Health Nanotechnology

REVIEW

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The power of deoxyribonucleic acid and bio-robotics in creating new global revolution: a review

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Abstract

The fourth industrial revolution is ushering in a new era for AI, big data, and omnipresent robots. The breakthrough in biotechnology, particularly the deep understanding of the genome, has led to the emergence of bio-robotics. DNA, which contains all genetic information, is used in big-data storage in a way similar to that of silicon chips. This has enabled the creation of DNA-based and DNA-encoded machines necessary for developing bio-robotics capable of mimicking human intelligence and performing human-like actions and beyond. Bio-robotics has the potential to bridge the gap between humans and machines. The advancement of genetic engineering and 3D/4D bio-printing technologies has made biotechnology's application far-reaching. This has paved the way for synthetic biology using the central dogma of molecular biology, to produce automated or bio-robot-assisted life-made products. Despite the important role of biologics in modern biotechnological endeavors, bio-robotics also pose some risks that necessitate cautiousness, particularly in certain areas. Therefore, it is crucial to thoroughly investigate future advancements in robotics and develop clear legal and ethical procedures to ensure the harmonious coexistence of Society in the 5.0 industrial revolution with automated industries and biotechnology research. Overall, bio-robotics is an up-and-coming field with the potential to transform many aspects of our lives. However, it is critical to be aware of the potential risks and take proactive measures to tackle upcoming challenges. Most importantly, bio-robotics should never be allowed to operate beyond human control.

Keywords DNA, Bio-printing, Bio-robotics, Synthetic Biology, DNA computation, Bio-robots-ethics

Introduction

In the early decades of the twenty-first century, there have been concerted efforts to integrate research based on the interconnectedness of nature, leading to the integration of nanotechnology, biotechnology, information technology, and new cognitive science-based technologies [117]. The fourth industrial revolution is characterized by the convergence of the physical, digital, and biological realms which is rapidly reshaping the current global economy. The international operating system is experiencing rapid change due to emerging technologies such as automation, omnipresent robotics, artificial intelligence (AI), machine-to-machine communication, the Internet of Things [46], and big data [68]. Consequently, with the emergence of a paradigm shift in the 5.0 industrial revolution, the integration of AI into daily human life seems essential with the aim of empowering human capacity through collaborative interaction at the core of the universe [125]. This necessitates wisdom in all fields to adapt to these sophisticated emerging technologies and ensure their sustainability and existence in the 5.0 industrial revolution [62].

The 4.0 industrial revolution envisions replacing subject (*human*)-object (*technical devices*) interaction with

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object-object interaction. The advancement of genetics and robotics in the USA points towards the goals of the 4.0 industrial revolution that are coming to fruition [48], facilitating the integration of physical and biological systems.

Biologists who adhere to dialectical materialism now consider the mechanical theory of the organism, previously accepted as a dogma in biology, as a narrow and insufficient perspective. In the past, the relationship between machines and organisms has been explored mainly from one angle: the structure and function of the organisms have been explained by comparing them to an existing machine. Philosophers and mechanist biologists have generally assumed the existence of machines or, when examining their design, have relied on human calculations. Machine movements are typically understood as geometric and measurable displacements. It is traditional to present the construction of the locomotive as a "marvel of science". The proposed solution that people have tried to defend has the advantage of demonstrating continuity with life through technology before emphasizing the break for which humans are responsible through science [28]. Scientific and engineering developments frequently highlight the shortcomings of traditional methods previously employed to comprehend, forecast, and regulate occurrences. As technological limitations are overcome, the fields of developmental biology and robotics offer new opportunities, leading to practical applications ranging from regenerative medicine to the development of useful synthetic living machines [23].

The recent progress in biotechnology, particularly genetic engineering, has resulted in the emergence of unpredicted outcomes. The field of bio-robotics has been significantly shaped by biotechnology, particularly through the integration or fusion of DNA, or nucleic acid with computer decoders, which has led to the creation of advanced humanoid robots. Studies have shown that biotechnology used to produce robots that behave like biological organisms, such as walking, moving, sensing their environment, adapting to changing situations, and working independently. This phenomenon signifies the merging of physical and biological boundaries, resulting in a new technological and social era that significantly impacts our current and future way of life. Computational biology, nanotechnology, biomaterials, and synthetic biology/microchips appear to hold the key for the future, with biotechnology serving as the foundation for these complex technologies. This study, therefore, aims to examine the breakthroughs in integrating biotechnology and bio-robotics for handling large amounts of data, to disseminate this knowledge to a wider audience. Furthermore, the ethical implications and practical applications of bio-printing technologies, synthetic biology, DNA computations, and the consequences of bio-robotics are discussed.

Biotechnology: the game-changing power of DNA molecule

Biotechnology, as defined by Verma et al. [137], is the application of the principles of engineering and biological sciences to create new products from raw materials of biological origin, aiming their unlimited potential for the benefit of humanity in various domains including food, health, animal life, energy, and the environment. This field has a significant impact on our daily lives, including our routine life, and future existence from birth to death.

In 1953, Watson and Crick made a groundbreaking discovery by identifying the chromosome located in the cell nucleus, which serves as the carrier for all hereditary information stored in DNA [138]. According to AlJame and Ahmad [7], the genome consists of the DNA collection from all chromosomes within the cell's nucleus that encodes, stores, replicates, and propagates genetic information across all living organisms. Watson and Crick's discovery unveiled the mysteries of DNA as a genetic material [137]. Structurally, DNA is composed of two strands, each containing four nucleotides: adenine (A), cytosine (C), guanine (G), and thymine (T) [3].

Understandably, the inherent capabilities of DNA are driving the extensive exploration of more advanced applications. Specifically, the advancement of genetic engineering which involves manipulating the DNA sequence in the genome [111] is facilitated by restriction enzymes that precisely cleave DNA at specific sites[26]. Additionally, DNA cloning expedited the comprehensive application of the genome for different purposes [140]. Moreover, the regular production of novel materials and equipment, chemicals, and reagents for DNA manipulation makes the significance of biotechnology in various sectors such as industry, healthcare, the environment, and agriculture [87]. The ability of scientists to investigate and manipulate the central dogma of molecular biology, both in vivo and in vitro conditions, enhances the diverse applications of DNA in biotechnology [112].

Similarly, the accessibility of sequenced genomes of different organisms globally plays a crucial role in the progress of biotechnology and DNA nanotechnology. This development is currently reshaping the interaction among professionals, researchers, patients, individuals, families, industry, and government [25].

Overall, DNA serves multiple purposes: it contains all the hereditary information of living organisms, acts as nourishment for living creatures, functions as a storage system capable of replacing hard disks, and also functions as a weapon that can distract the globe. DNA is thus everything that controls life in the biosphere.

Special Properties of DNA for Fabrication of Nano-materials

In addition to its role as the carrier of hereditary information, DNA possesses fascinating physical and chemical attributes that make it highly suitable for creating DNA-based and DNA-coded machines. Some of the properties include DNA oligomers or DNA origami, which are accessible for modification and play a role in conformational changes in stimulus-responsive DNA Nano-machines [114]. DNA has emerged as the primary building material for producing structurally complex and functional Nano-materials, thanks to its status as a well-understood polymer with precise nano-scale dimensions and the ability to be programmed with molecular recognition capabilities. Thus, it serves as a core resource for the self-assembly of highly specific and molecularly programmed materials in the realm of structural DNA nanotechnology [20]. DNA's simple rules for strand interactions allow for the construction of complex and mobile nano-devices with DNA-based molecular motors [144]. Additionally, DNA's remarkable capability for information processing enables the intricate spatial organization and dynamical reconfiguration of high-performance functional materials [17].

The distinctive features of DNA, such as its self-driving force at the micro/nano-scale, high specificity, and programmability, have opened extraordinary opportunities in diversified research disciplines, highlighting DNA as a core element in formulating intelligent and versatile micro/Nano robotic devices. Hence, DNA serves as a platform for the fusion of biological and machine elements [134]. Through DNA-made cages and wireframe nanostructures, complex, dynamic 2D and 3D geometries can be generated. These structures can be applied in the configuration of DNA on nanoparticle (NP) surfaces and organize nanoparticles (NPs) into specific supermolecular structures that can be implemented in biosensing and drug delivery applications [64].

Nano-particles are too small to be assembled into materials using conventional methods, but DNA molecules can be used to bind them together. This results in the formation of material aggregates with remarkable strength and stiffness. For instance, a novel material composed of hollow nano-particles and DNA exhibits exceptional strength, lightness, and resilience despite its minute component making it potentially valuable for building extremely sturdy medical and electronic devices [75].

Several 2D and 3D DNA nanostructures harmonized with optical, chemical, or magnetic triggers have been designed and assembled, and extensively used as versatile templates for molecular robots, Nano-sensors, and intracellular drug delivery systems. Furthermore, researchers have identified DNA origami-based nano-devices that can be induced and activated by magnetic fields [77, 78]. DNA nanostructures can be easily designed and manipulated to create specific responses in tiny Nano-machines for targeted applications [101]. According to Qian and Winfree [113], DNA computing takes advantage of the dynamic nature of DNA and its programmable capabilities. DNA's flexibility makes it an ideal option for creating long-lasting moving components [29]. Therefore, DNA nano-materials of varying sizes and shapes have been designed based on the classic Watson–Crick base-pairing method for molecular self-assembly. DNA nanotechnology has generated a plethora of structures uniquely suited for nano-scale patterning. In general, the unique nature of DNA contributes to the construction of different nano-machines with applications in the fields of medicine, chemistry, material physics, biogenetics, and data computing [79].

Physical and biological boundary fusion resulted in bio-robotics

Now, it is evident that the integration of biology and engineering is not just a concept but a concrete reality in today's world (https://fastercapital.com/content/DNA-Nanotechnology-and-Robotics--Disrupting-the-Market--DNA-Nanotechnology-and-Robotics-as-Catalysts-for-StartupGrowth.html. Accessed on 1 June 2024) [40]. Bio-robotics is the study of the interaction and functioning of robots and living things that break the boundary between biotic and abiotic creatures. It involves manipulating living organisms to serve as functional robots or components of robots. The field of robotics encompasses genetic engineering and the creation of living organisms from inanimate matter through genetic manipulation (Bionity.com) [22]. Bio-robotics combines the principles of physics and biology to create machines that can mimic and interact with biological systems. For example, soft robots are made from materials akin to the tissues and muscles found in living organisms, enabling them to move and interact with their surroundings more naturally compared to conventional robots [142].

Recently developed interactive robots simulate the behavior of living systems, enabling them to imitate actions observed in nature [35]. These robots are equipped with various senses, such as vision, hearing, touch, smell, and taste, as well as a sixth sense that allows them to perceive and respond to physical phenomena like temperature and pressure, and understand complex visual or auditory information [5]. In terms of UV vision, bio-robots also have the potential to perceive ultraviolet light similar to insects, birds, and many aquatic species, which use this ability for navigation on land, in the air, and underwater [121]. This capacity is valuable for developing navigation systems inspired by biological mechanisms, with bio-robots expected to detect UV light, unlike the human eye.

The fusion of physical and biological boundaries in robotics is exemplified by the development of bio-hybrid robots, which combine living and non-living components [90]. Some bio-hybrid robots, for example, employ living muscle cells to power their motions.

The ability to design and synthesize DNA frameworks of various shapes and effectively organize molecular components into complex assemblies has made bio-robots possible through nucleic acid nanotechnology. However, creating inorganic and hybrid material through programmable DNA templates is a different story that needs further investigation [59]. Conversely, there is a significant interest in the field of DNA nanostructure-driven materials science engineering, which employs DNA-based fabrication techniques such as metallization, mineralization, lithography, and casting to create self-assembling metal nano-particles. This exceptional assembly power of DNA to create robust inorganic compounds opens up novel possibilities for future applications. By harnessing the assembly power of DNA, researchers can explore uncharted territories in inorganic materials science and discover novel applications [59]. One significant aspect of DNA nanotechnology, particularly the DNA origami technique, is the ability to precisely control the shape and size of minerals and metals in the resulting object [38]. If successful, the engineering for the integration of DNA with inorganic matter could revolutionize not only for organic-based creatures but also for non-living substances. This breakthrough has the potential to significantly advance the progress of robotics, particularly in the context of factory automation and industrial applications.

Human genome project and bio-robotics

The Human Genome Project (HGP) spanned 13 years to sequence the entire human genome. The project revealed the presence of around 3 billion nitrogenous bases in the 23 pairs of human chromosomes containing instructions for over 30,000 genes responsible for the formation of human cells, tissues, organs, and the sustenance of life through protein expression [94].

The human genome project had a significant impact on advancing biotechnology research automation specifically in the field of robotics facilitating the automation of DNA cloning. Recent advancements in robotics have resulted in the development of automated DNA cloning systems [104]. This indicates the ability of robotics to comprehend DNA replication mechanisms and autonomously perform the replication process for DNA libraries. Currently, robots are can understand the complex enzymatic activity and temperature changes that occur during DNA replication [145].

Machine learning of bio-robotics to install human intelligence

Tamborini [131] postulated that the combinatorial practice of bionics, biomimetics, biorobotics, and all design strategies inspired by nature involves not just imitating nature, but also interpreting concepts. He also proposed that the ability to replicate complex locomotion systems in robots stems from this interpretive practice.

Human intelligence imitates machine learning by training from the surrounding environment [47]. Machine learning continues to play a fundamental part in the field of computational biology. Essentially, machine learning algorithms and processes have been integral in creating nano-robots using different materials like biosensors, motors, manipulators, power supplies, molecular computers, biochips, and nanoelectronics, microscopic level nanorobtos which have significant medical applications [55]. For example, Maasch et al. [83] reported stable, nontoxic peptide antibiotics identified through machine-learning-based encrypted peptide prospection.

DNA motors and computers

Molecular motors, which are distinct cellular enzymes, use chemical energy to mechanical work and perform various biological processes such as DNA replication and transcription [119], DNA supercoiling, intracellular transport, and in vivo ATP synthesis. Mechano-chemical coupled with molecular motors has opened the door to the development of artificially engineered motors [92]. Recent findings by Zhu [148] revealed the suitability of bio-robots in bridging biological results with engineering advancements.

Cutting-edge molecular robots are advancing with the help of computerized DNA motors, which can detect and process chemical information around them to produce a response that mimics certain properties of living cells (https://www.openaccessgovernment.org/computerised-dna-motors/133508/) [34]. Different designing methodologies have been developed to make enzymatic-based DNA circuits with plasticity, allowing them to exhibit memory and learning characteristics effectively [96].

Recent developments in bioelectronics and bio-robotics system

The science of bioelectronics and robotics is advancing toward the goal of creating unified interfaces between biological structures and artificial devices. There is a growing emphasis on developing machines that are both biocompatible and capable of mimicking life. In bioelectronics and robotics, there is a specific focus on applying these technologies for motor control and sweat sensing. Bio-mimicry, which involves drawing inspiration from natural systems, plays a crucial role in the design and construction of machines and electronics that are compatible with biological organisms, allowing their machines to perform similar functions as living cells [109]. The integration of rigid structural components, soft actuators, and flexible sensors enables the assimilation of physical materials and biological organisms, ultimately benefiting human users [109].

DNA-based modeling approaches and Robotic technologies

Advancements have been made in DNA nanotechnology, especially in the development of autonomous nano-scale robots in recent years. This exciting area shows great potential for various applications. A great breakthrough was made by Nickels and his research team when they introduced a self-assembling DNA "force clamp." This innovative tool enables for precise manipulation of objects at the nano-scale, opening up possibilities for conducting multiple tasks simultaneously [99]. A DNA robot was created that could operate independently and carry out a range of tasks including initiating, following a path, making turns, and halting on a DNA platform [81]. Wickham and his team took it a step further by creating a 100-nm DNA track, demonstrating a DNA motor that could autonomously move a load along the entire track, completing a complex 16-step journey with remarkable consistency [141]. A distinct "bipedal DNA walker" was unveiled, comprised of two DNA origami building blocks that mimicked the movement of kinesin proteins and could move forward and backward on a specific origami surface [76].

Scientists are currently pushing the limits of complexity, as evidenced by Gu et al. [56] creating a programmable DNA assembly line. In this intricate system, a "tensegrity-triangle walker" with manipulators was used to traverse a DNA origami platform and assemble cargo from specific cassettes. Thubagere and colleagues introduced the latest advancement, developing a sophisticated algorithm that allows DNA robots to accurately place two types of cargo in specific locations on a DNA origami platform [133]. This achievement signifies a major step towards the creation of highly functional and versatile DNA-based machines.

These advancements demonstrate the increasing complexity of DNA nano-robots. Ketterer and his team have shown the possibility of building intricate nano-machines using several DNA origami elements, indicating the potential for developing even more intricate structures [67]. In addition, researchers have investigated the possibility of robots interacting with each other, which could result in cooperative autonomous tasks [143]. The field of DNA nano-robotics is advancing rapidly, and with continual research, these miniature machines could have a significant impact on various aspects of synthetic biology and beyond.

Table 1 classifies different DNA robots based on their functionality. The categories consist of nano-scale mechanical tools for manipulation and measurement, information that relay robots for communication and control, tools for nano-medicine used as diagnostics and drug delivery, robots for photonics and plasmonics applications like sensing and diagnostics, externally driven robots for precise movement, and autonomous robots capable of complex tasks such as assembly lines, cargo sorting, and rudimentary computation. Each section describes the type of robot, and its functionality, and provides an example of its potential usage.

DNA-based computing and anticipating memory of bio-robotics to handle big data

Various software programs have been developed to analyze text data using statistical methods; however, performing similar tasks for biological data with conventional statistical software is challenging. Unlike images or text data sets, biological data are more complex encompassing various aspects of a living organism such as genetics, proteomics, metabolomics, which examines concentrations of different molecules, and neuroscience. Furthermore, the majority (99%) of the estimated trillion species, primarily consisting of micro-floras, have not been thoroughly studied. Therefore, the sheer volume of existing and future biological data makes it impractical to manage using ordinary data management systems. Consequently, AI methods are suitable for handling such extensive and complex data sets [68].

With the exponential increase of human-generated information globally, the storage capacity of silicon chips is proving to be insufficient [66]. In approximately two decades, the total digital information is expected to reach 3×1024 bits [106], and the global demand for data storage is estimated to be approximately 1.75×1014 GB by 2025. Conventional data storage media, which can only accommodate a maximum density of 103 GB/mm^3, will not be enough to meet the increasing data requirements cost-effectively, while also posing risks of data loss in the future [42].

Hence, the increasing need for alternative methods of data storage is recognized to accommodate the vast amount of data anticipated [124]. Scientists in the USA and Europe studying advanced synthetic biology have acknowledged the challenges associated with handling biological data. They are exploring the use of automated robots for repetitive and time-intensive biological

Table 1 Mechanisms of action, and applications of some types of robots

Classification	Type of robot	Mechanism of action	Example of application
Mechanical tools	Force clamp	Entropic DNA spring	Resolving, e.g., DNA conformational changes
	Pylons	DNA base stacking	Resolving DNA base stacking interaction
	Calipers	DNA hinge + interaction between the investigated species	Measuring, e.g., forces between nucleosomes and nucleosome unwrapping
Information relay	Networks	Base stacking (depends on ionic strength)	Large-scale movement
	Nano = actuator	DNA hybridization	Molecular regulation
	Domino arrays	Base stacking	Long-distance step-by-step movement
Nano-medicine	Imaging tools	Various conformational and structural transitions, DNA transient binding	Diagnostics, and payload Delivery, etc
	Pliers	Target molecule binding	Diagnostics, molecular computing
	Nano-robots	aptamer-protein interaction	Targeted and programmable drug delivery
	Capsules/cages	Strand displacement/pH-sensitive DNA strands/light/temperature/mRNA	Selective and controlled display/release of molecular cargo
Photonics/plasmonics	Metamolecules	Strand displacement/pH-sensitive DNA strands/azobenzene-modified strands/aptamer-binding	Sensors, diagnostics
	AuNR walkers/nanoclock	Strand displacement/DNAzyme	Complex nano-machinery
External-field driven	Robotic arms	Electric field	Nano-machines with rapid and controlled movement
	Nanohinge/nanorotor	Magnetic field	Nano-machines with rapid and controlled movement
	Swimmers	Magnetic field, thermophoresis	Guided drug delivery
Autonomous robots	Walkers/motors/robots	Strand displacement/toeholds/restriction enzyme driven	Nano-scale assembly lines, cargo-sorting, computing
	Rotary apparatus	Controlled DNA base stacking + Brownian motion	Toward bio = mimicking nano-machines
	Interacting dynamic robot populations	Binding through hybridization/toeholds, detection of signals such as miR	Toward safe, decision-making robotics

Source: (Nummelin et al. [101])

experiments and advocating for the development of specialized software to manage complex biological data [68]. The ongoing generation of massive amounts of data necessitates durable storage solutions that can withstand extreme environmental conditions, possess higher storage density, retain information for extended periods, and do so at low maintenance costs and energy efficiency [2, 51].

DNA computing is regarded as a superior alternative to silicon-based storage due to DNA's unique capability to regulate gene expression and control biochemical reactions. With its predictable pairing, nano-scale dimensions, and high-capacity coding capability, DNA is suitable for computing and diagnostic applications [82]. The necessary components and procedures for DNA storage already exist in nature, allowing for the adaptation of these mechanisms. This makes DNA-based information storage a potentially attractive supplement to the current electronic data storage methods shortly [18].

Genetic engineering can involve transferring human DNA into bacterial DNA or vice versa, enabling accurate reading, interpretation, and copying of information in the recipient organism [4]. The recent breakthrough in DNA research has led to the development of sub-computing techniques using DNA sequences, biochemistry, and hardware to encode genomes in computers. DNA computing relies on DNA nitrogenous bases (A, T, G, and C) for information representation instead of the traditional binary code (1 and 0), resulting in high speed, minimal storage requirements, and lower power consumption [97].

DNA, also known as organic memory, has been identified as a potential medium for storing large amounts of data with security properties like cryptography and stenography. DNA memory plays a fundamental role in striving to solve complex computational problems [37]. It is worth noting that next-generation molecular computers heavily rely on DNA computing to perform Boolean logic using DNA as their fundamental components, mainly due to its affordability, ease of synthesis, excellent biocompatibility, and high programmability [52]. Recent advances in synthetic biology, next-generation sequencing, DNA writing (synthesis), and reading (sequencing) have made synthetic DNA the most preferred medium for data storage [51]. DNA is considered suitable for data storage both in*vitro* through chemical synthesis and in vivo via 'molecular recorder' genetic systems that modify DNA as cells grow, divide, and change their gene expression [89].

Bio-robotics can benefit from the use of recently developed DNA computing technologies to store huge amounts of data. Specifically, about 700 terabytes (TB) of data can be stored in just one gram of DNA, a stark comparison to the 233 hard disks weighing a total of 151 kilos required to store the same amount of data [97]. According to Zhang [147], it is possible to store about 10 TB of data in one cubic cm of DNA, i.e. 10 TB/cm^{3}DNA. Additionally, DNA computing plays a vital role in the field of cryptography and/or steganography to enhance data security. By employing nucleotides (A, T, C, and G) instead of traditional 0 s and 1 s for encryption, DNA computation offers more randomness that results in more complex arrangements making it difficult for hackers to breach data [9]. Furthermore, DNA computing has emerged as a fundamental technology for encrypting images, ensuring comprehensive data storage and protection [8].

Principles of DNA computing

Researchers demonstrated evidence of DNA's potential to replace silicon-based processors in molecular computing [110]. They introduced a novel DNA computation model that effectively converted a chemical input into mechanical output using dynamic DNA-based motors.

DNA smart technologies allow the interactive exploration of rankings based on multiple attributes computed for a given data set. These techniques can accommodate sequences obtained from either the synthesis or sequencing process. The process of storing data in DNA involves three main steps: synthesizing synthetic DNA sequences (oligonucleotides) that contain the data as payload, incorporating the synthetic DNA with a storage solution, and sequencing to read the short DNA sequences from storage [51]. The utilization of DNA molecular nano switches that can be programmed, combined with stimuli-responsive conformational changes, allows for the encoding of information and visual representation using gel electrophoresis, which is helpful for data storage and processing [130].

Translation of information between binary and quaternary codes

Advancements in DNA computing and digital technology have allowed for the encoding of digital data into DNA sequences [98] and subsequent decoding back into digital data, as illustrated in Fig.1. A binary message can be decoded on a gel using a mixture of oligonucleotides in each lane that collectively form an 11-byte binary message spelling out "Hello world". The binary bit strings are interpreted from top to bottom, with the largest DNA segment corresponding to the most significant bit. The presence of a visible band in a lane indicates a binary 1, while the absence of a band indicates a binary 0. Although all lanes contain an equal amount of DNA, only the double-stranded pieces are visible when stained [58] as shown in Fig.2.

DNA coding and computing processes

The DNA coding algorithm has the potential to greatly improve the efficiency of DNA encoding and decoding, making it practical and facilitating the application of DNA encoding in image encryption [146].

Chargaff's rules of base pairing indicate that the nucleotides G and C always complement each other, as do A with T [54]. This complementary relationship is similar to the pairing of 0 and 1 in a binary system. As a result, 00, 11, 01, and 10 can be represented using these rules. The structural configurations indicate that there are a total of 24 possible DNA coding methods. However, the effective utilization of complementary relationships applies only to the four designated coding sets (Zhang and Tian [146]) (Table 2).

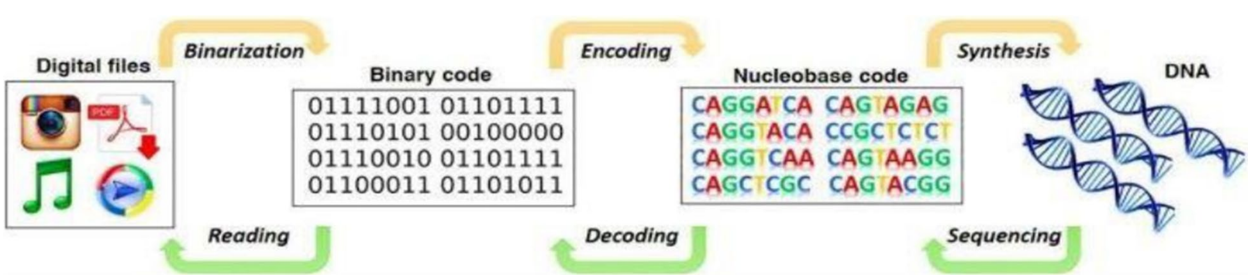

Fig. 1 DNA and coding (Source; El-Seoud [49])

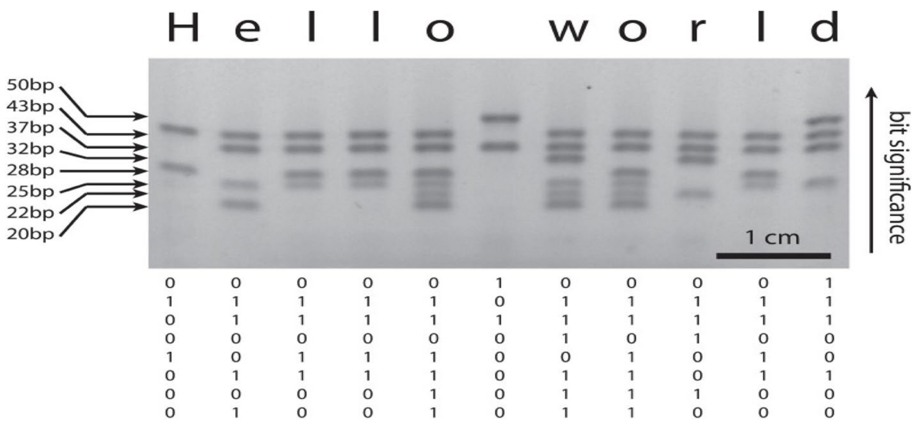

Fig. 2 Decoding a binary message on a gel. (Source: Halvorsen and Wong [58])

Recombinant DNA technology and the skyrocket in synthetic biology

Using synthetic DNA as a molecular blueprint for building synthetic systems is a modern and relevant strategy with various aims: i) generating a wide range of user-defined structures and functions in a generic and highly programmable manner; ii) constructing well-defined systems where all components are perfectly known and assembled; iii) studying living systems systematically; and iv) developing synthetic systems with life-like properties such as communication, adaptation, reproduction, or evolution [15]. The versatile DNA is harnessed to revolutionize the advancement of synthetic biology.

Synthetic biology, an emerging field, involves designing and building novel biological components, gadgets, and systems that do not exist in nature, as well as redesigning existing biological systems [32, 50]. This field allows for the replication of nature in laboratory settings, enabling the production of unlimited amounts of various products from raw materials, similar to altering a digital product by changing ones and zeros on a screen, where modification in DNA's code can alter a biological system (https://builtin.com/biotech/synthetic-biology) [129]. Currently, knowledge of genetic engineering creates desired synthetic genotypes, with resulting phenotypes tested using automated robots. Therefore, the integration of genetic engineering and automated robots simplifies the formation of different synthetic biology companies aiming at producing basic consumable products to replace existing and limited natural products. These synthetic products exhibit similar nutritional characteristics to their natural products [68].

Currently, there is a substantial investment from both government and private sectors in the establishment of synthetic biology companies. Countries like the USA and UK have numerous government and privately funded start-ups actively engaged in the practical production of commercially viable tools, services, and products (https://builtin.com/biotech/synthetic-biology [129]. Accessed on 19 August 2023). The expected output of these initiatives aims to generate sustainable, biodegradable, and eco-friendly products that align with the global sustainable development goals. Within the realm of synthetic biology, several companies (Tab s1) have the potential to collaborate for impactful advancements in industrial biotechnology and bio-economy. To influence synthetic biology and industrial biotechnology profoundly, a networked approach involving all stakeholders and infrastructures with sufficient long-term funding is crucial [33].

Table 2 Rules for encoding and decoding

Rule	Rule 0	Rule 1	Rule 2	Rule 3	Rule 4	Rule 5	Rule 6	Rule 7
00	A	A	T	T	C	C	G	G
01	C	G	C	G	A	T	A	T
10	G	C	G	C	T	A	T	A
11	T	T	A	A	G	G	C	C

Source (Lim [75])

Multidimensional bio-printing technologies for biomaterial fabrication

Additive manufacturing has grown into a "multi-x" era with terms like multi-part design, multi-material, multi-process, multi-mode, multi-scale, multi-dimension, and multi-function [10]. Bio-printing, which involves creating three-dimensional constructs filled with cells to mimic biological tissues, is crucial for applications beyond tissue engineering [65]. The first patent for 3D printing technology was granted to Hull in 1986 in the USA [63]. However, the static nature of 3D printed products limited their ability to address the mobile nature of tissues. To overcome this limitation, 4D printing technology has emerged allowing for conformational changes in printed structures through the use of stimuli-responsive biomaterials. Consequently, 4D printing technology facilitates the production of movable biomaterials, the fabrication of tissue structures capable of morphological changes in response to external stimuli after printing, and the compatibility of bio-printed products with natural cell forces. Furthermore, 4D bio-printing systems use stimuli-responsive biomaterials as potential bio-inks, which represent a significant breakthrough in the fields of actuation, bio-robotics, and bio-sensing [13].

3D and 4D printing technologies to fabricate soft robotics spare parts/body part

Soft robots are a novel type of robots that offer excellent adaptability and flexibility and are extensively used in various fields such as bioengineering, disaster recovery, industrial production, medical services, exploration, and surveying [77, 78]. Soft robotics focuses on developing duplicating machines that can mimic the elastic and rheological properties of biological tissues and organs, typically made of polymeric or elastomeric materials [107].

Soft magnetic structures with a non-uniform magnetization profile can be employed to achieve multimodal locomotion in confined spaces, but incorporating magnetic anisotropy directly into their body is challenging. However, the advent of the 3D printing method allows for the direct incorporation of magnetic anisotropy into printed soft structures, eliminating the need for time-consuming and bulky conventional methods of anisotropy production [11].

Researchers have used the 3D technology to create and print sheet-type and 3D-shaped soft sensors to develop soft sensors that can be incorporated into miniature robots. These sensors help the robots perceive their surroundings in physically challenging situations, enabling them to provide feedback, detect obstacles, measure inclination, and identify collisions, thereby enhancing the robot's adaptability in physically challenging environments [105].

Stimuli-responsive materials used as bio-inks for 4D bio-printing

Researchers proposed that transient DNA templates to "print" programmed particles provide a practical pathway for transferring materials from one substrate to another while maintaining spatial information intact. DNA printing involves decorating particles with arbitrarily designed patterns that break their symmetry allowing for their self-assembly into complex structures autonomously [116].

Researchers have shown the occurrence of stimuli-responsive materials that can respond to specific triggers, such as temperature, pH, humidity, electricity, magnetic fields, light, sound, or a combination of these stimuli [12, 139]. These materials are suitable for applications in 4D bio-printing technologies, as they can undergo conformational changes in response to stimuli and can serve as bio-inks in 4D bio-printing due to their compatibility and printability [13]. This helps the printed materials to detect their environment and exhibit different chemical and structural changes. Some examples of these recently developed stimuli-responsive materials that can be used in 4D bio-printing are presented as follows:

> Firstly, polymers made from poly (N-isopropyl acrylamide) (PNIPAM) are temperature-responsive, altered at relatively low temperatures (32^0C), and can changes in their physicochemical properties when the temperature fluctuates [139]. Secondly, pH detector materials exhibit structural and chemical modifications in response to changes in the pH levels of their environment. These responsive materials contain carboxyl, pyridine, sulfonic, phosphate, and tertiary amine groups, allowing them to release or absorb protons when there is a decrease or increase in pH [69]. Thirdly, humidity-responsive materials are cellulosic materials that indicate changes in humidity by altering their shapes and size [36]. The fourth is polyelectrolyte hydrogels, which are made of electric field-responsive materials that swell, shrink, erode, or bend if they detect an electric field in their surroundings [122]. Fifthly, light-responsive materials can capture optical signals using photo-chromic molecules and convert the photo-irradiation into a photoreaction within biomaterials [53]. The sixth category refers to materials that respond to sound waves, particularly audio waves at high sound levels [1]. The seventh category encompasses materials that are smart and versatile, capable of detecting multiple stimuli simultaneously with precision [31]. Hence, the full effectiveness of multiple stimuli response may be cost-effective and time innovative compared to the development of every stimuli-specific biomaterial [41].

To design effective 4D bio-printing, it is crucial to focus on effective mathematical modeling that provides essential information concerning the shape, properties, and function required for the printed materials [128]. It is essential to select suitable mathematical modeling for 4D printed materials based on factors such as print path, desired (final) shape, ink properties, and stimulus properties. Choosing the appropriate mathematical modeling is necessary for optimizing the structures of 4D bio-printed materials in a cost-effective and time-efficient manner [93].

Application of 3D/4D bio-printing

Robots require flexible actuation for effective communication with humans, other robots, or machines and the surrounding environment. However, there are challenges in finding commercially viable actuators. As a solution, a 3D printing technology platform is employed to fabricate a suitable silicon actuator with programmable bio-inspired architectures and motions. This actuator possesses a lead angle that facilitates elongation and contraction movements, similar to the fibrous architectures found in muscular hydrostats [120]. Therefore, the potential to manufacture diverse robotic components using 3D printing technology makes it possible to create robotics that closely resemble biologically inspired humans or animals, allowing for interactions with humans and their environment. Thus, the effectiveness of digital 3D printing technology has the potential to play a significant role in the development of bio-robotics that replicate human-like characteristics. This achievement marks a significant milestone in the technological era [11].

Bio-printers have been developed to fabricate different synthetic tissues, cells, and organs that play vital roles in innovative and auspicious strategies in the medical and pharmaceutical fields [136]. The significance of bio-printing technologies lies in their ability to generate nano-scale biomedical products that contribute to the development of nano-medicine [149]. The advent of 3D printing has addressed issues such as the deficit of donor organs, the production of replacement body parts, and the customization of medicine to satisfy individual body requirements. It has also opened up opportunities to manufacture rare and expensive medical equipment components, such as cardio stimulators and prefilled syringes for bone fractures at local hospitals instead of relying on imports. Additionally, fully printed organs have the potential to revolutionize drug testing by providing realistic human subjects, and there is even the potential to print food products [48].

To demonstrate the connection between humans and machines, researchers have developed a 3D printed biomimetic robotic hand called the 'Faive Hand'. This human tendon-controlled robotic hand has been integrated into robots capable of performing routine tasks including household activities [14]. Additionally, a Chinese company, Triastek, has publicized a 3D-printed drug product named T21, which has been proven to deliver the drug directly to the colon for the treatment of moderate to severe ulcerative colitis in humans [84, 85]. Furthermore, 3D printing has a wide range of applications, including gene therapy, cancer treatment, tissue engineering, osteogenesis (bone growth), and regeneration of skin and blood vessels [123]. In forensic science, 3D-printed skulls have played a "pivotal" role in securing murder convictions [84, 85].

Generally, the potential of four-dimensional bio-printing for various biomedical applications, such as tissue engineering, biosensors, actuators, and robotics, is remarkable. In essence, the goal of 4D bio-printing is to create intelligent and versatile materials for these specific purposes, with the potential to enhance the performance of existing materials. 4D bio-printing has been utilized in creating dynamic cellular structures for biomedical purposes, including crafting intricately complex and dynamic tissues for tissue engineering, developing biosensors for monitoring cell behavior and function, and potentially utilizing 4D printed actuators as bio-robots [13]. The integration of these applications could ultimately simplify everyday experiences.

Limitations and consequences of bio-printing

The uncontrolled development of food, medical equipment, and body parts raises concerns about abuse and safety. The primary focus is on ensuring that these creations adhere to moral and artistic standards. Additionally, the increased waste from bio-printing processes could put further strain on the environment. Therefore, it is necessary to build sustainable practices in tandem with the advancement of this technology. The ethical implications of bio-printing organs are significant in ensuring the safety and quality of printed organs, which is a complex task. The accessibility of replacement components may also influence how individuals prioritize their health maintenance. On the other hand, food printing has the potential to greatly influence traditional agriculture, potentially significantly displacing farmers and current food systems. Therefore, the social and economic consequences must be carefully considered [48].

DNA nanotechnology has generated a multitude of structures uniquely suited for nano-scale patterning. However, scalability, affordability, and recyclability are important preconditions for the industrial production and widespread use of DNA-based materials [116].

Application of bio-robotics

A robot or bio-robotics is a smart device created and designed to perform tasks with minimal human interventions, exceeding human capabilities [55]. The realization of the technology brings a core breakthrough for genetic engineering and proves the multidimensional application of biotechnology in various fields such as industry, agriculture, medicine, and the environment. By incorporating an automated DNA cloning system in biotech research, we can maintain uniform procedures and facilitate the rapid regeneration of substantial amounts. Some of the main applications of bio-robotics in sensitive issues are outlined below:

Role of Robotic DNA nanostructures in synthetic biology

Nanotechnology enables the development of advanced bio-robotic systems that can sense and actuate in innovative ways [57]. Biological molecular robots are designed to utilize the unique characteristics of biological molecules to carry out actions and respond to their environment [135]. The ability to program DNA nanostructures opens up possibilities for creating intelligent molecular robotics tailored to specific tasks, with potential applications in synthetic biology. These DNA nanostructures, which follow the rules of Watson–Crick base pairing, can be used in various fields such as therapeutics, diagnostics, and logic-gated Nano pills that respond to different stimuli like light, pH, and temperature. They can also be used for optical polarizers, sensors, capsules, autonomous cargo-sorting robots, rotary machines, precision measurement tools, and robotic arms directed by electric and magnetic fields [101].

Role of Bio-robots in medical biotechnology

Scientists have developed a magnetic system that can direct tiny DNA-based robots to move at a much faster rate than previously possible [72]. Robots with biomedical functionalities have recently been employed in various biomedical applications. Bio-robots and molecular robots have a wide array of functions within the biological sciences and are anticipated to minimize or replace human intervention. According to Ghosh and Dasgupta [55], bio-robots, particularly nano-robots, play a crucial role in detection systems and the study of infectious disorders, immune responses to infections, brain and neurological functions, as well as locomotion analysis. These functions are essential in the development of intelligent bio-robots capable of performing complex actions by simulating human intelligence. An example of such advancements is the use of lower-limb robotic exoskeletons, which serve as a powerful tool for addressing gait issues in individuals with walking impairments that can assist or function in the place of damaged skeleton [80].

Robots utilized in nano-medicine

Nano-robots made from biological materials typically operate at a sub-cellular scale. Their intricate design allows them to outperform conventional methods because of their distinct features such as loading cargo, resistance to breakdown, targeting specific sites, penetrating tissues, and reacting to stimuli [74].

Robots precision medicine

Currently, the application of DNA robotics seeks attention from start-up companies to develop accurate drug delivery systems in the precision medicine field. For example, DNA origami structures can be designed to open and discharge medications upon identification of specific molecular signals. This ensures that treatments are directed precisely to the intended location, minimizing side effects and optimizing effectiveness (https://fastercapital.com/content/DNA-Nanotechnology-and-Robotics--Disrupting-the-Market--DNA-Nanotechnology-and-Robotics-as-Catalysts-for-Startup-Growth.html. Accessed 1 June 2024) [40].

Creation of smart materials

DNA nanotechnology, when combined with robotics, enables the development of materials that can alter their characteristics in reaction to environmental triggers. Companies like SmartMatTech are investigating the feasibility of creating surfaces that can self-clean or change their texture. These innovations have the potential to be used across various industries, ranging from smart textiles to aerospace components that can adjust to different environments. In the next decade, DNA robots will play a crucial role in the manufacturing process by efficiently assembling materials at a nano-scale level with unparalleled precision (https://fastercapital.com/content/DNA-Nanotechnology-and-Robotics--Disrupting-the-Market--DNA-Nanotechnology-and-Robotics-as-Catalysts-for-Startup-Growth.html. Accessed on 1 June 2024) [40].

Role of Bio-robotics in smart diagnostics

The integration of DNA robotics and diagnostic tools referred to as Smart Diagnostics poised to revolutionize personalized health assessments. Through the analysis of minute biological indicators, these devices have the potential to detect early signs of diseases, customize treatment strategies, and monitor patient progress with unprecedented accuracy (https://fastercapital.com/content/DNA-Nanotechnology-and-Robotics--Disrupting-the-Market--DNA-Nanotechnology-and-Robotics-as-Catalysts-for-Startup-Growth.html. Accessed on 1 June 2024).

Application of Bio-robots in the environment

Chellapurath and colleagues introduced the concept of bio-inspired robotics to create adaptable organisms for future conservation initiatives [30]. These agents are designed to function in the natural environment with minimal disruption to the local inhabitants and the environment's balance.

Furthermore, a team of scientists created the Autonomous Robotic Environmental Sensor (ARES). ARES is a specially designed mobile robot with Omni wheel technology equipped with various sensors to collect data on the indoor environment from multiple locations independently. This helps reduce the need for numerous sensors, labor, and cost. Dyer et al. assert that the inclusion of DNA robots in environmental monitoring equipment enables the identification of pollutants with unparalleled accuracy and precision [45].

Robots in automation research work

Bio-inspired robots are widely used in many industries, such as medicines and architecture [132] and their affordability and ability to accommodate customized protocols took attention. Several indicators show that the robotics industry is moving towards commercialization. One indicator is the presence of innovative robotic products in the market, while another sign is the high demand for robotics from different companies and industries [24]. The robot grippers of the automated cell production platform AUTOSTEM have been specifically designed to handle multiple geometries with just one pair of grippers [102]. An example of this is seen in the use of automated robots, like Alpha Fold AI which has surpassed protein folding in proteomics, demonstrating that automated robots are now a pre-requisite for documenting vast scientific knowledge data [68]. However, several challenges must be addressed to advance sophisticated robotic technologies. These challenges include the pace and scope of innovation, providing proof for product/market fit, exploring different business models, scaling up robotics from the laboratory to the market, and developing innovative vehicle-related products for commercialization [24].

Bio-robotics, in collaboration with Bio-robots Universal System Software, combines various necessary tools, software, purification technologies, and enzyme technologies to revolutionize the automation of biotechnological research and development [88]. For example, a new method of DNA isolation from the saliva of epithelial cells has been incorporated into the Bio-Robot Universal System resulting in significant success [43]. Despite the availability of software for device control and automated processing, challenges related to functionalities, flexibility, and adaptability still pose potential challenges in achieving optimal solutions for automating biotechnology laboratory processes [21].

Since the automation of biotechnological laboratory processes is still in its infant stage, continuous research and innovation are necessary to overcome future challenges. This involves in-depth intensive research on the definitions of manuals and the transferability of each process within those manuals to automation. The main challenge lies in the geometry of robots to grip and de-cape flasks, tubes, and plates, as well as the size and storage of these materials. Ultimately, the role of robotics handling in biotechnological research should ensure the desired output and required quality [21].

Robotics platforms for enzyme screening and microbial research

Nano-bots, enzymes, and nano-motors, which are autonomous, vehicles, and consume biocompatible fuels, are particularly attractive to nanotechnology scaffolds. To effectively treat a variety of diseases, these smart nanostructures are widely used as drug delivery systems [39].

According to Orsi et al. [103], biological research efforts are transitioning from manual labor to automation in order to reduce labor intensity and increase the production of high-quality products. As a result, a combination of machine learning, artificial neural network genetic algorithms, and other similar tools are being utilized alongside high-throughput screening methods in the advancement of various enzyme engineering protocols [71], Mandeep et al., [86, 118]. Various Bio-robots and robotic platforms have been of great importance in enzyme and microbial research, particularly for enzyme screening. As an illustration, a biological robot was created to screen aspartate kinase III variants that are presented on the bacterial phage M13 [126].

Automated robotic platforms for the high-throughput screening of enzymes are currently under development and have been effectively employed in the screening of a variety of enzymes, including hydrolases, Baeyer–Villiger monooxygenase, dehalogenase, transaminase, and acylase. As an illustration, the investigation of cellulose cel5A expression in K. lactis was accomplished utilizing the fully automated robotic system RoboLector [95]. In a subsequent investigation, the RoboLector system was employed for the automatic and high-throughput screening of various upstream and downstream processing parameters [95].

According to Kovačević et al. [70], researchers demonstrated that a collection of mutated glucose oxidases presented on the surface of yeast cells underwent thorough screening using a high-throughput flow cytometry method. According to a separate study, Leferink and colleagues devised an automated system to screen libraries of plant monoterpene cyclases/synthases (mTC/S) expressed in*E. coli* [73]. A microfluidic platform utilizing droplets was created for screening engineered enzymes, capitalizing on the exceptional secretion capabilities of the yeast*Yarrowia lipolytica*. Five enzymes (endo-β−1,4-xylanase B and C; 1,4-β-cellobiohydrolase A; endoglucanase A; aspartic protease) derived from *Aspergillus niger* were specifically chosen for overexpression and secretion in their active forms within the crude supernatant of *Yarrowia lipolytica*. The enzymes were evaluated using a microfluidic system based on droplets [19]. Overall, the extraction and purification of enzymes from microbial sources are increasingly viable, potentially streamlining processes, improving research quality, and enhancing efficiency, ultimately leading to time and labor savings.

Findings from another study showed that a robotic platform was developed specifically for high-throughput screening, to conduct quantitative measurements at various compound concentrations or perform different assays under the same set of conditions (Michael et al., [91]).

As a limitation of automation research and the use of bio-robots for research, liquid handling robots are quite expensive and incompatible with the complex protocols which need to be updated in the future [60].

Opportunities for automated DNA cloning

High-throughput cloning is a technique in molecular biology that involves the assembly of a large number of DNA sequences, such as genes, to develop libraries and facilitate the screening of constructs, protein expression, or protein function. Through the incorporation and utilization of automation, researchers can expand and enhance their output to encompass hundreds or thousands of reactions, while also saving time and money through streamlined workflows and reduced volumes. Additionally, automating complex mixing processes can lead to improved reproducibility, minimizing the potential for manual errors (https://www.neb.com/en/applications/cloning-and-synthetic-biology/high-throughput-cloning-and-automation-solutions/. Accessed on 8 June 2024) [61]. The automated process for assembling DNA allows for the consistent and high-volume production of DNA devices, while also minimizing the potential for human error that can occur when manually pipetting repeatedly [104].

The discovery made by Bairy et al. [16], complete automation was achieved for all the processes related to cloning and in vivo expression screening. The study conducted by Bairy et al. [16] demonstrated that it is feasible to produce substantial amounts of soluble proteins, perform large-scale purification, and successfully crystallize these proteins through automated cloning using robots in*E. coli*.

Pavan and colleagues developed a primary DNA assembly evaluation (Q-metric) to evaluate the benefits of a particular automated method compared to traditional manual manipulations in terms of researchers' most important criteria: output, cost, and time [108]. According to these researchers, the process of capturing, defining, assembling design, and providing human and robotic liquid handling instructions is executed through the use of a software tool known as Puppeteer.

Recent studies have shown that automated robots are being utilized to manipulate the genetics of multicellular organisms, such as fruit flies and zebrafish embryos. The technology will help laboratories save time and resources, while also allowing them to efficiently carry out new and extensive genetic experiments that were not feasible with manual methods before [6]. Automation of the DNA assembly process has garnered significant interest in the execution of various DNA assembly methods and standards within the Synthetic Biology community, as advocated by [127]. The researchers have created a publicly available software package and showcased the effectiveness of DNA-BOT by concurrently constructing 88 compositions consisting of 10 genetic elements with precision and reasonable cost. They assessed the design space for a three-gene operon, specifically examining the promoter, ribosome binding site, and gene order. This demonstrates the efficacy, precision, and cost-effectiveness of DNA-BOT, rendering it accessible to the majority of laboratories and facilitating the widespread adoption of automated DNA assembly [127].

Challenges/Risks of bio-robotics and automated cloning

Bio-robotics lacks a detailed explanation of in vivo characteristics such as pharmaco-kinetics, structure-performance relationships, and circulating half-lives [27].

Cloning can present a variety of expected potential risks or challenges. Automated DNA cloning presents several challenges, including the potential misuse of cloning technology for bioterrorism, patent disputes, public hesitancy towards cloned products, and regulatory hurdles. Managing the toxicity and biosafety of cloning, as well as ensuring the efficiency of automated cloning in forensic science and identifying unintended consequences, such as ecological impact, are also significant challenges. Due to the complex legal and ethical issues surrounding gene cloning and intellectual property rights, the application of automated cloning may be difficult (https://fastercapital.com/content/DNA-Nanotechnology-and-Robotics--Disrupting-the-Market--DNA-Nanotechnology-and-Robot ics-as-Catalysts-for-Startup-Growth.html. Accessed on 1 June 2024) [40].

From a technical perspective, it is not possible to create a pipeline using just one large robotic platform. Instead, it requires a combination of several specialized robot platforms connected by mobile robot units to allow distributed workflows and complex scheduling. Additionally, there are numerous challenges in incorporating particular devices with different interfaces into liquid-handling stations, establishing efficient cloning workflows, and creating a flexible and user-friendly digital infrastructure for conducting automated experiments, including real-time data processing for loop closure [103].

Recently, there has been a breakthrough in cloning technology. Despite facing difficulties like scalability and regulatory obstacles, the potential for success is great on this path. Startups that effectively navigate these challenges are in a strong position to take the lead in the market. A startup has been able to provide DNA nanomachine components to a range of industries, including medicine and manufacturing, after successfully overcoming the obstacle of mass production (https://fastercapital.com/content/DNA-Nanotechnology-and-Robotics--Disrupting-the-Market--DNA-Nanotechnology-and-Robotics-as-Catalysts-for-Startup-Growth.html. Accessed on 1 June 2024) [40].

Bio-robots—ethics and responsibility

Bio-robotics is going to create a new revolution in the upcoming society of the 5.0 revolution. It seems that we may be destined to have artificial human beings. However, there is a chance that natural human beings will continue to exist while being in control of the production of artificial human beings [100]. The technology of robotics is making progressive and revolutionary advancements, which warrants special attention to the possible mega challenges that may emerge with this technology in the future [44].

The convergence of technological and biological aspects of AI gives rise to biotechnical AI [100]. However, AI systems have various drawbacks that require careful consideration and responsibility. These include embedded bias in AI, catastrophic forgetting, the potential threat to privacy breaches, and the intricate task of determining accountability for AI errors (i.e., whether it falls on AI's advice, the AI developer, or the company that owns the AI system).

Ultimately, any legal framework for autonomous AI must ensure that these systems are held accountable while ensuring their safe and secure operation in our society [115]. Bioethical issues highlight the importance of following the natural course of action for all bio-organisms, as they are created by nature itself. It is crucial to maintain the natural balance between living matter and non-living matter, and no one should alter it [100].

The author's mixed feelings; hopes and fears of the double edge of synthetic biology

The double sword of synthetic biology

Synthetic biology companies have been working intensively to implement the global sustainable development goals by bringing nature to the laboratory. The potential integration of bio-robotics with synthetic biology companies can completely replace the human workforce if bio-robots can store big data, mimic human activity through machine learning, perform tasks accurately, operate tirelessly, complete numerous assignments quickly, and generate desired products in both high quality and quantity. This advancement could raise concerns about the future of the global population, potentially leading to a decrease in human involvement in global activities. There is a possibility that humans could become obsolete, merely consuming products produced and supplied by bio-robots as slaves.

Mixed bag of 3D/4D bio-printing

The expansion and accessibility of 3D and 4D bio-printing presents future mega challenges, as it may lead to the easy availability of cells, tissues, organs, and even entire functional organisms. This advancement could potentially result in the commercialization of human body parts in supermarkets, and ethical dilemmas, particularly from religious and social perspectives. This clash could also involve conflicts between creationism and evolutionary beliefs and may raise issues concerning intellectual property rights. Additionally, the integration of bio-robotics, cloning, and advanced printing technology could lead to the exponential growth of bio-robotics globally, surpassing humans altogether.

Two-faced Coin of DNA computation

It is possible to store information in DNA or nucleic acid, making it as easy as copying documents onto a hard disk to install huge amounts of knowledge into every human or selected individual. Hence, human beings may no longer need to read several hard-copy documents, as there could be a straightforward process of knowledge installation for those who desire it and denied to others. The union of synthetic biology, quadruple codes, and binary codes could potentially create remarkable advancements in the world. This could have both positive and negative implications/consequences for the upcoming world. Positively, advanced artificial intelligence is expected to perform effectively, consistently, rapidly, and fruitfully, overcoming human weaknesses and limitations. On the other hand, negative implication of bio-robotics could lead to extreme destruction for the current world order.

Boon and bane of automated DNA cloning

Automated DNA cloning is anticipated to solve various man-made errors and problems in modern biotechnology research and applications. The concern is that automated DNA cloning may lead to extraordinary phenomena, risks, or the creation of unusual creatures on Earth. Imagine if the central dogma of molecular biology could be executed autonomously by bio-robots. What would happen if this capability could be integrated with a 3D printing machine? If genetic engineering becomes autonomous, what outcomes would arise? How likely is the production of biological weapons to increase? The control of biotech laboratories by bio-robotics could result in a different era in science. The other mega challenge is the administration of bio-robotics in the future world. We doubt whether granting bio-robotics administrative authority would enable them to control the biosphere. This could potentially result in conflicts and competition for global leadership/control. If we live long enough, we might witness a war between humans and bio-robotics fighting for control of the planet. Thus, humans should never let bio-robotics hold administrative positions.

Conclusion

The advancement in biotechnology progress has the potential to spark a new revolution that could drastically alter the existing lifestyle and overall living system on Earth. If DNA can effectively store large amounts of data and bio-robots can autonomously handle various technologies such as recombinant DNA, synthetic biology, and biotechnology, it is conceivable that the significance of humans in society may diminish. Moreover, the widespread availability of 3D and 4D bio-printed materials in the market could lead to different life eras. In our opinion, bio-robotics possesse the potential to transform human life, but it is crucial to establish clear policies based on societal norms, cultural values, and ethical considerations. Furthermore, it is important to define the governance of the bio-robotics system, addressing legal issues and responsibilities, and safeguarding intellectual property rights are crucial. More importantly, bio-robotics should never be allowed to operate without human control. It is imperative to construct bio-robotics in a way that aligns with natural human behavior to ensure the continuity and sustainability of a normal life.

Supplementary Information

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Supplementary Material 1.

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