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Review

Multifaceted Applications of Synthetic Microbial Communities: Advances in Biomedicine, Bioremediation, and Industry

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Abstract: The broad range of applications offered by synthetic biology and bioengineering has revolutionized the ability to design and redesign microorganisms to express specific functions, overcoming the limitations of natural biological systems. This advancement has been achieved through the use of mathematical models and genetic circuits, enabling the precise design of synthetic microbial communities. These are defined as artificially created communities through co-cultures of selected species that share similar characteristics and environments. Reprogramming an organism is carried out by inserting synthetic genetic circuits, which are designed in a controlled manner to obtain biotechnological products beneficial to humans, their health, and the environment. The potential applications in medicine, bioremediation, industry, and pharmaceuticals make the research of synthetic microbial communities a promising field for the future. However, the implementation of synthetic microbial communities carries potential risks, such as horizontal gene transfer and possible environmental impacts. It is crucial to carefully evaluate these functions and risks, considering biocontainment and the associated ethical and ecological implications.

Keywords: synthetic biology; microbial communities; bioengineering; genetic circuits

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1. Introduction

Microbial communities consist of diverse species interacting either individually or in multicellular aggregates. The collective functional capabilities of these communities are shaped by the interactions between individual cells within them [1]. Such interacting microbial populations, known as consortia, can evolve or develop new biological activities that impact their environment [2]. Leveraging the nature and adaptability of these communities holds promise for applications such as biofuel production, fine chemical synthesis, pharmaceuticals, and bioremediation [3]. Consortia are more effective than monocultures, because they enable the division of labor among populations, enhancing resilience against environmental changes and invasion by single species [4]. This division of labor reduces the biosynthetic burden and metabolic stress on individual microorganisms, while the coordination of nutrient availability and signal transduction supports specialized roles within the ecological network [5].

Synthetic biology is a design-driven discipline focused on engineering novel biological functions through the discovery, characterization, and repurposing of molecular parts. Synthetic biology is being used to create synthetic microbial communities, which are defined as

an artificial community created by mixing different selected species [6], designed to act as a model system that evaluates the roles of ecological, structural, and functional characteristics in a controlled manner [7,8]. That is why several applications of synthetic biology are found in vaccine development, molecular diagnostics, and cell-based therapeutics, emphasizing the technologies approved for clinical use or in active clinical trials [9].

Synthetic bacterial communities are of great importance for the study of microbial and ecological evolution, as they allow for rapid iteration between controlled laboratory experiments and theoretical models [10]. These communities have been used to compare different consortia that perform the same function, for example, the degradation of harmful molecules or their detection [8,11], the reduction of toxic compounds, and the measurement of their stability and long-term performance [7].

Synthetic biology and microbial communities represent rapidly advancing fields with significant implications for medicine, bioremediation, and industry. However, there is a lack of comprehensive reviews that consolidate recent developments and highlight practical applications while addressing ecological and ethical considerations. This article aims to fill this gap by providing an in-depth review of synthetic microbial communities, focusing on the use of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology, multifaceted applications, and practical implementations. The first section reviews the latest advancements in synthetic biology and microbial interactions. The second section discusses methodologies and tools used to design synthetic microbial communities, with a special emphasis on CRISPR technology and its advantages. The third section examines the applications of synthetic microbial communities in various fields such as medicine, bioremediation, and industry. The final section addresses the practical implementation of these communities, including risk assessment and biocontainment strategies.

2. Definition and Importance of Microbial Communities

2.1. Synthetic Microbial Communities

In 2012, Bernstein and Carlson defined synthetic microbial communities as "those composed of two or more populations of metabolically modified cells" [12], and these communities, unlike natural ones, are made with functions and complexities that are not present in natural ones, allowing for the generation of defined systems, meaning they develop functions that are not naturally present [8]. Likewise, they have the ability to maintain their stability and are used to study the necessary conditions in interactions with environmental competition and how their structure, function, and evolution react as complex dynamic systems [13].

The purpose of designing a synthetic microbial community is to produce a model community, focusing primarily on precision in selecting the species that will be part of that complex community, paying attention to the levels of diversity and their genetic and biological characteristics, such as cell adhesion, biomass production, substrate consumption, enzymatic activities, and the expression of their 16S rRNA phylogenetic markers [14,15]. A model community is one that represents or mimics the systemic behavior of natural communities, but under controlled and isolated conditions. A successful model community should resemble the target ecological community, be representative, and meet the four criteria that evaluate its suitability: (1) accessibility (ability to transplant the community from natural environments to controlled laboratory conditions); (2) manageability (describes the manipulability and controllability of community phenotypes); (3) stability (reproducibility of community phenotype and dynamics and long-term stability during propagation under laboratory conditions); and (4) reduced size (it should be as small as possible, though of sufficient size, to capture the effects of interest) [13].

A community can be more resilient to environmental challenges because of its division of labor and lower metabolic burden [16]. Therefore, organism engineering expands along with its capabilities, such as transferring amounts of DNA from one organism to another, since the pathways, precursors, and cofactors are known with greater specificity. It is known that enzymatic and protein machinery works to its own advantage if used correctly.

The design and improvement in efficiency at the organelle level depend on extra- and intracellular factors, which improve the catalytic efficiency and controllable biosynthesis, an example being the improvement or modification of the cell wall, which performs protein-based synthesis and increases the cell yield, affecting the physiological state and chemical production [3]. Therefore, biotechnological strategies eliminate unwanted phenotypes, metabolic pathways, and improve the cellular and consortium synthetic capacities.

Diversity can be manipulated in a designed community, allowing for the development of its structure and function in a controlled manner, and is influenced by local environmental stimuli and spatio-temporal changes [17], which are useful not only for maintaining community stability but also for developing and defining possible control points and bottlenecks [8], which also allow for visualizing and measuring the scope of its function.

2.2. Artificial Communities

Artificial communities are constituted by populations of wild communities that do not naturally coexist; therefore, their interaction is facilitated by the introduction of one community to another, either in the laboratory or under controlled conditions, enriching each other [13]. Microbial communities allow vegetation to exude substances from their roots that favor the presence of other microorganisms, forming consortia and functioning as an immune system against pathogens. Among the promoter bacteria that are artificially used in other cultures as biological nitrogen fixers are *Rhizobium* sp., *Bradyrhizobium* sp., *Azospirillum* sp., *Pseudomonas* sp., and *Agrobacterium* sp. [18,19].

These communities have a wide variety of functions to exploit, such as clinical, industrial, and environmental applications. A clear example is the transplantation of fecal microbiota from healthy donors and the reduction of diesel fuels or aromatic hydrocarbons, but with less efficiency than required for industrial processes [20].

Therefore, it is necessary to deduce and understand the eco-physiology of each population to which another will be introduced. Given the possible interactions that these consortia may have, they have been used in various areas such as renewable energy, bioremediation, or food processing [14], allowing for work with cultures of two or more microbial strains. Some are mutualistic symbionts of plants, such as nitrogen-fixing bacteria or mycorrhizal fungi, which play a fundamental role in nutrient cycles and soil organic regulation, allowing for the increased volume and efficiency of nutrient absorption by vegetation, improving plant health [21].

2.3. Semi-Synthetic Communities

Semi-synthetic communities are composed of metabolically modified communities that regulate or modify their metabolism and communities that are naturally in the environment. Both communities interact with each other, and both benefit through cooperation and task distribution [22], manipulating their genetic content, or by modifying their metabolism according to their type of interaction [12].

Bengtsson-Palme divided model systems based on criteria such as the following: whether they are of natural or synthetic origin, whether members lack the ability to produce essential metabolites produced by other consortium members, by the number of species, and their type of interaction. He did this to create two types of model communities: those based on synthetic mutants of multiple species and semi-natural communities [23].

The first hybrid systems, composed of wild and modified populations, were implemented for a microbial consortium consensus and used *E. coli* SD2 and *P. aeruginosa* in biofilms, where the microenvironment was manipulated with mutualism interaction. These were used because *P. aeruginosa* has the ability to form biofilms in the lungs of cystic fibrosis patients, and both bacterial species needed to be present at appropriate population densities; neither population could respond without a signal from the other. This characteristic was used as a logical gate; the input was the cell quantity of the two populations. Two genetic circuits (A and B) were used. Circuit A is powered by circuit B, and the output of circuit A forms a complex to activate a promoter that expresses the desired gene. The

quorum sensing (QS) components, LasI/LasR and RhlI/RhlR from *P. aeruginosa*, were used to detect the population density in their environment, catalyzing acyl-homoserine lactone (acyl-HSL) molecules, 3-oxododecanoyl-HSL, and butanoyl-HSL [24].

The regulator in circuit B is LasR and is activated by 3-oxododecanoyl-HSL, which is in turn emitted by circuit A. RhIR in circuit A is activated by the presence of butanoyl-HSL, which is produced by circuit B and catalyzed by RhlI. When acyl-HSL concentrations were low, the cell densities were reduced, but they increased as the densities of cells from circuits A and B increased. When the concentrations were high in both circuits, they produced a consortium response, corresponding to the emission of red and green fluorescence. This type of expression is tailored to minimal isolated expression, where no bacterial species can generate a response without a signal from the other, preventing a single population from self-activating in isolation.

Other communities are used for metabolic exchange. QS or resource-partitioning communities are constructed as artificial ecosystems with broad bioprocess technology potential for consortium engineering with environmental relationships, distribution, and species abundance [15], or they are constructed to be used as catalysts for the synthesis of more compounds of interest or in the identification of genes for morphological changes as in the case of *Synechococcus elongatus* and other bacteria, where researchers observed the reaction of overexpression or elimination of the morphological proteins FtsZ and MreB for possible use in morphological engineering for their systematic calculation and comparison [25], leading to minimized cells and imbalanced proportions in fusiform cells until flexible and controllable cell length regulation was achieved.

3. Interactions in Microbial Communities

In microbial communities, populations or organisms interact either cooperatively or competitively, leading to positive, negative, or neutral effects [26,27]. Figure 1 illustrates six possible microbial interactions within synthetic microbial communities; the color difference denotes different microbial strains, and the circles represent metabolites. It is a way to analyze the behavior between species and how one affects the other, which can drive their functions and community structure [8,26]. These interactions include symbiosis, where both microbial partners benefit, which is fundamental for cooperative metabolic exchanges and enhanced community stability. Commensalism involves one organism benefiting while the other is unaffected, often seen in nutrient-sharing scenarios [8], either at the level of promoters or signaling, by using QS systems, which is when a sufficient amount of the cell population or signal molecules accumulate; cells perceive this density around them, and cooperative intercellular communication takes place [21], which is linked to gene expression or toxins [16]. Competition occurs when microorganisms vie for limited resources, which can drive evolutionary adaptations and influence community structure. Predation, where one organism preys on another, helps control population sizes and maintain ecological balance. Amensalism describes a relationship where one organism is inhibited or destroyed while the other remains unaffected, often through the production of antimicrobial compounds. Lastly, no interaction signifies the coexistence of microorganisms without direct influence on each other, which can occur in highly diverse communities with niche differentiation [28].

A study investigating microbial community interactions explored the deodorizing capacity of *Lactobacillus paracasei* B1 in an airborne microbial community. *L. paracasei*, a bioagent composed of lactic acid bacteria (LAB), reduced airborne ammonia by 96.8% and sustained this effect for over 3 h. It also induced changes in the microbial community structure, resulting in a reduced diversity of pathogenic bacteria and their dissemination in the air. This mitigates the health risks associated with air pollution, establishing a foundation for applying and developing this bioagent to purify compost [29]. Metagenomic analyses have shown that the application of microbial inoculants and liquid obtained from compost fermentation resulted in reduced nematode diseases and decreased arsenic levels in the rhizosphere of Panax quinquefolium cultivation [30].

These interactions collectively contribute to the robustness and functionality of synthetic microbial communities, and understanding them is crucial for optimizing the community design for various applications [31].

An example of interaction in implemented consortia is seen between *Synechoccocus elongates* and *Pseudomonas putida*, where *S. elongates* produces sucrose from CO_2 and light, which *Pseudomonas* utilizes. *P. putida*, in turn, degrades and detoxifies 2,4-dinitriotoluene (2-4-DNT) while producing polyhydroxyalkanoates (PHA). Therefore, the optimization objective focuses on maximizing sucrose production in the presence of 2-4-DNT. Another example involves *Escherichia coli*, which uses glucose to produce acetate, a substrate that *Acinetobacter baylyi* consumes. Here, the optimization goal is to maximize biomass accumulation with *E. coli* while minimizing acetate levels [26]. In another example, the study examined how a synthetic microbial community, including bacteria and ectomycorrhizal fungi, contributes to phosphorus (P) acquisition and impacts the growth and productivity of *Pinus tabulaeformis* plantations under P deficiency. The synthetic microbial community was used to enhance the available P, alkaline phosphatase activity, root P concentration, and superoxide dismutase activity, thereby alleviating P stress. The study underscores the importance of microbial interactions for plantation management and development [32].

Given the above, interactions within synthetic communities are crucial for the design of genetic circuits. As previously mentioned, creating and designing a community is more complex than working with an individual organism. Therefore, understanding interactions not only within a single species but also among different species is essential [33].

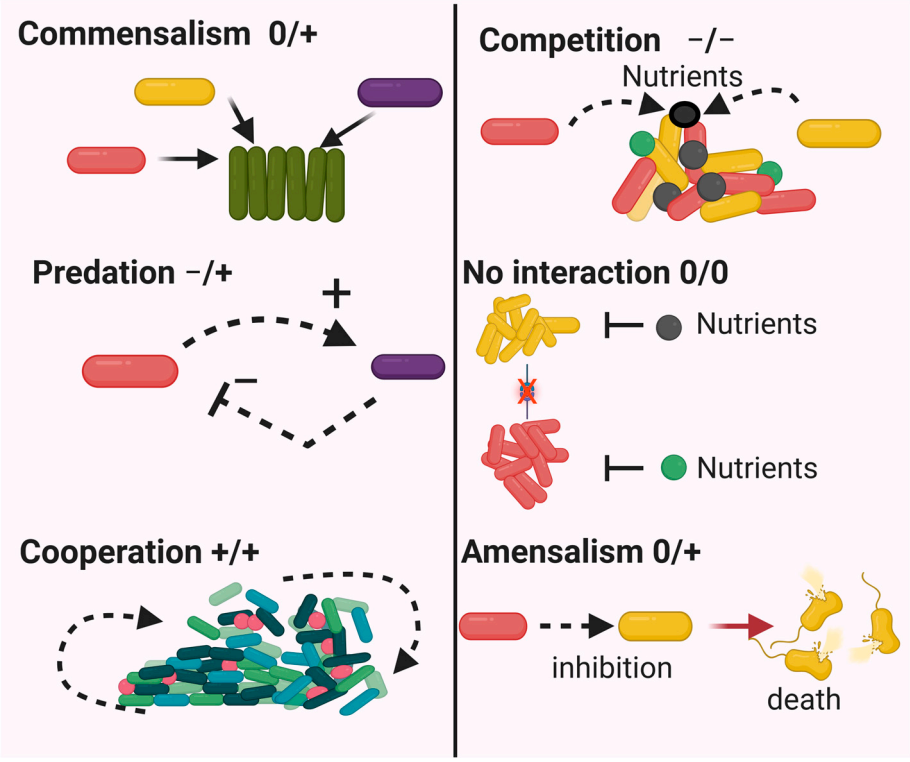

Figure 1. Microbial interactions. The six possible microbial interactions are depicted: commensalism, where one species benefits without harming the others; competition, where two or more organisms attempt to use the same nutrients or occupy the same niche; predation, where one organism benefits at the expense of another; no interaction, where organisms do not interact, benefit, or harm each other; cooperation, where organisms benefit from cooperation to increase their survival and individual abilities; and amensalism, where one microorganism damages another while suffering no alteration itself, and the antagonism of one affects the other.

4. Methodologies and Tools in Design of Synthetic Microbial Communities

Motivation for research lies in the creation of theoretical and experimental models to link them to natural systems and, thus, combine them with natural species without altering their metabolic networks, harnessing their full potential.

The primary use of synthetic microbial communities is in biotechnology; they have also been used for waste treatment in agriculture, fuel production, medicine, and biomaterials. However, for their construction and behavior programming, it is necessary to create new tools that can be used for building these synthetic communities [16]. Their application has led to the use and characterization of species from natural communities inhabiting different ecosystems and systems, even the human gut [34].

Different standards have been proposed to facilitate the certification of chassis organisms by compiling data on the following: their genomic sequence, capacity to evolve, efficacy on target, genetic stability (recombination, mutation, or insertion capacity), durability, phage and antibiotic sensitivities, traceability, antigenicity, energy metabolism, stress resistance, gene transfer capacity (donor receptor), and environmental conditions for their resistance, providing a profile for specific safety classifications and a standardized chassis. Furthermore, for specific control of the chassis organism, applying a genomic barcode to have control over synthetic organisms enhances the safety, traceability, and management of potential contingencies, as well as provides a catalog with specific information for each organism, making it more accessible. The study by de Lorenzo addresses specific points and problems that may arise from applying bio-orthogonal barcodes and possible chassis [35].

The tools are not limited to genetic modifications and can also be adjusted to environmental conditions [36] or add exogenous molecules like antibiotics or bacteriocins to control gene expressions [16]. As each organism depends on and relates to its environment, microbial communities exhibit improvements that monocultures do not, such as resistance to invaders, greater robustness to environmental disturbances, or better metabolic function to improve growth rates [31,37]. To resist these exogenous molecules, they encode and express inducers or signaling molecules in their genetic machinery to generate positive or negative interactions [38] that alter the expressions of specific genes by adjusting the concentrations of exogenous molecules [39]. However, to enable the precise control and design of microbial interactions for desired outcomes, the use of synthetic biology methodologies and tools is crucial for the creation of new genetic circuits in synthetic microbial communities. Here, we provide a brief overview of some of these application areas.

4.1. Computational Models

The design and testing of synthetic microbial communities involve several methodologies, including the use of genetic circuits and mathematical models. These communities are assembled using automated platforms that generate candidate systems from a set of genetic parts. The design process involves computational modeling to predict the behavior of microbial interactions and to select optimal configurations based on stability and performance criteria. Testing these communities often requires iterative cycles of model refinement and experimental validation. Comparative studies with natural microbial communities are conducted to assess the ecological relevance and performance of synthetic systems [40]. Based on computational models, syntrophic consortia are designed that predict genetic and metabolic networks based on the resource growth requirements [41,42], metabolic capabilities, and metabolite exchange rates of each microorganism, predicting how the system will behave [16].

Dynamic models track the consortium variables over time from initial values and behavior rates [41]. They predict how the population of each consortium member would change in response to a given stimulus or under a parameter that disturbs the system [16]. Modeling microbial communities aims to describe and predict the dynamics between species [17] without describing their intracellular metabolisms.

Designing synthetic consortia to execute complex tasks for the previously discussed applications requires navigating a complicated network of organisms and interactions

over time and space, a challenge that surpasses empirical methods. Computational techniques and mathematical modeling tools are essential for addressing these challenges and revealing aspects of microbial communities that are experimentally inaccessible. These models are fundamental in exploring ecologically and evolutionarily pertinent questions, such as assessing the effects of inter-species interactions and environmental factors on the emergence of cooperation, the coexistence of cooperators and cheaters, and the evolutionary outcomes of communities. Additionally, they are crucial for the rational design of synthetic consortia tailored for specific applications. The most commonly used techniques for modeling microbial communities are as follows: ecological theories of inter-species interactions (resource ratio theory and maximum power principle), population dynamics model, spatial modeling, individual-based modeling, genome-scale metabolic network modeling, steady-state model, dynamic models, and spatial–temporal models [43].

Microfluidic droplets are used to study the dynamics and functions of microbial communities, where a mixed culture is encapsulated in droplets, generating a controlled space for study. Microbial interaction networks in droplets (MINI-Drops) have been developed with automated computational methods coupled to microscopy and fluorescence [44]. This resulted in a spatial visualization method for microbial community interactions and their dispersion in mixed cultures.

Mathematical models are used for the design and modeling of adhesion molecules. Genetically modified adhesion molecules can be used to program or induce three-dimensional multicellular morphologies. These are regulated on the cell membrane, forming cell-to-cell or cell-to-extracellular matrix interactions, allowing for the creation of specific orthogonal formations to form different multicellular aggregates with varying morphologies, such as fibrous, spheroidal, or mesh-like structures [45]. This serves to create the desired materials that mimic the desired morphologies in biological systems, up to bacterial imprints or lithographies. For instance, Jin and Riedel-Kruse used *E. coli* for light-controlled promoter expression, producing proteins that adhered in biofilms to form lithographies at 25 μm [46]. This example illustrates that by programming and utilizing synthetic biology, one can define the space and position of cells wherever desired, controlling their morphology, functionality, signal transduction, and localization [16].

4.2. Importance of Genetic Circuits in Microbial Communities

A genetic circuit consists of an input, a coding sequence that reacts based on the input, and an output or terminator that provides the signal to terminate transcription and produce a functional protein. Different types of genetic circuits exist, such as the toggle switch [47] and oscillator types [48] as well as QS or autoinduction types, which are mechanisms of gene expression regulation based on a certain cell population size [49].

Genetic circuits are engineered to control microbial behaviors, while mathematical models, such as agent-based and dynamic models, are used to simulate community interactions and predict outcomes. These approaches facilitate the creation of stable, functional microbial consortia with applications in biotechnology and environmental management [50,51]. Promoters and transcription factors acting as genetic activators or repressors and modulated by chemical inducers have proven to be effective and versatile tools for constructing robust genetic circuits to create synthetic microbial communities [36,52]. Although limitations with promoters have led to the design complexity of networks being low, genetic part libraries and assembly have been created to search for additional orthogonal promoters [53].

The use of DNA assembly in genetic circuits makes this possible along with QS, where the emission and perception of chemical molecules coordinate gene expression responses [54]. By utilizing a signaling molecule, one can ascertain when the receptor of that molecule is activated, triggering promoter transcription in the receiving cell. This can have multiple inputs, activating pathways that regulate other pathways in the presence of external substances within a consortium, which is potentially superior to individual organisms [22]. There are also types of molecules that can be used as promoters or repressors, such as isopropyl-β-D-thiogalactopyranoside (IPTG) or anhydrotetracycline (aTc), which are inducer molecules [55].

Since some expressions serve for the survival or protection of microbial communities, like the expression of resistant genes in the presence of antibiotics (AmpR) [38], organisms with syntrophic exchanges can be designed. Together with the design of organisms with a minimal genome, where non-essential genes are removed [56,57], survival is possible, although it also depends on the resource distribution from other strains within the microbial community [16].

Cooperation between two microbial strains can be designed using synthetic biology, leveraging genetic editing tools to eliminate non-essential genes in each strain or selecting organisms that naturally cooperate with each other. For example, using an organism that produces a product or waste, which inhibits its metabolic reactions when accumulated to a certain level, thus deactivates the expression of some genes [8].

4.3. CRISPR

Another tool in the design of synthetic microbial communities is CRISPR technology [58]. The arms race between viruses and their hosts has driven the evolution of defenses and counterattack mechanisms [59]. One of these defense mechanisms is Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), which were discovered in the genome of *Haloferax mediterranei* [60]. Figure 2 illustrates the mechanism of action of CRISPR/Cas when a bacteriophage infects a bacterium, which was first observed in archaea [61]. This discovery led to the use of this mechanism as a powerful molecular tool for genetic editing [62].

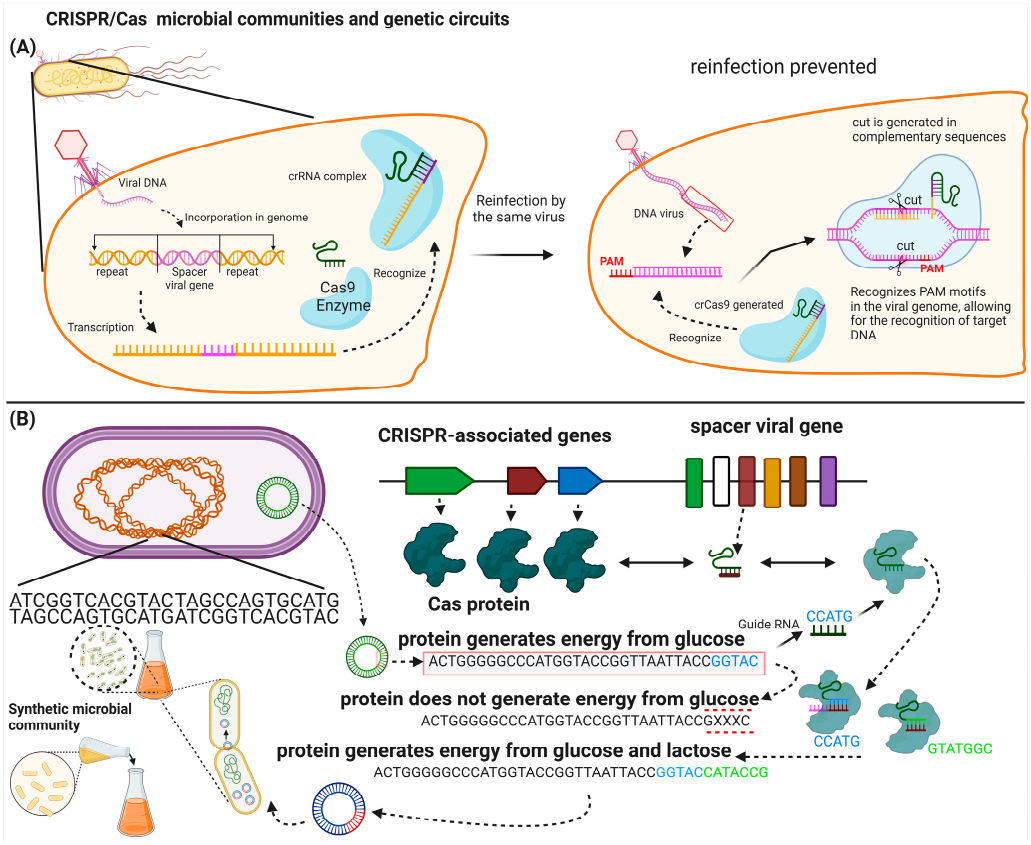

Figure 2. CRISPR technology utilized in synthetic microbial communities. (**A**) Palindromic repeat sequences in specific regions with foreign viral DNA are incorporated into a spacer within the genome of a bacterium, recruited by viral infection, and adhered to the genetic material as a defense mechanism. When encountering a complementary sequence of the virus during reinfection, the viral DNA, along with activated Cas9 protein, cuts the DNA of the reinfecting virus, rendering it useless for repair. Proto-spacer adjacent motif (PAM) sites are fragments that support the recognition and cleavage of DNA mediated by Cas9, located at the 3′ end, initiating DNA matching with the Cas9-directed sequence. (**B**) Design of bacteria generating energy from glucose and lactose. The bacterial

genome of this model organism is altered via CRISPR by creating a plasmid through a genetic circuit. The circuit comprises CRISPR-associated genes and viral spacer genes, generating Cas proteins and a guide RNA for modification. The activated Cas protein with guide RNA cuts at the recognition site and inserts the coding series for the protein of interest. Once the plasmid is ready, it is inserted into a bacterium in a synthetic community for horizontal gene transfer mechanisms.

CRISPR/Cas, as an advance in genetic engineering, has assisted in constructing biological genetic circuits that directly impact metabolic pathways, allowing for the redesign of organism systems and controlling their behavior based on other molecules or co-dependent factors. This precise control over genetic modifications facilitates the creation of microbial strains with optimized metabolic pathways, improving the efficiency of metabolic processes such as biosynthesis, degradation, and energy production. CRISPR's multiplexing capability allows for the simultaneous editing of multiple genes, which is essential for engineering complex traits and interactions within microbial consortia. This ability to modify multiple genetic targets in parallel accelerates the development of robust and stable synthetic communities. Additionally, CRISPR technology significantly enhances the design and implementation of metabolic engineering strategies in synthetic microbial communities, paving the way for innovative applications in biomedicine, bioremediation, and industry [16].

One study reported using the CRISPR-based approach for precise genome editing in complex bacterial communities. The study focused on the bacteria *Escherichia coli* and *Bacteroides thetaiotaomicron*, targeting specific genes such as lacZ in *E. coli* and BT2086 in *B. thetaiotaomicron*, and the researchers successfully demonstrated species-specific editing without disturbing the overall microbial community. Additionally, the ecological studies conducted include manipulating *B. thetaiotaomicron* in the mouse gut microbiome to understand its role in carbohydrate metabolism. This approach highlights the potential of targeted genome editing for studying microbial ecology, with applications in synthetic biology, environmental microbiology, and therapeutic interventions, enabling the precise manipulation of bacterial populations within their native environments [63].

4.4. Quorum Sensing (QS)

Two types of QS are known: Al-1 (acyl-homoserine lactone (AHL)), originally from the bacterium *Vibrio fischeri*, and other species with AHL homologous systems specific to each species, as they recognize and utilize the AHL they produce and multiple QS signals [49,64]. In *V. fischeri*, luminescence production on its cell membrane is controlled, increasing as the cell density rises to a specific amount. The LuxR regulator can be manipulated to control AHL sensitivity by modifying AHL binding sites or controlling the amount of LuxR [64,65]. This system is easy to use, as AHL passes through the cell membrane without needing a transporter.

The Al-2 system uses LuxS to synthesize Al-2 as a byproduct. In *E. coli*, the transporter used is LsrACDB, which is phosphorylated by the LsrK kinase. It then binds to the LsrR repressor, repressing the Lsr promoter regulated by luxs for lsr operon transcription and overexpression of LsrACDB, LsrK, LsrR, and LsrFG. This quickly captures Al-2 until it is depleted and allows LsrFG to metabolize more Al-2. The overexpression of LsrACDB and LsrK also causes rapid extracellular Al-2 absorption. Due to its complexity and transporter usage, the Al-1 system is a better option. However, its complexity also allows for the creation of regulatory control points by modifying or removing specific genes that are overexpressed in the cascade process [64].

5. Applications of Synthetic Microbial Communities

5.1. Biomedicine and Health

Microbial communities within the human body significantly impact physiology and health, performing essential functions. For instance, the human gut microbiota aids in the breakdown of indigestible polysaccharides, which is crucial for immune system development and homeostasis, and provides resistance against pathogenic bacteria [66,67]. Dysbiosis, or shifts in the microbial composition, is linked to numerous diseases, with

studies indicating strong associations between gut microbiota composition and complex diseases such as obesity, atherosclerosis, diabetes, and inflammatory bowel disease. Factors like diet, environment, and age also influence gut microbiota composition and structure [68]. Similarly, the oral cavity hosts complex microbial communities forming dental plaques, leading to diseases such as dental caries and periodontitis [69]. Although there is a growing industry aiming to enhance the health benefits of certain human-associated microbes, the systematic and validated use of synthetic microbial communities for disease treatment is in its early stages but holds significant potential [70]. The development of gut-on-a-chip technology lays the groundwork for constructing synthetic microbial communities to study intestinal physiology, digestive diseases, and drug development [71]. Synthetic ecology can also help in creating synthetic microbial consortia to restore balanced microbiota, such as in treating Clostridium difficile infections with fecal microbiota transplants, which are more effective than antibiotics [72]. Designing SMCs as an alternative to using natural communities from healthy individuals is another promising approach.

Synthetic biology has also become part of cancer treatment research, and in conjunction with genetic technologies, microbial consortia have been developed that can be implemented as suitable and less invasive therapies, where bacterial growth and gene expressions can be controlled [73,74]. Combining synthetic microbial ecology and nanotechnology, compounds like taxol, an effective cancer drug, are developed. Larger quantities are produced through biosynthesis by synthetic microbial communities, which were previously obtained from the barks of *Taxus brevifolia* or *T. baccata* [75] in limited amounts.

One cancer treatment approach is demonstrated in the work of Gurbatri et al., where T cells recognize tumor antigens, as shown in Figure 3, and activate proliferation [74]. However, when binding to PD-1 to PD-L1, they inhibit signaling, leading to reduced proliferation, thus inhibiting the programmed death of the cancer cell. Therefore, blocking CTLA and PD1 signaling is sought to allow T-cell proliferation, reducing immunosuppression and stimulating programmed cell death [76].

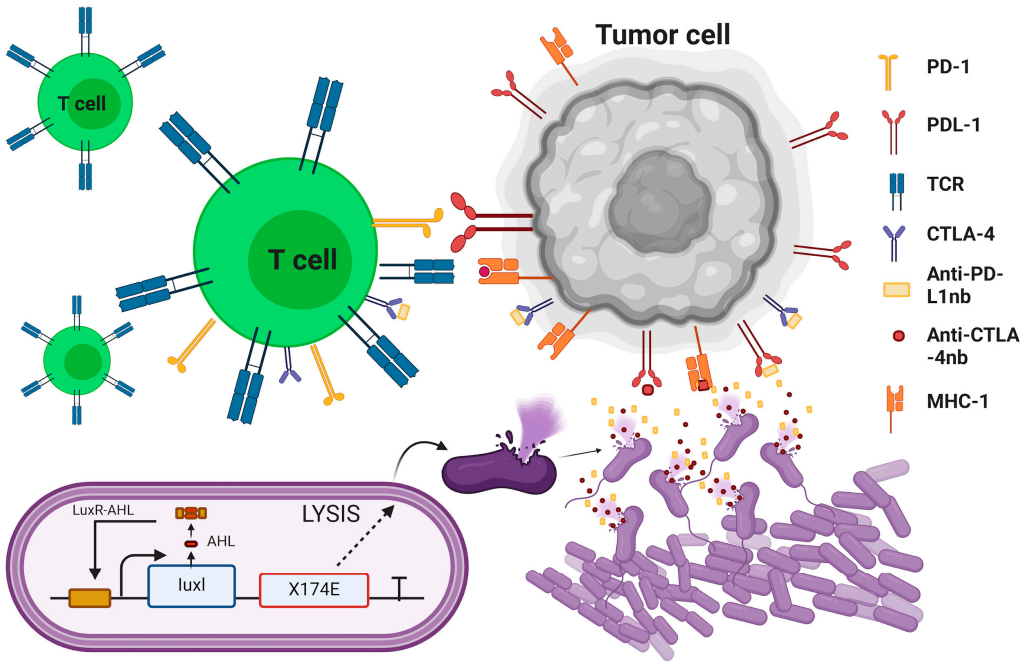

Figure 3. Tumor cells presenting to T cells and blockade of PD-1 and CTLA-4 signaling through bacterial lysis with a genetic circuit designed to release antibodies. This image was created as a summary of what was reported in [62,66].

It is known that there are bacteria that grow and cluster around malignant tissues without causing infections [73]. Therefore, a probiotic bacterium was designed to synthesize

and release antibodies to block immune system regulators used by cancer cells (Figure 3). This occurred when the bacterial count reached a critical level, inducing lysis in the tumor microenvironment, thus releasing the PD-L1- and CTLA-4-blocking antibodies [77], which are produced through a programmed genetic circuit [74]. The released antibodies (rCTLA-4nb and rPD-L1) bind to PD-L1 and CTLA-4 receptors, blocking them. This approach was tested in mice with efficient results. Moreover, due to their greater diffusion and rapid elimination through glomerular filtration, they provide a guarantee in reducing off-target effects [78].

The plasmid containing the genetic circuit was inserted into *E. coli* Nissle 1917, which, due to its quorum-like configuration, releases the antibody payloads. The circuit drives the transcription of the lux1 and X174E genes with a single promoter. The circuit was cloned into 3 plasmids with different copy numbers: "low" under sc101 (3–4 copies), "medium" under p15A (15–20 copies), and "high" under coE1 (70–100 copies). All were inserted into the EcN-lux genome for synchronized lysis (SLIC) and with GFP to track time-dependent fluorescence. It was observed that the plasmid with the lowest copy number produced the highest amount of GFP compared to the others with higher copy numbers.

This occurred because a higher number of copies of the X174E gene induces basal lysis. When injected into mouse tumors, lysis was achieved within 24 h, and a decrease in CD4 and CD3 regulatory T cells was observed. Their goal was to achieve tumor regression, and they reduced the treated tumors by 50%, while tumors in 50% of untreated mice grew even more. Additionally, mice receiving the treatment showed an increase in CD4, CD62L, CD44, and CD8 cells, suggesting an expansion of immunological memory. Thus, with a single injection, the treatment is likely to persist due to the adaptive immune response [73].

5.2. Bioremediation and Industry

The study on synthetic microbial communities for bioremediation and industry involved designing and testing communities composed of isolated or genetically engineered functional species. Specific methodologies included constructing synthetic microbial community with low complexity to model microbial interactions and using multiomics analyses to assess their efficiency.

Using synthetic microbial systems for bioremediation provides sustainable and cost-effective methods for cleaning soils, bodies of water, and oceans contaminated with hydrocarbons and organic and inorganic pollutants. This includes halophilic bacteria capable of degrading polycyclic aromatic hydrocarbons and oil from highly saline wastewater, as well as plasticizers like bisphenol and phthalates, and nanoparticles from commercial products found in herbicides or agricultural pesticides [79]. Before the development of synthetic microorganisms, aerobic degradation and catabolic pathways of Proteobacteria, Actinobacteria, and Firmicutes were already being used, which have regulatory networks and mechanisms for hydrocarbon tolerance [80]. This approach is slower than physicochemical methods but achieves the complete degradation of contaminants.

Recent interest in agricultural bio-inputs includes synthetic microbial communities for enhancing crop productivity, such as nitrogen-fixing bacteria and arbuscular mycorrhizal fungi in sugarcane. Despite their crucial role, few studies have explored the impact of synthetic microbial communities on sugarcane endophytic microbiota. Schwab et al., 2024 investigated the effects of synthetic microbial community inoculation on microbiota structure, revealing stable diversity but significant community differences between sugarcane varieties and plant organs (roots and culms) after one growth cycle (~360 days). This highlights potential applications for specific root and culm microbes in sugarcane cultivation [81].

A synthetic microbial community capable of efficiently degrading lignocellulose was constructed based on multiomics. This community was specifically designed for solid-state fermentation, focusing on corn straw. Optimal conditions included a 10% inoculum (w/v), 4% nitrogen source ratio, and a fermentation period of 23 days. Under these conditions, the cellulose, hemicellulose, and lignin degradation rates reached 34.91%, 45.94%, and 23.34%, respectively. Proteomic analysis highlighted enzymes such as lignin 1,4-β-xylanase, and β-xylosidase as crucial for this process. Corn straw fermentation primarily yields sugars and proteins [82].

Heavy metal-reducing microorganisms have been studied for their use in bioremediation. In research on bacterial diversities in CrO3-reducing biocathodes of fuel cells [83] using 454 pyrosequencing of the 16S rRNA gene, diversity was observed in the microbial community. It was noted that some identified genera were not associated with chromium oxide (CrO3) reduction. Therefore, it was argued that these characteristics were acquired due to the environment where they were found and their interaction within the community. They were able to remove 97.83% of pollutants in wastewater, leading to the development of an efficient, self-sustaining biocathode. This biocathode is cost effective, produces minimal sludge, and converts oxidized compounds into less harmful forms, making it suitable for use in the bioremediation of contaminated effluent water.

It has been demonstrated that microalgae can remove heavy metals due to components in their cell wall. They have an adaptive nature to grow under stress conditions without generating toxic sludge [84–86]. Immobilizing microalgae is considered a technique to improve the chemical and physical performances of metal absorption. Currently, such mechanisms are being studied and applied, but few industries use biological treatment for wastewater [87]. For instance, the bioremediation capacity of live *Chlorella* sp. was evaluated to remove dye effluents from textile companies using a cultivation methodology in small 3.0 L containers with an effective volume of 2.5 L, achieving successful results with an absorbance of 0.30, removing 97.2% of the present dyes, reducing the total organic carbon (COT) by 94.6% and the chemical oxygen demand (COD) by 95.4%, and stabilizing the pH [88]. The ability to resist heavy metals allows them to survive in such environments, as demonstrated by Marrero [89]. He showed the genes involved in each type of metal resistance, their chromosomal location, enzyme-mediated transformation, and their applications. Marrero describes two types of transformations: metal mobilization and immobilization.

The concentrations of heavy metals in different ecosystems have led to the selection of metal-resistant organisms. Thus, bioremediation is not achieved by a specific microbial species but by functional units acting together based on their biological activities, determining the speed and efficiency of treatment. The environmental changes in Antarctica have accelerated the proliferation of microbial communities colonizing affected areas. These communities have important characteristics such as surviving at low temperatures or low light intensities [90,91].

Microbial communities inhabiting the shallow waters of Potter Cove on King George Island are being studied for their biogeochemical responses and their ability to degrade small amounts of spilled diesel in coastal areas. These microbial communities were evaluated using DGGE (fingerprinting technique), and libraries of 16S rRNA gene clones were constructed. They found that the communities mainly consist of chemoheterotrophic bacteria capable of responding to climate change. Additionally, through studies, they found that genes encoding the biosynthesis of unsaturated fats are activated when exposed to cold as an adaptation mechanism. Thus, *Bizionia argentinensis* secretes peptidases from Pfam or Tigrfa as signal peptides for the Potter Cove communities [91]. Although not all functional genes have been assigned yet, they determined that JUB59T belongs to anaerobic denitrifying bacteria capable of assimilating and reducing nitrites and NO_2. They also found seasonal changes in the microbiome between three study areas, which would combine these communities and how they would respond to human activities. Increasing volumes of wastewater present a global environmental challenge, necessitating sustainable treatment methods due to the high costs and environmental impact. Microalgae–microbiome-based treatments offer a promising alternative by capturing carbon emissions and recovering resources, potentially achieving carbon neutrality in wastewater treatment. The synergistic interactions between microalgae and bacteria in synthetic microbial communities enhance carbon sequestration and nutrient recovery in treatment plants [40].

For soil bioremediation, synthetic microbial communities with Plant Growth Promoters (PGPs) have been implemented to meet food needs, prevent soil loss and degradation in agricultural crops, maintain yield, and avoid the use of chemical fertilizers [92]. Once these microbial communities were introduced into the soil, they showed difficulties in repro-

ducing (10^3–10^4 cells/gram of soil), which enhanced the cultivation of interest, prevented erosion, and made the soil more fertile without uncontrolled growth. Additionally, they participated in reducing the chemical compounds from fertilizers that contaminate water bodies, generating environmentally friendly products [93].

Microbial communities have been employed for water bioremediation due to its significant contamination. Therefore, *Candidatus brocadia*, an anammox bacterium, has been implemented for nitrogen removal in wastewater. These bacteria perform the process of nitrification by partially aerobically oxidizing ammonium to nitrite, which is then further reduced to molecular nitrogen.

These microorganisms were characterized from wastewater treatment plant sludge, collected from nitritation–anammox sequencing batch reactors. The most abundant species identified was *Thauera phenylacetica*, which degrades aromatic compounds under denitrifying conditions. Additionally, *Chloroflexi* OLB14 and *Anaerolineae* UTCFX1 and UTCFX3 were found. The genomes of these bacteria were assembled and assigned to *C. brocadia* to create the activated sludge microbial community. They were introduced into a 9 L reactor with an efficiency ranging from 30 to 90% at an ammonium concentration of 200 mg per L, using only 50 g of sludge residue [94].

In the degradation of aromatic compounds like aniline, which is toxic but used in the production of dyes, rubber, plastics, paint, and even pharmaceuticals, causing significant water pollution, bacteria isolated from marine sediments were used. *Desulfobacterium anilini* [95] and *Thiocapsa roseopersicina* DSM217, a hydrogen sulfide-consuming bacterium, were employed. This consortium was formed because sulfide inhibited the growth of *D. anilini*, creating a community where both bacteria could grow continuously, as *D. anilini* provided sulfide to *T. roseopersicina* [96]. This is a clear example of a microbial consortium with beneficial potential in water bioremediation.

Oil spills during transport or storage on offshore platforms are a severe problem for ecosystems and beaches. Therefore, synthetic bacterial consortia have been constructed for oil degradation using *Achromobacter* sp. P3, *Sphingobium* sp. P10, and *Rhizobium* sp. P14, which successfully degraded oil under optimal conditions [97]. These strains were collected from an oil field in China. The synthetic consortium was compared and used alongside another bacterial consortium, resulting in a 34.8% higher degradation than the original. Currently, over 100 genera of bacteria capable of oil degradation have been identified, providing a broader range for constructing synthetic consortia with an increased efficiency in bioremediation [98–100].

Aiming to refine the flavor compound profile in Chinese liquor fermentation, the focus was on shaping a synthetic microbial community's composition. Through the analysis of 80 fermentations, twenty key flavor compounds were identified, leading to the selection of six microbial strains noted for their high production of these compounds. A mathematical model was developed to predict how the structure of this synthetic microbial community influences the final flavor profile [101]. This approach offers a strategic method to exert targeted control over flavor compounds in fermented foods, highlighting its potential applicability across diverse food fermentation processes [102]. Synthetic microbial communities derived from the root microbiota of tea plants have been utilized to enhance the synthesis of theanine, a pivotal factor influencing tea taste and quality, by regulating nitrogen homeostasis and theanine production [103].

Synthetic microbial community biosensors utilize genetically engineered or natural microbial communities to detect and convert biosignals into digital outputs, potentially revolutionizing biosensing technology. The construction workflow involves selecting microbial candidates, constructing and validating the mathematical model that is developed to predict the structure of this synthetic sensor, and detecting biosignals. These biosensors offer enhanced sensitivity, specificity, cost effectiveness, and real-time monitoring capabilities. They hold promise for applications in agriculture, food management, biotherapeutic development, home sensing, and urban and environmental monitoring initiatives. Future advancements aim to optimize the mathematical model developed to predict how the

structure of this synthetic biosensor influences real-time and remote environmental monitoring in dynamic settings [104]. Recent advancements in genetically encoded biosensors encompass various types, including fluorescent protein-based, nucleic acid-based, allosteric transcription factor-based, and two-component system-based biosensors. These biosensors are constructed with specific frameworks tailored to their detection mechanisms. They have been instrumental in creating versatile microbial cell factories for producing high-value chemicals, showcasing significant progress in biosensor applications in bioproduction [105].

Synthetic microbial communities in plants play a crucial role in regulating plant growth and productivity by revealing interactive dynamics among community elements. The effectiveness of co-inoculation with multiple species varies across different scenarios. In some cases, co-inoculation enhances survival in soil, resulting in synergistic effects that amplify host benefits. A combination of PGP *Bacillus subtilis* GB03 and *B. amyloliquefaciens* IN937a enhanced plant growth and induced disease resistance in *Arabidopsis thaliana*. Co-inoculating cotton with various PGP microorganisms increases its production. However, co-inoculating tomato (*Lycopersicon esculentum* Mill.) with *Bacillus pumilus* WP8 and *Erwinia persicinus* RA2 did not demonstrate superior efficacy over individual inoculations in controlling tomato wilt caused by *Ralstonia solanaceum* Rs 1115 under field conditions [106].

Desertification threatens soil carbon accumulation due to climate change and human activities. Synthetic bacterial communities offer promise by enhancing soil microbiomes for improved plant growth. A study on desertified land in the Loess Plateau over two years found that the introduction of synthetic bacterial communities enriched beneficial bacteria, increased the biodiversity, and reshaped bacterial community structures, especially in the soil surface (0–10 cm). Synthetic bacterial communities also enhanced bacterial network complexity and outperformed chemical fertilizers, influencing nutrient availability and ecosystem functions significantly. Synthetic bacterial communities have potential to restore ecosystems in degraded soils [107].

The model cyanobacterium *S. elongatus* PCC 7942 was engineered to secrete a large portion of the carbon it fixes as sucrose, as this carbohydrate can be utilized by many other microorganisms. Therefore, the ability of sucrose-secreting cyanobacteria to serve as a flexible platform for constructing light-driven synthetic consortia was tested, combining them with three disparate heterotrophs: *Bacillus subtilis*, *E. coli*, or *Saccharomyces cerevisiae*. Comparing the different microbial communities in co-cultures revealed general design principles for building robust autotroph/heterotroph consortia. The consortia stabilized when exposed to heterotrophic sucrose, which persisted and, in some cases, affected the interaction between consortia, benefiting from one another. The programmed photoproduction of S. elongatus exported 85% of photosynthetically fixed carbon as sucrose by expressing CscB+. This supported the growth of *E. coli*, *S. cerevisiae*, and *B. subtilis*. Additionally, *E. coli* expressed genes for the biosynthesis of alpha-amylase and poly-beta-hydroxybutyrate (PHB) from *S. elongatus* sucrose [108].

From organic substrates and wastewater contamination, microbial consortia were synthesized, in this case, *Shewanella oneidensis*, *B. subtilis*, and *E. coli*, to generate energy in microbial fuel cells. These convert the chemical energy of compounds into electrical energy through their metabolism, offering advantages over current energy generation technologies due to higher efficiency and operation at room and low temperatures [109]. This can meet energy needs in certain U.S. sectors where high temperatures prevent energy consumption and is a potential option for diversifying energy fuel with microbial consortia and their biosynthesis.

6. Bioethics: Potential Risks in Implementing Synthetic Microbial Communities

The applications and advancements of synthetic, semi-synthetic, and artificial communities offer significant opportunities for development but come with strengths and challenges for implementation [20]. The creation and use of synthetic microorganisms may pose risks within habitats and ecosystems. Therefore, all their functions should be analyzed to identify potential chemical and biotechnological risks, where horizontal gene transfer could be concerning, leading to ecosystem changes and posing a danger to unmodified organisms [110].

The implementation of synthetic microbial communities may not be well received by the general public due to expectations generated by synthetic biology use and fears of complications affecting other biological and environmental processes such as biogeochemical cycles (carbon, phosphorus, sulfur, nitrogen, and oxygen) [111].

Another potential risk in using synthetic microbial communities is lacking adequate biocontainment to prevent a solution to one problem or specific treatment in a patient from becoming a pathogen. Thus, autotrophic biocontainment is sought by adding only the specific substance to activate it and allow its proliferation [9].

7. Conclusions

Synthetic biology combined with bioengineering has successfully redesigned microorganisms to express characteristics or functions different from their natural state. This is achieved through mathematical models and genetic circuits focused on designing a model community and synthetic microbial communities. This community selects specific species with genetic and biological features tailored to the intended application. Additionally, it is crucial to analyze the interactions among microbial communities and between these communities and their environment to ensure their utility.

Essential tools for the development of synthetic microbial communities include CRISPR, microfluidics, and adhesion molecules, among others. These tools enable the design or redesign of microorganisms for specific purposes. Based on their functions, synthetic microbial communities have applications in various fields. They can be applied in medicine through the implementation of genetic circuits for cancer treatment, in bioremediation by using microorganisms to reduce heavy metals in water or soil, and in the industry and pharmaceutical sectors, among others.

While the use of these microorganisms offers numerous benefits, it also comes with risks that need careful consideration. It is essential to assess all functions to identify potential chemical and biotechnological risks. Horizontal gene transfer could be particularly concerning, leading to ecosystem alterations and posing risks to unmodified organisms. Therefore, a comprehensive understanding of these synthetic communities' functions and potential impacts is essential for their safe and effective implementation.

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