SRYAHWA PUBLICATIONS

Journal of Biotechnology and Bioengineering
ISSN: 2637-5362 | Volume 8, Issue 1, 2025
https://doi.org/10.22259/2637-5362.0801002

RESEARCH ARTICLE

Biohybrid Microrobots: A New Frontier in Targeted Drug Delivery and Precision Therapeutics

Ubaid Ahmad

Multidisciplinary and Interdisciplinary School, Chiang Mai University, Chiang Mai 50200, Thailand.

Received: 18 February 2025 Accepted: 14 March 2025 Published: 19 March 2025

Corresponding Author: Ubaid Ahmad, Multidisciplinary and Interdisciplinary School, Chiang Mai University, Chiang Mai 50200, Thailand.

Abstract

Biohybrid microrobots, integrating living biological components with synthetic materials, represent a cutting-edge approach to advancing medical treatments, particularly in drug delivery. These microrobots leverage natural biological systems, such as bacteria, algae, or mammalian cells, in combination with synthetic components like nanoparticles and polymers to achieve targeted, efficient, and responsive therapeutic delivery. Key mechanisms like pH sensitivity, temperature responsiveness, and enzyme-triggered release enhance their ability to release drugs precisely at the site of need, offering solutions for localized therapy and reducing side effects. Despite their promising applications, challenges related to biocompatibility, stability, scalability, and regulatory concerns remain. Future advancements, including enhanced propulsion systems, AI integration, and improved targeting mechanisms, hold the potential to overcome these hurdles. Biohybrids are poised to revolutionize drug delivery, disease diagnosis, tissue repair, and regenerative medicine, offering a new frontier in personalized and efficient healthcare.

Keywords: Biohybrid Microrobots, Targeted Drug Delivery, Drug Release Mechanisms, Bacterial-Powered Microrobots Enzyme-Triggered Release.

1. Introduction

A particular family of microrobots known as biohybrids microbots combines synthetic and biological components, utilizing the advantages of both materials [1]. The term “bio” usually refers to living things or cells that are inherently able to move, sense, or interact biologically with their surroundings, such as bacteria, algae, or even mammalian cells. The term “hybrid” describes the synthetic materials such as metals, polymers, and nanoparticles that give the biohybrid microrobot structural support, improve functioning, and allow for precise control over its behavior [2].

The biological component gives the microrobots a degree of freedom and natural motion that makes it challenging for them to explore the body with entirely synthetic equipment [2]. For instance, bacterial-driven microrobots move by using flagella or pili and can travel through physiological fluids as shown in Fig. 1 [3]. Conversely, synthetic materials are employed to improve the of payload, provide and maintain structural integrity, and shield biological components from degradation within the body [4].

The review shed light on the design and functionality of biohybrid microrobots, which can be improve to perform precise drug delivery to the affected area in the body. This capability increases the efficacy of therapeutic by minimizing potential off-target effects. Moreover, the review explain how biohybrids are being utilized in diagnostics and provide the detection of diseases earlier with high accuracy. Additionally, this review paper also covered the potential applications of biohybrids in tissue repair and regeneration, with particular focus organ regeneration, wound healing and cancer treatment.

Challenges that scientists face while integrating biohybrid microrobots also discussed in this review.

Citation: Ubaid Ahmad. Biohybrid Microrobots: A New Frontier in Targeted Drug Delivery and Precision Therapeutics. Journal of Biotechnology and Bioengineering. 2025;8(1):15-26.

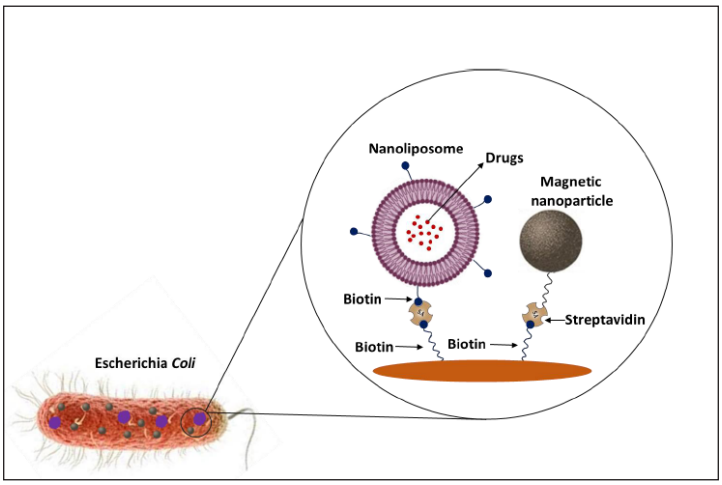

Figure 1. *Schematic representation of a biohybrid microrobot system using Escherichia coli as a biological carrier. The system integrates nanoliposomes loaded with drugs, which are functionalized with biotin for targeted attachment. A magnetic nanoparticle, conjugated with streptavidin, enables external magnetic guidance and control. This approach combines bacterial motility with nanotechnology for targeted drug delivery.*

2. The Evolution of Microrobots

The origin of the field microbotics can be traced back to the development of robotics and engineering technologies [5]. In the early 1980 and 1990 researcher and developer started to navigate the possibilities of creating miniature machines capable they could perform the challenging tasks that were once thought impossible due to size limitations [6]. The applications of the these early microrobots were limited to industries and military purposes [7]. Small, mechanically operated robots that could perform basic movements but lacked the fine control necessary for complex jobs were among the earliest examples.

More complex systems were made possible by advancements in materials science, microfabrication, and control systems as the area of microrobotics advanced. In the late 1990s and early 2000s, microelectronics and nanotechnology grew rapidly [8]. Scientists and engineers started considering microrobots for complex tasks. These robots could perform delicate jobs, especially in medicine. They offered possibilities like targeted drug delivery, diagnostic imaging, and even microsurgeries. A turning point in the development of microbots was the introduction of their medical application [9]. Researchers started creating robots that could navigate the human body and carry out functions including monitoring physiological conditions, administering medications to a specific tissues or cells, and helping with minimally invasive procedures [10]. This advancement led the foundation for current biohybrid microbots.

Biohybrid microrobots represent a significant step forward from traditional synthetic microrobots. For mobility and task execution, biohybrid microrobots use living biological components, in contrast to conventionally built robots that only use mechanical systems [11]. These biological components can be microorganisms like bacteria or algae or even mammalian cells, which have natural capabilities to detects and react to surrounding environment [11]. Certain metals, nanoparticles, and polymers are used as synthetic part in biohybrid microbots that provide more stability to the strictures , increase the capacity for payloads [12] . Because of the combination of biological and synthetic components, biohybrid microrobots are able to carry out tasks with greater precision and flexibility than solely synthetic robots.

Table 1. *Key milestones and contributions in the development of microbots*

Year	Researchers	Milestones / Contributions	[References]
2001	Drefus *et al.*	Developed the first microrobot, breaking time-reversal symmetry with a propagating wave along its lumped structure	[13]
2007	Bell *et al.*	Fabricated and controlled the smallest artificial helical bacterial flagella	[14]
2007	Behkam *et al.*	Developed the first hybrid micro-biorobots by coupling with *Serratia marcescens* bacteria	[15]
2009	Ghosh *et al.*	Reduced the size of artificial bacterial flagella by 30 times in length	[16]
2013	Magdanz *et al.*	Created hybrid micro-biorobots by coupling with sperm cells	[17]
2013	Hiroshi Yamaoka	Development of swarm microrobots for environmental sensing	[18]
2014	Khalil *et al.*	Developed microrobots based on propagation of planar waves through a flexible tail	[19]

3. Design and Functionality of Biohybrid Microrobots

The design and functionality of biohybrid microrobots depend on the seamless integration of biological materials and synthetic components. This section explains the components that make up biohybrid microrobots, their propulsion mechanisms, and how they can be used for precise drug delivery.

3.1 Biological Components

The biological components of biohybrid microrobots are essential to their natural abilities, such as motility, environmental sensing, and interaction with biological systems as discussed in *table 2*. Below are the main biological elements commonly used in biohybrids:

3.1.1 Microorganisms (bacteria and algae)

3.1.2 Bacterial based Biohybrid Microbots

Bacteria are often used in biohybrids microbots due to their ability to self-propel through liquid environments using flagella or pili [20]. These hair-like structures extend from the bacterial surface and rotate, propelling the organism forward. The motility of bacteria can be harnessed to power biohybrid microrobots. For example, Escherichia coli (E. coli) and Salmonella have been used to power microrobots that navigate through body fluids, including blood and mucus [11, 21]. The bacteria's inherent motion allows the microrobots to travel toward specific targets, such as cancer cells or infected tissue, enhancing their ability to deliver drugs precisely [22].

3.1.3 Algae based biohybrid microbots

Algae are another biological component used for propulsion in biohybrid microrobots [23]. Algae-based robots often use the natural flagella or cilia movement to propel themselves in aqueous environments. One of the key advantages of algae is their ability to perform photosynthesis, which can provide an energy source for the microrobots to move autonomously [1]. In addition, certain species of algae have been used for the controlled release of drugs as they respond to changes in light or other environmental stimuli [24].

3.2 Mammalian Cells

Mammalian cells, such as red blood cells (RBCs) or endothelial cells, can be incorporated into biohybrids for their superior biocompatibility and ability to interact with human tissues [25]. RBCs are often used as a surface coating or part of the payload delivery system in biohybrids due to their natural ability to circulate through the body's vasculature without triggering an immune response [26]. These cells can also be engineered to carry specific molecules (such as antibodies or peptides) that target diseased tissue, including tumors or infected sites [25].

3.3 Enzymes and Biological Catalysts

Some biohybrid microrobots utilize enzymes to carry out specific reactions or trigger drug release [27]. These enzymes can act as biocatalysts that help break down certain substances in the body or trigger the release of encapsulated drugs when exposed to specific environmental conditions [28]. For instance, urease-powered microrobots can use the enzyme urease to convert urea into ammonia, which generates propulsion in the bladder, helping to treat bladder cancer by releasing chemotherapy agents in a localized manner [29].

Table 2. *Biological components and their functions in biohybrid microbots*

Biological Components	Function in biohybrid microbots	Examples [References]
Algae	Provides autonomous movement via phototaxis or flagella; used in propulsion systems	*Chlamydomonas reinhardtii*, *Spirulina* [1]
Bacteria	Used for propulsion, typically via flagella or other motility mechanisms	*Serratia marcescens*, *Escherichia coli* [30]
Sperm Cells	Provide motility and directional movement when integrated into biohybrids	Mammalian sperm cells, such as those from mice or humans [31]
Cilia	Used for propulsion and movement in micro-scale robots or biohybrid systems	Ciliated cells (e.g., *Paramecium*) [32]
Muscle Cells	Can generate movement via contractions, often used for actuation in biohybrids	Cardiac or skeletal muscle cells [33]
Yeast Cells	Can serve as biological motors or generate biofuels in biohybrid applications	*Saccharomyces cerevisiae* (baker's yeast) [34]

3.4 Synthetic Components

The synthetic materials used in biohybrid microrobots play a crucial role in providing structural stability, enhancing the robot's functionality, and facilitating its interaction with biological systems [1]. Here are the main synthetic materials used in biohybrid microrobots also shown in *table 3*.

3.4.1 Polymers

Polymers are commonly used in biohybrids microbots to provide structural integrity and flexibility [35]. Polymers can be engineered to form the outer shell or framework of the microrobot, offering protection to the biological components inside [36]. They also allow for customization in terms of size, shape, and surface properties. Common polymers include polyethylene glycol (PEG), polylactic acid (PLA), and polystyrene, all of which are biocompatible and easy to modify. Polymers are also used to encapsulate drugs, protecting them from premature degradation or release [37]. These polymers can be designed to release drugs in response to specific environmental stimuli, such as changes in pH, temperature, or enzymatic activity [38].

3.4.2 Nanoparticles

Nanoparticles, including gold, silica, and liposomes, are commonly integrated into biohybrids microbots to carry and deliver therapeutic agents such as drugs, nucleic acids, or imaging agents [39]. These nanoparticles can be functionalized with targeting ligands, such as antibodies or peptides, which allow the biohybrid to home in on specific cells or tissues [26]. Gold nanoparticles, for example, are particularly useful in photothermal therapy, where they are heated by near-infrared light to kill cancer cells selectively [40]. Nanoparticles can also serve as carriers that protect sensitive drugs from degradation until they reach their intended site of action [41]. By combining these particles with biological components, biohybrids can offer both targeted drug delivery and controlled release, improving the therapeutic outcome.

3.4.3 Metals and Magnetic Materials

Magnetic nanoparticles or metal components are used in biohybrids to allow for external control over the movement of the robot [46]. These magnetic materials can be remotely controlled via external magnetic fields, enabling precise navigation of the microrobot to its target location. This is particularly useful for applications where the microrobot needs to navigate through difficult-to-access areas, such as the brain or deep tissue structures [47]. Metals like titanium or stainless steel can also be used to enhance the durability and stability of biohybrids, especially in environments where mechanical strength is required [48].

Table 3. *Synthetic components and their functions in biohybrid microbots*

Synthetic components	Function in biohybrid microbots	Example [References]
Polymers (e.g., PDMS, PLA)	Flexible, biocompatible, moldable, lightweight; used for structural support	Frameworks for robots, soft actuators, sensors [42]
Nanoparticles (e.g., gold, silver)	Magnetic, optical, and catalytic properties; enhance robot control and sensing	Magnetic propulsion, drug delivery, sensing components [43]
Hydrogels	Biocompatible, water-retentive, adaptable to various environments	Soft actuators, responsive sensors, biocompatible coatings [44]
Carbon nanotubes	Strong, electrically conductive, and flexible; used in sensing or actuation	Actuators, sensors, and propulsion mechanisms [2]
Magnetic materials	Controlled remotely via magnetic fields; enable precise movement	Magnetic actuators, robots controlled by external fields [45]

4. Propulsion and Control Mechanisms

One of the key advantages of biohybrid microrobots lies in their ability to move autonomously or be guided by external forces. The propulsion and control mechanisms of biohybrids depend on both biological motility and synthetic control systems. These systems can be broadly divided into biological propulsion, external field control, and hybrid control mechanisms.

4.1 Biological propulsion

Many biohybrids rely on the natural motility of biological components. For example, bacteria use flagella to propel themselves through fluids [49]. The movement is driven by the rotation of these flagella, which creates a pushing force that propels the bacterium in a specific direction. This propulsion system can be harnessed in biohybrids to enable them to travel through biological environments, such as the bloodstream or the lymphatic system [50].

Similarly, algae-based biohybrids use the flagella or cilia of algae to propel themselves forward. The biological propulsion systems offer unique advantages, such as self-regulation and the ability to move efficiently in complex environments [1].

4.2 Magnetic fields

Magnetic fields are commonly used to control the movement of biohybrid microrobots as shown in

Fig. 2 [45]. By embedding magnetic materials (e.g., iron oxide nanoparticles) in the microrobots, external magnetic fields can be used to steer them through the body [43]. This is especially useful when precise navigation is required, such as targeting a tumor or infected site.

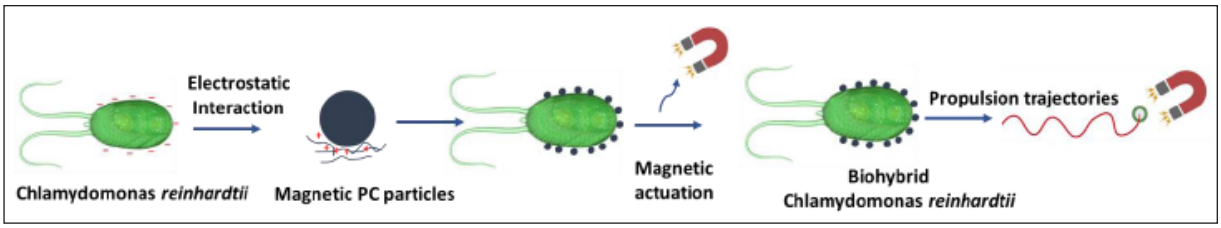

Figure 2. *Illustration of a biohybrid microrobot system using Chlamydomonas reinhardtii. The microalgae interact electrostatically with magnetic PC particles, enabling magnetic actuation. Once hybridized, the biohybrid Chlamydomonas reinhardtii can be externally controlled using a magnetic field, allowing precise propulsion and navigation*

4.3 Electric and Light Fields

Other external fields, such as electric fields (electrophoresis) or light (optical tweezers), are also used for propulsion and movement control [51]. Electric fields can be used to move particles or cells within a liquid, while light can be harnessed to activate light-sensitive biological components in some biohybrids, driving them toward specific locations as illustrated in Fig. 3 [51].

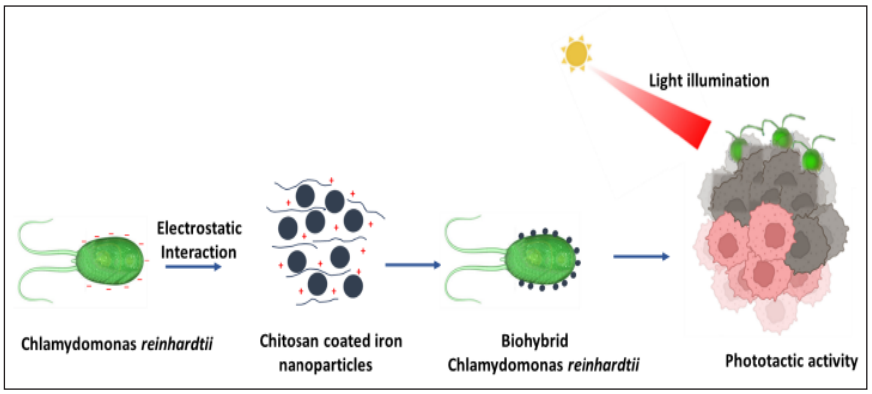

Figure 3. *Schematic representation of a biohybrid microrobot using Chlamydomonas reinhardtii functionalized with chitosan-coated iron nanoparticles through electrostatic interaction. The biohybrid exhibits phototactic activity, allowing light illumination to guide it toward targeted areas, such as tumor sites.*

5. Drug Delivery Mechanisms

The main mechanisms for drug delivery in biohybrids are as follows:

5.1 pH Sensitivity

Certain environments in the body, such as tumors or inflamed tissue, have distinct pH levels [52]. Biohybrids can be designed to release drugs when they encounter low pH conditions, which are typical of acidic environments like tumors or infected tissues. Polymers and nanoparticles with pH-sensitive linkages can break down in response to this acidic environment, releasing the drug only where it is needed [53].

5.2 Temperature Sensitivity

Temperature-sensitive materials can be used in biohybrids to trigger drug release in response to changes in body temperature [54]. This is particularly useful for localized treatments, such as applying heat to a cancerous tumor to release chemotherapy agents.

5.3 Enzyme Triggered Release

Some biohybrids use enzymes as triggers to release drugs. Enzymes can break down certain bonds or polymers that hold the drug, enabling its release when the microrobot reaches a particular location in the body [27].

6. Applications in Drug Delivery

Biohybrid microrobots have emerged as one of the most promising platforms for advanced drug delivery systems. The main advantages of using biohybrid microrobots for drug delivery include targeted therapy, reduced side effects, and the ability to deliver drugs in response to specific environmental triggers [55]. Below, we explore in detail how biohybrid microrobots are revolutionizing drug delivery across various applications.

6.1 Targeted Drug Delivery

Biohybrid microrobots can be engineered to target specific cells or tissues based on their surface

properties or through the use of biological targeting moieties. For instance, surface modifications with antibodies, peptides, or ligands allow biohybrids microbots to recognize and bind to specific receptors on the surface of target cells, such as cancer cells or infected cells [56]. The biological component, such as bacteria or mammalian cells, can help the microrobots identify the correct tissue, enhancing their ability to navigate to the desired site.

In cancer therapy, biohybrids can deliver chemotherapeutic agents directly to tumor cells, reducing the need for high doses that affect healthy tissue [25]. For example, macrophage powered microrobots can be directed toward tumors due to their ability to recognize tumor-specific environments, such as the low-oxygen conditions often found in tumor sites as illustrated in Fig.4 [57]. This selective targeting not only improves drug delivery but also minimizes the adverse side effects commonly associated with chemotherapy.

Magnetic nanoparticles embedded in biohybrids can be manipulated using external magnetic fields to guide the microrobots toward specific locations within the body [58]. This is particularly useful for targeting deep tissue structures, such as brain tumors or organs, that are otherwise difficult to access. By using external magnets, researchers can steer the biohybrids to the intended site and achieve precise control over drug delivery [59].

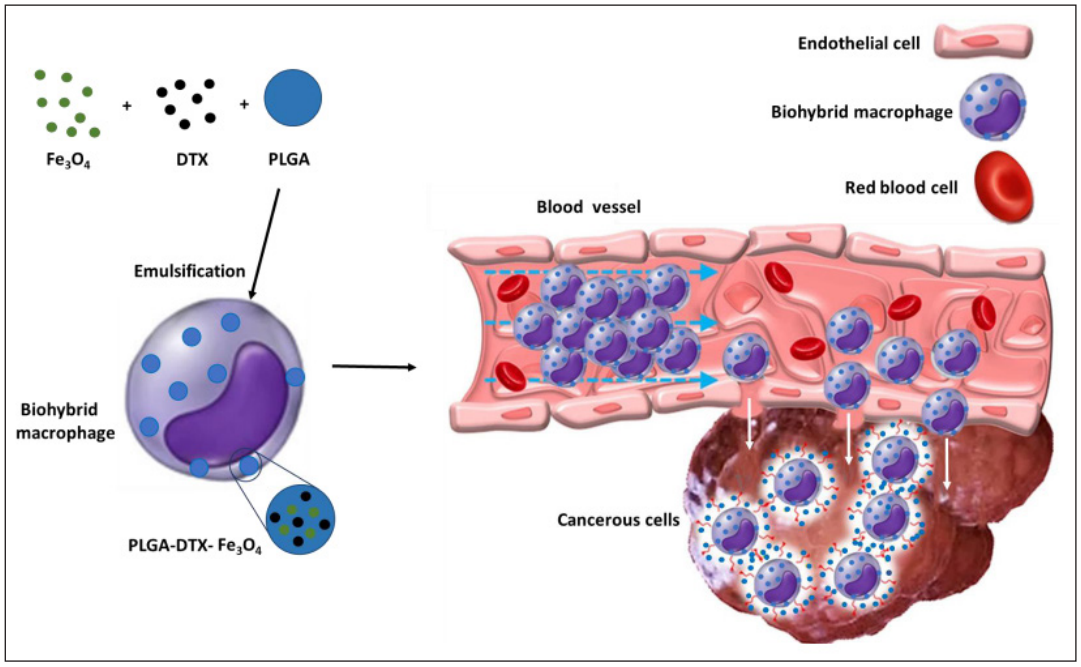

Figure 4. *Schematic of a biohybrid macrophage-based drug delivery system. Macrophages loaded with PLGA-DTX-Fe_3O_4 nanoparticles travel through the bloodstream and accumulate at tumor sites, guided by external magnetic fields for targeted drug delivery.*

6.2 Localized Delivery

Biohybrid microrobots offer a powerful method for localized drug delivery, which is essential for treating diseases that are confined to specific regions of the body.

Tumors often present challenges for conventional drug delivery due to their complex and heterogeneous nature [60]. Biohybrids can be designed to release therapeutic agents directly at the tumor site, bypassing the need for widespread drug distribution. For instance, biohybrids can be engineered with cancer-targeting ligands on their surface, such as antibodies that recognize specific tumor antigens [61]. Additionally, the ability of biohybrids to navigate through the tumor microenvironment using natural motility (e.g., bacterial flagella or ciliary movement) allows them to penetrate tumor tissues more effectively than traditional drug carriers [44].

In the case of bacterial or viral infections, biohybrids can target the site of infection, ensuring that antibiotics or antiviral agents are released where they are most needed. For example, biohybrids microbots functionalized with antibiotics or antimicrobial peptides can be directed toward infected tissues or organs, releasing their payload directly onto the pathogen or inflamed tissue [62]. This strategy reduces the need for systemic antibiotic administration, which can contribute to antibiotic resistance and damage to healthy tissues. *Table 4* explain various applications of biohybrid microbots.

Table 4. *Applications and key outcomes of biohybrid microbots in drug delivery and cancer therapy*

Micro/Nanorobots	Target Applications	Key Outcomes	References
DOX-loaded ZIF-8 nanoparticles coated E. coli MG1655	Drug delivery	Enzyme protection - pH-responsive drug release	[63]
ZIF-8 functionalized chlorella loaded Fe3O4 nanoparticles	Drug Delivery	Antibacterial activity - Magnetic field enhancement	[64]
Fe3O4 nanoparticles with DOX-loaded pine pollen micromotor	Drug delivery	Magnetic targeting - High adaptability	[65]
DOX-loaded urease-powered nanomotors	Drug delivery	Self-propelling in urea - Urea-dependent toxicity	[66]
Ultrasound-responsive SonoBacteriaBot (DOX-PFP-PLGA@EcM)	Drug delivery	Ultrasound-triggered release - Targeted cancer therapy	[67]
Paclitaxel-loaded peptide nanotubes coated microalgae	Drug Delivery & anticancer activity	Fast movement - Significant tumor reduction	[68]
IRONSperm	Drug delivery & anticancer activity	Magnetic targeting - Sustained drug release	[69]
Urease-immobilized Janus platelet micromotor (JPL-motor)	Drug Delivery, antibacterial, & anticancer	Targeted movement - Enhanced cancer cell attachment	[70]
Magnetic nanoparticles@ MSC biohybrid microbots (BHM-MSCs)	Cancer therapy	Targeted stem cell delivery - Effective anticancer effects	[71]
Anti-HER2 aptamer-functionalized tetrahedral framework nucleic acid (tFNA)	Cancer therapy	HER2-targeting - Prolonged blood circulation	[72]
CuS nanodots-loaded biohybrid magnetic helical Spirulina microrobot	Anticancer & antibacterial activity	NIR-induced photothermal effect - Magnetic targeting	[73]

7. Challenges and Limitations of Biohybrid Microrobots

While biohybrid microrobots hold great promise in revolutionizing medical treatments across several biomedical fields, there are still a number of challenges and limitations that must be addressed before they can be widely adopted in clinical practice. These challenges span from issues related to biocompatibility, stability, and control to manufacturing, scalability, and regulatory concerns. Below, we discuss these challenges in detail and explore the potential solutions and considerations moving forward.

7.1 Biocompatibility

Biocompatibility is one of the most significant concerns when developing biohybrid microrobots for clinical applications.

7.1.1 Immune Response

Living biological components, particularly bacteria or mammalian cells, may be recognized by the body's immune system as foreign invaders, leading to an immune response. This can result in inflammation, tissue damage, or the premature clearance of the microrobots from the body. For instance, bacterial microrobots could trigger an immune reaction due to the release of bacterial byproducts or pathogen-associated molecular patterns (PAMPs) [3]. The immune system may target and neutralize these microrobots before they can deliver their therapeutic payload effectively.

Solutions to this issue include modifying the surface of biohybrids with biocompatible coatings (e.g., polyethylene glycol, PEG) to reduce immune recognition or incorporating cells that are derived from the patient's own body, which would reduce the likelihood of an immune response.

7.1.2 Toxicity

The synthetic components of biohybrids microbots, such as nanoparticles, polymers, or metals, may also cause toxicity if they accumulate in the body or are not fully biodegraded [74]. For instance, some metal nanoparticles can accumulate in organs like the liver or kidneys, leading to long-term toxicity. Additionally, synthetic materials used in the biohybrids may leach harmful chemicals into the surrounding tissues [74].

Addressing this challenge requires the development of materials with proven biocompatibility and biodegradability. Materials that break down into non-toxic byproducts upon reaching the end of their therapeutic lifecycle are preferred. Extensive

preclinical and clinical testing is essential to assess the safety profiles of new biohybrids before they can be used in humans.

7.1.3 Long Term Effects

The long-term impact of biohybrids in the human body is another major concern, particularly when dealing with living biological components [28]. While bacteria or algae may be programmed to self-destruct or degrade after completing their task, the long-term persistence of these living organisms could lead to unintended consequences. There is also the potential for microbial resistance or the development of new pathogenic strains, particularly in the case of bacterial-based biohybrids [3].

Researchers must carefully design biohybrids to include fail-safe mechanisms, such as self-limiting growth or rapid degradation, to minimize the risk of unintended persistence or spread of biohybrids in the body.

7.2 Stability and Control

Biohybrid microrobots, particularly those with living cells or microorganisms, face challenges related to maintaining their viability and functionality over time once they are inside the body [2]. The living biological components must remain viable, active, and functional while also interacting seamlessly with the synthetic materials. Environmental factors such as pH, temperature, and ionic strength, as well as interactions with the immune system, can affect the stability and motility of the biohybrids [75].

Ensuring stability may require the development of advanced encapsulation techniques to protect the biological components from the harsh conditions of the body. Researchers are exploring techniques such as nanocoating, hydrogels, or biomaterials that provide a stable environment for the biological components within the microrobots [76].

7.3 Manufacturing and Scalability

The production of biohybrid microrobots at a scale sufficient for clinical applications remains a significant challenge [2]. The combination of living biological components with synthetic materials introduces complexities related to the manufacture, quality control, and scalability of biohybrids microbots [77]. integrating living cells or microorganisms with synthetic components, requires sophisticated fabrication techniques [78]. For instance, bacterial-based microrobots need to be cultured in specific condition, and their growth must be controlled to avoid contamination or variability in performance [78]. On the other hand, the integration of synthetic materials such as polymers or nanoparticles requires precision engineering to ensure that they function as intended within the biohybrid structure.

Achieving reproducibility and consistency across batches of biohybrids is challenging and critical for ensuring therapeutic efficacy and safety. Current manufacturing processes need to be optimized to facilitate large-scale production while maintaining high-quality standards.

7.4 Cost Considerations

The costs associated with developing and manufacturing biohybrid microrobots are still high, particularly due to the complexity of their design, the need for specialized materials, and the labor-intensive processes involved in cell culture and microrobot fabrication [28]. Scaling up production for clinical use could make these technologies prohibitively expensive, particularly for routine healthcare applications.

Economies of scale, improved automation in manufacturing, and the use of less expensive materials or simplified biohybrid designs may help reduce production costs. In addition, advances in bioprinting and microfluidics may lead to more cost-effective and scalable production methods.

7.5 Ethical and Regulatory Issues

The incorporation of living biological components in medical devices and treatments raises a range of ethical and regulatory concerns that must be addressed before biohybrid microrobots can be widely adopted in clinical settings [28].

The use of living cells or microorganisms in biohybrids microbots may raise ethical questions, particularly regarding the potential for unintended consequences [79]. For example, the release of genetically modified organisms (GMOs) or bacteria into the body could have unforeseen effects on human health, the environment, or microbial communities within the body. There are also concerns about the long-term impact of using living components in medical devices, including potential ecological consequences if biohybrids were to escape into the environment [2].

8. Future Directions of Biohybrid Microrobots

Biohybrid microrobots have already demonstrated significant promise in various biomedical applications, from drug delivery to diagnostics. However, their potential to revolutionize healthcare is far from fully realized. As research and technology continue to advance, biohybrids are poised for

further breakthroughs that could transform medicine. Below, we explore several exciting future directions for biohybrid microrobots, including technological innovations, integration with artificial intelligence (AI), their role in personalized medicine, and the path toward clinical translation.

8.1 Technological Innovations

The future of biohybrid microrobots will be heavily influenced by advancements in materials, propulsion systems, and drug delivery mechanisms [2]. As these systems evolve, we can expect improvements in their efficiency, precision, and versatility.

8.2 Advanced Propulsion Systems

One of the major challenges for biohybrid microrobots is achieving efficient and precise propulsion [77]. While many current biohybrids use biological components for propulsion, future advancements may lead to more sophisticated, hybrid propulsion systems. For example, biohybrids may incorporate engineered external propulsion systems like magnetic or electric fields, which could enable better steering and control, even in deep tissues or organs [80]. Magnetic nanoparticles or motors could be embedded in the synthetic components to enable external magnetic fields to guide and control the movement of the biohybrids microbots more accurately [81].

8.3 Better Targeting Mechanisms

Improved targeting of biohybrid microrobots will be critical to their success in clinical applications. One future direction is the development of highly selective targeting strategies, which can deliver therapeutic agents to specific tissues or even individual cells [82]. For instance, biohybrid microbots could be functionalized with novel biomarkers or ligands that bind with high specificity to certain receptors or antigens expressed on the target cells [56]. The use of advanced targeting moieties such as aptamers, monoclonal antibodies, or peptide-based ligands could allow biohybrids microbots to distinguish between normal and diseased cells with greater precision [83].

Another innovation is the use of multimodal targeting, where biohybrid microbots could incorporate multiple mechanisms for recognition and binding, such as dual-receptor targeting (e.g., targeting both tumor-specific markers and immune checkpoints) [84]. This would further enhance the precision of the drug delivery, ensuring that the biohybrids reach only the desired target tissues and minimize off-target effects.

8.4 Integration with AI and Sensors

In the future, biohybrids could be equipped with AI algorithms that allow them to make real-time decisions based on environmental cues [85]. For example, biohybrids microbots could assess the local pH, temperature, or the presence of certain biomarkers, and adjust their behavior accordingly to optimize therapeutic outcomes. AI could also be used to help biohybrids navigate complex environments within the body, learning how to avoid obstacles (like immune cells or blood vessels) and follow the most efficient paths to their targets [28].

Additionally, machine learning techniques could help biohybrid microbots learn from their interactions with the body, improving their functionality over time [86]. This would make biohybrid microbots more robust and adaptable in dealing with unpredictable biological environments, thus increasing their therapeutic success rate.

9. Conclusion

The field of biohybrid microrobots represents a transformative leap in biomedical technology, combining the advantages of both biological systems and synthetic engineering to offer highly effective, targeted, and efficient solutions for a wide range of medical challenges. These biohybrids are poised to revolutionize not only drug delivery but also disease diagnosis, tissue repair, and regenerative medicine. By integrating living organisms—such as bacteria, algae, or mammalian cells with synthetic materials like polymers, nanoparticles, and metals, biohybrids gain unique capabilities, including motility, environmental sensing, and responsiveness to stimuli. These functionalities enable the precise targeting and delivery of therapeutic agents directly to affected tissues, minimizing side effects and improving treatment efficacy.

In this review, we have explored the design and functionality of biohybrid microrobots, their diverse applications in drug delivery, and their potential to tackle complex biomedical problems. Key innovations such as improved targeting, drug release mechanisms, and propulsion systems are already being developed to enhance the effectiveness of these systems. Furthermore, the integration of AI and sensors offers the exciting possibility of creating “smart” biohybrids capable of adaptive, real-time decision-making, further improving their precision and responsiveness in clinical settings.

However, significant challenges remain before biohybrid microrobots can be widely used in clinical

settings. Issues such as biocompatibility, stability, scalability, and regulatory approval need to be addressed. Overcoming these barriers will require continuous research, innovative engineering solutions, and collaboration across multidisciplinary fields. Moreover, the ethical and regulatory frameworks around the use of living biological components in medical technologies must evolve to ensure the safe and responsible use of biohybrids.

Statements and Declarations

Ethics Approval: This study does not contain any studies with human or animal subjects performed by any of the authors.

Consent for Publication: Not applicable.

Competing Interests: The authors declare no competing interests

Clinical Trial Number: not applicable

Funding: No funding is available for this study

10. References

1. Zhang, F., et al., Biohybrid microalgae robots: design, fabrication, materials, and applications. Advanced Materials, 2024. 36(3): p. 2303714.
2. Lin, Z., T. Jiang, and J. Shang, The emerging technology of biohybrid micro-robots: a review. Bio-Design and Manufacturing, 2022: p. 1-26.
3. Chen, M., et al., Microbe-material hybrids for therapeutic applications. Chemical Society Reviews, 2024.
4. Kim, J., et al., Advanced materials for micro/nanorobotics. Chemical Society Reviews, 2024.
5. Abbott, J.J., et al., Robotics in the small, part I: microbotics. IEEE Robotics & Automation Magazine, 2007. 14(2): p. 92-103.
6. Petroski, H., Invention by design: How engineers get from thought to thing. 1996: Harvard University Press.
7. Bogue, R., Miniature and microrobots: a review of recent developments. Industrial Robot: An International Journal, 2015. 42(2): p. 98-102.
8. Cressler, J.D., Silicon Earth: Introduction to microelectronics and nanotechnology. 2017: CRC Press.
9. Wang, B., et al., Trends in micro-/nanorobotics: materials development, actuation, localization, and system integration for biomedical applications. Advanced Materials, 2021. 33(4): p. 2002047.
10. Huda, M.N., H. Yu, and S. Cang, Robots for minimally invasive diagnosis and intervention. Robotics and Computer-Integrated Manufacturing, 2016. 41: p. 127-144.
11. Alapan, Y., et al., Microrobotics and microorganisms: Biohybrid autonomous cellular robots. Annual Review of Control, Robotics, and Autonomous Systems, 2019. 2(1): p. 205-230.
12. Bahaar, H., et al., From Concept to Creation: Micro/Nanobot Technology from Fabrication to Biomedical Applications. Engineered Science, 2024. 32: p. 1346.
13. Dreyfus, R., et al., Microscopic artificial swimmers. Nature, 2005. 437(7060): p. 862-865.
14. Kim, D.H., et al. Three-dimensional control of engineered motile cellular microrobots. in 2012 IEEE International Conference on Robotics and Automation. 2012. IEEE.
15. Behkam, B. and M. Sitti, Bacterial flagella-based propulsion and on/off motion control of microscale objects. Applied Physics Letters, 2007. 90(2).
16. Ghosh, A. and P. Fischer, Controlled propulsion of artificial magnetic nanostructured propellers. Nano letters, 2009. 9(6): p. 2243-2245.
17. Magdanz, V., S. Sanchez, and O.G. Schmidt, Development of a sperm-flagella driven micro-bio-robot. Advanced Materials, 2013. 25(45): p. 6581-6588.
18. Suzuki, R., et al. Shapebots: Shape-changing swarm robots. In Proceedings of the 32nd Annual ACM Symposium on User interface Software and Technology. 2019.
19. Khalil, I.S., et al., Magnetic propulsion of robotic sperms at low-Reynolds number. Applied Physics Letters, 2016. 109(3).
20. Tovey, S., et al., SwarmRL: Building the Future of Smart Active Systems. arXiv preprint arXiv:2404.16388, 2024.
21. Zhang, H., et al., Review of the applications of micro/nanorobots in biomedicine. ACS Applied Nano Materials, 2024. 7(15): p. 17151-17192.
22. Zhang, Z., et al., Micro-/Nanorobots in antimicrobial applications: recent progress, challenges, and opportunities. Advanced Healthcare Materials, 2022. 11(6): p. 2101991.
23. Shchelik, I.S., J.V. Molino, and K. Gademann, Biohybrid microswimmers against bacterial infections. Acta Biomaterialia, 2021. 136: p. 99-110.
24. Zhong, D., Z. Du, and M. Zhou, Algae: a natural active material for biomedical applications. View, 2021. 2(4): p. 20200189.
25. Banskota, S., P. Yousefpour, and A. Chilkoti, Cell-based biohybrid drug delivery systems: The best of the synthetic and natural worlds. Macromolecular Bioscience, 2017. 17(1): p. 1600361.

26. Mohammadi, M.R., et al., Biohybrid nanoparticles to negotiate with biological barriers. Small, 2019. 15(34): p. 1902333.
27. Xu, Y., et al., Micro/nanorobots for precise drug delivery via targeted transport and triggered release: A review. International Journal of Pharmaceutics, 2022. 616: p. 121551.
28. Zarepour, A., et al., Biohybrid Micro/Nanorobots: Pioneering the Next Generation of Medical Technology. Advanced Healthcare Materials, 2024. 13(31): p. 2402102.
29. Hortelão, A.C., Enzyme Powered Nanomotors Towards Biomedical Applications. 2021.
30. Hussein, H., et al., Actuation of mobile microbots: a review. Advanced Intelligent Systems, 2023. 5(9): p. 2300168.
31. Liua, X., C. Wanga, and Z. Zhanga, Biohybrid microrobots driven by sperm. Untethered Small-Scale Robots for Biomedical Applications, 2023: p. 63.
32. Lim, S., et al., Fabrication, control, and modeling of robots inspired by flagella and cilia. Bioinspiration & Biomimetics, 2022. 18(1): p. 011003.
33. Gao, L., et al., Recent progress in engineering functional biohybrid robots actuated by living cells. Acta Biomaterialia, 2021. 121: p. 29-40.
34. Pu, X., et al., 3D Bioprinting of Microbial-based Living Materials for Advanced Energy and Environmental Applications. Chem & Bio Engineering, 2024.
35. van Dongen, S.F., et al., Biohybrid polymer capsules. Chemical Reviews, 2009. 109(11): p. 6212-6274.
36. Soto, F., et al., Smart materials for microrobots. Chemical Reviews, 2021. 122(5): p. 5365-5403.
37. Vilar, G., J. Tulla-Puche, and F. Albericio, Polymers and drug delivery systems. Current Drug Delivery, 2012. 9(4): p. 367-394.
38. Almeida, H., M.H. Amaral, and P. Lobão, Temperature and pH stimuli-responsive polymers and their applications in controlled and selfregulated drug delivery. Journal of Applied Pharmaceutical Science, 2012(Issue): p. 01-10.
39. Ju, S. and H.-Y. Cho, Biohybrid Nanoparticle-Based In Situ Monitoring of In Vivo Drug Delivery. Biosensors, 2023. 13(12): p. 1017.
40. Kim, H.S. and D.Y. Lee, Near-infrared-responsive cancer photothermal and photodynamic therapy using gold nanoparticles. Polymers, 2018. 10(9): p. 961.
41. Mitchell, M.J., et al., Engineering precision nanoparticles for drug delivery. Nature Reviews drug discovery, 2021. 20(2): p. 101-124.
42. Ricotti, L. and T. Fujie, Thin polymeric films for building biohybrid microrobots. Bioinspiration & Biomimetics, 2017. 12(2): p. 021001.
43. Zhou, H., et al., Magnetically driven micro and nanorobots. Chemical Reviews, 2021. 121(8): p. 4999-5041.
44. Sun, L., et al., Biohybrid robotics with living cell actuation. Chemical Society Reviews, 2020. 49(12): p. 4043-4069.
45. Quashie, D., et al., Magnetic bio-hybrid micro actuators. Nanoscale, 2022. 14(12): p. 4364-4379.
46. Mestre, R., T. Patiño, and S. Sánchez, Biohybrid robotics: From the nanoscale to the macroscale. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 2021. 13(5): p. e1703.
47. Iacovacci, V., et al., Medical Microrobots. Annual Review of Biomedical Engineering, 2024. 26.
48. Holzmeister, I., et al., Artificial inorganic biohybrids: The functional combination of microorganisms and cells with inorganic materials. Acta Biomaterialia, 2018. 74: p. 17-35.
49. Bastos-Arrieta, J., et al., Bacterial biohybrid microswimmers. Frontiers in Robotics and AI, 2018. 5: p. 97.
50. Zhang, J., et al., Self-propelling micro-/nano-motors: Mechanisms, applications, and challenges in drug delivery. International Journal of Pharmaceutics, 2021. 596: p. 120275.
51. Carlsen, R.W. and M. Sitti, Bio-hybrid cell-based actuators for microsystems. Small, 2014. 10(19): p. 3831-3851.
52. Swietach, P., et al., The chemistry, physiology and pathology of pH in cancer. Philosophical transactions of the royal society B: Biological Sciences, 2014. 369(1638): p. 20130099.
53. Raman, R. and R. Langer, Biohybrid Design Gets Personal: New Materials for Patient-Specific Therapy. Advanced Materials, 2020. 32(13): p. 1901969.
54. Kashyap, S., S. Kirtania, and S. Banerjee, Smart Biomaterials for Thermal Regulation in Biomedical Applications, in Engineering Materials for Efficient Energy Storage and Conversion. 2024, IGI Global. p. 377-418.
55. Li, J., et al., Biohybrid micro-and nanorobots for intelligent drug delivery. Cyborg and Bionic Systems, 2022.
56. Jahromi, L.P., et al., Chemically engineered immune cell-derived microrobots and biomimetic nanoparticles: emerging biodiagnostic and therapeutic tools. Advanced Science, 2021. 8(8): p. 2002499.
57. Wang, W., et al., Engineering versatile nano-bacteria hybrids for efficient tumor therapy. Coordination Chemistry Reviews, 2023. 488: p. 215178.

58. Bente, K., et al., Biohybrid and bioinspired magnetic microswimmers. Small, 2018. 14(29): p. 1704374.
59. Zhu, S., et al., Biohybrid magnetic microrobots: An intriguing and promising platform in biomedicine. Acta Biomaterialia, 2023.
60. Rosenblum, D., et al., Progress and challenges towards targeted delivery of cancer therapeutics. Nature Communications, 2018. 9(1): p. 1410.
61. Fontana, F., R. Bartolo, and H.A. Santos, Biohybrid Nanosystems for Cancer Treatment: Merging the Best of Two Worlds. Bio-Nanomedicine for Cancer Therapy, 2021: p. 135-162.
62. Li, J., et al., Antimicrobial micro/nanorobotic materials design: From passive combat to active therapy. Materials Science and Engineering: R: Reports, 2023. 152: p. 100712.
63. Li, Y., et al., Biohybrid bacterial microswimmers with metal-organic framework exoskeletons enable cytoprotection and active drug delivery in a harsh environment. Materials Today Chemistry, 2022. 23: p. 100609.
64. Gu, B., et al., Metal organic framework-loaded biohybrid magnetic microrobots for enhanced antibacterial treatment. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2024. 685: p. 133295.
65. Sun, M., et al., Magnetic biohybrid micromotors with high maneuverability for efficient drug loading and targeted drug delivery. Nanoscale, 2019. 11(39): p. 18382-18392.
66. Hortelão, A.C., et al., Enzyme-powered nanobots enhance anticancer drug delivery. Advanced Functional Materials, 2018. 28(25): p. 1705086.
67. Du, M., et al., Establishment of ultrasound-responsive SonoBacteriaBot for targeted drug delivery and controlled release. Frontiers in Bioengineering and Biotechnology, 2023. 11: p. 1144963.
68. Ha, L., et al., Phototactic Biohybrid Microrobot Using Peptide Nanotubes-Coated Microalgae for pH-Responsive Active Drug Delivery. Advanced NanoBiomed Research, 2024. 4(10): p. 2400042.
69. Magdanz, V., et al., IRONSperm: Sperm-templated soft magnetic microrobots. Science advances, 2020. 6(28): p. eaba5855.
70. Zhou, H., et al., Untethered Microgrippers for Precision Medicine. Small, 2024. 20(11): p. 2305805.
71. Gundersen, R.A., et al., Generation of magnetic biohybrid microrobots based on MSC. sTRAIL for targeted stem cell delivery and treatment of cancer. Cancer Nanotechnology, 2023. 14(1): p. 54.
72. Ma, W., et al., An intelligent DNA nanorobot with in vitro enhanced protein lysosomal degradation of HER2. Nano Letters, 2019. 19(7): p. 4505-4517.
73. Gong, D., et al., CuS nanodots-loaded biohybrid magnetic helical microrobots with enhanced photothermal performance. Materials Today Chemistry, 2022. 23: p. 100694.
74. Shivalkar, S., et al., Nanoengineering of biohybrid micro/nanobots for programmed biomedical applications. Colloids and Surfaces B: Biointerfaces, 2023. 222: p. 113054.
75. Wang, Z., et al., Soft Bio-Microrobots: Toward Biomedical Applications. Advanced Intelligent Systems, 2024. 6(2): p. 2300093.
76. Azar, A.T., et al., Medical nanorobots: Design, applications and future challenges, in Control Systems Design of Bio-Robotics and Bio-mechatronics with Advanced Applications. 2020, Elsevier. p. 329-394.
77. Webster-Wood, V.A., et al., Biohybrid robots: recent progress, challenges, and perspectives. Bioinspiration & Biomimetics, 2022. 18(1): p. 015001.
78. Murali, N.,et al., Advanced Biomimetic and Biohybrid Magnetic Micro/Nano-Machines. Advanced Materials Technologies, 2024. 9(19): p. 2400239.
79. Mestre, R., et al., Ethics and responsibility in biohybrid robotics research. Proceedings of the National Academy of Sciences, 2024. 121(31): p. e2310458121.
80. Ricotti, L., et al., Biohybrid actuators for robotics: A review of devices actuated by living cells. Science robotics, 2017. 2(12): p. eaaq0495.
81. Xu, R. and Q. Xu, A Survey of Recent Developments in Magnetic Microrobots for Micro-/Nano-Manipulation. Micromachines, 2024. 15(4): p. 468.
82. Zhao, Z., et al., Targeting strategies for tissue-specific drug delivery. Cell, 2020. 181(1): p. 151-167.
83. Shivalkar, S., et al., Strategies in design of self-propelling hybrid micro/nanobots for bioengineering applications. Biomedical Materials, 2023. 18(6): p. 062003.
84. Zhang, H., et al., Dual-responsive biohybrid neutrobots for active target delivery. Science Robotics, 2021. 6(52): p. eaaz9519.
85. Dong, H., et al., AI-enhanced biomedical micro/nanorobots in microfluidics. Lab on a Chip, 2024. 24(5): p. 1419-1440.
86. Salehi, A., et al., Advancements in Machine Learning for Microrobotics in Biomedicine. Advanced Intelligent Systems, 2024: p. 2400458.