

Research Perspective

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Synthetic Microbial Communities: Redesigning Genetic Pathways for Enhanced Functional Synergy

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Molecular Microbiology Research, 2024, Vol.14, No.1 doi: [10.5376/mmr.2024.14.0005](https://doi.org/10.5376/mmr.2024.14.0005)

Received: 22 Dec., 2023

Accepted: 31 Jan., 2024

Published: 18 Feb., 2024

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Preferred citation for this article:

Song R.S., Sun K., Wang Y.X., Liu S.K., and Bu Y.Y., 2024, Synthetic microbial communities: redesigning genetic pathways for enhanced functional synergy, *Molecular Microbiology Research*, 14(1): 39-48 (doi: [10.5376/mmr.2024.14.0005](https://doi.org/10.5376/mmr.2024.14.0005))

Abstract This study aims to summarize recent advancements in genetic engineering, focusing on the interactions within microbial communities and their implications for improved functionality. Significant progress has been made in the field of synthetic biology, particularly in the design of synthetic microbial communities. Recent studies have demonstrated the use of control engineering concepts to analyze and design microbial systems, enhancing their functional output. The development of robust synthetic communities using quorum sensing and other interaction motifs has shown promise in creating stable and efficient microbial consortia. Additionally, programmable ecological interactions within synthetic consortia have been engineered to achieve specific population dynamics and functional outcomes. Advances in genome-centric metagenomics have provided deeper insights into the metabolic pathways and synergistic networks within microbial communities, revealing novel metabolic interactions and evolutionary insights. Furthermore, the integration of systems biology and synthetic biology approaches has been pivotal in understanding and manipulating the human microbiome for therapeutic and diagnostic applications. The redesign of genetic pathways within synthetic microbial communities holds significant potential for various industrial, environmental, and health-related applications. By leveraging advanced genetic engineering techniques and a deeper understanding of microbial interactions, it is possible to create microbial consortia with enhanced functional synergy. These developments pave the way for innovative solutions in bioremediation, chemical production, and human health, highlighting the importance of continued research in this rapidly evolving field.

Keywords Synthetic microbial communities; Genetic pathway redesign; Genetic engineering; Microbial interactions; Quorum sensing; Synthetic biology; Human microbiome; Metabolic pathways

Synthetic microbial communities (SynComs) are engineered consortia of microorganisms designed to perform specific functions or produce desired outcomes. Unlike natural microbial communities, which are often complex and difficult to manipulate, SynComs offer a controlled environment where interactions between species can be precisely managed. The importance of SynComs lies in their potential to enhance productivity and stability in various applications, ranging from industrial biotechnology to environmental restoration and agriculture (Karkaria et al., 2021). For instance, SynComs can be designed to improve crop resiliency by enhancing plant-microbe interactions, thereby increasing crop productivity under adverse environmental conditions (Souza et al., 2020). Additionally, SynComs can be used to create distributed systems that mitigate issues often found in engineering monocultures, especially as functional complexity increases (Karkaria et al., 2021).

Genetic pathway redesign involves modifying the genetic circuits within microbial communities to achieve enhanced functional synergy. This can be accomplished by engineering specific genetic parts and pathways to optimize interactions between different microbial species. For example, quorum sensing mechanisms can be employed to control interactions such as competition and cooperation within the community, thereby stabilizing the system and enhancing its overall functionality (Li et al., 2022). The division of labor among different strains within a community can also reduce the metabolic burden on individual members, leading to more efficient production processes. Moreover, synthetic biology tools and strategies, such as genome mining and bioinformatics,

can be used to identify and optimize biosynthetic pathways for the production of natural products with improved properties (Kang et al., 2020).

The primary objective of this study is to provide a comprehensive overview of the current state of research on synthetic microbial communities and the redesign of genetic pathways for enhanced functional synergy. By synthesizing findings from multiple studies, this paper aims to highlight the methodologies, tools, and strategies that have been developed to design and optimize SynComs. The significance of this review lies in its potential to guide future research and applications in various fields, including biotechnology, agriculture, and environmental science. By understanding the principles and techniques involved in creating robust and efficient SynComs, researchers can develop more effective solutions to complex biological and ecological challenges. This study propose directions for future research, thereby contributing to the advancement of synthetic biology and microbial engineering.

1 Synthetic Microbial Communities

1.1 Definition and characteristics

Synthetic microbial communities (SynComs) are engineered consortia of microorganisms designed to perform specific functions or exhibit particular traits. These communities are constructed by co-cultivating two or more microbial species under controlled environmental conditions. The design of SynComs leverages principles from both synthetic biology and microbial ecology to create systems with high biological processing efficiencies. This is achieved through the division of labor among community members, which reduces the metabolic burden on individual microorganisms and enhances overall functionality (Liang et al., 2022).

1.2 Examples and applications in various fields

SynComs have broad applications across multiple fields, including biotechnology, agriculture, and medicine. In biotechnology, SynComs are used to create distributed systems that mitigate issues found in monocultures, especially as functional complexity increases. For instance, they can be designed to include competition for nutrients and use quorum sensing to control interactions, thereby producing stable and robust communities (Karkaria et al., 2021). In agriculture, SynComs are tailored to enhance crop resiliency and productivity by selecting microorganisms with traits beneficial for plant health, such as robust colonization and stress resistance (Souza et al., 2020). In medicine, SynComs are explored for their potential to rewire the human microbiome, offering novel therapeutic and diagnostic interventions. Tools like biosensors and engineered bacteria can be used to modulate the microbiome environment, thereby improving health outcomes (Ezzamouri et al., 2021).

1.3 Advantages over natural microbial communities

SynComs offer several advantages over natural microbial communities. One significant advantage is the ability to design and control the community composition and interactions, which can lead to more predictable and stable outcomes. This controlled environment allows for the optimization of microbial traits and functions, enhancing the overall efficiency and effectiveness of the community (Liang et al., 2022). Additionally, SynComs can be engineered to perform specific tasks that natural communities may not be capable of, such as producing particular metabolites or degrading environmental pollutants. The use of computational methods, including machine learning and artificial intelligence, further enhances the design and optimization of SynComs, making them more effective in achieving desired outcomes (Martins et al., 2023).

By leveraging the principles of synthetic biology and microbial ecology, SynComs represent a powerful tool for advancing various scientific and industrial applications, offering enhanced functional synergy and efficiency compared to their natural counterparts.

2 Redesigning Genetic Pathways

2.1 Overview of genetic pathway engineering

Genetic pathway engineering is a cornerstone of synthetic biology, aiming to rewire and optimize metabolic and

regulatory networks within microbial systems. This process involves the modification of existing genetic circuits or the introduction of new pathways to enhance or introduce desired functionalities. The integration of control engineering principles has significantly advanced the field, providing robust frameworks for the analysis and design of these synthetic systems (Perrino et al., 2021). The primary goal is to achieve improved production of natural products, biofuels, pharmaceuticals, and other valuable compounds by leveraging the inherent capabilities of microbial hosts (Alam et al., 2021).

2.2 Techniques and tools for genetic modification

Several advanced techniques and tools have been developed to facilitate genetic modifications in microbial systems. Among these, CRISPR-Cas systems have emerged as a powerful tool for precise genome editing, allowing for targeted modifications with high efficiency. Synthetic biology also employs modular genetic circuits, which can be designed, built, and tested iteratively to achieve desired outcomes (Kumar et al., 2022). The use of photosynthetic microorganisms as hosts for synthetic biology applications has been explored, although the genetic engineering tools available for these organisms still lag behind those for heterotrophic hosts (Vavitsas et al., 2021). Additionally, bioinformatics and genome mining techniques are crucial for identifying and manipulating biosynthetic gene clusters, enabling the discovery and production of novel natural products (Alam et al., 2021).

2.3 Case studies of successful genetic pathway redesign in microbial communities

Several case studies highlight the successful redesign of genetic pathways in microbial communities. For instance, the development of synthetic microbial communities using quorum sensing to control interactions has demonstrated the potential for creating stable and robust systems that can perform complex functions (Karkaria et al., 2020). Another example is the use of growth-coupled selection schemes to accelerate the development of cell factories, enabling deep rewiring of metabolic networks for enhanced bioproduction (Orsi et al., 2021). Furthermore, the integration of synthetic biology and systems biology approaches has shown promise in human microbiome studies, where engineered microbes can be used to modulate host responses and improve health outcomes (Ezzamouri et al., 2021).

In summary, the redesign of genetic pathways in microbial communities is a rapidly evolving field, driven by advances in synthetic biology and genetic engineering tools. These innovations hold great potential for enhancing the functional synergy of microbial systems, leading to significant improvements in various biotechnological applications.

3 Enhanced Functional Synergy

3.1 Definition of functional synergy in microbial communities

Functional synergy in microbial communities refers to the cooperative interactions among different microbial species that result in enhanced collective functionality compared to the sum of their individual contributions. This synergy can manifest in various forms, such as improved metabolic efficiency, increased resilience to environmental stresses, and enhanced production of desired metabolites. The concept is rooted in the ecological principle that diverse microbial communities can exploit a wider range of resources and environmental niches, leading to more robust and efficient systems (Marin et al., 2021).

3.2 Mechanisms through which genetic redesign enhances synergy

Genetic redesign in synthetic microbial communities can enhance functional synergy through several mechanisms:

Quorum Sensing and Communication: Engineering microbial strains to communicate via quorum sensing can synchronize their activities, leading to more coordinated and efficient metabolic processes. For instance, quorum sensing modules can be used to control bacteriocin interactions, ensuring stable community dynamics and enhanced functional output (Karkaria et al., 2020).

Metabolic Pathway Engineering: By modularizing and optimizing metabolic pathways, synthetic biology enables the creation of microbial consortia where each member specializes in a specific part of a metabolic process. This division of labor can lead to more efficient resource utilization and higher overall productivity. For example, the co-fermentation of different substrates by engineered microbes can significantly boost biohydrogen production (Hu et al., 2020)

Cross-Feeding Interactions: In some synthetic communities, non-metabolizing members can support metabolizing ones through cross-feeding interactions. This can involve the exchange of metabolic intermediates that enhance the overall degradation or production capabilities of the community. An example is the synergistic biodegradation of n-alkanes by a consortium of *Dietzia* sp. and *Pseudomonas stutzeri*, where metabolic intermediates are exchanged to improve degradation efficiency (Hu et al., 2020).

Ecological Interaction Modulation: Synthetic biology allows for the precise tuning of ecological interactions such as competition, exploitation, and mutualism. By engineering these interactions, researchers can create consortia with desired dynamic behaviors and enhanced functional outcomes. For instance, engineered *E. coli* strains can be programmed to exhibit different interaction modes, such as synergy or competition, depending on the initial conditions and engineered modules (Li et al., 2022).

3.3 Examples of enhanced functional outcomes

Increased Metabolite Production: Synthetic microbial communities have been designed to enhance the production of valuable metabolites. For example, the modularization of metabolic pathways combined with growth-coupled selection schemes has been shown to significantly improve the bioproduction capabilities of cell factories (Figure 1) (Orsi et al., 2021). **Improved Degradation of Pollutants:** Engineered microbial consortia can achieve more efficient degradation of environmental pollutants. The synergistic interaction between *Dietzia* sp. and *Pseudomonas stutzeri* in n-alkane biodegradation is a prime example, where the presence of a non-degrading member enhances the overall degradation efficiency through metabolic cross-feeding (Hu et al., 2020).

Figure 1 compares the classical "design-build-test-learn" (DBTL) pipeline (top) with the "growth selection-based" DBTL cycle proposed in this study (bottom) (Figure 2). Both cycles are supported by the same technologies in the "design" and "build" phases. However, the novel pipeline changes in the "test" and "learn" phases, making them faster due to the absence of -omics analyses (shorter red and purple arrows). If necessary, the new cycle can incorporate adaptive laboratory evolution within its "test" phase (longer red arrow) (Orsi et al., 2021).

This improved DBTL cycle significantly accelerates the "test" and "learn" phases by reducing the reliance on -omics analyses. It allows for more flexible and adaptive experimental designs, enhancing efficiency and shortening cycle times. This new approach provides an effective pathway for rapid iteration and optimization in microbial engineering, improving the adaptability of laboratory evolution.

Enhanced Biohydrogen Production: The co-fermentation of antibiotic fermentation residue and fallen leaves by a synthetic microbial community has been shown to significantly increase biohydrogen production. This enhancement is attributed to the synergistic effects of microbial activity, enriched hydrogen-producing bacteria, and the expression of key functional genes (Yang and Wang, 2021). By leveraging these mechanisms and examples, synthetic microbial communities can be strategically designed to achieve enhanced functional synergy, leading to more efficient and robust biotechnological applications.

4 Applications and Implications

4.1 Industrial biotechnology

Synthetic microbial communities have shown significant potential in various industrial biotechnology applications, including biofuel production and bioremediation. The design of these communities often involves selecting appropriate microbial partners to optimize metabolic interactions and enhance overall productivity. For instance,

the pairing of phototrophic and heterotrophic microbes can facilitate sustainable growth and efficient bioproduction. A study demonstrated that a synthetic community of *Synechococcus elongatus* and *Escherichia coli* K-12 could sustain heterotrophic growth in minimal media, highlighting the potential for biofuel production (Zuñiga et al., 2020). Additionally, genome-scale metabolic models (GEMs) have been applied to design synthetic microbial communities for bioremediation, providing novel strategies for environmental cleanup (Wang et al., 2023). These models enable high-throughput simulations to predict metabolic flux distributions and optimize microbial interactions for effective pollutant degradation.

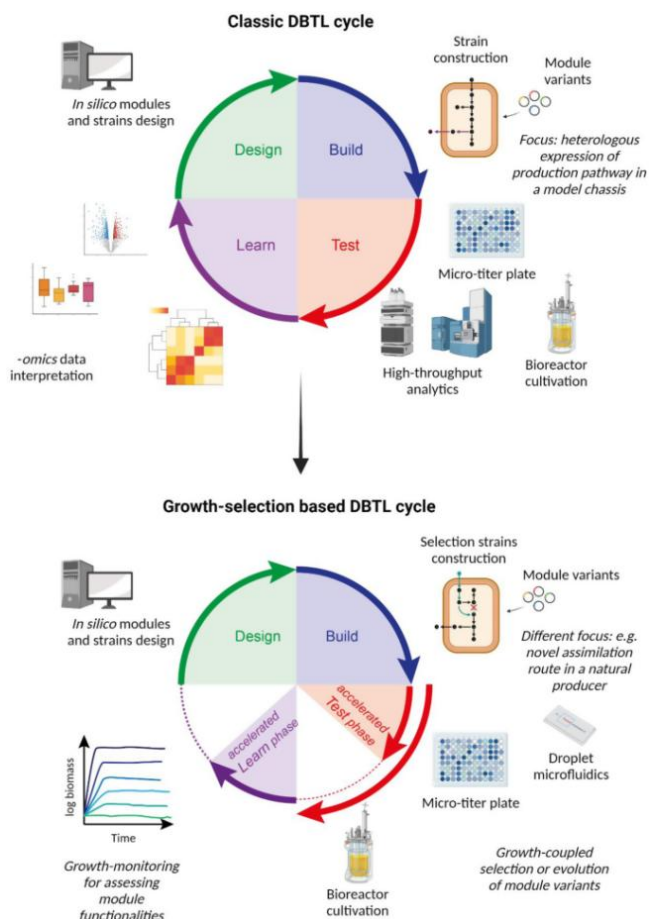


Figure 1 The classical "design-build-test-learn" (DBTL) pipeline (top) compared to the "growth selection-based" DBTL cycle proposed in this study (bottom) (Adopted from Orsi et al., 2021)

Image caption: The "design" and "build" phases are supported by the same technologies in both cycles. Nevertheless, the novel pipeline changes in the "test" and "learn" phases, which become faster in their execution due to the lack of omics analyses (shorter red and purple arrows). In case of necessity, the new cycle can host adaptive laboratory evolution within its "test" phase (longer red arrow) (Adapted from Orsi et al., 2021)

4.2 Agricultural biotechnology

In agricultural biotechnology, synthetic microbial communities are being explored to enhance soil health and promote plant growth. Microbial communities play a crucial role in plant-microbe interactions, contributing to crop productivity and resilience under adverse environmental conditions. The use of synthetic microbial communities (SynComs) involves designing inoculants with beneficial traits for robust colonization and specific functions that support plant development. Recent advances in computational methods, such as machine learning and artificial intelligence, have improved the screening and identification of beneficial microbes, leading to the development of SynComs that enhance crop resiliency (Souza et al., 2020). Furthermore, network analyses of

functional core microbiomes have identified key microbial species that control rhizosphere microbiomes and suppress pathogens, offering potential applications in agroecosystems (Toju et al., 2020).

4.3 Medical applications

Synthetic microbial communities also hold promise for medical applications, particularly in modulating the gut microbiome and treating diseases. The ability to monitor and model metabolite exchange in dynamic microbial consortia is crucial for understanding community-level behaviors and designing consortia with novel functions. For example, an in-silico model of a synthetic microbial community consisting of sucrose-secreting *Synechococcus elongatus* and *Escherichia coli* W demonstrated the importance of spatial organization and metabolite exchange in predicting colony fitness (Sakkos et al., 2023). This approach can be applied to engineer designer consortia for personalized probiotics and disease treatment (Figure 2). Additionally, the framework for scoring species within a microbial community based on their functional roles can be used to design functional core microbiomes for medical applications, such as organizing gut microbiome processes and functions (Toju et al., 2020).

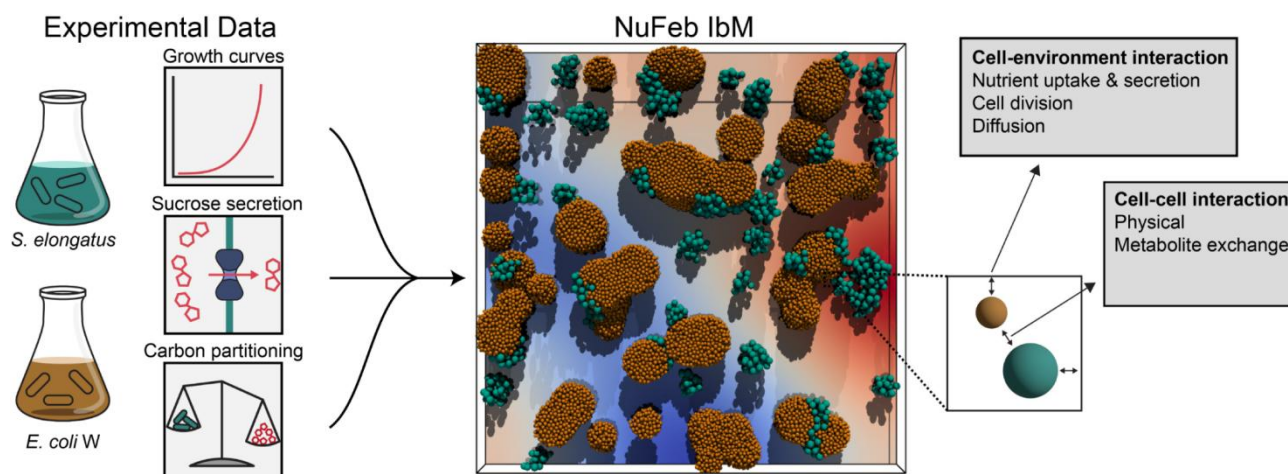


Figure 2 Study overview diagram (Adopted from Sakkos et al., 2023)

Image caption: Experimental growth, sucrose secretion, and biomass apportionment data were used to construct an Individual-based NUFEB model of an *S. elongatus* and *E. coli* consortium (Adapted from Sakkos et al., 2023)

The research from Sakkos et al. (2023) provides an overview of constructing an Individual-based NUFEB model for a consortium of *Synechococcus elongatus* and *Escherichia coli*. Experimental data, including growth curves, sucrose secretion, and carbon partitioning, were gathered from cultures of *S. elongatus* and *E. coli*. These data are crucial for modeling the interactions and behavior of the microbial consortium. The NUFEB (Newcastle University Frontiers in Environmental Biology) model simulates the dynamics of the consortium by integrating cell-environment interactions, such as nutrient uptake, secretion, cell division, and diffusion, along with cell-cell interactions like physical contact and metabolite exchange. This model provides insights into the interactions between the two species within their environment, optimizing conditions for mutual growth and productivity. The visual representation underscores the complexity of interactions and highlights the importance of both environmental and interspecies factors in shaping the consortium's dynamics. This integrative approach facilitates a deeper understanding of microbial consortia, potentially advancing biotechnological applications.

The redesign of genetic pathways in synthetic microbial communities offers numerous applications and implications across industrial biotechnology, agricultural biotechnology, and medical fields. By leveraging computational models and advanced screening methods, researchers can optimize microbial interactions and enhance the functional synergy of these communities for various practical applications.

5 Challenges and Limitations

5.1 Technical challenges in genetic pathway redesign

Redesigning genetic pathways within synthetic microbial communities presents several technical challenges. One significant issue is the complexity of engineering multiple strains to work synergistically. For instance, ensuring stable interactions and functional outputs in a co-culture system requires precise control over genetic elements and environmental conditions (Karkaria et al., 2020). Additionally, the integration of control engineering principles with synthetic biology has shown promise but also highlights the need for advanced tools to analyze and guide the design of these systems (Perrino et al., 2021). Another technical hurdle is the optimization of metabolic pathways to reduce the metabolic burden on individual strains, which is crucial for maintaining high productivity and stability (Liang et al., 2020). Furthermore, the modularization and growth-coupled selection of synthetic modules are essential for accelerating cell factory development, yet these processes are intricate and require sophisticated strategies (Orsi et al., 2021).

5.2 Ecological and ethical considerations

The introduction of synthetic microbial communities into natural or semi-natural environments raises several ecological and ethical concerns. One major issue is the potential for horizontal gene transfer, which can lead to unintended consequences such as the spread of engineered traits to native microbial populations (Martins et al., 2023). This could disrupt existing ecosystems and lead to unforeseen ecological impacts. Additionally, the long-term stability and colonization of synthetic communities are challenging to ensure, as environmental stressors and microbial evolution can alter community composition over time (Martins et al., 2023). Ethical considerations also arise from the manipulation of microbial communities, particularly regarding the potential risks and benefits to human health and the environment. The use of synthetic biology in human microbiome studies, for example, necessitates careful evaluation of the potential impacts on human health and the ethical implications of such interventions (Bekiaris and Klamt, 2021).

5.3 Regulatory and safety issues

The deployment of synthetic microbial communities is subject to stringent regulatory and safety considerations. Regulatory frameworks must address the potential risks associated with the release of genetically modified organisms (GMOs) into the environment. This includes assessing the potential for gene flow to non-target species and the ecological consequences of such events (Martins et al., 2023). Safety issues also encompass the containment and control of synthetic communities to prevent unintended spread and persistence in non-target environments. Moreover, the development of synthetic biology-inspired strategies for engineering microbial natural product biosynthetic pathways must comply with regulatory standards to ensure the safety and efficacy of the resulting products (Alam et al., 2021). The rational design of microbial consortia for bio-based production processes further necessitates robust regulatory oversight to mitigate potential risks and ensure compliance with safety protocols (Bekiaris and Klamt, 2021).

In summary, while the redesign of genetic pathways in synthetic microbial communities holds great promise for various applications, it is accompanied by significant technical, ecological, ethical, regulatory, and safety challenges. Addressing these challenges requires a multidisciplinary approach, integrating advanced engineering principles, ecological insights, and stringent regulatory frameworks to ensure the safe and effective deployment of these innovative systems.

6 Emerging Technologies and Their Potential Impact

6.1 Prospects for integrating synthetic microbial communities into broader biological systems

The field of synthetic microbial communities is rapidly evolving, driven by advancements in synthetic biology, control engineering, and computational methods. These emerging technologies are poised to significantly enhance the functional synergy of microbial systems, offering new avenues for biotechnological applications. The

integration of synthetic microbial communities into broader biological systems holds immense potential for various applications. One promising approach is the use of control engineering principles to design and analyze microbial systems. By applying control theoretical concepts, researchers can guide the design of synthetic biology systems in microbial cells, leading to more robust and predictable outcomes (Perrino et al., 2021).

Another key development is the automated design of synthetic microbial communities. This methodology leverages computational tools, such as Bayesian methods, to identify robust candidates for stable community compositions. These communities can mitigate issues often found in monocultures, especially as functional complexity increases (Karkaria et al., 2020). Additionally, the construction of environmental synthetic microbial consortia based on engineering and ecological principles can enhance biological processing efficiencies and reduce the metabolic burden on individual members (Liang et al., 2022). The integration of synthetic microbial communities into industrial microbial systems is also gaining traction. Advances in CRISPR-based genome editing and chromosomal integration techniques enable the reliable expression of genes and pathways, facilitating large-scale and long-term fermentation processes (Li et al., 2019). Furthermore, the development of synthetic biology-inspired strategies for engineering microbial natural product biosynthetic pathways can lead to the discovery of new natural products with enhanced biological properties (Alam et al., 2021).

6.2 Long-term vision for the field and potential breakthroughs

The long-term vision for the field of synthetic microbial communities involves harnessing the synergies between systems biology and synthetic biology to address complex biological challenges. For instance, the study of human microbiome communities using next-generation sequencing and computational tools can reveal novel therapeutic and diagnostic interventions. By rewiring the microbiome environment with engineered bacteria and biosensors, researchers can improve human health outcomes (Ezzamouri et al., 2021). One potential breakthrough is the application of synthetic biology tools to engineer microbial communities for biotechnological processes. These tools can expand the functions performed by microbial consortia, enabling the bioproduction of medicines, biofuels, and biomaterials from inexpensive carbon sources (McCarty and Ledesma-Amaro, 2019). Additionally, the development of computational approaches, such as ASTHERISC, for designing multi-strain communities can maximize the thermodynamic driving force for product synthesis, offering new principles for bio-based production processes (Bekiaris and Klamt, 2021).

In summary, the integration of synthetic microbial communities into broader biological systems and the continued advancement of synthetic biology tools hold great promise for the future. These technologies have the potential to revolutionize various fields, from industrial biotechnology to human health, by enabling the creation of more efficient, stable, and functional microbial systems.

7 Concluding Remarks

7.1 Summary of key points

Synthetic microbial communities (SynComs) have emerged as a powerful tool for enhancing functional synergy in various applications. These communities leverage the natural interactions between microbial species to create robust and stable systems that can outperform monocultures in terms of productivity and functional complexity. The design and engineering of SynComs involve sophisticated methodologies, including computational modeling, quorum sensing, and genetic pathway integration, to ensure stability and desired interactions. In agricultural contexts, SynComs have shown promise in improving crop resiliency and productivity by harnessing beneficial plant-microbe interactions. Additionally, advances in synthetic biology and control engineering have facilitated the integration of complex genetic pathways, enabling the production of valuable biochemicals and pharmaceuticals.

7.2 The overall impact of synthetic microbial communities on science and industry

The development of synthetic microbial communities has had a profound impact on both scientific research and

industrial applications. In science, SynComs have provided deeper insights into microbial ecology and the intricate interactions within microbial ecosystems. They have also advanced our understanding of plant-microbe interactions, leading to innovative strategies for enhancing crop performance under various environmental conditions. In industry, SynComs have revolutionized biotechnological processes, enabling the efficient production of biofuels, biochemicals, and pharmaceuticals from renewable resources. The ability to design and control microbial consortia has opened new avenues for sustainable and cost-effective bioproduction, waste treatment, and environmental remediation.

7.3 Call for continued research and collaboration in the field

Despite the significant advancements, the field of synthetic microbial communities is still in its nascent stages, and there is a pressing need for continued research and collaboration. Future studies should focus on optimizing the design and stability of SynComs, exploring new genetic pathways, and developing more sophisticated computational models to predict community dynamics. Interdisciplinary collaboration between microbiologists, synthetic biologists, computational scientists, and engineers will be crucial in overcoming current limitations and unlocking the full potential of SynComs. Additionally, there is a need for standardized protocols and frameworks to facilitate the reproducibility and scalability of SynCom applications in various industries. By fostering a collaborative and innovative research environment, we can accelerate the development of SynComs and their transformative impact on science and industry.

Acknowledgments

We extend our sincere thanks to two anonymous peer reviewers for their invaluable feedback on the initial draft of this paper.

Funding

This Project was provided by the Innovation Team Foundation of the Ministry of Education of China (IRT_17R99) and the Scientific Research Foundation of Zhejiang A&F University (2016FR006).

Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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