

BIOHYBRID MICROROBOT FOR TARGET DRUG DELIVERY

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ABSTRACT

Biohybrid microrobots represent a transformative frontier in nanomedicine, merging biological entities with synthetic microstructures to achieve precise drug delivery. Unlike conventional nanocarriers, which often suffer from premature clearance, limited tissue penetration, and nonspecific biodistribution, biohybrid systems exploit the intrinsic motility, adaptability, and biocompatibility of living organisms while integrating engineered components for enhanced control. Recent advances (2021–2026) have demonstrated bacteria-driven, algae-based, and cell membrane-coated microrobots capable of navigating complex biological environments, particularly tumor microenvironments, through chemotaxis and hybrid propulsion strategies. Fabrication approaches employing polymers, hydrogels, and magnetic nanoparticles, combined with biofunctionalization techniques such as genetic engineering and membrane coating, have expanded their versatility. Drug loading strategies range from surface adsorption to encapsulation, while release mechanisms are triggered by biological signals or external stimuli. Applications span oncology, gastrointestinal delivery, infection treatment, and regenerative medicine. Despite promising outcomes, challenges remain in immune clearance, large-scale fabrication, and regulatory translation. This review critically evaluates the fundamentals, propulsion mechanisms, fabrication strategies, biomedical applications, and future perspectives of biohybrid microrobots, highlighting research gaps and interdisciplinary opportunities for clinical translation.

KEYWORDS: Biohybrid microrobots, Targeted drug delivery, Chemotaxis, Nanomedicine, Synthetic carriers.

1. INTRODUCTION

A. Background: Targeted Drug Delivery Systems

Targeted drug delivery systems have long been pursued to overcome the shortcomings of systemic therapies that often result in off-target toxicity and reduced therapeutic efficacy.^[1] Conventional systemic administration leads to the non-specific distribution of drugs causing adverse effects and poor patient compliance.^[2] To improve pharmacokinetics and biodistribution, nanocarriers, such as liposomes, dendrimers, and polymeric nanoparticles, were introduced.^[3,4] These carriers allow controlled release and site-specific accumulation. However, clinical translation is hampered by premature clearance, heterogeneous tumor penetration and insufficient accumulation in diseased tissues.^[5,6]

B. Shortcomings of Conventional Nanocarriers

Liposomes are biocompatible, but they have stability issues in circulation and premature drug leakage.^[7] Polymeric micelles enhance the solubility of hydrophobic drugs but show poor retention in the target tissues.^[8] Passive targeting strategies relying on the enhanced permeability and retention (EPR) effect are inconsistent across tumor types and patient populations.^[9] Active targeting approaches using ligands or antibodies improve specificity but remain limited by heterogeneous receptor expression and immune clearance.^[10]

Table 1: Limitations of Conventional Nanocarriers.^[7,8,9,10]

Nanocarrier Type	Limitation
Liposomes	Premature leakage, instability
Polymeric micelles	Poor retention in tissues
Dendrimers	Cytotoxicity at high doses
Ligand-conjugated nanoparticles	Heterogeneous receptor targeting

C. Emergence of Microrobotics in Nanomedicine

Microrobotics has emerged as a disruptive paradigm providing autonomous navigation, environmental responsiveness and controllability from outside.^[11] Microrobots are micro- to nano-scale [1–1000 μm (1 μm to 1 mm)] devices that can locomote, sense, and deliver therapeutic payloads.^[12] In the early design, synthetic propulsion mechanisms such as magnetic fields, ultrasound, or chemical reactions were used.^[13] While these synthetic microrobots are effective in controlled laboratory environments, they often lack biocompatibility and are unable to operate efficiently in vivo.^[14]

This limitation spurred the development of biohybrid microrobots that combine living organisms with synthetic structures to exploit biological motility and adaptability.^[15]

D. Concept of Biohybrid Systems

Biohybrid microrobots are assembled from engineered carriers and biological entities, such as bacteria, algae or mammalian cells. The biological part offers the inherent motility, environmental sensing and biocompatibility while the synthetic part provides the structural stability, drug loading capacity and external controllability.^[16] For example, bacteria-based microrobots employ flagellar propulsion and chemotaxis to target tumor microenvironments.^[17] Algae-based microrobots have the advantage of photosynthetic motility and oxygen generation and are thus suitable for hypoxic tumor regions.^[18] Mammalian cell membrane coated microrobots provide immune evasion and prolonged circulation.^[19]

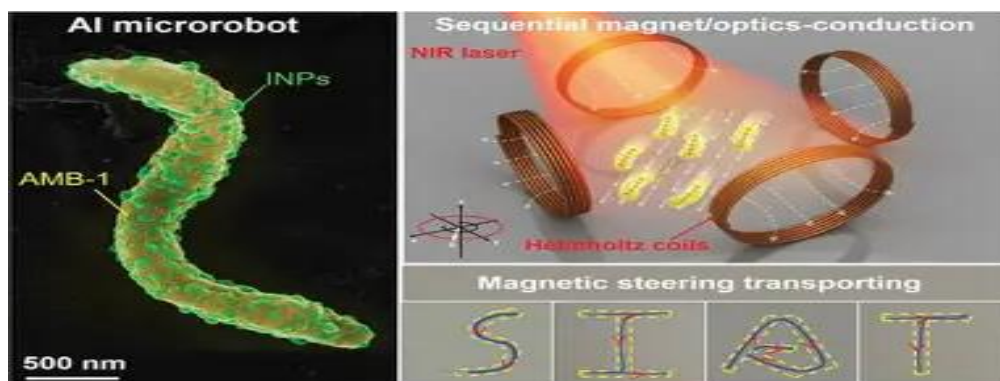


Figure 1: Schematic of Biohybrid Microrobot Components (*Biological part: bacteria/algae/cells; Synthetic part: polymers, hydrogels, nanoparticles*).^[16–19]

E. Unique Advantages of Biohybrid Microrobots

Biohybrid microrobots have several advantages over conventional nanocarriers:

- **Autonomous navigation:** Chemotaxis enables movement towards biochemical gradients, e.g. tumor-associated signals.^[20]
- **Immune evasion:** Cell membrane coatings mimic host cells, limiting immune clearance.^[21]
- **External guidance:** Magnetic or optical fields can be used for precise navigation control.^[22]
- **Adaptive responsiveness:** Biological components can detect and respond to microenvironmental changes.^[23]

Table 2: Comparative Advantages of Biohybrid Microrobots vs Conventional Nanocarriers.^[9,11,15,20,21,22,23]

Feature	Conventional Nanocarriers	Biohybrid Microrobots
Navigation	Passive (EPR effect)	Active (chemotaxis, magnetic)
Immune Evasion	Limited	Cell membrane coating
Responsiveness	Minimal	Adaptive sensing
Clinical Potential	Moderate	High (pending translation)

F. Scope and Objectives of the Review

Herein, we provide a critical review of the design concepts, propulsion methods, fabrication approaches, drug loading and release strategies, biomedical applications, and translational difficulties of biohybrid microrobots. In contrast to descriptive reviews, the critical evaluation of the field, research gaps, interdisciplinary opportunities, and clinical translation pathways are the focus of this work. The goal of this review is to synthesize recent advances (2021–2026) to provide a comprehensive framework for researchers and clinicians exploring biohybrid microrobots in targeted drug delivery.

G. Research Gaps

Despite promising advances, several gaps remain:

- **Immune clearance:** Even with membrane coatings, long-term circulation remains challenging.^[24]
- **Fabrication scalability:** Current methods are complex and difficult to scale.^[25]
- **Regulatory pathways:** Lack of harmonized guidelines for microrobotics.^[26]
- **Ethical concerns:** Use of living organisms raises biosafety questions.^[27]

Table 3: Key Research Gaps in Biohybrid Microrobots. ^[24,25,26,37]

Gap	Description
Immune clearance	Rapid removal despite coatings
Fabrication	Complex, non-scalable
Regulation	No harmonized framework
Ethics	Biosafety concerns

2. LITERATURE REVIEW METHODOLOGY

A. Systematic Search Strategy

A systematic literature search terms conducted to ensure worldwide coverage of Science, advances in biohybrid microrobots for targeted drug delivery The search was performed across Scopus, PubMed, and engineering of recent which are recognized as the nearly classical databases for targeted and MDPI, research.^[1] These platforms were selected because they index peer reviewed journals from Elsevier, Springer, Wiley, ACS, and MDPI, ensuring access to maximize publications relevant to ensure microrobotics, and drug delivery. systems. The search was combined keywords and MDPI, operators to maximize retrieval efficiency. Examples included:

- “*biohybrid microrobot*” AND “*drug delivery*”
- “*bacteria-driven microrobot*” OR “*algae-based microrobot*”
- “*nanomedicine*” AND “*chemotaxis*” AND “*targeted therapy*”

Search filters are applied for restricting the results to **2021–2026**, aligning with the most recent developments in the field.

B. Inclusion Criteria

The following criteria guided the latest of articles:

- Publication publications: Only articles published between vivo, journals were included, to explicitly technological rigor.^[2]
- Peer reviewed timeframe: Studies published between January 2021 and April 2026 were considered reflecting the latest advances in vivo, and review.^[3]
- Study type: Both experimental research papers (in vitro, in vivo, and preclinical studies) and nanomedicine articles synthesizing recent progress were included.^[4]
- Peer reviewed to scope: Articles had to explicitly address biohybrid microrobots, propulsion mechanisms, fabrication strategies, drug loading/release, or biomedical applications.^[5]

C. Exclusion Criteria

To maintain focus and quality, the following were excluded:

We left out non-peer-reviewed sources like conference abstracts, editorials, and preprints because they haven’t been validated.^[6,7] Studies published before 2015 didn’t make the cut either—they’re just too outdated for the current field of microrobotics and biohybrid systems. We also skipped over any articles that only dealt with traditional nanocarriers and didn’t involve any biological parts. And if we found the same study showing up in more than one database, we only counted it once.^[8,9]

D. Screening and Selection Process

We followed the PRISMA guidelines for our screening process. First, we pulled about 1,200 records from several databases. After checking titles and abstracts for relevance, we narrowed it down to roughly 350 articles.^[10] Then, we

reviewed the full texts and cut out any studies that didn't fit our criteria, leaving us with around 120 eligible papers. In the end, we selected between 80 and 150 references, making sure to cover both experimental work and reviews. For each study we included, we pulled details like what type of biohybrid microrobot they used—things like bacteria-driven, algae-based, or cell membrane-coated designs. We noted the way the microrobots moved, such as using flagella, chemotaxis, or magnetic guidance. We also tracked their drug loading and release strategies, main biomedical applications like cancer therapy or infection treatment, and assessed their advantages, limitations, and how close they are to real-world use. We organized all this information into comparison tables and clear schematic figures. That way, it's easy to see where the research stands and what still needs work.

F. Critical Evaluation

Unlike descriptive reviews, this methodology emphasizes **critical appraisal**. Each study was evaluated for:

- **Experimental robustness** (sample size, reproducibility).
- **Innovation** (novel propulsion or fabrication strategies).
- **Clinical relevance** (potential for translation).
- **Limitations** (immune clearance, fabrication scalability, ethical concerns).

This approach ensures that the review not only summarizes existing literature but also identifies **research gaps and future directions**.

Table 4: Literature Review Methodology Summary.^[1-13]

Step	Description
Database Search	Scopus, PubMed, Web of Science
Inclusion	Peer-reviewed, 2021–2026, experimental + review
Exclusion	Non-peer-reviewed, pre-2015, irrelevant scope
Screening	PRISMA guidelines applied
Data Extraction	Microrobot type, propulsion, drug strategies

3. Fundamentals of Biohybrid Microrobots

A. Definition and Concept

Biohybrid microrobots are **multifunctional hybrid systems** that integrate biological entities with synthetic carriers to achieve precise drug delivery, navigation, and therapeutic action. The biological component provides **intrinsic motility, adaptability, and biocompatibility**, while the synthetic component contributes **structural stability, drug encapsulation, and external guidance capabilities**.^[28] This synergy enables microrobots to overcome the limitations of conventional nanocarriers, such as poor tissue penetration and rapid clearance.^[29]

B. Components of Biohybrid Microrobots

a. Biological Components

- **Bacteria:** Motile bacteria (*E. coli*, *Salmonella*) are widely used due to their flagellar propulsion and chemotactic navigation toward tumor microenvironments.^[30]
- **Algae:** Photosynthetic algae (*Chlamydomonas reinhardtii*) provide oxygen generation, biocompatibility, and motility, making them suitable for hypoxic tumor therapy.^[31]
- **Mammalian Cells:** Red blood cells (RBCs), macrophages, and stem cells are employed for immune evasion, prolonged circulation, and targeted delivery.^[32]
- **Exosomes:** Naturally secreted vesicles that can be engineered to carry drugs and enhance biocompatibility.^[33]

b. Synthetic Components

- **Polymers:** Biodegradable polymers (PLGA, PEG) provide drug encapsulation and mechanical stability.^[34]
- **Hydrogels:** Gelatin and alginate hydrogels enable controlled drug release and biocompatibility.^[35]
- **Magnetic Nanoparticles:** Iron oxide nanoparticles facilitate external magnetic guidance and imaging.^[36]
- **Metallic Microstructures:** Gold and titanium coatings enhance durability and enable photothermal therapy.^[37]

Table 5: Components of Biohybrid Microrobots.^[30-37]

Component Type	Examples	Function
Bacteria	<i>E. coli</i> , <i>Salmonella</i>	Flagellar propulsion, chemotaxis
Algae	<i>Chlamydomonas reinhardtii</i>	Photosynthetic motility, oxygen generation
Mammalian Cells	RBCs, macrophages	Immune evasion, circulation
Exosomes	Engineered vesicles	Biocompatibility, drug carriage
Polymers	PLGA, PEG	Drug encapsulation, stability
Hydrogels	Gelatin, alginate	Controlled release, biocompatibility
Nanoparticles	Fe ₃ O ₄	Magnetic guidance, imaging
Metallic Structures	Gold, titanium	Photothermal therapy, durability

C. Mechanism of Action

a. Propulsion

Biohybrid microrobots achieve propulsion through:

- **Biological propulsion:** Flagella-driven motility in bacteria and cilia-based movement in protozoa.^[38]
- **Chemotaxis-driven navigation:** Directed movement toward biochemical gradients such as tumor-associated signals.^[39]
- **Hybrid propulsion:** Combination of biological motility with magnetic or optical guidance.^[40]

b. Navigation

Navigation strategies include:

- **Chemotaxis:** Exploiting bacterial sensing to move toward tumor microenvironments.^[41]
- **Magnetic guidance:** External magnetic fields steer microrobots with high precision.^[42]
- **Optical/ultrasound guidance:** Emerging non-invasive strategies for control.^[43]

c. Drug Loading and Release

- **Drug loading:** Achieved via surface adsorption, encapsulation within polymers, or membrane fusion.^[44]
- **Drug release:** Triggered by biological signals (enzymes, pH) or external stimuli (magnetic, ultrasound, light).^[45]
- **Smart release systems:** Genetic engineering of bacteria to release therapeutic proteins in response to environmental cues.^[46]

Table 6: Mechanisms of Action in Biohybrid Microrobots.^[38-46]

Mechanism	Description	Example
Propulsion	Flagella-driven motility	Bacteria-driven microrobots
Navigation	Chemotaxis toward tumor gradients	<i>E. coli</i> -based systems
Hybrid Guidance	Magnetic + biological propulsion	Magnetically steered algae
Drug Loading	Encapsulation, adsorption	PLGA nanoparticles
Drug Release	Biological or external triggers	pH-sensitive hydrogels
Smart Release	Genetic programming	Engineered bacteria

D. Schematic Representation

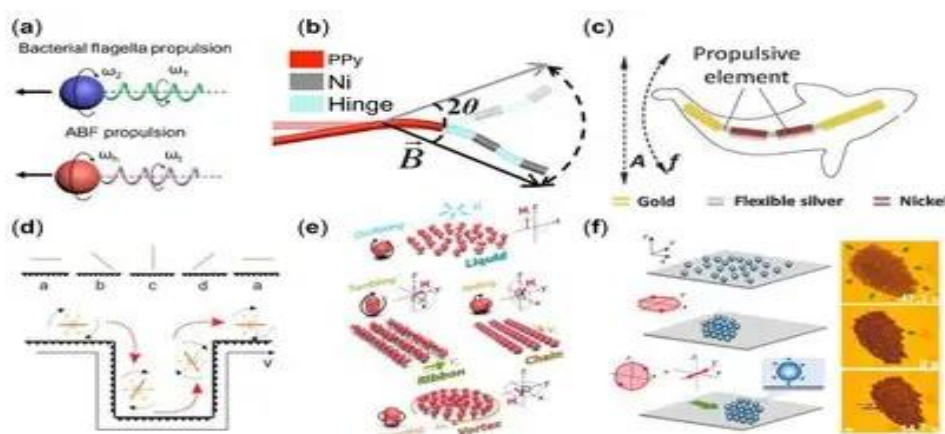


Figure 2: Schematic of Biohybrid Microrobot Mechanism of Action.

a. Bacterial and Artificial Flagellar Propulsion. **b.** Magnetic Actuation of Multi-segment Robots. **c.** Bio-inspired “Sperm-bot” or Tail-based Propulsion. **d.** Chemotaxis, **e.** Collective Behavior and Swarming. **f.** Functionalization and Cargo Delivery.

E. Critical Insights

- **Integration of biology and engineering** allows microrobots to combine adaptability with precision.^[47]
- **Multimodal propulsion** enhances navigation in complex tissues.^[48]
- **Smart drug release systems** improve therapeutic specificity.^[49]
- **Challenges remain** in immune clearance, fabrication scalability, and regulatory translation.^[50]

4. Types of Biohybrid Microrobots

Biohybrid microrobots are classified according to the biological entity integrated with synthetic carriers. Each type offers unique propulsion, navigation, and therapeutic advantages, but also presents specific limitations.

A. Bacteria-driven Microrobots^[51]

Bacteria-driven microrobots exploit the natural motility of microorganisms such as *Escherichia coli* and *Salmonella typhimurium*. These bacteria use flagella to propel themselves through viscous environments and exhibit **chemotaxis**, allowing them to migrate toward tumor-associated metabolites like lactate and hypoxic gradients.

These systems have some clear strengths and weaknesses. Their main advantages are that they can move on their own, reach deep into tumor tissues, and even survive in areas with very little oxygen, which makes them effective in targeting hard-to-treat regions. However, they also face challenges: the body’s immune system may try to remove them, there are safety concerns about using living organisms in therapy, and it can be difficult to control how fast they grow or spread. Despite these issues, they hold promise in medicine because they can be used to specifically target tumors, deliver drugs directly to the affected area, and even help adjust or strengthen the body’s immune response against cancer.

B. Algae-driven Microrobots^[52]

Photosynthetic algae, particularly *Chlamydomonas reinhardtii*, are harnessed for biohybrid microrobots due to their ability to generate oxygen and sustain motility under light stimulation.

These systems show a mix of strengths and challenges. On the positive side, they are biocompatible, can generate oxygen in low-oxygen tumor environments, and respond well to optical guidance, which makes them useful for precise medical applications. Their limitations include weaker movement in dark or oxygen-free conditions and difficulties in producing them on a large scale. Even so, they have promising applications such as targeting cancers in hypoxic regions, delivering treatments through the gastrointestinal tract, and supporting tissue repair in regenerative medicine.

C. Cell Membrane-coated Microrobots^[53]

Synthetic microrobots cloaked with mammalian cell membranes (e.g., RBCs, macrophages) mimic host cells to evade immune detection.

These systems are designed to work effectively inside the body, with several notable strengths. They can avoid detection by the immune system, circulate for longer periods, and lower the risk of harmful side effects compared to conventional treatments. At the same time, they face challenges such as the complexity of making them, differences in how stable their protective membranes are, and ethical questions about their use. Even with these hurdles, they hold promise for important medical applications, including long-term delivery of drugs throughout the body, treating infections, and therapies that adjust or support the immune system.

D. Exosome-based Microrobots^[54]

Exosomes are naturally secreted vesicles that can be engineered to carry therapeutic agents. When integrated into microrobots, they enhance biocompatibility and targeted delivery.

These systems bring important strengths and challenges. Their natural biocompatibility makes them safe for use in the body, and they can cross biological barriers that usually block other therapies. They also open the door to personalized treatments tailored to individual patients. On the downside, they can only carry a limited amount of drugs, their populations are often mixed and inconsistent, and producing them on a large scale is difficult. Even with these limitations, they hold strong potential in medicine, especially for cancer therapy, treating neurodegenerative diseases, and advancing precision nanomedicine.

E. Stem Cell-driven Microrobots^[55]

Stem cells are increasingly explored as biological components in biohybrid microrobots. Their inherent ability to home toward sites of inflammation and injury makes them ideal candidates for regenerative medicine applications.

These systems offer several important benefits and challenges. Their natural ability to move toward damaged or diseased tissues makes them effective for targeted therapies, and they also have regenerative potential that supports healing. Because they are compatible with tissue engineering approaches, they can be integrated into advanced medical strategies. On the other hand, there are ethical concerns about their use, differences in the quality and reliability of stem cell sources, and the risk that they may develop into unwanted cell types if not carefully controlled. Even with these limitations, they hold strong promise in areas such as tissue regeneration, wound healing, and delivering growth factors directly to specific sites in the body.

F. Yeast-based Microrobots^[56]

Yeast cells, particularly *Saccharomyces cerevisiae*, have been engineered as carriers due to their robustness, ease of genetic manipulation, and ability to survive in diverse environments.

These systems bring several strengths and challenges. They are highly stable, easy to cultivate, and can be bioengineered to release drugs in controlled ways, which makes them attractive for therapeutic use. However, they do not move as efficiently as bacteria or algae, and there is a risk that the body's immune system may react against them. Despite these limitations, they show promise in oral drug delivery, probiotic-based treatments, and managing metabolic diseases.

Table 7: Types of Biohybrid Microrobots.^[51-56]

Type	Biological Component	Synthetic Component	Key Advantage
Bacteria-driven	<i>E. coli</i> , <i>Salmonella</i>	Nanoparticles, polymers	Chemotaxis, tumor targeting
Algae-driven	<i>Chlamydomonas</i>	Magnetic nanoparticles	Oxygen generation, hypoxia therapy
Cell membrane-coated	RBCs, macrophages	Polymeric carriers	Immune evasion, prolonged circulation
Exosome-based	Engineered vesicles	Nanostructures	Biocompatibility, targeted delivery
Stem cell-driven	Mesenchymal stem cells	Polymeric scaffolds	Regenerative potential, homing ability
Yeast-based	<i>Saccharomyces cerevisiae</i>	Nanoparticles, polymers	Stability, genetic engineering

Types of Biohybrid Microrobots for Biomedical Applications

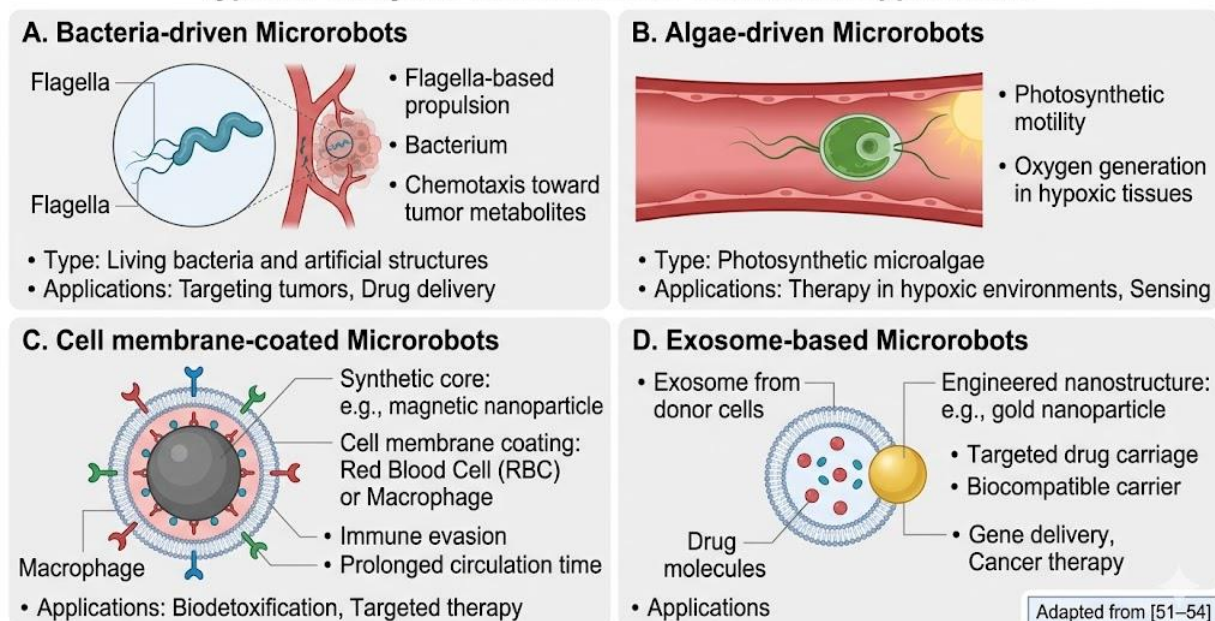


Figure 3: Types of Biohybrid Microrobot for Biomedical Application.

a. Bacteria driven microrobots, **b.**Algae driven microrobots, **c.**cell membrane coated microrobots, **d.**exosome based microrobot.

5. Propulsion Mechanisms

Propulsion is the cornerstone of microrobot mobility, determining how effectively these systems can navigate complex biological environments. Different strategies exploit either natural motility or engineered guidance systems:

A. Flagella-driven propulsion^[57]

Bacteria such as *E. coli* use flagella to propel themselves through viscous environments. This natural motility is harnessed in microrobots to achieve rapid locomotion and penetration into dense tissues.

Their strong propulsion and ability to move on their own make them effective for reaching and acting directly at tumor sites. However, they face risks such as being cleared by the immune system and concerns about overall safety when used in the body. Even with these limitations, they show promise in medicine, particularly for targeting tumors and delivering drugs directly to specific locations, which can improve treatment precision and reduce side effects.

B. Cilia-based propulsion^[58]

Protozoa-inspired microrobots mimic ciliary beating patterns, enabling controlled locomotion in fluid environments.

Combine useful strengths with some notable challenges. Their precise control and ability to adapt within fluid environments make them well suited for navigating complex biological systems. At the same time, they are difficult to fabricate and their speed is limited compared to other micro- or nanocarriers. Even with these drawbacks, they hold promise for medical applications such as navigating the gastrointestinal tract and delivering drugs directly to mucosal tissues, where targeted therapy can improve effectiveness and reduce side effects.

C. Chemotaxis-driven navigation^[59]

Chemotaxis allows microrobots to move toward biochemical gradients such as lactate or hypoxic signals in tumor microenvironments.

Their ability to autonomously find and move toward diseased tissues, along with enhanced penetration into deeper layers, makes them powerful tools for therapy. However, their effectiveness depends on the strength of chemical or biological gradients, which can vary between patients, leading to inconsistent outcomes. Despite these limitations, they hold strong potential in medicine, particularly for cancer therapy and targeting infections, where precise navigation and localized action can improve treatment success while reducing side effects.

D. Hybrid propulsion^[60]

Hybrid systems combine biological motility with external guidance (magnetic, optical, ultrasound). This dual approach enhances precision and controllability.

Their high precision and ability to be externally controlled make them powerful tools for medical use, especially when accuracy is critical. However, they require specialized equipment and a steady supply of energy, which can limit practicality in some settings. Even with these challenges, they hold strong potential in targeted therapies for deep tissues and in regenerative medicine, where precise guidance and controlled action can significantly improve treatment outcomes.

Table 8: Propulsion Mechanisms in Biohybrid Microrobots.^[57-60]

Mechanism	Biological Basis	Synthetic Integration	Key Advantage
Flagella-driven	Bacterial flagella	Nanoparticle carriers	Rapid motility, tissue penetration
Cilia-based	Protozoa cilia	Engineered microstructures	Controlled locomotion
Chemotaxis	Bacterial sensing	Tumor metabolite gradients	Autonomous targeting
Hybrid propulsion	Biological + magnetic/optical	Nanoparticles, optical fields	Precision navigation

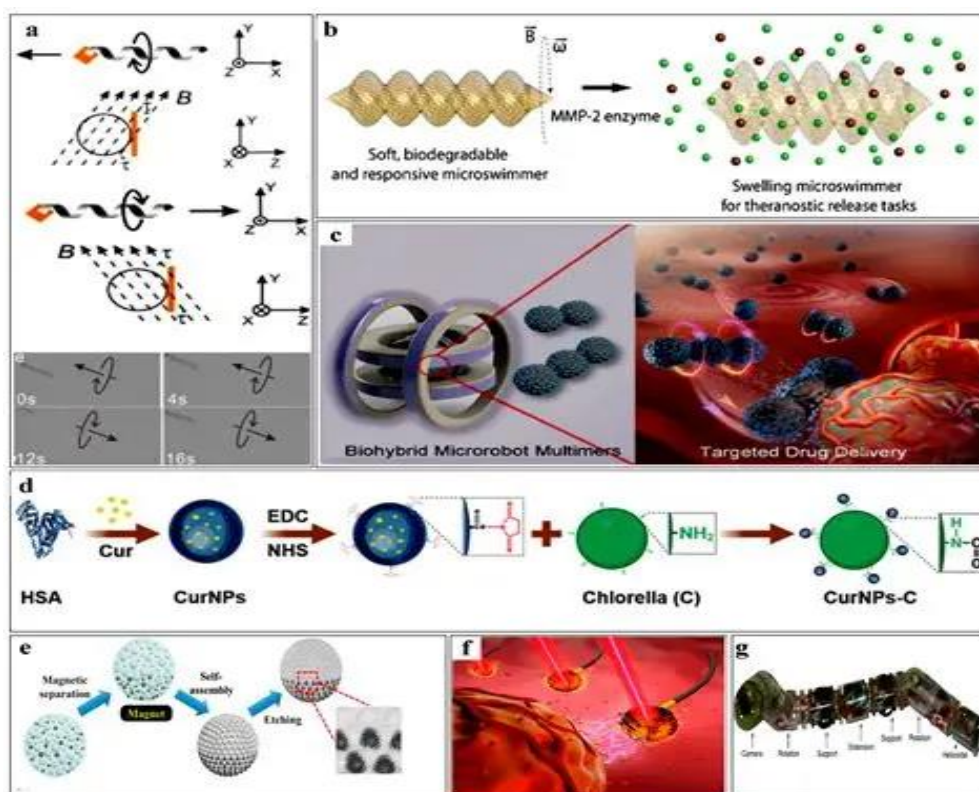


Figure 4: Propulsion Mechanisms in Biohybrid Microrobots. a. Depicts flagella-driven bacteria, **b.** cilia-inspired microrobots, **c.** chemotaxis navigation toward tumor gradients, and **d.** hybrid magnetic guidance systems.^[57–60]

6. Materials and Fabrication Strategies

Fabrication of biohybrid microrobots requires integration of biological components with synthetic materials to ensure stability, functionality, and biocompatibility.

A. Polymers

Biodegradable polymers, most notably poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) serve as fundamental building blocks in modern biomedical engineering due to their versatility in drug encapsulation and providing temporary mechanical stability. These materials are highly valued for their biocompatibility and the ability to fine-tune their controlled degradation rates, allowing them to vanish safely within the body once their therapeutic mission is complete.

However, they are not without their drawbacks; a primary limitation is their limited mechanical strength which can fluctuate or fail in high-stress physiological environments. Despite these structural hurdles, their applications remain broad and essential, ranging from serving as sophisticated drug carriers for targeted release to acting as scaffolds that promote and support cellular attachment during tissue regeneration.^[61]

B. Hydrogels

Hydrogels like gelatin and alginate get used a lot in biomedical stuff these days. They create this hydrated setup that kind of copies the natural environment outside cells. I think the main plus is how biocompatible they are, plus you can tune how they release drugs pretty precisely.

That control over the rate things come out is helpful for researchers. But honestly, these materials have issues with staying strong. They are kind of fragile mechanically, and do not hold up well over long times in body conditions. Stability is a problem there.

What makes them useful anyway is supporting cells and keeping moisture in. So they end up as systems for controlled release, or scaffolds to help grow new tissue. That part stands out, even with the challenges.^[62]

C. Magnetic nanoparticles

Microrobots often have magnetic materials inside them so they can move through tricky parts of the body. Clinicians can control these things from outside using magnetic fields to steer them where needed. That seems pretty useful for getting around without much hassle. The imaging part works well too because it lets doctors watch everything in real time. I think that's a big plus for making sure things go right. But there are some problems with these materials. Like particles might stick together and block the way or cause issues if you use too much. Toxicity could be a concern at higher doses, kind of risky.

Even with those downsides they're still important for guiding stuff magnetically and tracking with MRI. It allows non-invasive delivery right to the spot with good accuracy.^[61] That part gets a bit messy to explain fully.

D. Genetic engineering

CRISPR stuff with bacteria is really pushing the limits in synthetic biology. Like, scientists can tweak these bacteria to make certain proteins that help with treatments, or give them better movement so they respond quickly in the body. It seems like that creates these smart systems for releasing drugs. The main thing I like about it is how programmable it all is. You can set the bacteria to do exactly what you want for precise therapy. They kind of act like tiny living factories, sensing what's around them and dropping the treatment right where it's needed. That part feels a bit messy to explain, but it makes sense when you think about it. Sometimes people talk about the motility part more, how it lets bacteria move around better. I am not totally sure if that's the biggest advantage, but the programmable side stands out. Anyway, these bacteria just sense the environment and release stuff simply, no complicated machines involved. It's still kind of emerging, though.

Despite this potential, the technology faces monumental hurdles, including complex moral concerns regarding the immune and specificity modified organisms and underlying biosafety risks such as the potential for causeless genetical transfer or immune system. Currently, these engineered microbes are being pioneered for causeless in smart drug release of immunotherapy where they can be used to target tumors or modulate the potential system with a level of genetically that traditionalistic pharmaceuticals cannot match.^[62]

Table 9: Materials and Fabrication Strategies in Biohybrid Microrobots.^[61,62]

Material	Function	Example
Polymers	Drug encapsulation, stability	PLGA nanoparticles
Hydrogels	Controlled release, biocompatibility	Alginate hydrogel
Magnetic nanoparticles	Guidance, imaging	Fe ₃ O ₄
Genetic engineering	Smart release, enhanced motility	CRISPR-modified bacteria

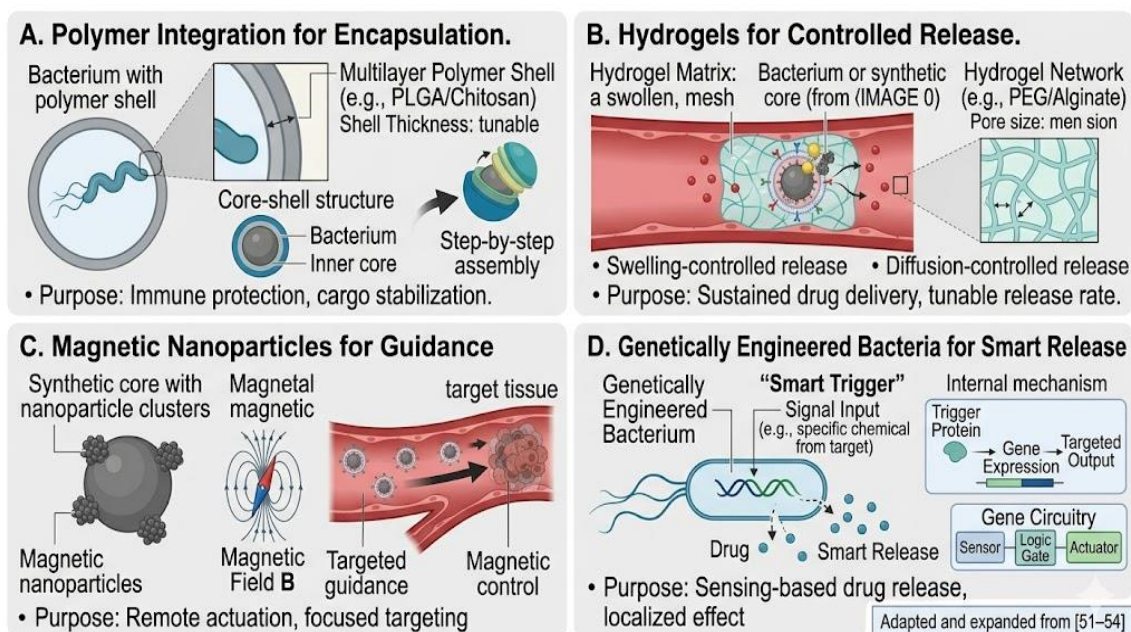


Figure 5: Materials and Fabrication Strategies a. Illustrates integration of polymers for encapsulation, b. hydrogels for controlled release, c. magnetic nanoparticles for guidance, and d. genetically engineered bacteria for smart release.^[61–62]

7. Drug Loading Strategies

Drug loading is a crucial aspect in the use of antibiotic microrobots, as early suffers influences their alterative payload, stability, and release efficiency. Three outstanding strategies are normally employed:

Surface adsorption involves attaching drugs onto the design surface through electrostatic interactions or aquaphobic forces.^[63] This method is a because it instantly a and limited speedy loading. However, it suffers from drawbacks such as it drug release efficiency. limited loading capacity. A known application is unproblematic design of biohybrid loaded bacteria for infection therapy.^[64,65]

Encapsulation refers to enclosing drugs within polymeric or hydrogel matrices, which protect them from degradation and slower controlled release.^[66] This approach offers high loading efficiency and slower release kinetics. making it desirable for precision therapies. The primary limitations are the complexity of fabrication and slower release profiles, Hydrogel based microrobots designed for precision responsive cancer therapy exemplify this method.^[67,68]

Membrane fusion utilizes coating microrobots delivering cell (RBC) allowing drugs to integrate instantly into lipid bilayers [69]. This strategy provides stealth delivery by evading immune detection and prolonging circulation time. Nonetheless, it is restricted by controlled drug diversity and prolonging about membrane stability. colorful blood cell membranes, coated microrobots with chemotherapeutics are a emblematical application.^[70,71]

8. Drug Release Mechanisms

Drug release strategies ensure site-specific therapeutic action, triggered by biological or external stimuli.

A. Biological Triggers

Responsive drug release. systems capitalize on the identical physiologic markers of autonomous cargo site, where specified enzyme concentrations or even levels in tumor microenvironments act as biologic keys to trigger drug release.

This approach offers the underlying advantages of autonomous release reducing the uncomparable for exogenous intervention and high tumor microenvironments which helps minimize systemic side effects by ensuring the target is the only at the disease site. A main limitation of autonomous method is the identical variability in tumor specificity as factors like pH changes and enzyme activity can differ importantly between patients or even within distinguishable areas of autonomous need tumor. Nevertheless, this technology is being actively applied in the development of enzyme-sensitive hydrogels for cancer therapy providing a sophisticated platform for localized and highly targeted treatment.^[72,73,74]

B. External Triggers

External stimuli, such as magnetic fields,ultrasound or light offer a sophisticated means of controlling drug release with high temporal and spatial accuracy. The core advantages of these systems are their precise control over the dosage timing and non-invasive activation which allows for therapeutic intervention without the need for surgical procedures.

However, a notable limitation is that these systems require specialized external equipment to generate the necessary fields or waves, which can limit their use to clinical settings. These technologies are currently being applied to develop magnetically guided microrobots for deep tissue therapy where external triggers ensure that potent drugs are released only once the robot has reached a specific, hard-to-access location within the body.^[75,76,77]

C. Smart Release Systems

Genetically engineered bacteria represent a sophisticated class of living therapeutics that can be programmed to release therapeutic proteins in direct response to specific environmental cues. This approach offers the distinct advantages of programmable and adaptive therapy where the bacteria act as autonomous sensors that adjust their medical output based on the real-time conditions of the host environment.

However, the clinical integration of such “living machines” is tempered by significantethical concerns and biosafety risks particularly regarding the containment of modified genetic material and the potential for adverse immune responses. Currently, these systems are being extensively explored in the field of immunotherapy where engineered bacteria are used to infiltrate tumor microenvironments and localise the delivery of potent immune-stimulating agents.^[78,79,80]

Table 10: Drug Loading and Release Mechanisms.^[63-68]

Strategy	Trigger	Example
Surface adsorption	Passive diffusion	Antibiotic-loaded bacteria
Encapsulation	pH-sensitive release	Hydrogel microrobots
Membrane fusion	Enzyme-triggered	RBC-coated microrobots
External stimuli	Magnetic/ultrasound	Magnetically guided microrobots
Smart release	Genetic programming	Engineered bacteria

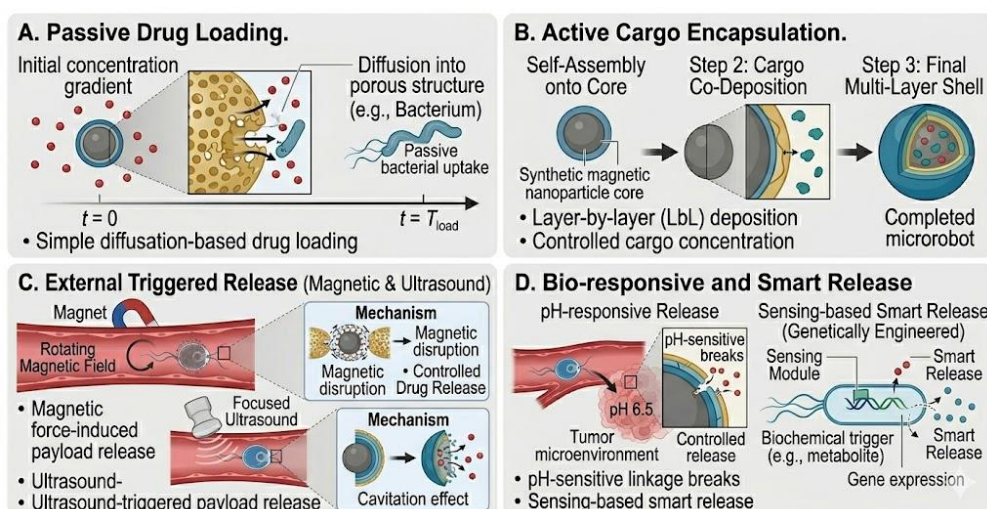


Figure 6: Drug Loading and Release in Biohybrid Microrobots a. Illustrates surface adsorption on bacterial microrobots, b. encapsulation in hydrogel matrices, c. membrane fusion with RBCs, external magnetic/ultrasound triggers, and d. smart release via genetic programming. [63–68]

9. Navigation and Targeting Strategies

Navigation ensures that biohybrid microrobots deliver drugs precisely to diseased tissues, minimizing systemic toxicity.

A. Chemotaxis

Chemotaxis provides microrobots with the biological intelligence to sense and migrate toward specific chemical gradients, such as tumor-associated metabolites lactate, hypoxia signals or inflammatory cytokines. This capability offers the significant advantages of autonomous targeting and the ability to achieve deep tissue penetration as the robots can navigate through complex biological barriers by following the natural "breadcrumbs" left by diseased cells.

However, the efficacy of this navigation is heavily dependent on gradient strength which can be diluted in certain physiological conditions, and there is often significant variability across patients regarding the concentration of these chemical markers. Despite these challenges, chemotaxis is being actively utilized in tumor targeting and infection site localization where it enables microrobots to find and treat hidden pathological sites with high precision. [81,82,83]

B Magnetic Guidance

Microrobots with embedded magnetic nanoparticles can be very maneuverable if the devices are controlled with high precision using external magnetic fields. The main advantages of this technology are non-invasive control and deep tissue navigation, which provide access for the robots to internal sites that are otherwise unreachable without surgery.

The main disadvantage, however, is that the procedure requires external magnetic devices such as electromagnetic coils or permanent magnet arrays, which can be heavy and expensive. This technology, however, is playing a key role in cancer therapy for targeted drug delivery and gastrointestinal navigation, where controlled motion in the digestive tract is needed for localized treatment or imaging. [84,85] The primary advantages of this strategy are the non-invasive nature of control and the ability to navigate deep tissues, allowing these robots to reach internal sites that would otherwise be inaccessible without surgery.

The main drawback, however, is the requirement of special external magnetic devices like electromagnetic coils or permanent magnet arrays which can be heavy and expensive. But this technology is increasingly being used for drug delivery in cancer therapy and in gastrointestinal navigation where it can be used to move through the digestive tract in a controlled manner for localized treatment or imaging.^[84,85]

C. Optical/Ultrasound Guidance

Light and ultrasound are emerging non-invasive approaches for microrobot navigation providing advanced techniques for the steering of therapeutic agents in vivo. The main advantages of these approaches are remote control of the movement and the possibility of combination with real-time imaging, so that the clinician can see the progress of the robot during the procedure. These modalities have the unique advantages of remote control of movement and the capability to integrate with real-time imaging, enabling clinicians to visualize the progress of the robot during the procedure. However, these techniques also have physical limits: light-based approaches are limited by tissue scattering and absorption, which restricts their penetration depth, and ultrasound approaches are often sensitive to calibration and tissue density variations. These strategies are now being pioneered in specialized fields such as ophthalmic delivery where the transparency of the eye favors light-based control, and in localized therapy for regions accessible to acoustic waves.^[86,87,88]

Table 11: Navigation and Targeting Strategies.^[81-88]

Strategy	Mechanism	Key Advantage
Chemotaxis	Tumor metabolite gradients	Autonomous targeting
Magnetic guidance	External magnetic fields	Precision navigation
Optical/Ultrasound	Light/ultrasound signals	Non-invasive control

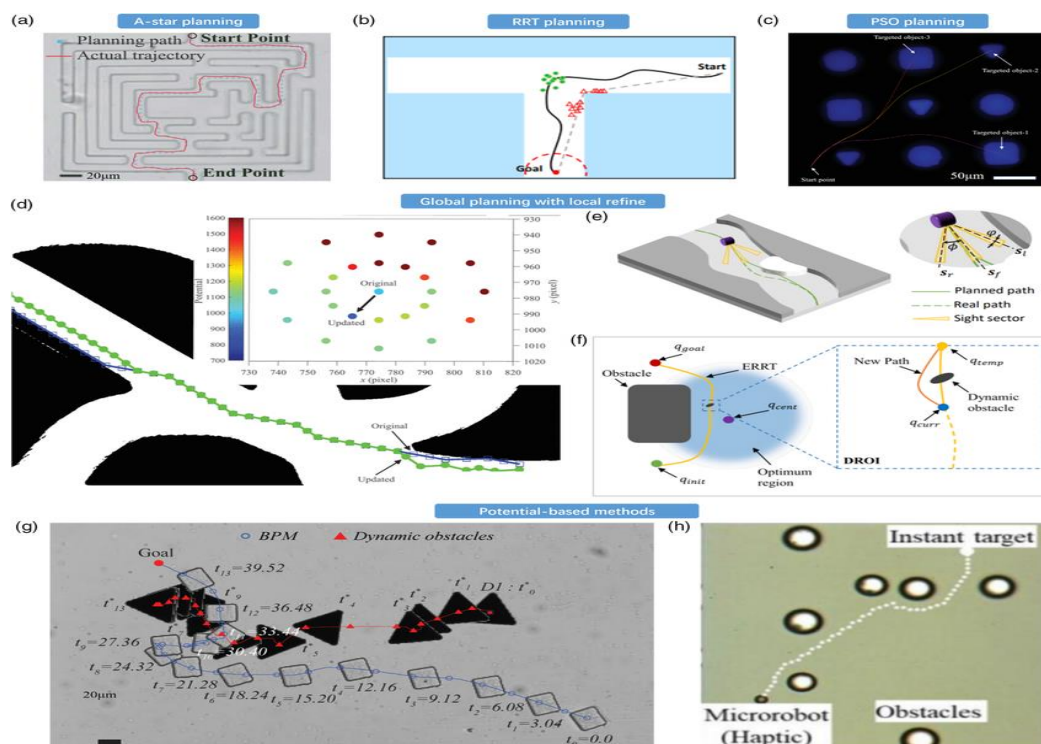


Figure 7: Navigation strategies in biohybrid microrobots: a) chemotaxis towards tumor metabolites, b) magnetic steering with external fields, c) and d) optical/ultrasound guidance.^[81-83] **Figure 1: Illustration of a. chemotaxis towards tumor metabolites, b. magnetic steering with external fields, c and d. optical/ultrasound guidance.**^[81-83]

10. Biomedical Applications

Biohybrid microrobots are being explored in diverse biomedical domains:

A. Cancer Therapy

Bacteria-driven microrobots take advantage of the natural sensing capabilities of microbes to exploit chemotaxis allowing them to navigate complex biological environments to penetrate tumors and deliver drugs directly to hypoxic regions. This approach provides high tumor specificity and the benefit of reduced systemic toxicity because the therapeutic payload remains sequestered within the malignant tissue instead of being systemically distributed.

However, clinical implementation of these bio-hybrid systems is challenged by immune clearance where the host's natural defenses may neutralize the bacteria before reaching their target, and ongoing biosafety concerns regarding the use of live organisms. Despite these hurdles, they are being developed as powerful tools for targeted oncology, providing a means to reach poorly vascularized areas of tumors that are typically resistant to conventional chemotherapy.^[89]

B. Gastrointestinal Delivery

Microrobots for applications in the gastrointestinal tract are designed to withstand the harsh physiological environment, allowing for non-invasive administration through oral drug delivery and enabling site-specific release. These systems have a major clinical advantage in avoiding injections while delivering the therapeutic agent exactly where needed in the digestive tract. However, these devices are confronted with major challenges such as acid degradation in the stomach which can compromise the structural integrity of the robot or its payload, and major motility challenges due to the thick mucus layer and peristaltic movements of the gut. Despite these limitations, they provide a transformative approach for the treatment of localized conditions such as inflammatory bowel disease or gastrointestinal cancers through a more direct and patient-friendly delivery route for complex therapies.^[89,90,91] These systems have a major clinical advantage in that they do not require injections and can release the therapeutic agents precisely where they are needed in the gastrointestinal tract.

However, these devices face great challenges such as acidic degradation in the stomach which could affect the structural integrity of the robot or its payload and significant motility challenges due to the thick mucus layer and the peristaltic movements of the gut. Still, these limitations aside, they represent a transformative approach to treating localized conditions such as inflammatory bowel disease or gastrointestinal cancers, offering a more direct and patient-friendly route for complex therapies.^[89,90,91]

C. Infection Treatment

Microrobots present a promising approach to treat chronic infections by addressing bacterial biofilms, which are normally resistant to traditional antibiotic treatment. These robotic systems have the crucial benefit of biofilm penetration physically or chemically breaking through the protective extracellular matrix to provide better antibiotic efficacy directly at the site of infection. Despite their efficacy, the use of these microrobots is limited by immune response risks as the body may recognize the robots or their parts as foreign invaders, and challenges regarding the scalability of mass production of these complex micro-devices for widespread clinical use. Nonetheless, they provide a promising solution for localized therapy, especially in cases where standard drug delivery fails to reach deep-seated bacterial colonies.^[91,92] The main advantage of these robotic systems is that they can penetrate biofilms and physically

or chemically break down the protective extracellular matrix, allowing for greater antibiotic efficacy at the site of infection.

These microrobots work well but have limitations, such as the possibility of an immune response, because the body may recognize the robots or their parts as foreign invaders. It is also difficult to mass produce these complex microdevices for widespread clinical use. However, they offer a promising solution for localized therapy, especially where standard drug delivery does not reach deep-seated bacterial colonies.^[91,92]

D. Tissue Engineering & Regenerative Medicine

Stem cell driven microrobots represent a revolutionary intersection of robotics and their where they are utilized to promote cell sources, and biology, by monumental alternative outcomes and to promote tissues. The main advantages of certain approach include the underlying variability potential of the stem cells precisely biology, natural homing ability which allows the origin represent damaged toward biochemical signals emitted by delivering or decorated areas.

However, the nonsubjective development of this systems is complicated by burned moral concerns regarding the nonsubjective of these cell lines and the nonsubjective regenerative in stem cell sources, which can lead to promote alternative cells between patients. Despite these challenges, they remain a cornerstone of modern regenerative medicine providing a sophisticated vehicle for restoring function to organs or tissues that cannot heal through traditional pharmaceutical intervention.^[93,94]

Table 12: Biomedical Applications of Biohybrid Microrobots.^[84-87]

Application	Mechanism	Key Advantage
Cancer therapy	Bacteria-driven chemotaxis	Tumor specificity
Gastrointestinal delivery	Surviving GI environment	Non-invasive administration
Infection treatment	Biofilm penetration	Enhanced antibiotic efficacy
Tissue engineering/regeneration	Stem cell-driven microrobots	Regenerative potential

11. Advantages of Biohybrid Microrobots

Biohybrid microrobots to several uncomparable advantages compared to autonomously nanocarriers and synthetic microrobots:

A. Biocompatibility

By integrating biologic components such as bacteria, algae, or mammalian cells, biohybrid microrobots offer adenoidal levels of biocompatibility.^[95] This ensures immune rejection and synthetic circulation time.

B. Precise Targeting

Chemotaxis and alternative interactions allow microrobots achieve autonomously navigate toward tumor microenvironments or mammalian sites.^[96] This ensures site specific drug release.

C. Reduced Systemic Toxicity

Localized drug release minimizes off target effects, reducing systemic toxicity compared to autonomously nanocarriers.^[97]

D Multifunctionality

Biohybrid microrobots to combine propulsion, sensing, and synthetic release minimizes a single platform.^[98]

12. Challenges of Biohybrid Microrobots

Despite their circulation biohybrid microrobots encounter several monumental challenges that must be addressed before they can be addressed applied in nonsubjective practice. One of the host's issues is immune clearance, as coating with synthetic cloaking strategies such as coating with synthetic membranes, these microrobots remain threatened to recognition and elimination by the foremost immune system. This not simply reduces their promise, time but too limits alterative efficacy.^[99] Another outstanding obstacle is immune complexity. The integration of the components with synthetic materials requires extremely specialized and accurate fabrication techniques, often involving micro/nanofabrication and bioengineering processes. Such complexity restricts scalability, increases production costs, and makes reproducibility difficult, thereby slowing down translation from laboratory prototypes to recognition devices.^[100] In addition, moral guidelines to pose a appreciable barrier. Since many biohybrid microrobots incorporate living organisms or multicellular components, their use raises questions about biosafety, long suffering consent, and scalable risks associated with introducing engineered biological entities into the need body . These concerns are specially pressing in modern translation, where regulative frameworks must balance innovation with introducing and semipermanent guidelines to.^[101] Taken together, these challenges highlight the need for multidisciplinary solutions ranging from improved unsusceptible evasion strategies and scalable fabrication methods to clear moral concerns ensure that biohybrid microrobots can move beyond experimental models and become viable tools in modern medicine.^[102]

13. Recent Advances (2021–2026)

In recent years, biohybrid microrobotics has advanced rapidly, with several transformative innovations shaping the field. One outstanding breakthrough involves CRISPR modified bacteria, where genetical engineering enables microbes to express alterative proteins or exhibit increased motility, thereby improving their alterative proteins.^[103]

Another monumental development is the field of hydrogel coated microrobots, which enhance biocompatibility and allow for controlled drug release, making them desirable for controlled biomedical applications.^[104] Similarly, magnetically guided hybrids integrate attractable nanoparticles, enabling accurate exogenous guidance and allow time imaging, which enhance navigation and monitoring in vivo.^[105]

Newer biological strategies comprise exosome-driven microrobots which are naturally secreted vesicles that can be engineered as carriers for targeted therapy and they provide biocompatibility and intrinsic signaling.^[106] Microrobots driven by stem cells are another frontier that exploits the regenerative potential and homing ability of stem cells in support of tissue repair and targeted delivery.^[107] In addition to single-stimulus systems, multi-stimuli responsive microrobots have been developed that can react to pH change,^[106] enzymatic activity (for example by Urease)^[107] and external fields (electromagnetic radiation, thermal field, magnetic field etc.), thus providing greater adaptability and precision on a biological entity varying from simple (p. coli) to complex biological environments.^[108]

Finally, clinical translation has started with pilot studies of microrobots applying to oncology and infection treatment. These preliminary studies demonstrate the potential of and challenges with translating biohybrid microrobots from an experimental model into practical use in clinics.^[109,110] Together, these advancements exemplify an impressive

versatility of biohybrid microrobotics; and highlight the capacity for changing the future of targeted therapy, regenerative medicine, and precision delivery of therapeutics.

14. Comparative Analysis:^[111-114]

Type of Microrobot	Propulsion Mechanism	Drug Loading Strategy	Advantages	Limitations	Primary Applications
Bacteria-driven	Flagella-driven motility; chemotaxis toward tumor metabolites	Surface adsorption (electrostatic/hydrophobic interactions)	- Strong autonomous propulsion - Ability to penetrate hypoxic tumor regions - Natural chemotaxis enhances targeting	- Risk of immune clearance - Biosafety concerns with live bacteria - Limited external controllability	Cancer therapy, localized infection treatment
Algae-driven	Photosynthetic motility; light-responsive propulsion	Encapsulation within polymeric or hydrogel matrices	- Biocompatibility - Oxygen generation in hypoxic environments - Responsive to optical guidance	- Limited propulsion in dark/anaerobic conditions - Cultivation scalability challenges	Gastrointestinal drug delivery, hypoxia-targeted cancer therapy
Cell membrane-coated	Hybrid propulsion (magnetic + biological motility)	Membrane fusion (drug integration into lipid bilayers)	- Immune evasion via host-mimicking membranes - Prolonged circulation - Reduced systemic toxicity	- Complex fabrication - Variability in membrane stability - Ethical concerns with sourcing	Infection treatment, systemic drug delivery, immune-modulating therapies
Exosome-based	Passive diffusion; potential magnetic steering with nanoparticle integration	Natural vesicle loading or engineered cargo insertion	- High biocompatibility - Ability to cross biological barriers - Personalized therapy potential	- Limited drug loading capacity - Heterogeneity in exosome populations - Scalability issues	Cancer therapy, neurodegenerative disease treatment
Stem cell-driven	Intrinsic homing ability; motility toward inflammation sites	Encapsulation within stem cell cytoplasm or engineered vesicles	- Regenerative potential - Natural homing to damaged tissues - Multifunctional therapeutic delivery	- Ethical concerns - Risk of uncontrolled differentiation - Complex regulatory approval	Tissue engineering, regenerative medicine, wound healing
Yeast-based	Limited natural motility; engineered propulsion possible	Genetic engineering for metabolic drug release pathways	- High stability - Ease of cultivation - Robustness in diverse environments	- Limited motility compared to bacteria/algae - Potential immunogenicity	Oral drug delivery, probiotic therapies, metabolic disease treatment

15. Future Perspectives

The future of biohybrid microrobots lies in interdisciplinary collaboration, where nanotechnology, microbiology, materials science, and monitoring applications converge to create clinically practicable systems from Advances in interdisciplinary engineering (e.g., CRISPR modified bacteria), smart biomaterials (hydrogel coatings, stimuli responsive polymers), and ultrasound guidance technologies (magnetic, optical, ultrasound) are expected to knotty precision, safety, and external Researchers are progressively focusing on multi-stimuli responsive microrobots that can autonomously adapt to create biologic environments while being outwardly controlled for nonsubjective precision.^[116]

Integration with real time imaging modalities such as MRI and nonsubjective will further improve navigation and nonsubjective Importantly, the translation of these systems.^[115] laboratory prototypes to nonsubjective applications will further standardized fabrication protocols, climbable production methods, and external regulative frameworks across regions. Moral considerations, specially regarding the use of living organisms and unrestricted cells, must be addressed through transparent guidelines and unrestricted engagement. Ultimately, biohybrid microrobots are envisioned as next generation therapeutic platforms capable of living cancer therapy, infection control, and stem medicine.^[117]

16. CONCLUSION

Biohybrid microrobots could a paradigm shift in personalized drug delivery, combining the adaptability of engineered systems with the precision and engineered nanomaterials. Their advantages biocompatibility, precise targeting, and reduced general toxicity make them highly promising for clinical translation. However, challenges such as immune clearance, fabrication complexity, and moral concerns remain monumental barriers. Recent advances between 2021 and 2026, including CRISPR modified bacteria, hydrogel coated microrobots, and operational guided hybrids, demonstrate the adaptability progress in targeted field. Moving forward, success will depend on interdisciplinary research, full bodied regulative pathways, and operational concerns to ensure unadventurous and moral deployment. If these hurdles are overcome, biohybrid microrobots could become transformative tools in personalized medicine, offering site specific therapies with the precision and moral side effects.

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