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Trends in Biotechnology

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Opinion

Perspective on the development of synthetic microbial community (SynCom) biosensors

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Synthetic microbial community (SynCom) biosensors are a promising technology for detecting and responding to environmental cues and target molecules. SynCom biosensors use engineered microorganisms to create a more complex and diverse sensing system, enabling them to respond to stimuli with enhanced sensitivity and accuracy. Here, we give a definition of SynCom biosensors, outline their construction workflow, and discuss current biosensing technology. We also highlight the challenges and future for developing and optimizing SynCom biosensors and the potential applications in agriculture and food management, biotherapeutic development, home sensing, urban and environmental monitoring, and the One Health foundation. We believe SynCom biosensors could be used in a real-time and remote-controlled manner to sense the chaos of constantly dynamic environments.

Highlights

Synthetic microbial community (SynCom) biosensors allow for the use of genetically edited or natural microbial communities in a biosensing system to capture and convert biosignals into digital outputs.

The workflow of SynCom biosensor construction contains three basic modules, including selection of microbial target candidates, construction and validation of SynComs, and detection of biosignals.

SynCom biosensors have the potential to revolutionize biosensing technology by improving sensitivity, specificity, cost effectiveness, and real-time monitoring capabilities.

Significance of developing biosensors

In the Anthropocene era, hazards such as heavy metals, organic pollutants, and pathogens threaten our lives and environments [1–3]. However, routine methods of detection, which largely rely on enzymatic and physiochemical spectrometry, have limitations such as manual sample collection, cost, lack of real-time feedback, and secondary pollution risks [4–6]. For example, although atomic absorption spectrometry can accurately detect heavy metals, expensive equipment and complicated operations are still required [1]. Thus, there is an urgent need for innovative, cost-effective, and reliable technologies that can detect and respond to targets in a precise, timely, and actionable manner [2,3].

Microorganisms are highly versatile and can survive in various adverse conditions such as extreme temperatures, high salinity levels or pH, and environments with high concentrations of toxic chemicals. Therefore, they can be applied as an easy, rapid, and inexpensive biosensor alternative to pinpoint existing environmental hazards [7]. Microbial biosensors have been used as bioreporters of diverse compounds due to their practical applications online, *in vitro*, and in dose–response analyses since the 1990s [5,8]. As a result, the development of microbe-based sensing technology has gained increasing popularity over enzymatic and physiochemical sensors. However, applying natural microorganisms or components in microbial biosensors faces limitations, including a short lifespan and difficulties in achieving high levels of sensitivity and precision [9,10]. These constraints represent significant obstacles to further progress in various fields, such as agriculture [11,12], bioremediation [2,13], bioproduction [14,15], and therapeutics [8,16].

To mitigate the drawbacks of microbial biosensors, we introduce the concept of synthetic microbial community (SynCom) biosensors. This approach involves engineering microbial strains or using natural microbiomes. The interactions between SynCom individuals can range from simple

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nutrient exchange to complex communication and coordination of behaviors to different stimuli [12,17,18]. Although the process of SynCom design is still in its early stages [19], the novelty of these biosensors is in their ability to detect multiple substances simultaneously with great sensitivity, effectiveness, and adaptability.

The proposed SynCom biosensors would take advantage of the flexibility, sensitivity, suitability, and multifunctionality of **engineered microorganisms** (see Glossary). Modern equipment can accept and connect the biosignals generated from living microorganisms, enabling real-time and remote control of the SynCom biosensing system. However, the workflow for designing a SynCom biosensor, such as microbial target selection, biodigital transformation, and biosensing equipment, poses a significant knowledge gap. To address this challenge, we propose a set of design criteria for constructing SynCom biosensors, providing a unique perspective for the biosensing field and highlighting the implications of this emerging technology.

Microbial-based biosensors and the advantages of unitizing SynCom

Generally, biosensors consist of input, output, and chassis components, which allow them to sense, compute, and respond to changes in detecting biotic and abiotic targets [4,20]. Based on the presence of microbial components or organisms in the chassis, microbial biosensors can be classified into three distinct groups: cell-free biosensors, whole-cell biosensors, and consortia biosensors (Box 1). These microbial-based biosensors currently have distinct advantages and limitations that cannot be ignored.

Cell-free biosensors are activated when a target substance binds to a protein transcription factor that activates the expression of a reporter construct [9]. Although these biosensors have high throughput and rapid workflows, they have limitations such as short lifetimes, low energy efficiency, and high dependence on environmental conditions like temperature, pH, and nutrients

Box 1. Cell-free, whole-cell, consortia, and SynCom biosensors

A cell-free biosensor (an alternative approach to those containing living cells) can be freeze-dried for long-term storage and detects a range of different physiochemical and biological compounds [9,10]. The primary advantages of cell-free biosensors include their high throughput, fast workflow, quick response time, flexibility, and low cost. However, they have some limitations, including lower sensitivity compared with biosensors that use living cells, less durability, limited specificity, and lower capacity due to the absence of amplification and signal amplification properties of living cells.

A whole-cell biosensor is a biosensing platform based on living cells, which may be nongenetically or genetically engineered and is composed of a sensing module and a reporting module [4,21]. The main advantages of whole-cell biosensors are their high sensitivity, which is due to the cells' ability to amplify signals and provide real-time monitoring of cellular processes, specificity, versatility, and biocompatibility. However, the use of whole-cell biosensors has some limitations, including their complexity, sensitivity to environmental factors that may affect their stability, ethical concerns related to genetic engineering, and the cost of production and maintenance.

A natural consortia biosensor refers to a biosensor system consisting of multiple strains or species of microorganisms that work together to detect and respond to specific signals or analytes. The key advantages of this biosensor are its robustness, low cost, eco-friendliness, and complexity, as natural microorganisms have evolved to survive and respond to a range of environmental conditions. However, there are some limitations, including limited specificity due to environmental fluctuations and difficulties in maintaining the microorganisms in laboratory conditions, ethical concerns related to the use of living organisms, and challenges in interpreting results due to the complex responses of the microbial consortia.

A SynCom biosensor is an innovative biosensor technology that employs genetically engineered or natural microbial communities in a biosensing system to capture and convert biosignals from living microorganisms into digital outputs [11]. The core advantage of SynCom biosensors is their ability to address the limitations of cell-free, whole-cell, and consortia biosensors while enhancing their benefits, such as specificity, multifunctionality, modularity (ease of customization by adding or removing microbial strains), and robustness (ability to withstand environmental fluctuations). However, similar to natural consortia biosensors, SynCom biosensors have some complexity and stability issues as well as ethical concerns.

Glossary

Biodigital convergence: a multidisciplinary field that integrates concepts and practices from artificial neural networks, evolutionary algorithms, genetic programming, mathematical biology, and information science. It visually represents biosignals from living organisms with high fidelity through symbolic production and the development of devices and interfaces.

Engineered microorganisms: an artificial microbial consortium created using top-down and bottom-up approaches. This involves utilizing genetically edited and naturally isolated microbial species, integrating multidisciplinary technologies such as synthetic biology, ecological modeling, and artificial intelligence for comprehensive analysis and manipulation.

Logic gate: a basic electronic component that performs basic logical operations such as AND, OR, NOT, and others. In biology, logic gates are applied to model gene regulatory networks, with genes acting as inputs and outputs, and their interactions modeled using Boolean logic, similar to digital circuits.

Microfluidic biosensor: a type of biosensing platform that integrates microfluidic technologies with biosensing mechanisms to detect and analyze specific target molecules or analytes in biological or environmental samples. For example, an ultrasensitive bacterial sensor was constructed for detecting arsenic and mercury, leading to significant improvements in detection limit and output [5].

Nanowire wearable biosensor: a type of biosensing platform that incorporates nanowire-based sensing elements into wearable devices for real-time monitoring of physiological parameters. For example, a bioelectronic ammonia sensor made by *Geobacter sulfurreducens* was constructed to detect ammonia concentrations [47].

One-Health: an integrated unifying approach to balance and optimize the health of people, animals, and the environment (https://www.who.int/news-room/questions-and-answers/item/one-health). It promotes collaboration and cooperation among professionals in human, animal, and environmental health to address health issues that impact these interconnected systems.

Paper-based biosensor: a type of biosensing platform that uses paper as a substrate for detecting biological or chemical targets. For example, a

[9,10]. Whole-cell biosensors are a cost-effective and user-friendly approach to assessing target analytes without complex sample preparation [4,5,21]. For example, an encapsulated microbial sensor cell array with a three-cascade amplifier **logic gate** was developed to detect arsenic and mercury in water [5]. Their ultrasensitive bacterial sensors significantly improved detection limits and outputs for both substances. However, a single living cell has limited functionality and lacks reproducibility [4,5,21]. Some biosensors constructed based on consortia have been proven efficient in analyzing nutrient metabolism *in vivo* and identifying water pollution and pesticides [13,21,22]. Such consortia biosensors are composed of multiple species of microorganisms that work together to detect a target analyte. Each species performs a specific function in the biosensing process, such as signal transduction, amplification, or reporting. The interactions between the species can be complex and are not fully understood, making it difficult to engineer and optimize the biosensor's performance. Another drawback is the uncertainty associated with community construction, as microbial species might be selected randomly from their natural habitats. As a result, the biosignals detected by these consortia biosensors may be unstable and difficult to control.

By contrast, SynCom biosensors will be constructed based on synthetic communities of microorganisms that are engineered to have well-defined functionalities and interactions [23,24]. Each member of a SynCom has a specific role to play in the biosensing process, and the interactions between the members are designed and controlled. Through genome-editing and microbiome-engineering approaches, SynCom systems can sense a wide range of input targets such as optical, electrical, and ecological biosignals due to the configuration of multispecies functionalities and interactions [20,25]. In summary, SynCom biosensors can maintain and combine the benefits of cell-free, whole-cell, and consortia biosensors, including high-throughput workflows, rapid sensing capabilities, and user-friendly interfaces. By leveraging SynCom in biosensing platforms, the performance of microbial-based biosensors can be significantly enhanced, particularly in terms of multifunctionality and adaptability in complex environments [26].

Construction of SynCom biosensors

SynCom biosensors have potential to revolutionize biosensing technology, but their construction is challenging. Question-driven experiments, sequencing technologies, database investigation, and computational platforms are all required for construction [27–32]. To address this difficulty, we propose a conceptual workflow to ensure that SynCom biosensors are generated with desired functions and can be utilized for further applications. This workflow involves selecting microbial target candidates, validating the SynCom, acquiring biosensing signals, and transforming **biodigital convergence**.

Selection of microbial target candidates

The core aspect of SynCom biosensors is their ability to use engineered microorganisms, including simple genetic elements, multiple strains, cocultured species, or various assembled communities [13,22,33]. This increases the ability of biosensors to respond to a broader range of stimuli and produce a more accurate response than other microbial-based biosensors. Therefore, the selection of microbial target candidates is the primary step (Figure 1A). Once the key microbial functions are identified, candidates can be prioritized based on their abundance, functional potential, and known or predicted roles in the microbiome. The process can start with microbiome characterization through metagenomics-enabled microbial surveillance [27]. Later, identification of critical microbial functions can be achieved by utilizing techniques like high-throughput spatial multiomics [30] and genome-scale metabolic models [17]. Finally, the prioritization of microbial candidates can be determined through processes such as circuit-guided synthetic acclimation [15] and multimetabolite crossfeeding coculture systems [7].

biosensing system based on freeze-dried paper could be used for rapid prototyping of complex gene circuits [58].

Steady-state nanochannel biosensor: a type of biosensing platform that uses nanochannels made of solid-state materials, such as silicon or graphene, to detect biomolecules. For example, a digital immunoassay scheme was reported capable of quantifying a target protein in complex biofluids associated with the use of solid-state nanopores [59].

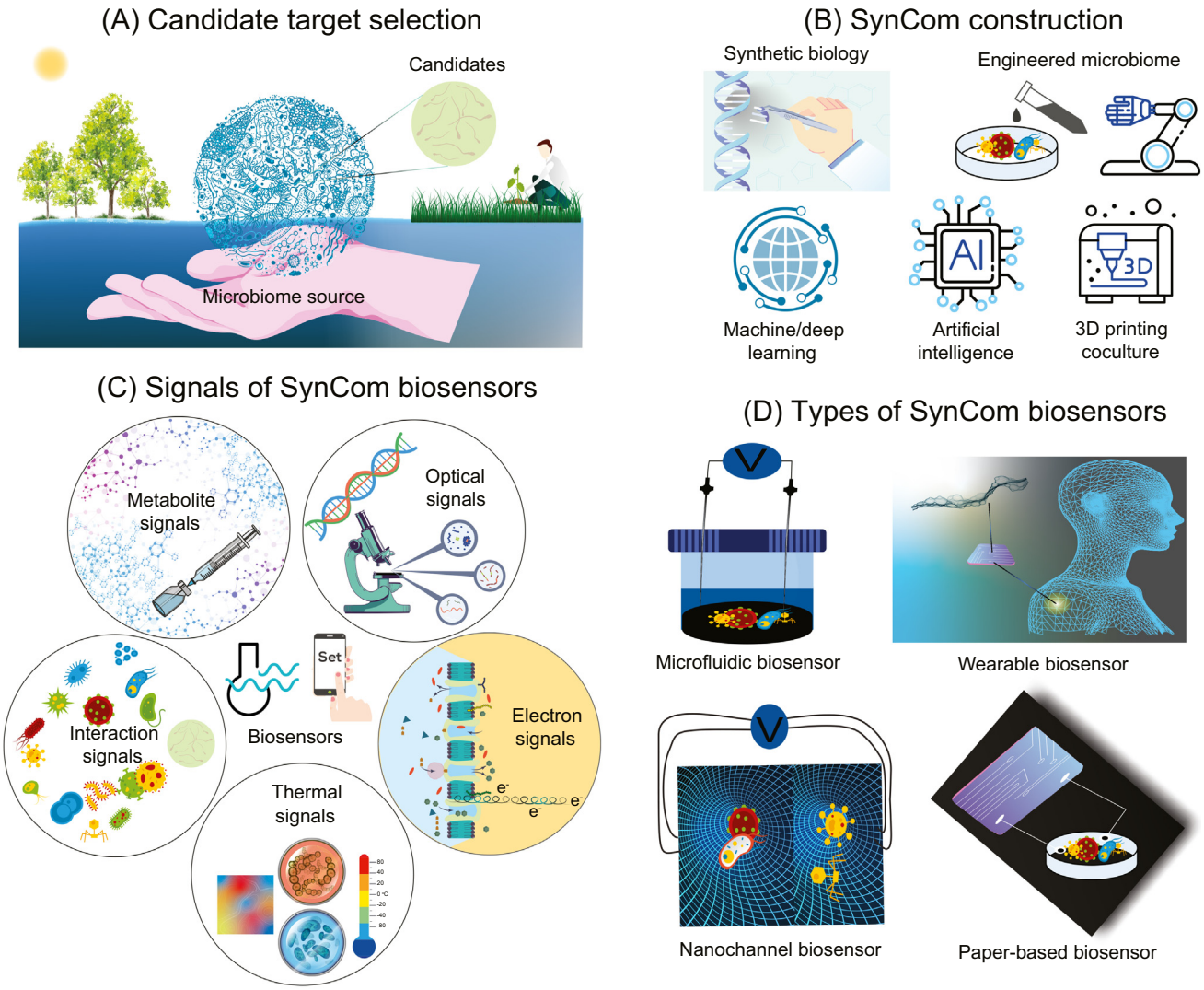

Figure 1. Conceptual construction of synthetic microbial community (SynCom) biosensors. (A) Candidate target selection. (B) SynCom construction includes advancements like synthetic biology, engineered microorganisms, machine/deep learning, artificial intelligence and 3D printing of coculture. (C) SynCom biosensors can emit metabolic, optical, electron, thermal, and interaction signals. These signals can be engineered within different SynCom biosensor modules. (D) SynCom biosensor types, include microfluidic, wearable, nanochannel, and paper-based biosensors. These biosensors can be developed to integrate with Internet of Things (IoT) networks.

The number of strains can be assembled into a SynCom for enhanced functionalities depending on the community complexity, desired function, and the biosensing technology. Successful assemblies of SynCom have been reported with several to hundreds of microbial strains [11,17,18]. However, it is important to note that a complex SynCom can pose challenges, such as potential interactions and interference among the different strains, which can increase the cost and technical requirements of the biosensor system. For example, a consortium comprising alginate-utilizing *Vibrio* sp. dhg and 3-hydroxypropionic acid (3-HP)-producing *Escherichia coli* strains were designed for the direct conversion of alginate to 3-HP [15]. Another community, with two Cr(VI)-reducing strains, *Paenarthrobacter nitroguajacolicus* C1 and *Pseudomonas putida* C2, and an atrazine-degrading strain, *Paenarthrobacter ureafaciens* AT, was built for the

detection of organic pollutants and heavy metals [34]. Additionally, a 193-genome SynCom was studied to predict functional inter-dependencies in the *Arabidopsis* root microbiome [17]. Therefore, the number of strains in a SynCom should be carefully considered and optimized for the intended application of the biosensor.

Construction and validation of SynCom

Next, we could generate a wide variety of functional SynCom based on the microbial candidates and validate their functions step by step. The first step is to identify the desired function or capability required, such as detecting a specific environmental pollutant or producing a particular metabolite. Next, microbial functional groups should be determined based on complementary metabolic capabilities and interactions [11]. These groups can be constructed using various microorganisms, such as producers and consumers, electroactive microorganisms, quorum-sensing microorganisms, and cooperative or competitive microorganisms. Producers and consumers can be used to detect the concentration of metabolites [35], while electroactive microorganisms can generate a measurable current by transferring electrons to the nonelectroactive microorganisms [36]. Microbes that communicate via quorum sensing can be constructed to detect specific molecules that trigger quorum sensing [15]. Cooperative or competitive microorganisms can be used to detect the presence of specific analytes under particular environmental conditions, such as a contaminated site [34].

Constructing SynComs requires careful consideration of the interactions between microorganisms and optimizing their metabolic capabilities to achieve the desired detection sensitivity and specificity. To achieve this, synthetic biologists increasingly use approaches such as computational models and modular DNA parts to engineer microbial consortia [19]. For example, a DNA-editing system called the DART system has precise manipulation of microorganisms without isolation from their living habitats [24]. This approach would reduce the time for the validation of SynCom. Another study proposed the design of a synthetic microbial wine community that uses a feedback control system to maintain responses with individual members [25]. This control system, which includes individual gene-circuit regulation and population-level control, can improve the feedback efficiency in SynCom biosensors. Also, a 3D printing microbial biosensor has been developed for the simultaneous detection of multiplex foodborne bacteria single strand (ss)DNA by smartphone [37]. This technology solves the reproducibility and long-term stability problems encountered in the biosensing technologies [38]. The advances in synthetic biology, engineered microorganisms, and 3D printing coculture will allow for rapid development and testing of SynCom candidates with specific capabilities [19,24,25,38,39] (Figure 1B).

Acquisition of biosignals in SynCom biosensors

Optimizing the design of biosensors and preparing the samples carefully is crucial for reliable detection in SynCom biosensors. The detectable signals of SynCom biosensors are diverse, such as microecological interaction signals [27,40,41], metabolite signals such as cofactors [14], electrochemical shuttles [42], and quorum-sensing molecules [43], and electron transfer signals via electroactive microorganisms [44] (Figure 1C). These biosignals can be engineered to be detected via different reporters like fluorescent [37], luminescent [5], thermal [45], colorimetric [46], electronic [47], or metabolic [14] systems.

The selection of the appropriate signal to magnify by SynCom fundamentally depends on how they respond to their associated biotic/abiotic targets, such as pathogens, heavy metals, and organic pesticides. For example, the detectable signals of SynCom biosensors could be designed based on the microecological interaction signals of quorum-sensing molecules [15,19]. Some microorganisms produce peptide-based electronics, which can be directly measured with the

electrochemical system. After receiving the target signals, SynCom will perform a series of reactions, including response, quantification, and visualization [43,48]. A study of bacteria-powered biobatteries using multiple species demonstrated an enhanced performance through their optimized synergistic interactions [49]. In other situations, a target analyte is used to observe changes in microbial respiration activity, which can be further measured with an electrochemical transducer [42]. Thus, different modules of SynCom biosensors will work together to transform captured signals from a microbial biosensing system into digital signals for real-time reporting.

There is still a concern about the interference of signals in any biosensing system that uses multiple strains. However, with careful selection of strains and optimization of SynCom biosensors, minimizing or eliminating signal interference is possible [33,43,48]. For example, one strain could produce a fluorescent signal while another produces a luminescent signal. The distinct signals from different strain modules will be allocated in one SynCom biosensing system but have nonoverlapping outputs [50]. Another approach is to use synthetic biology to engineer strains that respond to specific signals, such as carbon metabolites, but do not respond to other signals in the environment [23]. Overall, while interference of signals can be a concern, with careful selection of strains and optimization of the biosensing system, it is possible to reliably detect signals of individual strains in a SynCom biosensor. Through the use of engineering approaches, a smart SynCom biosensor could be well-designed with biosensing function and biodigital readability across organic and inorganic substrates in biological, digital, and cyber-physical system integrations [6,51].

Applications of SynCom biosensors

Compared with other microbial-based biosensors like cell-free and whole-cell biosensors, SynCom biosensors can provide a more robust and reliable response by engineering the microbiome to produce different signals in response to a specific stimulus. This capability is particularly valuable in complex environments where multiple stimuli may be present. Additionally, SynCom biosensors can be designed with more functional modules to identify and quantify multiple analytes simultaneously. Moreover, SynCom biosensors can demonstrate increased stability and longevity compared with consortia biosensors. This is because the interactions between the strains in a SynCom are carefully engineered, which can reduce the likelihood of one strain outcompeting another or overgrowing.

SynCom biosensors provide a more stable and reliable response over time due to their ability to detect different targets compared with other microbial-based biosensors. These biosensors can be produced in various forms, such as **paper-based biosensors** [52,53], **microfluidic biosensors** [5], **steady-state nanochannel biosensors** [54], and **nanowire wearable biosensors** [8,38,47] (Figure 1D). For example, a microfluidic biosensor was designed to detect multiple foodborne bacterial pathogens in milk and water samples for food safety analysis [37]. Another biosensor utilizing protein nanowires from electroactive microorganisms showed improved performance in detecting ammonia across a wider concentration range [47]. In microbial therapy scenarios, an approach leveraging transcriptional repressors to control bacterial gene expression demonstrated promising potential [45]. Additionally, engineered microbial biofilms has been used as a flexible biomaterial that can produce electricity from evaporating water, providing a potential source for evaporation-based electricity generation [36]. These technology-based biosensors will have wide-ranging applications in agriculture and food production [35,52], biotherapeutic development [16], and home sensing [8].

Moreover, SynCom biosensors have the potential to be applied in tracking and analyzing various aspects of urban and natural environments, providing valuable information for public health and safety measures [5,36,55]. For instance, these biosensors can be utilized for detecting heavy

metal and organic pollutants, enabling the development of practical SynCom biosensors for environmental monitoring [2,5,34]. By identifying areas of concern and informing policy decisions related to the **One Health** foundation [56], SynCom biosensors can contribute to the overall goal of improving global health. In summary, SynCom biosensors will offer a powerful tool for detecting various targets with high specificity and accuracy, making them suitable for applications in different fields, including agriculture, industry, healthcare, and environmental monitoring.

Challenges of SynCom biosensors

Designing SynCom biosensors capable of effectively detecting a broad range of analytes and functioning in diverse environments beyond the laboratory is a complex task. This requires a comprehensive understanding of microbial physiology and ecology, allowing communication and coordination among multiple species. While challenging, this underscores the need to advance biosensing technology. In addition to the design complexities, integrating SynCom biosensors with internet networks and cloud-based analytics represents a substantial challenge. Such integration demands specialized expertise in hardware engineering, software development, and data science. It also requires significant investment in personnel, equipment, and software licenses. In addition, organizations must approach the development of integrated systems with care and precision, ensuring the systems are reliable, scalable, and secure. Ensuring regulatory compliance is also critical. Standardization and validation protocols must be established to guarantee the safety and reliability of SynCom biosensors. This involves adhering to rigorous regulatory oversight and ensuring that the technology is transparent, accessible, and beneficial to all. Addressing these challenges necessitates a considerable investment in technology, infrastructure, and regulatory compliance, but the potential benefits make the effort worthwhile.

While developing and optimizing biosensors can be expensive, the cost-effectiveness of SynCom biosensors is relative to the application and alternative technologies available for that application. In the previous section, we mentioned that SynCom could be engineered to generate different signals like fluorescent and luminescence within different biosensing modules. This indicates that SynCom biosensors offer promising prospects for decreasing the need for expensive equipment. In the meantime, it is important to consider biosafety risks of SynCom biosensors before their release into the market. To address this, suicide genes or linguistic barriers can be incorporated into the biosensor design to ensure biosafety [20]. These genetic elements are programmed to encode toxic products that can eliminate the biosensor cells or consortia if released into the environment and prevent the SynCom biosensors from persisting and potentially causing harm in nature. This approach ensures that the SynCom biosensors self-destruct or lose their functional properties after completing their intended task, minimizing the risk of unintended consequences.

To deploy SynCom biosensors in various environments beyond the laboratory, challenges such as maintaining the viability of living microorganisms, developing synthetic platforms with long-term stability, seamlessly integrating biology with minimal equipment and resource requirements, automating processes to minimize the need for experienced professionals, and mitigating potential biosafety risks must be approached [4,16,35]. Collaboration between academia, industry, and regulatory agencies is crucial to develop guidelines and standards for their development and use. The development of secure, reliable, and scalable data networks is also critical for successful implementation. Overall, overcoming these challenges is necessary to unlock the full potential of SynCom biosensors in various fields.

Outlook for SynCom biosensors

Despite the challenges associated with developing SynCom biosensors, recent breakthroughs in metabolic modeling [17], synthetic biology [25], artificial intelligence [6], microbiome engineering

[15,24], consortia design [7], genome mining [31], machine and deep learning applications in microbiome research [32], and the perspective of the Internet of Things (IoT) [8,57] have shown promise for the development and adoption of SynCom biosensors. By pinpointing biological properties that limit selectivity, labor of division, and dynamic range, we can improve the overall sensing performance of biosensors.

By customizing these biosensors to detect specific molecules or parameters, they can transmit biosensing information through cellular signals to the designated platform in real time. For instance, an IoT-enabled SynCom biosensor that is programmed to detect a specific plant pathogen could provide real-time warning to growers so they can respond with an appropriate control method. Industry 4.0 encompasses a new industrial revolution in which advanced manufacturing systems are interconnected with information technologies [6]. The future availability of IoT will allow the system to monitor the parameters at regular intervals, so an IoT-enabled microbial system can be applied to accomplish the communication between users and the monitoring system [57].

This opinion article outlines a set of principles and guidelines for constructing SynCom for biosensing applications, which includes community composition, interaction dynamics, and environmental context considerations. We have highlighted the advantages of SynCom biosensors over traditional biosensing approaches. Additionally, we provide a workflow for the proposed biosensors to ensure the desired functions and further applications, which will refresh the knowledge of biosensing areas. Integrating SynCom biosensors with IoT technology will have the potential to revolutionize several fields, such as agriculture and food management, biotherapeutic development, home sensing, urban and environmental monitoring, and the One Health foundation [40,56].

Concluding remarks

In summary, SynCom biosensors have the potential to revolutionize fields such as healthcare, environmental monitoring, and food safety. However, practical implementation of the technology requires further optimization and refinement. Increasing biosensors' sensitivity and limits for detecting low levels of targets in complex samples is a key priority. Addressing biosensor specificity and potential crossreactivity with other targets and developing more stable and durable biosensors that can function in harsh environmental conditions are other priorities for future research. These priorities require researchers to address outstanding questions (see Outstanding questions), including how SynCom biosensors advance beyond other microbial-based sensors, effective manipulation of the biosensing system, biosafety concerns, and improving accessibility and performance. Recent breakthroughs in synthetic biology, engineered microorganisms, and artificial intelligence can facilitate the development of SynCom biosensors. Besides, successful construction of biosensors requires interdisciplinary collaboration between academia, industry, and regulatory agencies. By addressing these questions, the full potential of SynCom biosensors can be unveiled, leading to significant biotechnological innovations and transformative impacts on society.

Outstanding questions

How can microbial consortia be controlled and manipulated in a biosensing system, particularly regarding growth conditions and function?

How can the biosafety of SynCom biosensors be defined?

What are the challenges and potential solutions for improving the accessibility and performance of microbial biosensing approaches, including the biomanufacturing of SynCom biosensors and signal acquisition from consortia?

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Declaration of interests

None are declared by the authors.

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