut microbiota can increase community stability. Furthermore, competitive interactions between host-associated microorganisms and harmful invaders can protect the host from pathogen invasion and diseases[32] or can be used as the selective force to promote the biosynthesis of new and more efficient antimicrobials.[33] In contrast to commensalism, amensalism (or unidirectional competition) is a type of species interaction in which one strain is harmed or inhibited by inter-species relationship while the other one remains unaffected. Amensalism occurs for example between acid lactic bacteria and food spoilage bacteria, with the former producing antimicrobial compounds preventing the growth of undesirable spoilage bacteria.[34] Predation is another type of antagonistic interaction. Predation of bacteria by bacteriophages can be used as a tool to selectively modify and modulate the structure and composition of microbial communities.[35–37]

Interaction motifs are defined by different communication mechanisms, such as quorum sensing (QS). The QS is based on the production and detection of signaling molecules, known as autoinducers, whose concentration is correlated to the density of the secreting cells of the same population. When a threshold level for the signaling molecules is reached, the communicating microorganisms initiate a coordinated modification in their gene-expression profiles, synchronizing each other and thus function as a multicellular organism.[38] Interspecies QS through the secretion of the specific autoinducer-2 (AI-2) can also promote communication between two different populations, such *E. coli* and *Vibrio harveyi*.[39] QS can coordinate both cooperative and competitive interactions.[40] For example, QS stabilized cooperation by preventing the growth of quorum-defective cheaters in *Chromobacterium violaceum* population.[41] Quorum-controlled antimicrobials can also regulate interspecies competition in *Pseudomonas aeruginosa-Burkholderia multivorans* coculture.[42]

One of the QS-controlled microbial behaviors is the biofilm formation. In the biofilm, microorganisms form a surface-associated consortia assembled in a self-produced extracellular polymeric matrix, which confers higher microbial stress resistance and an ideal environment for microbial interactions.[43] Thanks to this attribute, biofilm plays a key role in the formation of functional microbial landscapes with high level of organization (for further discussion, **see** the article of Davide Ciccarese et al.). Even if aerobic granular sludge (AGS) microbial communities are not *sensu stricto* biofilms in a sessile state, they are considered as spherical biofilms in suspension composed of self-immobilized cells,[44] that enable multifunctionality through niche differentiation and decrease of pollutant toxicity felt by the community members.[45] Furthermore, biofilms can have applications in biofertilizer usage for improving crop productivity.[46,47] For example, fungal-bacterial biofilms (FBBs) including nitrogen-fixing bacteria (*Acetobacter*, *Azotobacter*, *Bradyrhizobium*, and *Rhizobium*) and the saprophytic fungus *Acremonium* sp., were used as biofertilizer and enhanced the growth of leguminous and non-leguminous plants.[48]

A property of microbial communities that emerges from the presence of interaction motifs and functional redundancy is the robustness.[49] In the presence of environmental fluctuations, multiple functionally-redundant and phylogenetically-distinct taxa per functional guild can compensate the reduced activity and population size that some species may experience during the perturbation.[50] For example, in a bioreactor designed for the removal of soluble mercury from wastewater, Von Canstein et al.[51] reported that increasing the diversity of mercury-reducing bacteria in biofilm resulted in higher mercury removal efficiency under changing environmental conditions. In another study, microbial community redundancy was the main driver to ensure continuous methane production in 1L-anaerobic digesters under salinity disturbance.[52] Furthermore, in a full-scale activated sludge under fluctuating solid retention times (SRTs), a complete functional recovery, coupled to a new structural stable state, was obtained thanks to functional redundancy.[53]

6.03.3 Microbial Diversity Manipulation: From Natural Ecosystems to Confined Environments

Manipulation strategies of microbial diversity vary with the type of (eco)-systems and their associated microbial communities and the target functions (**Fig. 1**).

Microbial communities present in natural ecosystems (i.e., environmental habitats or host-associated environments) can be manipulated in their native and local state preserving three-dimensional spatial heterogeneity and connections with the natural settings determined by the random environmental factors.[54] This approach is referred to as *in situ*, *in vivo* manipulation, as defined previously. The fundamental objectives of *in situ* biodiversity management are to control human health, to improve ecosystem functioning and the delivery of natural capital and ecosystem services,[55] as well as to achieve ecological restoration of impacted ecosystems or improve agricultural plant productivity. *In situ* manipulation strategies encompass the propagule pressure[56] (also known as invasion or colonization pressure) and the selection pressure. The propagule pressure is defined here as the release of allochthonous or exogenous living organisms and their establishment in the autochthonous or native community (e.g., fecal microbiota transplantation (FMT),[57] soil bioaugmentation[58] and the addition of bacteriophages as bio-control agents against plant pathogens[59]). The selection pressure is defined here as the deliberate modifications of physico-chemical conditions of the ecosystem

Strategies and variables	Types of microbial ecosystems			
	Natural ecosystem	Open, engineered ecosystems	Confined ecosystems with mixed, undefined cultures	Confined, artificial ecosystems
Manipulation	*In vivo*, *in situ*	*In vivo*, *ex situ*	*In vitro*	*In vitro*
Starter microbial source	Autochthonous communities	Any environmental communities (native or non-autochthonous)	Any environmental samples, enriched cultures	Synthetic microbial consortia, pure cultures (wild-type or mutants)
Biodiversity manipulation output	Autochthonous manipulated communities (can include non-native microbial strains from targeted propagule pressure)	Selected environmental communities (using engineering design and modulation of operating parameters and/or bioaugmentation)	Enriched, functionally-stable cultures maintained in bioreactors	Pure or mixed, functionally-stable cultures maintained in bioreactors
Targeted methods to analyze communities	Top-down approaches (e.g., meta-omics tools and molecular systems ecology): community-level modeling, network inference of inter-species interactions and identification of keystone community members		Community-scale metabolic modeling; Single-cell techniques and genome-scale modeling (after laboratory isolation)	Bottom-up approach (synthetic ecology and single-cell techniques); Community-scale modeling of synthetic consortia

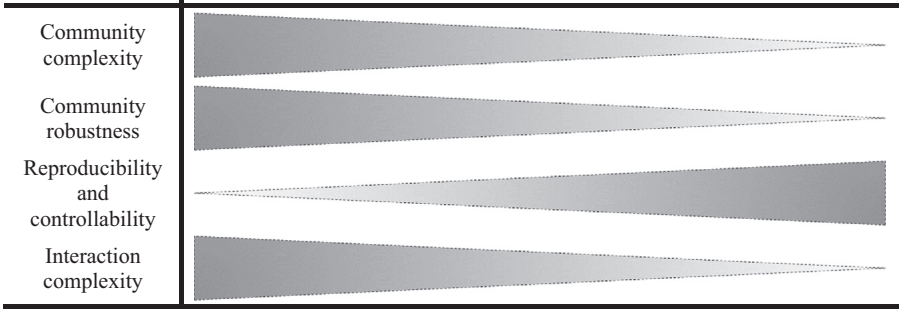


Figure 1 Manipulation strategies of microbial diversity according the type of (eco)-systems and their associated microbial communities.

that drive changes in microbial community composition and structure caused by deterministic fitness differences (e.g., addition of chemicals that can selectively prevent or stimulate the growth of native microorganisms (e.g., antibiotics, organic amendments (biostimulation), prebiotics), soil management and agricultural practices). Soil management (e.g., no or reduced soil tillage) and cropping/agricultural practices (e.g., intercropping, crop rotation, cover crops or crop species mixtures) have been proven to have positive effects in agriculture, supporting a diverse and active soil biota, while increasing the crop yield.[60] The use of targeted and sustainable agricultural practices that foster specific microbes with beneficial traits (e.g., those promoting plant growth, implementing biotic or abiotic stress tolerance, etc.), will help paving the way for "smart farming" practices.[61]

In situ microbial communities are usually analyzed with a top-down approach, using multiple meta-omics approaches to examine the composition, the interaction networks and the overall behavior of the system under undisturbed conditions or in response to various perturbations at the community level.[50,62,63] *In situ* techniques enable to shape a natural microbial community in its native state, with its co-evolution history and the intrinsic adaptation of native microorganisms to local conditions, with lower perturbation of the natural ecosystem compared to *ex situ* approaches.[64] Nonetheless, this approach has to deal with the difficulties to control a natural microbial community with a high complexity in terms of composition, metabolism and dynamics.

Natural microbial communities can also be manipulated through selective forces imposed by the engineering of constructed environments to favor specific ecological guilds and steer the functions of the community. This approach is referred to as *ex situ*, *in vivo* manipulation since microorganisms are maintained and selected outside their native habitat. Typical examples of engineered, open ecosystems are activated sludge systems or constructed wetlands in which the manipulation of microbial community diversity and functionality are performed through specific engineering designs (e.g., selection of bioprocess operational parameters, sizing and configuration of process units).[45] The resulting engineered microbial communities are dedicated to a specific biotechnological application commonly found in wastewater treatment plants, such as denitrification, phosphate removal or organic matter oxidation processes. In engineered, open ecosystems for wastewater treatment, the selection pressure is imposed by controllable

parameters (hydraulic and solid residence times, aeration, volumetric organic loading rates, etc.) and acts on the incoming sewage or wastewater microbial community to achieve a microbial engineered ecosystem with stable target functionalities.

For the production of a specific product using industrial microbial-driven processes and biorefinery, *ex situ*, *in vitro* biodiversity manipulation (i.e., under laboratory conditions) are performed in confined environments (e.g., bioreactors under different kinetic modes) with the development of efficient and robust microbial biocatalysts. Two main strategies can be used to obtain a microbial consortium from laboratory incubations: (i) the enrichment or community culture approach,[65] starting from a complex naturally-occurring community to achieve a functionally-stable consortium with the desired trait and (ii) the assembly of synthetic consortia from microbial isolates using the synthetic ecology approach.[50]

Using the first approach, the resulting communities have reduced size and complexity, turned in higher tractability while retaining the core of the native interactions to perform the desired function.[64] On the other hand, lower complexity can be associated to lower functional redundancy and stability since other ruled out bacteria can play a key role in ensuring microbial community robustness (e.g., rare biosphere[50,66]). Starting from natural systems (e.g., rumen liquor, contaminated soil), laboratory domestication and enrichment techniques down-select for simplified and stable consortia by promoting growth of organisms of interest under controlled laboratory conditions. These methods allow ending up with a functionally-stable enriched consortium composed of functional strains of interest and screened off from the non-functional ones. Common strategies to obtain enriched consortia are selective growth medium composition, dilution-to-extinction, toxicity-to-extinction or dilution-to-stimulation.[67–70] Laboratory isolation of microbial strains from mixed cultures is the ultimate result of enrichment techniques that will be used as pure biocatalysts in axenic food or medical biotechnologies or as building blocks for the construction of synthetic microbial communities.

The second approach focuses on the combination and stable assembly of two or more microbial strains using the bottom-up approach to artificially construct *de novo* synthetic microbial consortia. *In vitro*, simplified and defined consortia can be constructed, using wild type or genetically modified microorganisms, enabling the assembly of *de novo* consortia for novel applications.[71] The simplest form of synthetic community is a co-culture defined as a consortium made up of two operational taxonomic units. The artificial consortia afford high tractability, reproducibility and controllability and can be used for several applications, from fundamental research on ecological questions (e.g., biodiversity-ecosystem function,[72] biodiversity-ecosystem stability[73], inter-species interactions mechanisms[74,75]) to novel applications in chemical and energy industry, agriculture and healthcare.[8] However, only culturable microorganisms can be included in synthetic consortia and often they have to be characterized a priori (single-cell genomics) if specific outcomes need to be achieved. For their relative simplicity, they suffer from relatively low stability under long term maintenance and low representativity because isolating pure strains and mixing them to form a consortium may neglect important interactions and mechanisms occurring in natural communities.[64]

6.03.4 Translation of Microbial Diversity Manipulation Into Practical Applications

As explained in the previous section, there are different approaches to manipulate microbial communities, from the construction of artificially-assembled microbial consortia, to the deconstruction of natural communities or the direct manipulation of naturally-occurring microbiomes *in situ*. Each approach deals with different communities of different size, complexity and functionality in order to provide different services to society, such as intrinsic ecosystem services or commercial biotechnical applications in the agro-environmental, industrial or medical disciplines. In this section, we will give an overview of the multiple applications offered by microbial community manipulation, from large-scale natural communities to synthetic co-cultures.

6.03.4.1 Applications in Natural Ecosystems (*In Situ* Manipulation)

Environmental and host-associated microbiomes are dynamic and complex that play key roles in regulating soil or aquatic ecosystems or the physiology of animal and plants.[76] Soil and plant-associated microbiomes (i.e., rhizosphere, root or leaf-associated microbial communities) have been found to be crucial in supporting plant health by enhancing the disease-suppressive ability of microbial community members or improving plant phenotypes such as productivity or fitness. Perturbations of well-balanced microbiomes can result in deleterious changes to the hosts and its surroundings, such as reduced plant productivity or human/plant fitness. Manipulating natural microbiomes *in situ* offers exciting opportunities to steer microbial communities toward a particular functional and structural state. In agriculture, land use practices and agricultural diversification, such as no-till, intercropping, cover crops, crop rotation, residue management or organic fertilization, can improve soil quality and alter the diversity of its associated microbiome.[4,77–79]

6.03.4.1.1 Soil Biodiversity and Agricultural Productivity

Nutrient availability and niche dimensionality rely on land use practices which therefore affected microbial diversity and selected for different microbial life strategies based on the universal adaptive strategy theory (i.e., the Competitor, Stress tolerator and Ruderal life strategy scheme (C-S-R)).[80] The diversity of C-inputs from cover crops boosted microbial productivity and selected for species with a wider metabolic ability and moderate growth rate (ruderals). In the absence of cover crops, no-till selected for a greater diversity and slow-growing microorganisms (stress tolerators), whereas the conventional tillage shifted the community toward a lower diversity and selected for fast-growing competitors.[80] Similarly, Hartman and colleagues showed a pronounced effect of different management types (conventional vs. organic) and tillage intensities (reduced vs. intensive tillage) on composition

of soil and root bacterial and fungal communities. Tillage influences soil bacterial and root fungal communities, whereas soil fungal and root bacterial communities were affected mainly by management type. Taxonomically different microorganisms resulted from different cropping practices, which also influenced the co-occurrence networks between community members.[61]

6.03.4.1.2 In Situ Bioremediation of Contaminated Soils

In situ microbiome manipulation can be also a strategy for beneficial outcomes in bioremediation of polluted environments. This can be attained either by adding specific nutrients to selectively favor indigenous species with degrading abilities (biostimulation[81]) or by introducing microbial pure cultures or consortia with the desired catalytic abilities (bioaugmentation[82]). An example of commercialized consortium for use in bioaugmentation is KB-1 (SiREM, Ontario, Canada), a well-defined enrichment culture derived from a TCE-contaminated site that dechlorinates PCE through trichloroethene (TCE), *cis*-dichloroethene (cisDCE), and vinyl chloride (VC) to the non-toxic ethene.[83] KB-1 has been successfully used as a commercially-available bioaugmentation inoculum to enhance biodegradation of chlorinated solvents at many contaminated sites.[84]

6.03.4.1.3 Plant-Associated Microbiomes

In order to maintain, preserve and improve plant or soil-associated microbiomes, chemical-based manipulation method (i.e., biostimulation), propagule pressure (i.e., bioaugmentation) and bacteriophage treatment are innovative alternatives to conventional pesticide treatments in the control of plant diseases. The use of organic amendments has gained attention because chemical-based manipulation methods are reported to improve soil suppressiveness to plant pathogens. For instance, the application of composted almond shells stimulates the activities of specific species (e.g., *Pseudomonas* spp.) acting as biocontrol agents in avocado crops and enhanced the suppressiveness of soils against the pathogen *Rosellinia necatrix*.[85,86] Similarly, Tomihama et al.[87] used rice bran-based organic fertilizers for the amendment-induced disease suppression of the pathogenic *Streptomyces* spp. causing potato common scab disease frequently detected in long-term potato monocultures. The reduction in the disease was associated with the increase in the relative abundance of antagonistic actinomycetes against *Streptomyces* spp. producing the virulent phytotoxin, thaxtomin A. Beyond biostimulation approaches, bioaugmentation formulations have successfully been used in the forms of pure cultures, artificial mixed cultures or undefined, complex microbial communities (i.e., soil transplantation). In both greenhouse and field experiments, specific plant growth-promoting rhizobacteria (PGPR) in isolation or in polycultures induced systemic resistance to black rot in Chinese cabbage.[88] In this regard, PGPR strains are already commercially available for broad-spectrum disease suppression, such as Kodiak (*Bacillus subtilis* GB03) (Gustafson, Inc, Plano, TX, USA) for biological control of *Rhizoctonia* spp., *Fusarium* spp., and *Aspergillus* spp. or Serenade (*B. subtilis* QST 713) (Bayer CropScience, Germany) for suppression of *Botrytis* spp., *Sclerotinia* spp., *Xanthomonas* spp., and *Erwinia* spp. Furthermore, Liu et al.[89] showed that the use of mixture of different beneficial strains can exhibit higher level of biocontrol of multiple plant diseases and plant-growth promotion than each strain in isolation.

The whole microbial community from a healthy soil can also be transplanted to a disease-conducive soil in order to restore the soil microbiome to a healthy state and prevent the use of insecticides.[90,91] In a six-year-old field experiment, Wubs and colleagues showed higher plants biodiversity and ecosystem health after healthy soil transplantation to a dysbiotic one.[92] Similarly, the total foliar microbiome transplant from healthy mint species onto fungicide-dependent threatened plants, resulted in significant disease reduction thanks to the establishment of beneficial communities of endophytes.[93]

Plant diseases, especially in the phyllosphere, can also be controlled by bacteriophage therapy. Phages are very specific toward bacterial hosts. Therefore, by exploiting this predator (phages) - prey (bacteria) interaction, bacteriophages can be used to selectively modify the composition of microbial communities. This approach has found applications in controlling bacterial plant diseases[94] and tailor-made phage cocktails can be used to selectively remove specific disease-causing bacteria.[95]

6.03.4.1.4 Human-Associated Microbiomes

Like in soil or plants, the human microbiome can be manipulated using selection or propagule pressure. The human microbiome has a crucial role in ensuring host health and preventing diseases,[96] and *in situ* human microbiome manipulation is especially applied on the gut microbiome for treatment of diseases. Prebiotics administration (molecule-based) represents an effective strategy to promote gut health by stimulating beneficial gut bacteria (e.g., soluble corn fiber stimulates *Bifidobacteria*[97]) and preventing pathogenic bacteria from invading the gastrointestinal tract. BiomeBliss, from MicroBiome Therapeutics (New Orleans, LA), has recently been launched as clinically-tested prebiotic blends made with natural plant-based ingredients (i.e., polyphenol antioxidants from blueberries; inulin from agave and beta-glucan from oats) that ensure nourishment and protection of human gut microbiome. Another example of molecule-based therapeutics, which successfully completed Phase I clinical study, is the EB8018 (Enterome)[98] for the treatment of the Crohn's disease, a chronic inflammatory disease of the gastrointestinal tract.

On the other hand, the use of probiotics as cells-based approach represents a very remarkable strategy to treat inflammatory (e.g., ulcerative colitis), metabolic (e.g., obesity), and infectious (e.g., *Clostridium difficile* infection (CDI)) diseases directly or indirectly associated with dysbiosis of gut microbiome.

The use of probiotics to treat gastro-intestinal diseases encompasses two main approaches which differ in the way probiotic formulations are designed. The first approach relies on fecal materials of healthy human donors to benefit from human commensal bacteria with or without preliminary enrichment. The second approach involves the rational design of synthetic consortia from pure microbial collections without the need of direct sourcing of healthy fecal materials.

Within the first approach, the colonic microbiota present in stool specimens from healthy, screened human donors can be either directly transferred to sick patients (Faecal microbiota transplants (FMT)) or first screened and purified before patient

administration. FMT has shown highly successful cure potential for patients with recurrent CDI.[57,99] In fact, the reestablishment of intestinal microorganisms after healthy donor-feces infusion (in particular, *Bacteroidetes* and *Firmicutes* species), resulted in an increase in microbial diversity and guaranteed colonization resistance against CDI.[100] Moreover, the use of freeze-dried oral capsules for FMT represents a new promising method of administration compared to the traditional ones (i.e., colonoscopy, nasoduodenal infusion and enema), often inconvenient for patients.[101] Despite FMT effectiveness, there is still some concern regarding the transferring of uncharacterized members with undesired functions, potentially risky for the recipients. Colonic microbiota from stool specimens can be screened and purified from undesired microorganisms to end up with a safer feces-derived community. For example, Seres Therapeutics (Cambridge, MA) developed SER-109, a stool-derived oral microbiome therapeutic for the prevention of CDI in adults with multiply recurrent CDI. SER-109 is composed of nearly 50 encapsulated species of *Firmicutes* spores fractionated from stool specimens in which vegetative microbiota were eliminated with ethanol.[102] SER-109 is currently in a Phase III clinical study. SER-287 (in a Phase Ib study, Seres Therapeutics) is another example of a microbiome therapy containing a consortium of live bacterial spores for the ulcerative colitis and other forms of inflammatory bowel disease treatment.

The second approach involves the rational design of probiotic formulations whose composition is based on the prevalence of commensal bacteria in healthy individuals. It is a fermentation-based approach which enables standardized and scalable modular manufacturing and bypasses the need for fecal donor material, reducing patient risk of transmission of potential pathogens. Examples of rationally-defined consortium of human microbiome-derived bacteria are SER-262 (Seres Therapeutics), VE303 (Vedanta Biosciences, Cambridge, MA) and Evivo (Evolve BioSystems, Davis, CA). SER-262 (Phase Ib clinical study) is a rationally-defined mixture of spores from 12 different bacterial species, manufactured using anaerobic fermentation for the prevention of recurrence of CDI. VE303 is another rationally-designed consortium in powder form constructed out of commensal bacterial strains from healthy humans to restore gut microbiome resistance against pathogens, including *C. difficile*. Evivo (Evolve BioSystems, Davis, CA) is the first clinically-proven probiotic for babies which helps to release nutrients in breast milk and creates a protective environment in new-born gut microbiome, improving its function.[103,104] It contains lactose and activated *Bifidobacterium longum* subsp. *infantis* EVC001, selected for its ability to digest the full breadth of human milk oligosaccharides (HMOs).

Successful manipulations of non-gastrointestinal, human microbiomes have also been achieved by several biotechnological companies. For example, AOBiome Therapeutics (Cambridge, MA) released Mother Dirt, a skin cosmetic containing beneficial ammonia-oxidizing bacteria (AOB) that naturally populate skin microbiome. The product application ensures the restoration of skin microbiome undermined by soaps and other personal care products.

6.03.4.2 Applications in Open Engineered Ecosystems (*Ex Situ*, *In Vivo* Manipulation)

Through environmental and ecological engineering, microbial community can be manipulated in engineered, open ecosystems in which operational parameters and process configuration can act as selective forces on the community. These selected microbial communities find applications especially in environmental biotechnology and biorefinery processes.

A typical example is represented by the aerobic granular sludge (AGS) technology for wastewater treatment. Aerobic granules are dense and compact engineered microbiomes generated from stress-induced microbial self-immobilization,[105] which allows simultaneous removal of carbon, nitrogen, phosphorus and other contaminants in a single reactor unit with significant space and cost savings.[106] The aerobic granulation can be initiated by different selection pressures carried out in sequencing batch reactors (SBRs), such as starvation conditions, the decrease of settling time and hydraulic retention time (HRT) or the increase of hydrodynamic shear forces. Alternating anaerobic-aerobic phases combined with high shear force and short settling time are strong selective forces for the formation of granules containing (i) an anoxic/anaerobic core for denitrifying, anaerobic ammonium oxidation (Anammox) and polyphosphate-accumulating (PAOs) organisms, (ii) an intermediate layer for denitrifying microorganisms and (iii) the outer layer occupied by nitrifiers and heterotrophic, aerobic bacteria involved in the organic matter degradation.[45]

In water resource recovery facilities, clean water production is coupled to the maximization of resource recovery and production of value-added by-products such as biopolymers or biofuels. An example is the production of polyhydroxyalkanoates (PHAs), microbial storage polymers, obtained from renewable resources.[107] Open mixed microbial cultures are enriched for PHA-storing bacteria by providing a selective pressure within the process called the feast and famine strategy: during the feast period, the microbes are exposed to high concentration of short fatty acid (VFAs) which are assimilated and stored into polymers; during the famine period the bacteria consumed the stored substrates to gain energy for the growth.

Finally, high rate algal ponds (HRAP) are open, paddlewheel-mixed, raceway ponds designed for wastewater treatment and resource recovery in the form of microalgal biomass for use as protein-rich feed or biofuel production.[108] They offer an efficient and cost-effective replacement of traditional waste stabilization pond systems (WSPs) or conventional wastewater treatment technologies.[109] Their performance relies on a mutualistic interaction between bacteria and microalgae with the latter releasing oxygen that is immediately available to bacteria to oxidize the organic content. Thanks to the mechanical mixing through paddlewheels, non-motile colonial algal genera (e.g., *Micractinium*, *Pediastrum* and *Scenedesmus*) can grow and form large microbial flocs with a diameter greater than 100 μm, allowing an easy and cost-free harvesting by gravity sedimentation.[109] Furthermore, other operational factors can be appropriately chosen to improve algal productivity, such as higher ponds depth, shorter hydraulic retention time, recycling algal biomass or CO_2 addition.[110–112] In HRAP treating municipal wastewater, high microalgal diversity with multiple functional traits has also been shown to stabilize the microalgal biomass productivity thanks to the mutualistic adaptation to fluctuating environmental factors.[113]

6.03.4.3 Applications in Confined Environment (*Ex Situ*, *In Vitro* Manipulation)

The use of *in vitro* biodiversity manipulation has been carried out in confined environments (typically bioreactors) to develop the full potentialities of microbial activities under defined conditions to reach more controllable outputs and reproducible functional outcomes. The construction of gnotobiotic (or synthetic) ecosystems from known microbial populations ensures reduced complexity, higher reproducibility and controllability of their dynamics. This strict *in vitro* bottom-up approach is complemented by the enrichment or community culture method that generates interacting and simplified microbial communities under controlled environmental conditions able to catalyze a desired functional trait through artificial selection. Synthetically-assembled communities and artificial selection of microbial communities both hold great promises in biorefining and industrial processes.

To improve the enzymatic hydrolysis of lignocellulosic materials, the application of organic salts (ionic liquids (ILs)) is a promising eco-friendly pre-treatment process. The use of ILs involves subsequent washing steps to remove the residual salt that causes enzymatic inhibition in the following steps of lignocellulose hydrolysis. The use of halotolerant lignocellulose-degrading microbial consortia, with their associated enzymes, has been proposed as an alternative approach to reduce the bio-process costs. For this purpose, stable bacterial consortia for lignocellulose degradation under saline conditions has been artificially constructed by enriching a salt marsh soil microbiome on wheat straw, through the dilution-to-stimulation method.[114] In another example to valorize the cellulosic fraction of lignocellulose, a sludge sample collected from an anaerobic digester was artificially selected (dilution-to-stimulation method) to end up with an anaerobic consortium able to produce hydrogen from different cellulosic feedstocks.[115]

In the last decade, synthetic communities have been constructed for several practical applications spanning from the production of bioenergy to nutraceuticals or drugs. For instance, bioelectrochemical systems (BESs) are electrochemical cells that use microorganisms attached to electrodes as biocatalysts to perform oxidative (bioanode) and/or reductive (biocathode) reactions. A BES is called a microbial fuel cell (MFC) if it produces net electrical power and is called a microbial electrolysis cell (MEC) if electrical power is provided to allow a certain reaction, otherwise not thermodynamically favourable.[116] Liu and colleagues designed and constructed a synthetic three-species microbial consortium for electricity generation from sugars.[117] Two fermenting species (engineered *E. coli* and *B. subtilis*) were used to produce lactate and riboflavin as a carbon source and an electron shuttle, for the exoelectrogenic *Shewanella oneidensis*. The consortium produced stable power generation for up to 15 days with energy conversion efficiency over 50%. Likewise, using CO_2 and voltage source, synthetic co-cultures of Fe(0)-corroding strain IS4 with *Methanococcus maripaludis* or *Acetobacterium woodii* could perform hydrogenotrophic synthesis of methane and acetate, respectively.[118]

Another promising application of synthetic communities is the production of medium-chain carboxylic acids (MCCAs) and higher alcohols by fermentative synthetic cultures grown on syngas, a waste-derived mixture of CO, H_2, and CO_2, generated from gasification of renewable carbonaceous feedstocks. For example, Diender et al.,[119] using synthetic co-culture of *Clostridium autoethanogenum* and *C. kluyveri*, produced a mixture of C_4 and C_6 fatty acids and their respective alcohols using solely CO or syngas as a substrate.

A typical use of synthetic microbial consortium in the production of nutraceuticals is the one consisting of *Ketogulonicigenium vulgare* and *Bacillus megaterium*. This co-culture has been widely used in industry for the production of 2-keto-L-gulonic acid (2-KLG), the immediate precursor of vitamin C.[120] By integrating system biology analyses (i.e., time series metabolomic and metaproteomic profiling), it was revealed that the sporulation and cell lysis of *B. megaterium* facilitated *K. vulgare* to grow better and produce more 2-KLG.[121] Using four-cooperating engineered *E. coli*, Jones and colleagues developed a synthetic consortium collectively expressing 15 different enzymes and transcription factors for the *de novo* production of the anthocyanin molecule, calistephin. This cell-based compartmentalization strategy allowed the division of the biosynthetic labor and the reduction of the metabolic burden across the community members.[5] Another example of microbial partnership for metabolic pathway division is the co-culture of *E. coli* and *Saccharomyces cerevisiae* for the production of oxygenated taxadiene from xylose as sole carbon source. The presence of *S. cerevisiae* guaranteed an efficient cytochrome P450 expression for monooxygenase-catalyzed bioconversion. Moreover, the authors developed a mutualistic carbon-source model to ensure a stable and controllable microbial composition.[122]

Finally, synthetic communities can be employed to enhance or induce the production of antimicrobial peptides. For example, co-cultivating *Lactococcus lactis* with the yeast *Yarrowia lipolytica* resulted in higher nisin production by *L. lactis* thanks to the presence of the yeast that consumed the inhibiting lactic acid.[123] Likewise, co-culture of *Streptomyces* sp. PTY087I2 with different human pathogens (i.e., *B. subtilis*, *Staphylococcus aureus* and *P. aeruginosa*) resulted in increased production of three antibiotics, i.e., granaticin, granatomycin D, and dihydrogranaticin B.[124]

6.03.5 Conclusions

Microbial communities represent a unique and irreplaceable resource. They have a critical role in protecting and enhancing human health, crop production or regulating biogeochemical fluxes of the major elements of the biosphere. The advances in microbiome-based technologies, environmental engineering and synthetic microbial ecology have paved the way for biodiversity engineering and the possibility to harness and control microbial communities in their natural environments, in open, engineered ecosystems or in confined environments. Over the last years, different strategies have been developed to manipulate and modulate microbial communities *in vivo* or to assemble individual microbial populations *in vitro*. These strategies have found their applications in different sectors, spanning from industrial and environmental to plant and medical biotechnology.

The challenges that humanity is facing in the 21st century gave several initiatives to improve our knowledge on microbial community activities and dynamics and exploit their full potential (e.g., Unified Microbiome Initiative (UMI); International Microbiome Initiative (IMI), Earth Microbiome Project).[125–127] Current issues such as increased food demand, environmental degradation, shortage of natural resources, pollution and plant/human diseases can now be tackled by manipulating microbiomes present in their natural ecosystems (e.g., *in situ* rhizosphere microbiota manipulation for increased crop yield or defense against pathogens) or by exploiting defined consortia in confined environments (e.g., use of defined consortia for production of fuels and chemicals starting from carbon-based renewable materials).

Thanks to the recent advances in molecular systems microbiology and the development of new-generation technology platforms for high-resolution microbial ecology studies, a collaborative, cross-disciplinary research effort, from ecological to bioprocess and metabolic engineering, will pave the way for predictable microbial diversity manipulation and new microbial-driven solutions to tackle the current environmental challenges we are facing at the nexus of food, water and energy.

See Also: 6.04 Functional Microbial Landscapes; 6.13 Bioaugmentation of Chlorinated Ethene-Contaminated Groundwater.

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