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REVIEW ARTICLE

DAWN OF SYNTHETIC BIOLOGY ENGINEERING LIFE AT THE MICROSCOPIC SCALE: A REVIEW

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Abstract

Synthetic biology, converging biology, engineering and computer science, allows the design of new biological systems, promising revolutions in healthcare, agriculture and environmental sustainability. Its core principles—modularity, abstraction hierarchies, orthogonality, predictability, and standardization—enable systematic biological engineering. Modularity breaks complex systems into manageable parts, while abstraction hierarchies organize these parts by complexity. Orthogonality ensures independent function of synthetic components and predictability is achieved through modeling and computation. Standardization promotes reproducibility and collaboration. Mechanistically, synthetic biology manipulates DNA, designs genetic circuits and metabolic pathways and applies physical and computational principles. Techniques like PCR and DNA sequencing construct recombinant DNA. Genetic circuits control gene expression and metabolic engineering optimizes pathways. Integrating Artificial Intelligence (AI) and Machine Learning (ML) accelerates innovation by analyzing data, predicting protein structures and automating experiments, improving drug and therapy development.Synthetic biology can address global challenges like infectious diseases, climate change and food security, in addition to the potential applications in the medical and pharmaceutical sectors. By understanding its principles and using advanced technologies, researchers can realize the field's potential for a better future.

Keywords: Abstraction hierarchies, AI, DNA, ML, modularity, orthogonality, PCR.

INTRODUCTION

Synthetic biology is a groundbreaking area within biotechnology that combines engineering and biological principles to create and build novel biological components, devices, and systems[1]. This interdisciplinary field has advanced quickly, fueled by progress in genetic engineering, computational biology, and systems biology[2]. While synthetic biology holds potential for diverse applications, from environmental solutions to industrial biotechnology, its applications within the pharmaceutical industry are particularly promising and impactful[3]. The capacity to engineer biological systems at the microscopic level provides unparalleled opportunities for creating new therapeutics, vaccines and diagnostic tools[4]. Synthetic biology allows for the precise manipulation of genetic material, enabling the development of customized microorganisms that can produce complex pharmaceuticals that were previously challenging or impossible to synthesize. This concise review will examine the fundamental concepts of synthetic biology, emphasize significant technological developments, and discuss its current and future applications in pharmaceutical development. This exploratory review aims to discuss the innovative field of synthetic biology, focusing on the creation and engineering of life at the microscopic level, with a particular emphasis on its use in pharmaceutical applications.

Foundational principles of synthetic biology

Synthetic biology is an interdisciplinary field that combines principles from biology, engineering and computer science to design and construct new biological entities or redesign existing biological systems for useful purposes[5]. This field has emerged as a powerful approach to understanding and manipulating biological systems, offering the potential to revolutionize various sectors, including healthcare, agriculture and environmental management[6]. The foundational principles of synthetic biology are rooted in the systematic and standardized manipulation of genetic material, enabling the creation of novel biological functions and systems[7].

One of the core principles of synthetic biology is the concept of modularity, which involves breaking down complex biological systems into smaller, manageable parts or modules[8]. These modules, often referred to as "biological parts," can be standardized and recombined in various ways to create new functions. This approach is akin to using interchangeable parts in mechanical engineering, allowing for the rapid prototyping and testing of new biological designs[9]. The Registry of Standard Biological Parts, also known as the BioBrick registry, is a key resource in this regard, providing a collection of standardized DNA sequences that can be used to build synthetic biological systems. Another fundamental principle is the use of abstraction hierarchies to manage the complexity of biological systems. Abstraction in synthetic biology involves organizing biological components into different levels, such as parts, devices and systems. This hierarchical approach simplifies the design process by allowing synthetic biologists to focus on one level of complexity at a time, without being overwhelmed by the details of lower levels. For example, a genetic circuit can be designed at the device level using standardized parts, without needing to consider the intricate molecular interactions at the part level. The principle of orthogonality is also crucial in synthetic biology. Orthogonality refers to the ability of synthetic biological components to function independently of the host organism's native biological processes. This ensures that the introduced synthetic systems do not interfere with the host's natural functions, thereby reducing the risk of unintended consequences. Achieving orthogonality often involves designing synthetic components that use unique molecular interactions or pathways that are not present in the host organism. Synthetic biology also emphasizes the importance of predictability and reliability in the design and construction of biological systems. This is achieved through the use of mathematical modeling and computational tools to predict the behavior of synthetic biological systems before they are constructed. By simulating the interactions and dynamics of biological components, synthetic biologists can identify potential issues and optimize designs for desired outcomes. This predictive approach reduces the trial-and-error aspect of biological experimentation, making the engineering of biological systems more efficient and reliable. In addition to these principles, synthetic biology relies heavily on the concept of standardization. Standardization involves creating uniform protocols and measurement techniques to ensure that biological parts and systems can be reliably reproduced and shared among researchers. This is essential for the collaborative nature of synthetic biology, as it allows researchers from different backgrounds and institutions to work together effectively. Standardization also facilitates the scaling up of synthetic biological systems for industrial and commercial applications. Overall, the foundational principles of synthetic biology modularity, abstraction, orthogonality, predictability and standardization provide a robust framework for the systematic engineering of biological systems. These principles enable synthetic biologists to design and construct novel biological functions with precision and reliability, paving the way for innovative solutions to some of the most pressing challenges in medicine agriculture, and environmental sustainability[10-17]. Table 1 elucidates the fundamental principles underpinning synthetic biology: Modularity: This means breaking down complex biological systems into smaller, manageable parts. It could be viewed like building with a blocks game, where each block is a piece that can be used to create something bigger.

Abstraction Hierarchies: This involves organizing biological parts into different levels, such as parts, devices, and systems. It's like organizing a library where books are sorted into sections, shelves and individual books, making it easier to find what is needed.

Table 1: Depiction of foundational principles of synthetic biology with examples.

Principle	Description	Example
Modularity	Breaking down complex biological systems into smaller, manageable units.	BioBricks: Standardized DNA sequences used to build genetic circuits. For example, BioBricks have been used to create bacteria that produce biofuels[1].
Abstraction Hierarchies	Organizing components into different levels of complexity, enabling the design of genetic circuits at the device level.	Biosensors: Using abstraction hierarchies, scientists have developed E. coli that glow green in the presence of lead, simplifying the detection of lead contamination[2].
Orthogonality	Ensuring synthetic components function independently of the host organism's native processes, often achieved through unique molecular interactions.	Orthogonal tRNA: Engineered tRNA molecules that do not interact with the host's native tRNA, allowing for the incorporation of non-natural amino acids into proteins[3].
Predictability and Reliability	Designing functional systems with predictable and reliable behavior, using mathematical modeling and computational tools to simulate and optimize designs.	CRISPR-Cas9: The use of CRISPR-Cas9 for gene editing relies on predictable and reliable targeting of specific DNA sequences to make precise genetic modifications[1].
Standardization	Standardizing protocols and measurement techniques to facilitate reproducibility and sharing of biological parts and systems.	Gibson Assembly: A standardized method for assembling DNA fragments, widely used in synthetic biology for constructing complex genetic constructs[4].

Orthogonality: This ensures that synthetic biological parts work independently from the host organism's natural processes. It's like adding a new app to your phone that doesn't interfere with the phone's existing functions.

Predictability and reliability: This is about using mathematical models and computer tools to predict how synthetic biological systems will behave. It's like using a weather forecast to predict the weather, helping scientists design experiments that are more likely to succeed.

Standardization: This involves creating uniform methods and measurements so that biological parts can be reliably reproduced and shared among researchers. It's like having a standard recipe that anyone can follow to bake the same cake, ensuring consistency and collaboration. Table 2 shows the experiments that highlight the progressive advancements in synthetic biology, showcasing the ability to design and construct organisms with entirely synthetic genomes[18-22]. Each step builds on previous knowledge, pushing the boundaries of what is possible in creating life from basic biological components.

Table 2: Key experiments performed to achieve complete synthetic organisms[18-22].

Year	Experiment	Description
2010	Creation of JCVI-syn1.0	Scientists at the J. Craig Venter Institute (JCVI) created the first cell with a synthetic genome. They started with Mycoplasma cells, destroyed their DNA and replaced it with DNA designed on a computer and synthesized in a lab.
2016	Development of JCVI-syn3.0	JCVI researchers stripped down the synthetic organism to its minimum genetic components, creating a cell with only 473 genes, the simplest living cell known at the time.
2021	JCVI-syn3A	Scientists identified seven additional genes needed for normal cell division, creating JCVI-syn3A, which grows and divides more uniformly. This variant has fewer than 500 genes.
2018	BaSyC Project	Researchers from the Netherlands formed the Building a Synthetic Cell (BaSyC) group, aiming to construct a cell-like system that can grow and divide within ten years.
2019	Synthetic Yeast Genome Project (Sc2.0)	The Sc2.0 project aimed to synthesize the entire genome of Saccharomyces cerevisiae, a model organism in genetics and biotechnology.

Science behind synthetic biology

Synthetic biology utilizes the systematic and standardized manipulation of genetic material to generate new biological functions and systems. A mechanistic understanding of this field requires a thorough examination of molecular biology, biophysics and computational modeling that support these engineered systems. Central to synthetic biology is the manipulation of DNA, the molecule containing genetic information. DNA is composed of nucleotides, each consisting of a phosphate group, a sugar molecule and a nitrogenous base. The order of these bases (adenine, thymine, cytosine, and guanine) dictates the genetic instructions. Synthetic biologists employ techniques like polymerase chain reaction (PCR) to amplify DNA sequences and DNA sequencing to read these sequences. DNA manipulation frequently involves restriction enzymes, which cleave DNA at specific sequences and ligases, which connect DNA fragments. This enables the creation of recombinant DNA molecules, which can be introduced into host organisms through processes like transformation, transfection or electroporation. The design of synthetic biological systems frequently uses the concept of genetic circuits, which are analogous to electronic circuits. These circuits comprise promoters, ribosome binding sites, coding sequences and terminators. Promoters are DNA sequences that initiate transcription, the process by which RNA polymerase creates messenger RNA (mRNA) from a DNA template. Ribosome binding sites are sequences that facilitate the binding of ribosomes to mRNA, initiating translation, the process by which proteins are synthesized from mRNA. Coding sequences are the portions of DNA that encode proteins and terminators signal the end of transcription[22-32]. The behavior of genetic circuits can be modeled using differential equations that describe the rates of transcription, translation and degradation of mRNA and proteins. For example, the rate of change of mRNA concentration ((m)) can be described by the equation:

$dtdm=\alpha-\beta m$

The variable α represents the transcription rate, while β represents the mRNA degradation rate. The rate at which protein concentration (p) changes can be expressed analogously:

$$dtdp=\gamma m-\delta p$$

In these equations, γ represents the translation rate, while δ represents the protein degradation rate. Numerical solutions to these equations allow for predictions of genetic circuit behavior under varying conditions. Beyond genetic circuits, synthetic biology also encompasses the engineering of metabolic pathways. Metabolic pathways are sequential chemical reactions within a cell, each catalyzed by a specific enzyme. These pathways can be engineered for the production of valuable compounds, including pharmaceuticals, biofuels, and industrial chemicals. Metabolic pathway design frequently utilizes stoichiometric models, which detail the balance of reactants and products in each reaction. These models can be represented as systems of linear equations, solvable through techniques like Flux Balance Analysis (FBA). FBA optimizes metabolite flow within a reaction network to maximize the production of a target compound.

The physical principles underpinning synthetic biology are grounded in thermodynamics and kinetics. Thermodynamics dictates the stability and equilibrium of biological molecules, whereas kinetics describes the rates of biochemical reactions[22-32]. The Gibbs free energy (ΔG) of a reaction determines its spontaneity. A spontaneous reaction requires a negative ΔG. The

Gibbs free energy change for a reaction can be calculated using the equation:

$$\Delta G=\Delta H-T\Delta S$$

where (\Delta H) is the change in enthalpy, (T) is the temperature, and (\Delta S) is the change in entropy. Enzyme kinetics, on the other hand, is described by the Michaelis-Menten equation:

$$v=Km+[S]Vmax[S]$$

The equation v = (V_{max}[S])/([S] + K_m) expresses the relationship between reaction rate (v), maximum reaction rate (V_{max}), substrate concentration ([S]) and the Michaelis constant (K_m). This equation illustrates how the reaction rate is influenced by both the substrate concentration and the enzyme's attraction to the substrate. Computational tools are essential in synthetic biology for designing and analyzing biological systems. Bioinformatics tools facilitate the analysis of genomic and proteomic data, enabling the identification of genetic elements and predictions of protein structure and function. Machine learning (ML) algorithms can model the behavior of genetic circuits and metabolic pathways based on empirical data. Computational models allow for simulations of biological system dynamics, enabling synthetic biologists to test hypotheses and refine designs prior to laboratory experimentation. The convergence of synthetic biology with other fields, such as nanotechnology and materials science, has facilitated the creation of innovative applications. For instance, synthetic biology can engineer bacteria to produce nanomaterials with specific properties, like improved conductivity or biocompatibility. These nanomaterials have diverse uses, including drug delivery, biosensing and tissue engineering. In pharmaceutical applications, synthetic biology allows for the production of intricate drugs that are challenging to synthesize using conventional chemical methods. For example, the production of artemisinin, an antimalarial drug, has been enhanced using engineered yeast strains. These strains have been genetically modified to express the enzymes necessary for artemisinin biosynthesis from simple sugars. Optimizing this pathway involved employing metabolic engineering techniques to balance the flow of intermediate compounds and maximize the final product yield. The advancement of synthetic biology also presents significant ethical and safety considerations. The release of genetically modified organisms (GMOs) into the environment requires careful management to prevent unforeseen ecological consequences. The possibility of synthetic biology being misused for bioterrorism or the creation of dangerous biological agents necessitates strict regulatory oversight. Researchers must comply with biosafety and biosecurity guidelines to ensure the responsible and safe application of synthetic biology. In conclusion, synthetic biology is a rapidly advancing field that integrates principles from biology, engineering, and computer science to design and build novel biological systems. The mechanistic understanding of synthetic biology encompasses DNA manipulation, the design of genetic circuits and metabolic pathways, and the application of physical and computational principles[22-38]. This interdisciplinary approach enables the development of innovative solutions for a wide range of applications, from pharmaceuticals to nanotechnology, while also necessitating careful consideration of ethical and safety issues.

Using synthetic biology in pharmaceutical applications: A model guide

Synthetic biology is revolutionizing the pharmaceutical industry by providing innovative solutions for drug discovery, development and production. Theoretically, several concepts must be born in mind when aiming to transfer this technology into the industry. This guide outlines the steps involved in leveraging synthetic biology for pharmaceutical applications, focusing on practical and actionable strategies. Before delving into specific applications, it is essential to grasp the foundational principles of synthetic biology, which serve as the starting point for any synthetic biology project. These principles include, as stated earlier some concepts that must be familiar before excursion of new research. Synthetic biology hinges on several core principles. Modularity involves the decomposition of complex biological systems into smaller, manageable parts, simplifying analysis and manipulation. Abstraction hierarchies organize these components into hierarchical levels, enabling a systematic approach to biological complexity. Orthogonality ensures the independent function of synthetic components within the host organism, minimizing unintended interactions and maximizing control. Predictability and reliability are achieved through mathematical modeling and computational tools, allowing for accurate prediction and optimization of system behavior. Standardization of protocols and measurement techniques promotes reproducibility, collaboration, and rapid advancement in the field. By understanding and applying these principles, researchers can effectively design and implement synthetic biology projects, driving innovation in various fields, including medicine, agriculture and environmental science. The first step in applying synthetic biology to pharmaceuticals is identifying specific needs within the industry. These can include drug discovery, production, personalized medicine, vaccine development and disease modeling. Once the needs are identified, the next step is designing synthetic biological systems to address these needs. This involves selecting biological parts, constructing genetic circuits and modeling and simulating the systems. After designing the synthetic systems, the next step is building and testing them in the lab. This includes DNA assembly, transformation, screening and selection and functional testing. Once a functional synthetic system is developed, it needs to be optimized and scaled for industrial use. This involves optimization, fermentation and bioprocessing and purification. Ensuring that the synthetic biology applications comply with regulatory standards is crucial. This includes safety assessments, regulatory approval and quality control. For pharmaceutical applications, clinical trials are essential to validate the efficacy and safety of the new drugs or therapies. This involves preclinical studies, Phase I, II and III trials and Phase IV trials. After successful clinical trials, the final step is bringing the synthetic biology-based pharmaceutical product to market. This involves manufacturing, distribution and marketing. To illustrate these steps, there are a few case studies that have successfully implemented synthetic biology breakthroughs in pharmaceutical applications. As mentioned earlier, Artemisinin production, CAR-T cell therapy and synthetic vaccines are examples of how synthetic biology has revolutionized the pharmaceutical industry. The future of synthetic biology in pharmaceuticals holds immense potential, with advancements in gene editing, synthetic microbiomes, biosensors and personalized therapies. Synthetic biology offers a powerful toolkit for transforming pharmaceutical applications[17,33-41]. The integration of modularity, abstraction hierarchies, orthogonality, predictability, and standardization ensures that these synthetic systems are designed and implemented with precision and reliability, paving the way for a new era in medicine.

Leveraging AI and ML in synthetic biology for pharmaceutical applications

Artificial Intelligence (AI) and Machine Learning (ML) are transforming synthetic biology, particularly in the pharmaceutical industry. These technologies enhance the design, development and production of new drugs and therapies. The following sectionsoutlineshighlights on steps on how to effectively integrate AI and ML into synthetic biology for pharmaceutical applications[42-57].

1. Understanding the Role of AI and ML in synthetic biology

AI and ML can process vast amounts of biological data, identify patterns and make predictions that are beyond human capability. In synthetic biology, these technologies are used to:

- **Analyze Genomic Data**: AI and ML can analyze large genomic datasets to identify potential drug targets.
- **Predict Protein Structures**: These technologies can predict the 3D structures of proteins, which is crucial for drug design.
- **Optimize Metabolic Pathways**: AI and ML can optimize the metabolic pathways in microorganisms to enhance the production of pharmaceuticals.
- **Automate Experimentation**: AI-driven automation can streamline the Design-Build-Test-Learn (DBTL) cycle in synthetic biology.

2. Data Collection and Preparation

The first step in using AI and ML in synthetic biology is collecting and preparing data:

- **Genomic Data**: Genomic sequences from public databases or through sequencing projects are collected.
- **Phenotypic Data**: Data on the observable characteristics of organisms, such as growth rates and metabolite production are gathered.
- **Experimental Data**: Data from laboratory experiments, including results from genetic modifications and metabolic engineering are collected.

Data preparation involves cleaning and organizing the data to ensure it is suitable for analysis. This includes removing duplicates, filling in missing values and standardizing formats.

3. Building Predictive Models

Once the data is prepared, the next step is building predictive models using AI and ML:

- **Feature Selection**: The most relevant features (variables) that influence the outcome of interest should be identified. For example, in drug discovery, features might include gene expression levels and protein interactions.
- **Model Selection**: Appropriate ML algorithms based on the type of data and the problem at hand should be choosen carefully. Common algorithms include decision trees, random forests, support vector machines and neural networks.
- **Training and Validation**: The models on a subset of the data should be trained and their performance on a separate subset must be validated. This helps ensure the models can generalize to new, unseen data.

4. Integrating AI and ML into the DBTL Cycle

The DBTL cycle is a core process in synthetic biology and AI and ML can enhance each stage:

- **Design**: AI is used to design genetic constructs and metabolic pathways. For example, AI can predict the effects of gene edits on metabolic fluxes.
- **Build**: The construction of genetic circuits is automated using robotic systems controlled by AI algorithms.
- **Test**: ML is used to analyze experimental data and identify successful constructs. High-throughput screening techniques can generate large datasets that ML algorithms can quickly analyze.
- **Learn**: ML is applied to learn from experimental results and refine the design process. This iterative learning helps improve the accuracy and efficiency of synthetic biology projects[58].

5. Case Study Concept: AI-Driven Drug Discovery

A practical example of AI and ML in synthetic biology is AI-driven drug discovery:

- **Target Identification**: AI algorithms analyze genomic and proteomic data to identify potential drug targets. For instance, deep learning models can predict which proteins are involved in disease pathways.
- **Compound Screening**: Virtual screening using AI can evaluate millions of compounds to identify those most likely to bind to the target protein. This reduces the need for extensive laboratory testing.
- **Lead Optimization**: AI models can predict the pharmacokinetic and pharmacodynamic properties of drug candidates, helping to optimize their efficacy and safety.
- **Clinical Trials**: AI can analyze patient data to identify suitable candidates for clinical trials and predict potential side effects.

6. Optimizing Metabolic Pathways

In pharmaceutical production, optimizing metabolic pathways in microorganisms is crucial for efficient drug synthesis:

- **Pathway Design**: AI can design metabolic pathways by predicting the effects of gene edits on metabolic fluxes. This involves using constraint-based models and flux balance analysis.
- **Strain Optimization**: ML algorithms can analyze experimental data to identify genetic modifications that enhance production yields. Techniques like adaptive laboratory evolution can be guided by AI to evolve strains with desired traits.
- **Process Optimization**: AI can optimize fermentation conditions and bioprocess parameters to maximize production efficiency. This includes adjusting factors like temperature, pH and nutrient concentrations.

7. Automating Laboratory Processes

Automation is a key benefit of integrating AI and ML into synthetic biology:

- **Robotic Systems**: AI-driven robotic systems can automate repetitive tasks such as pipetting, colony picking and DNA assembly. This increases throughput and reduces human error.
- **High-Throughput Screening**: AI can control high-throughput screening platforms to rapidly test thousands of genetic constructs. ML algorithms analyze the results to identify successful variants.
- **Data Management**: AI can manage and analyze large datasets generated by automated experiments, providing insights that guide further research.

8. Ensuring Data Security and Ethical Compliance

With the integration of AI and ML, ensuring data security and ethical compliance is essential:

- **Data Privacy**: Robust data privacy measures must be implemented to protect sensitive genomic and patient data.
- **Ethical Considerations**: Ethical concerns related to genetic modifications and AI decision-making should be addressed. This includes obtaining informed consent and ensuring transparency in AI algorithms.
- **Regulatory Compliance**: Compliance with regulatory standards for data handling and synthetic biology practices must be ensured. This includes adhering to guidelines from bodies like the FDA and EMA.

9. Future Directions

The future of AI and ML in synthetic biology holds immense potential:

- **Advanced AI Models**: Developing more sophisticated AI models that can handle complex biological data and make more accurate predictions.
- **Integration with other technologies**: Combining AI and ML with other emerging technologies like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and nanotechnology to create more powerful synthetic biology tools.
- **Personalized Medicine**: Using AI to develop personalized therapies based on individual genetic profiles, leading to more effective and targeted treatments.
- **Sustainable Production**: Leveraging AI to optimize the production of pharmaceuticals in a sustainable and environmentally friendly manner.

AI and ML are powerful tools that can significantly enhance synthetic biology, particularly in pharmaceutical applications. By following the steps outlined in this guide, researchers and companies can harness the potential of these technologies to develop innovative drugs, optimize production processes and automate laboratory workflows[42-58]. The integration of AI and ML ensures that synthetic biology projects are more efficient, accurate and scalable, paving the way for groundbreaking advancements in medicine.

CONCLUSIONS

Synthetic biology, a burgeoning field at the intersection of biology, engineering, and computer science, has emerged as a powerful tool for engineering life at the microscopic scale. By systematically manipulating genetic material and applying principles of modularity, abstraction, orthogonality, predictability and standardization, researchers are able to design and construct novel biological systems with unprecedented precision. The integration of advanced computational tools, such as ML and AI, further enhances the capabilities of synthetic biology, enabling the prediction, optimization and automation of complex biological processes. The potential applications of synthetic biology are vast and far-reaching, with significant implications for healthcare, agriculture and environmental sustainability. In the pharmaceutical industry, synthetic biology is revolutionizing drug discovery, development and production. By engineering microorganisms to produce therapeutic compounds, researchers can accelerate the development of novel drugs and reduce production costs. Additionally, synthetic biology can be used to create personalized medicines tailored to the specific genetic makeup of individual patients. However, the rapid advancement of synthetic biology also raises important ethical considerations. As scientists gain increasing control over the fundamental building blocks of life, it is imperative to carefully consider the potential risks and benefits of this technology. Rigorous ethical guidelines and international cooperation are essential to ensure the responsible and beneficial use of synthetic biology. In the future, synthetic biology is poised to continue its trajectory of innovation, with exciting developments on the horizon. The integration of emerging technologies, such as CRISPR-Cas9 gene editing and synthetic organelles, will further expand the capabilities of this field. By addressing grand challenges, such as climate change, food security and infectious diseases, synthetic biology can play a pivotal role in shaping a sustainable and prosperous future.

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AUTHOR'S CONTRIBUTION

Eissa ME: conceived the idea, writing the manuscript, literature survey, formal analysis, critical review.

DATA AVAILABILITY

Upon request, the accompanying author can furnish the empirical data used to bolster the findings of the study.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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