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Review

Advancements in Micro/Nanorobots in Medicine: Design, Actuation, and Transformative Application

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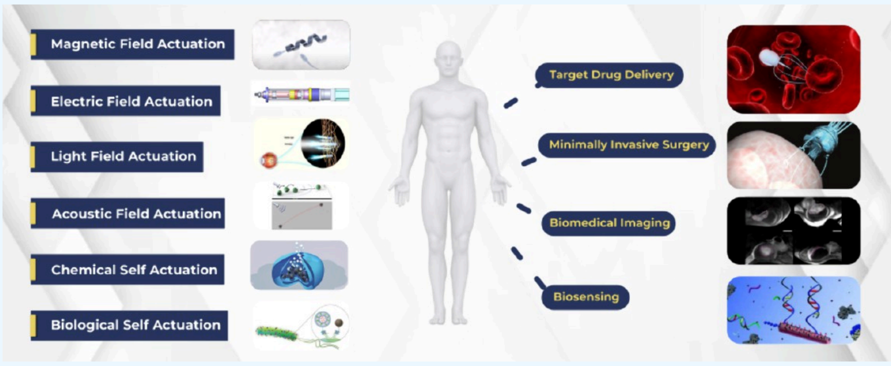

ABSTRACT: In light of the ongoing technological transformation, embracing advancements that foster shared benefits is essential. Nanorobots, a breakthrough within nanotechnology, have demonstrated significant potential in fields such as medicine, where diagnostic and therapeutic applications are the primary focus areas. This review provides a comprehensive overview of nanotechnology, robots, and their evolving role in medical applications, particularly highlighting the use of nanorobots. Various design strategies and operational principles, including sensors, actuators, and nanocontrollers, are discussed based on prior research. Key nanorobot medical applications include biomedical imaging, biosensing, minimally invasive surgery, and targeted drug delivery, each utilizing advanced actuation technologies to enhance precision. The paper further examines recent progress in micro/nanorobot actuation and addresses important considerations for the future, including biocompatibility, control, navigation, delivery, targeting, safety, and ethical implications. This review offers a holistic perspective on how nanorobots can reshape medical practices, paving the way for precision medicine and improved patient outcomes.

1. INTRODUCTION

By manipulating matter at the atomic and molecular levels, nanotechnology enables the creation of materials with a startlingly wide range of sophisticated features. This fast-growing field of study has enormous potential across various industries, including electronics, construction, and healthcare. The development of nanotechnology spurs significant scientific advancements in the medical sciences.[1] The discipline of nano oncology has emerged due to the application of nanotechnology in oncology, and nanoparticles have entirely transformed the drug delivery industry due to their ease of design. Drug-loaded nanoparticles can protect our healthy cells by explicitly targeting malignant cells. Above all, these nanoparticles can get through our body's physiological barrier because of their small size.[2] Also, nanotechnology is used for minimally invasive surgery, biomedical imaging, biosensing, and more medical applications.

Nanotechnology is utilized to create diagnostic systems, and nanomedicine is the branch of medicine used to diagnose and treat illnesses. The material can be measured at the nanoscale thanks to technologies like electrochemiluminescence.[3] Nanoprobes such as quantum dots, plasmonic nanoparticles, magnetic nanoparticles, nanotubes, nanowires, and multifunctional nanomaterials can be used for cellular imaging in medical diagnosis. High volume/surface ratio, surface tailor ability, multifunctionality, and inherent features are benefits of employing nanoprobes.[4,5] Additionally, nanotechnology aids drug development, enhances drug distribution within the body, and targets specific therapeutic sites. It can also be included to improve the effectiveness of traditional medical procedures.[6] Nowadays, robot technology is leading in every sector. Scientists and engineers try to make different types of robots

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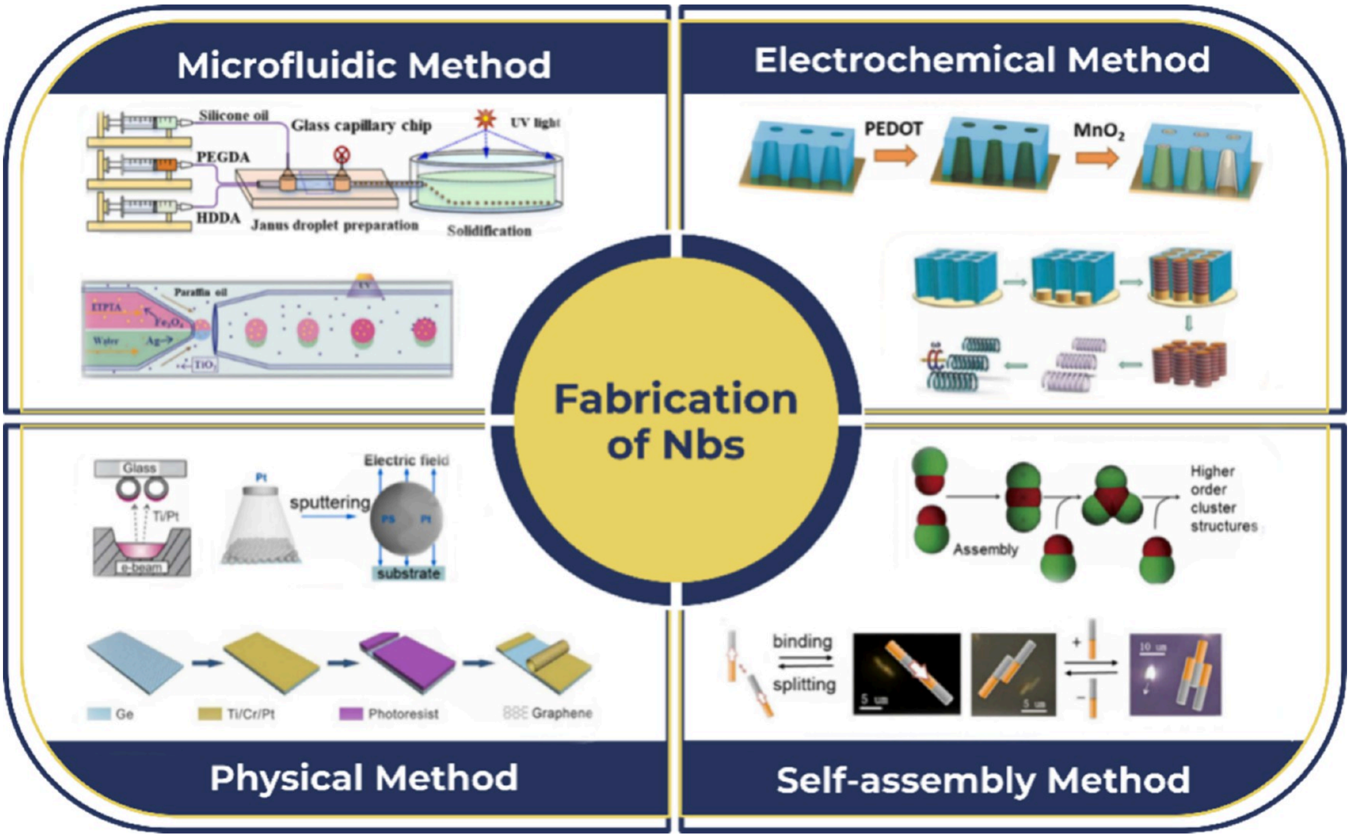

Figure 1. Schematic diagram of fabrication methods of micro/nanorobots.

using nanotechnology. As a result of nanotechnology, they can make nanorobots. Creating machines or robots with components at or near the scale of a nanometer (10^{-9} meters) is known as nanorobots or simply nanobots.[7] Nanoid robotics, also known as nanorobotics or nanobotics, is an emerging technology sector. Specifically, nanorobotics (as opposed to microrobotics) is the engineering discipline of nanotechnology that deals with the design and construction of nanorobots that have devices made of molecular or nanoscale components and range in size from 0.1 to 10 μm.[8]

The history of robotics goes from ancient dreams to modern reality. The earliest known example of a robotic device dates back to ancient Greece (Leonardo Da Vinci's), where Archytas of Tarentum built a mechanical bird that could fly. The Industrial Revolution of the 18th and 19th centuries saw the development of several machines that could perform repetitive tasks, such as the Jacquard loom and the cotton gin. These machines were not robots, but they paved the way for developing automated machinery that would later be used in factories. The early robots, the first programmable robots, were created in 1954 by George Devol and Joseph Engelberger. The Unimate robot was used to lift and stack hot metal parts in a General Motors factory. In the late 20th and early 21st centuries, robots began to move beyond the factory and into the home. Robots like the Roomba vacuum cleaner and the iRobot Create educational robot made it possible for people to experience the benefits of robotics in their daily lives. And the future of robotics is bright, with exciting possibilities in healthcare, space exploration, and environmental monitoring.[9] Robots are becoming increasingly sophisticated, capable of learning, adapting, and working collaboratively with humans. Robots will play an increasingly important role in our lives in the future.[10]

The creation of nanorobots/microrobots was prompted by the swift expansion of robot technology's uses in health and medical science. Nanorobots are controlled nanoscale devices that carry out bodily functions. They are highly accurate, versatile, and flexible. Sensors and motors make up nanorobots.[11] When trouble-making intruders are present, they undergo conformational changes that trigger the release of an agent that works against them. Even smaller nanorobots operate at the breathtaking nanoscale, ranging from 1 to 100 nm (1 billionth of a meter). Also, nanorobots require specialized microscopy techniques for observation.[12]

The concept of nanorobots was first introduced by Richard Feynman in 1959 in his talk "There's Plenty of Room at the Bottom", where he highlighted their potential in treating cardiac conditions.[13] Building on this, Robert Freitas conducted pioneering research on "respirocytes", artificial red blood cells designed for therapeutic purposes. Recent advancements in bioinformatics, robotics, nanostructuring, medicine, and computing have driven the development of nanorobots and microrobots, especially for drug delivery systems. These robots exist in various forms, such as respirocytes, microbivores, surgical nanorobots, and cellular repair nanorobots, each tailored to specific medical applications.[14] Carbon, known for its exceptional strength and inertness, is a critical material for constructing the external surfaces of nanorobots, providing structural durability and shielding them from immune system attacks. Advanced microscopy techniques like Atomic Force Microscopy (AFM) and Scanning Electron Microscopy (SEM) are indispensable tools for studying and refining the molecular structure of nanorobots. These techniques allow researchers to

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visually and tactilely analyze their design and functionality, ensuring optimal performance. Despite these advancements, nano robots' precise creation, control, and navigation remain significant challenges, requiring further technological and scientific breakthroughs.[15]

Robotic systems have significantly increased human awareness, interaction, manipulation, and transformation of our surroundings. In particular, a revolution in the medical applications of robotic technologies to improve healthcare has been made possible by the convergence of multiple technologies.[16] Medical robot devices are made for settings and tasks related to illness prevention and treatment. They need intelligent materials with small bits for intricate and accurate operations and to match with the human body. Technological advancements in motors, control theory, materials, medical imaging, and improved surgeon/patient acceptance have all contributed to the explosive rise of medical robots.[17]

The emergence of nanorobots is a significant development in biomedical engineering that has the potential to completely transform healthcare.[18] The field of micro/nanorobots has seen extensive review efforts, with many articles focusing on specific aspects such as fabrication techniques, actuation mechanisms, or biomedical applications. While these reviews provide valuable insights into individual components of the field, there is a lack of comprehensive integration that holistically connects the design, manufacturing processes, actuation mechanisms, and diverse biomedical applications of micro/nanorobots. This manuscript aims to fill this gap by offering a multidimensional review that synthesizes these elements into a unified framework. First, the review highlights the complex procedures used in their design and manufacture, such as chemical etching, thin layer deposition, electrode placement, and soft lithography. Next, we highlight the wide range of biomedical uses that nanorobots make possible, including minimally invasive surgery, precise target drug administration, and state-of-the-art biomedical imaging and biosensing technologies. Moreover, the article clarifies the many actuation processes that drive nanorobots into motion, whether by fuel-dependent self-propulsion or external field actuation. Lastly, the authors explore the prospects and problems in this emerging sector, focusing on important topics, including delivery and targeting accuracy, control and navigation, biocompatibility, and safety and ethics.

2. DESIGN AND FABRICATION OF NANOROBOTS

Nanorobot design takes into account many important factors, including biocompatibility, functionality, size, and shape.[19] Nanorobots must have specific functions suited to their intended uses and be small enough to maneuver through biological settings and engage with molecules and cells. Furthermore, making sure that an object is biocompatible is crucial to avoiding adverse reactions when it is used on living things.[20] The fabrication of nanorobots necessitates specific methods able to precisely and consistently create structures at the nanoscale.[21] Soft lithography, electrodeposition, thin film deposition, and chemical etching are fabrication processes. Each method adds something unique to the fabrication process concerning resolution, scalability, and material compatibility. The available fabrication techniques are intrinsically tied to micro- and nanorobot device design.[22] Figure 1 shows the fabrication methods of micro/nanorobots.

Although there has been some stability in the development of microfabrication methods over the past ten years, these technologies are still actively being pursued, and the design limitations they generate have not been thoroughly studied.[23] The procedures utilized in conventional microfabrication, including lithography, thin-film deposition, chemical etching, and electrodeposition, will be briefly highlighted in this section. The traditional fabrication techniques created for the semiconductor industry are the foundation of most micro- and nanofabrication techniques. Therefore, anyone starting a research and development career in the micro/nano domain must thoroughly understand these methodologies. Fabrication of micro/nanorobots is a very complex process. Fabrication of micro/nanorobots is done by following the process. Such as Soft lithography, thin film deposition, chemical etching and electrodeposition.[24] The advancement in the creation of nanorobots is never-ending. In two studies published in 2014, two fabrication methods were also provided. Researchers in Bao et al.[25] created nanorobots from platinum and carbon nanotubes (CNTs) using the focused ion beam (FIB) technology. Hayakawa et al. experimented with inserting an infrared laser into cells to create a puncture site and generate heat.[26]

2.1. Soft Lithography.

Lithography is a planographic printmaking process in which a design is drawn onto a flat stone (or prepared metal plate, usually zinc or aluminum) and affixed using a chemical reaction. Transferring a computer-generated design onto a substrate (silicon, glass, GaAs, etc.) is called lithography.[24] The underlying thin layer (oxide, nitride, etc.) is then etched using this pattern for various uses (doping, etching, etc.). While photolithography, which uses an ultraviolet light source for lithography, is the most commonly used method in microelectronic fabrication, X-ray and electron-beam lithography are two other options that have garnered significant interest in the Micro-Electro-Mechanical Systems (MEMS) and nanofabrication fields.[27] Developing a photomask is the first step after the computer layout for a particular manufacturing sequence. Origami designs inspired Huang et al. They used a one-step photolithography approach to use the hydrogel's self-folding upon hydration to create microswimmers with various 3D topologies. The gel composites were strengthened with magnetic nanoparticles.[28]

Phic procedures (using e-beam or optical pattern generators) produce a thin (about 100 nm) chromium layer on a glass plate with the required pattern.[29] The first step in the photolithography process is spin-coating the substrate with a photoresist once the desired material has been deposited. This polymeric photosensitive material can be spun onto the wafer in liquid form; adhesion promoters like hexamethyldisilane (HMDS) are typically utilized before the resist is applied. The final resist thickness, usually 0.5−2.5 μm, depends on the photoresist viscosity and spinning speed. Positive and negative photoresists are the two available types.[30] In the succeeding development stage, UV-exposed areas with a positive resist will dissolve, whereas those with a negative photoresist will stay exposed after development. The photoresist is spun on the wafer, and then the substrate is soft-baked (5−30 min at 60−100 °C) to improve adhesion by eliminating solvents from the resist. After that, the photoresist is exposed to a UV source while the mask is positioned about the wafer. The photoresist is developed in a manner akin to that of developing photographic film following exposure. The resist is then hard-baked (20−30 min at 120−180 °C) to enhance adhesion

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even more. The hard-bake phase completes the photolithography sequence, which transfers the intended design onto the wafer. Following the etching of the underlying thin film, the photoresist is removed using acetone or another organic solvent.[31] In 2013, lasers made it possible to fabricate nanorobots. A construction process using an optical tweezer laser beam is proposed, coupled with a manipulation technique, for a robot whose components are inside the nanoscale but whose overall body size is in the microscale. Fukada et al. have also achieved translation speeds of 100 μm/s and rotation speeds of 1140 deg/s using holographic optical tweezers.[32]

2.2. Thin Film Deposition. Micro- and nanofabrication technologies make considerable use of thin-film deposition and doping. Most of the constructed structures are made of materials different from the substrate and are either modified or deposited using different methods.[33] Oxidation, doping, chemical vapor deposition (CVD), physical vapor deposition (PVD), and electroplating are some of these methods. A material undergoes oxidation when it reacts with oxygen to produce an oxide layer on its surface.[34] This technique is frequently used to change a material's surface characteristics, including improving adhesion or resistance to corrosion. For instance, silicon wafers can be thermally oxidized to create a layer of silicon dioxide (SiO_2), which is used in microelectronics as a passivation or insulating layer.[35]

Doping is adding impurities to a semiconductor material to change its electrical characteristics. This method is critical to producing semiconductor devices because it allows for exact control over the conductivity and carrier concentration of materials.[36] Common dopants are substances that are integrated into the semiconductor substrate's crystal lattice, such as phosphorus (P), arsenic (Ar), and boron (Br). In CVD, a thin layer of material is deposited on a substrate surface through the chemical reaction of precursor gases.[37] With its ability to precisely manage film composition, thickness, and uniformity, it can be applied to a variety of situations. In semiconductors, CVD is widely used to deposit materials such as silicon nitride (Si_3N_4), SiO_2, and several thin-film metals for electrodes and interconnects. PVD refers to methods in which a substance is physically transferred, usually via sputtering or evaporation, from a solid source to a substrate.[38] PVD is a commonly employed technique for the uniform and high-purity thin-film deposition of metals, alloys, and other materials. Thin-film transistors in display technology, protective coatings in tribology, and mirror-reflection coatings are a few examples of applications. By running an electric current through a solution containing metal ions, a thin coating of metal is deposited onto a substrate through the process of electroplating.[39] This process is widely utilized in applications including corrosion protection, decorative coatings, and semiconductor device metallisation because it gives exact control over the thickness and composition of the deposited metal layer.[40] Various methods for depositing thin material layers on a substrate are combined to form thin film deposition. Electrodeposition is one of these methods that is used extensively, particularly for applications where exact control over the film's thickness, content, and shape is needed.[41]

2.2.1. Electrodeposition. Electrodeposition is a popular thin-film deposition technique in which an electric current is applied to place a material onto a conductive substrate. To create a consistent and cohesive layer on the substrate, metal ions in an electrolyte solution must be reduced by this procedure. Electrodeposition presents several benefits, namely its ease of use, economic feasibility, and capacity to attain precise regulation of the film's characteristics through the manipulation of variables like current density, electrolyte composition, and deposition duration.[42]

Various metal and polymer materials can create microrobots with different three-dimensional geometries by electrodeposition, also known as electrochemical deposition.[43] Electrodeposition is, therefore, a practical technique for creating microrobots. This method can be readily modified to meet the requirements of microrobots of different sizes and does not require expensive equipment or exacting testing conditions.[44] Redox reactions can be used instead of the usual method of applying an electric current to deposit the substance.[45] Template-assisted electrochemical deposition (TAED) can be used to create helical topologies in addition to the tubular micro motors for which it has been commonly utilized. Li et al. presented a representative example by creating magnetic helical nanomotors cloaked in platelet membrane.[46] Figure 2 shows the Fabrication of magnetic nanowires by TAED and some examples.

2.2.2. Membrane Template-Assisted Electrodeposition. Membrane Template-Assisted Electrodeposition is a specific type of electrodeposition in which a porous membrane template guides the deposition process. This method makes it possible to create nanostructured films with particular morphologies and patterns that are hard to do with conventional electrodeposition.

Using thin-film micropores, a variety of materials, including polymers, metals, semiconductors, and carbon, are synthesized into desired tubular or nanowire shapes in membrane template-assisted electrodeposition.[53] These micropores serve as reactors, enabling the necessary micromachines to be synthesized. The membrane micropores are perfect for mass-producing microrobots with comparable nanostructures because of their high micropore density and monodispersed diameter.[54] Trace-etchable polycarbonate membranes and alumina membranes are common membrane materials. The diameter of the particles matches the diameter of the micropores, and the length of the created microrobots is proportionate to the electrical charge.[55] The created nanostructures can be solid or hollow, depending on the material's characteristics and the pore walls' chemical makeup. Electrodeposition with membrane templates offers a low-cost and effective way to manufacture nanowires, nanotubes, or helical micro motors. This section covers the preparation of nanowires, nanotubes, and helically organized micro motors using membrane-template-assisted electrodeposition.

The first to create bimetallic gold (Au)−platinum (Pt) nanowires, measuring 370 nm in diameter and 2 um in length, were Paxton et al.[56] These nanowires moved along the axial platinum end direction in a 2−3% aqueous hydrogen peroxide (H_2O_2) solution at a velocity of up to 10 times the body length per second. Electrodeposition with membrane template assistance was the primary method to create these bimetallic nanowire motors. Later on, an enhanced electrodeposition technique for creating bimetallic nanowire motors was suggested by Fournier-Bidoz et al.[57] A silver (Ag) or gold (Au) coating was first physically vapor deposited on one side of the membrane to serve as the working electrode. After assembling the membrane in a Teflon plating bath, the metal layer was covered with a flat aluminum (Al) sheet that served

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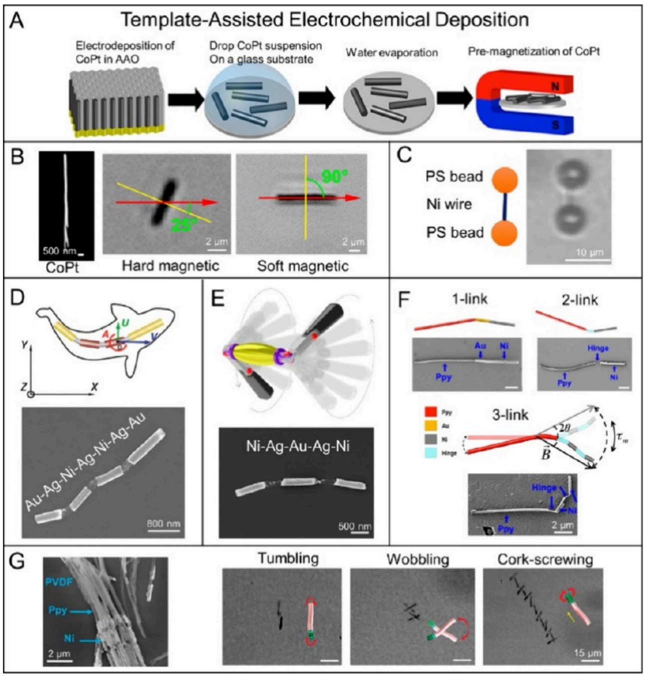

Figure 2. A) CoPt nanowires are synthesized using a template-assisted electrodeposition process. B) The magnetization angle of hard-magnetic CoPt nanowires aligns with the short axis (yellow). In contrast, soft-magnetic CoNi nanowires align with the direction of the magnetic field (red). Reproduced with permission from the ref[47] Copyright 2019 American Chemical Society. C) The dumbbell-shaped MagRobot is composed of a nickel nanowire (Ni NW) connected to two polystyrene (PS) microbeads. Reproduced with permission from ref 48. Copyright 2016 Wiley-VCH Verlag GmbH and Co. KGaA, Weinheim. D) A fish-like nano swimmer exhibits traveling-wave motion when subjected to an oscillating magnetic field. Reproduced with permission from ref 49. Copyright 2016 Wiley-VCH Verlag GmbH and Co. KGaA, Weinheim. E) A two-arm nano swimmer can freestyle swimming. Reproduced with permission from ref 50. Copyright 2017 American Chemical Society. F) SEM images show 1-, 2-, and 3-link microswimmers, with the 3-link microswimmer demonstrating traveling-wave propulsion under an oscillating magnetic field. Reproduced with permission from ref 51. Copyright 2015 American Chemical Society. G) PVDF-Ppy-Ni nanoeels exhibit three distinct motion modes, as illustrated in the SEM image provided. Reproduced with permission from ref 52. Copyright 2019 Wiley-VCH Verlag GmbH and Co. KGaA, Weinheim.

as a conductive contact for the following electrodeposition. The different desirable metal elements are usually deposited after a sacrificial layer of copper (Cu) or Ag has been put. After physically polishing or chemically etching the Ag/Au substrate and sacrificial layer away, the aluminum oxide membrane is dissolved by immersing it in a sodium hydroxide solution. Once the nanowire motor has been centrifuged and rinsed several times, it is extracted from the template and gathered. It was utilized to create threaded rod-like nanowire motors by depositing several metals one after the other into an alumina membrane that had nanoscale micropores.

At the unattached nickel (Ni) end of the bimetallic nanorods, H_2O_2 underwent oxidative breakdown to produce oxygen (O_2), which propelled the nanorods toward consistent circular motion. This bimetallic nanorod produces its energy through the catalytic breakdown of H_2O_2 into O_2 and water (H_2O). The interfacial tension gradient, bubble recoil, viscous Brownian ratcheting, and autoelectrophoresis underpin the nanorods' driving concept, translating chemical energy into the mechanical energy needed to move the system. Based on the Tafel plots produced by the reaction of H_2O_2 on the cathode and anode on several metal ultramicroelectrodes, Ambulo et al.[58] calculated the potentials of the cathode and anode on each metal with similar reaction rates. The bipolar electrochemical driving mechanism of the bimetallic nanorods was further confirmed by predicting all possible directions of motion of the bimetallic assemblies based on the electrochemical mechanisms of the bimetals.

The fundamental idea of membrane template-assisted electrodeposition and electrodeposition is using electric current to deposit material onto a substrate. By adding a membrane template to the conventional electrodeposition technique, Membrane Template-Assisted Electro deposition allows for more control over the nanostructure of the film. Membrane template-assisted electrodeposition is a sophisticated form of electrodeposition that provides extra capabilities for nanoscale patterning and structuring of the deposited material. Both techniques are essential to thin-film deposition; choosing one will depend on the application's needs.[59]

2.3. Chemical Etching. Further to thin film etching, the substrate (silicon, glass, GaAs, etc.) must frequently be removed in micro- and nanofabrication to form different mechanical structures (beams, plates, etc.). Selectivity and directionality are two crucial aspects of any etching process. The ability of the etchant to distinguish between the layer to be etched and the masking layer is known as selectivity. The etch profile beneath the mask determines directionality. An isotropic etch produces a semicircular profile beneath the mask because the etchant hits the material in all directions at the same rate. An anisotropic etch produces straight sidewalls or other noncircular features, with the dissolving rate dependent on specific directions. The different etching methods can also be separated into wet and dry groups. Due to the lateral undercut, wet etchants can only achieve a minimum feature size greater than 3 μm. Photoresist and Si_3N_4 are the two most popular masking materials for the wet oxide etch. Essential subjects in micro- and nanofabrication are isotropic and isotropic wet etching of crystalline (silicon and gallium arsenide) and noncrystalline (glass) surfaces.

2.4. Two-Photon Polymerization (TPP). TPP is a cutting-edge fabrication technique that enables the creation of intricate micro- and nanostructures with high accuracy.[60] This method exploits the simultaneous absorption of two photons to start polymerization, which allows for the formation of 3D structures at micro/nanoscale. The accuracy of TPP stems from its nonlinear absorption process, which confines the polymerization to the focal point of the laser beam, thus providing a higher resolution than traditional single-photon polymerization methods. This capability makes TPP particularly suitable for developing micro- and nanorobots, which require intricate and precise designs to function effectively in complex environments such as biological systems.[60−62]

Recently, over the years, the TPP fabrication technique has been explored for the fabrication of micro/nanorobots with applications in minimally invasive surgery, targeted drug delivery, and other biomedical applications. Palagi et al. developed a microswimmer that navigates through viscous biological fluids driven by light-induced stimuli. These microswimmers, fabricated using TPP, exhibit high portability and can be steered with great accuracy.[63] Furthermore, researchers integrate functional materials into TPP for

Table 1. Recent Advancements of Fabrication Techniques in Biomedical Applications

Serial no.	Fabrication technique	Material used	Application of nanorobots	Refs
1	Photolithography	Photoresist	High-resolution patterning for microfluidic devices	67
2	Electron-beam lithography	Polymers, metals	Analyte sensing and cellular dynamics	68
3	X-ray lithography	Poly(methyl methacrylate) (PMMA)	Enhanced precision for MEMS applications	69
4	Soft lithography	Polymethyldisiloxane (PDMS), SU-8	Rapid prototyping for microfluidics	70
5	TPP	Photopolymer resins	3D nanostructures with submicron resolution	71
6	Thin film deposition	Metal oxides, polymers	Atomic layer deposition for ultrathin conformal coatings	72
7	Chemical etching	Silicon	X-ray imaging and spectrum detection systems	73
8	Bioinspired fabrication	Biomimetic hydrogels, peptides	Self-assembling nanorobots for biocompatible applications	74
9	Laser ablation	Metals, ceramics	High precision in creating nanotextured surfaces	75
10	3D Printing	Polymers, bioinks	Bioprinting of organ-on-chip systems	76
11	Inkjet printing	Conductive inks, biomaterials	Flexible electronics and sensors for healthcare	77
12	Electrospinning	Polymers, nanofibers	Production of nanofiber scaffolds for tissue engineering	78
13	Self-assembly	Lipids, polymers	Nanorobots for drug delivery through guided assembly	79
14	Focused ion beam lithography	Metals, semiconductors	Nanosculpting for device customization	80
15	Micromolding	Thermoplastics, PDMS	Creation of microscale implants	81
16	Electrochemical deposition	Metals, conductive polymers	Development of electrochemical sensors	82
17	Sol−gel process	Silica	Controlled porosity for drug delivery vehicles	83
18	Plasma etching	Silicon, polymers	Enhancement of surface properties and device performance.	84
19	Nanoimprint lithography	Thermoplastics, resists	Reduced membrane befouling, enhanced device performance	85
20	Magnetron sputtering	Metal films	Enhanced mechanical and optical properties	86

fabricated micro- and nanorobots. Incorporating magnetic nanoparticles allows for the remote control of nanorobots using external magnetic fields, enabling precise positioning and movement within the body.[64]

Similarly, incorporating fluorescent dyes or quantum dots facilitates real-time tracking and imaging of nanorobots, which is crucial for monitoring their behavior and interactions in vivo.[65] Haken et al. fabricated a biodegradable microswimmer for theragnostic cargo delivery and release to specific sites within the body. These microrobots are designed to degrade after execution of their function, minimizing probable long-term side effects. They exhibited the accuracy of TPP in creating complex, biodegradable structures that can navigate the body's complex vascular system, showcasing the method's potential to revolutionize targeted drug delivery.[66] As research proceeds, the combination of TPP with advanced materials and technologies is expected to expand the applications of micro and nano robots, opening new frontiers in medicine, environmental science, and beyond. Table 1 illustrates the recent advancements in fabrication techniques in biomedical applications.

3. ACTUATION OF NANOROBOTS

Micro/nanorobots are an emerging robotics field that has grown quickly in the last several decades. Macroscale robots can only be used in certain situations, such as small-space tasks. Feynman[87] initially proposed employing microrobots in medical care in 1959. It has been suggested that human bodies may be implanted with nanorobots, which could kill different diseases and proliferate themselves. Scientists are becoming more and more excited about the field of micro- and nanorobot research. Micro/nanorobots and biomedicine can tackle issues that conventional medicine cannot address, and this combination is predicted to spark a new medical revolution. As a result, researchers and scientists are still investigating and studying micro and nanorobots. However, because of their small size, micro/nanorobots are challenging to create, assemble, and maneuver. They cannot use specific conventional robotic theories and technologies. The micro/nanorobot movement in fluids is in the regime of low Reynolds numbers when an object shrinks to the micro/nanoscale.[88] The inertial force is minimal in this situation, and the viscous force is predominant. Because of this, micro/nanorobots require constant power to operate. Micro/nano robots, however, are complex to load with power sources like batteries and engines because of their small size. As a result, actuation technologies have been central to micro- and nanorobot research.

Transforming energy is one approach to operating micro/nanorobots to achieve motion. To carry out work duties flexibly and effectively at the micro/nanoscale, micro/nanorobots can transform magnetic, optical, audio, or other types of energy into kinetic energy or actuation force. Actuation technologies already used for micro/nanorobots can be categorized into two groups based on the various actuation mechanisms. External magnetic, electric, optical, and audio fields are examples of external field actuation. The other is self-actuation, encompassing many techniques such as chemical and biological self-actuation. Micro/nano robots employ various actuation techniques, contributing to their complexity compared to conventional macroscale robots. Research on micro/nanorobot actuation technologies is crucial and profound because the choice of actuation techniques for various micro/nanorobots will directly impact motion.[89] Table 2 provides a comparative overview of nanorobots based on their type, size, materials, propulsion mechanisms, and biomedical applications. It highlights advancements and variations in nanorobot design and functionality to guide future research and development.

3.1. External Field Actuation.

Applying external forces to regulate the motion and functionality of nanorobots is known as external field actuation. This technique uses different fields, such as light, acoustic, electric, or magnetic, to power and guide nanorobots inside the body remotely. Because they can precisely manage their depth of tissue penetration and allow focused navigation across complex biological contexts, magnetic fields are very desirable. Acoustic fields provide propulsion through ultrasonic waves, whereas electric fields can

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Table 2. Quantified Comparison of Various Nanorobots/Microrobots

Serial no.	Study/author	Year	Type of robot	Size range	Material uses	Propulsion mechanism	Biomedical application	Refs
1	Weiden and Bastings	2021	DNA origami	1−10 nm	DNA	Chemical reaction	Controlled drug delivery	90
2	Zhang et al.	2022	Micro Nanorobots	10−40 nm	Lipid-based materials	Ultrasound waves	Drug delivery to tumor cells	91
3	Andhari et al.	2020	Multicomponent magnetic Nanorobot.	10−100 nm	Magnetic particles	Magnetic fields	Tumor targeting and destruction	92
4	Li et al.	2022	Biohybrid micro − nanorobots	50−200 nm	Biological tissues, e.g. erythrocytes, leukocytes, microorganisms	Microfluidic	Performing microsurgeries, targeting diseased cells	93
5	Ning et al.	2018	Chemically powered robots	5−50 nm	Metallic nanoparticles	Catalytic reaction	Gene therapy	94
6	Arque et al.	2022	Self-propelled nanomotor	2−20 nm	Polymeric	Self-electrophoresis	Treatment of bacterial infection	95
7	Huang et al.	2008	Photothermal nanorobot	10−50 nm	Gold nanoparticles	Photothermal effects	Cancer cell ablation	96
8	Dong et al.	2016	Light-driven TiO_2-Au Janus micromotors	15−80 nm	Semiconductor materials	Light activation	Photocatalytic therapy, drug delivery	97
9	Wang and Zhang	2020	Untethered micro/nanorobots	10−50 nm	Titanium dioxide, gold, barium titanate, lipid based materials	Acoustic waves	Diagnostics imaging, drug delivery, biosensing	98
10	Li et al.	2022	pH responsive nanoparticle	20−100 nm	pH sensitive polymers	pH changes	Programmable antibiotics release for targeted microbial activity	99
11	Sanchez Moreno et al.	2018	Thermal-sensitive nanoparticles	10−60 nm	Thermal-sensitive polymers, iron oxide, gold particles	Temperature changes	Drug delivery, thermal therapy	100
12	Volpatti et al.	2020	Nanosensors	25−100 nm	Carbon nanotubes, platinum, gold	Glucose oxidation	Glucose monitoring in diabetes patients, insulin delivery	101
13	Kushwaha et al.	2022	Biodegradable nanorobots	10−50 nm	Zinc oxide, silver, gold, biodegradable polymers	Enzymatic degradation	Wound healing by the generation of reactive oxygen species, bacterial tidal effect by the materials used	102
14	Robert D. Crapnell and Craig E. Banks	2021	Nanoparticle-based biosensors	1−100 nm	Conductive polymers, gold	Electrochemical gradients	Biosensing, e.g., for detecting bacterial pathogens	103
15	Zhou et al.	2021	Electromagnetic micro nanorobots	1−50 nm	Electromagnetic materials	Electromagnetic fields	Surgery, ablation, biopsies, image guided procedures	104
16	Hortelão et al.	2017	Urease-powered nanomotors (nanobots)	200−300 nm	Silica	Silica is driven by enzymes like catalase, that respond to H_2O_2, producing thrust and propulsion for the nanobots	For increasing percision of targeting Doxorubicin (DOX) for cancer cells of the bladder	105
17	Xu et al.	2021	Mg microrobots	5 μm	Magnesium core with poly (lactic-*co*-glycolic acid) (PLGA) and hyaluronic acid layers	Chemical propulsion by generation of hydrogen (H_2) gas from gastric acid	To enhance the delivery and effectiveness of PLGA and hyaluronic acid for ther treatment of rheumatoid arthritis by directly aiming inflamed joint tissues	106
18	Nguyen et al.	2015	Bacteriobot	800 nm	Bacteria (*Salmonella typhimurium*) and liposome	Flagella movement of *Salmonella typhimurium* and its chemotactic behavior allows it to actively move to and penetrate tumor cells using chemical gradients of the tumor cells	For increased penetration as well as targeted and controlled release of paclitaxel for breast cancer cells	107
19	Li et al.	2016	PEDOT/Au microrobots	5 μm	Enteric coated magnesium core	Chemical propulsion by generation of H_2 gas in acidic pH and self-propulsion at neutral pH	For target deliver of magnesium to the intestine	108
20	Wang et al.	2022	Pt-coated mesoporous silica	200−300 nm	Gold nanorods in silica shell	Thermophoretic self-propulsion and biological chemotaxis	Form improvement if drug delivery and penetration of cisplatin in treatment of colorectal cancer	109
21	Wu et al.	2021	Silica nanobottle (Si NB) robots	200 nm	Chitosan coated zinc core	Chemical propulsion by generation of H_2 gas from gastric acid	For effective delivery of clarithromycin for treating stomach ulcers and even cancer	110

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Table 2. continued

Serial no.	Study/author	Year	Type of robot	Size range	Material uses	Propulsion mechanism	Biomedical application	Refs
22	Karshalev et al.	2019	TiO_2/PLGA /Fe-Se@chitosan-coated Mg microspheres	5 μm	Magnesium core with iron oxide, eudragit and gold layers	Chemical propulsion by generation of H_2 gas from gastric acid	For targeting of iron and selenium to the intestine	111
23	Park et al.	2019	Degradable hyperthermia microrobot (DHM)	40 μm	Silica core with magnetite nanoparticles (Fe_3O_4), drug loaded gelatin methacryloyl and PLGA	Magnetic actuation	For aiming 5-fluorouracil (5-FU) to cancer cells and inducing hypothermia in cancer cells	112
24	Villa et al.	2018	Superparamagnetic/catalytic microrobots (PM/Pt microrobots)	5 μm	Paramagnetic polystyrene bead core with functionalized surface and platinum coating	Oxygen bubbles generated from decomposition of H_2O_2 from platinum coating and magnetic field actuation.	To enhace the specificity and reduce the sytemic side effects in delivering DOX to breast cancer cells	113
25	Wei et al.	2019	Biomimetic micromotor toxoid	20 μm	Magnesium core with erythrocyte membrane coating, loaded with ovalbium	Chemical propulsion by generation of H_2 gas from gastric acid	To improve the delivery and effectiveness of staphylococcal α-toxin and other therapeutic agents via oral route into the small intestine	114
26	Kim et al.	2020	Retrievable intraocular bilayer hydrogel microrobot	200 μm	Fe_3O_4 nanoparticles with an upper layer of poly(N-isopropylacrylamide) and a lower layer of carboxymethyl cellulose (CMC)	Magnetic field actuation	For delivery of drugs in treating intraocular conditions and retrieval of nanoparticles from the eyes, postsurgery for monitoring treatrment	115
27	Yan et al.	2015	Porous hollow helical microswimmers	5–8 μm	Fe_3O_4 nanoparticles with a porous and hollow helical shell having a biocompatible coating	Magnetic actuation of the helical microswimmers	Spirulina, not specified	116
28	Alapan et al.	2018	Soft erythrocyte-based bacterial microswimmers	6–8 μm	Erythrocyte membranes to which *E. coli* bacteria has been attached	Magnetic actuation along with, flagella movement of *E. coli*	For targeted delivery of doxorubicin to cancer cells	117
29	Peng et al.	2018	Poly (ethylene glycol)-b-polystyrene (PEG-PS) polymersome-based Janus nanomotors	300 nm	Platinum core, functionalized with polyethylene glycol (PEG)	Oxygen bubbles generated from decomposition of H_2O_2 from platinum coating	For therapeutic penetration and delivery of fluorescein sodium salt to the endothelium of cancer cells	118
30	Wan et al.	2019	Nitric oxide nanomotors	80 nm	Mesoporous silica nanoparticles (MSNs) with manganese dioxide (MnO_2) and biomimetic cell membrane layer, derived from red blood cells	Generation of gas bubbles by the decomposition of nitric oxide on the MnO_2 surface of nanparticle	For target delivery of nitric oxide to various cells including joint muscle cells and cancer cells	119

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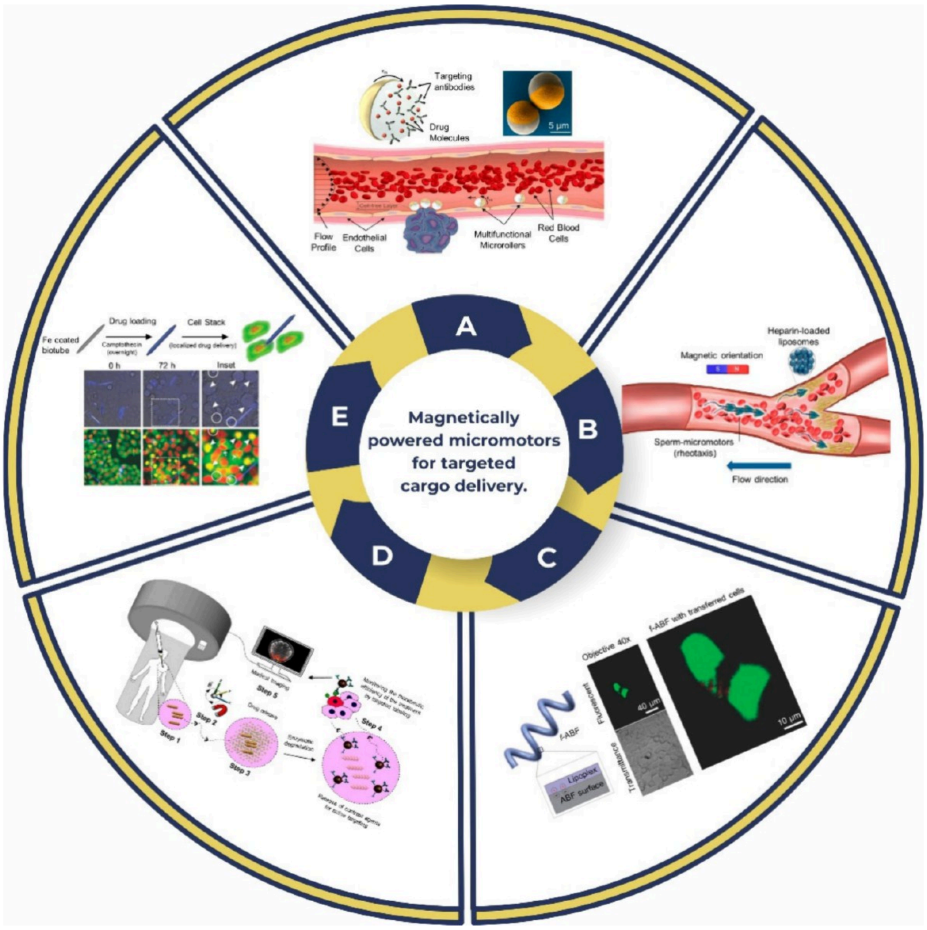

Figure 3. (A) Fe-coated camptothecin-loaded magnetic tube for killing HeLa cells. White circles highlight dead cells. (B) Controllable navigation and targeted transport of antibodies inside blood flow by using Janus micropropellers. (C) Sperm-based MagRobots are capable of delivering heparin-loaded liposomes through flowing blood. (D) pDNA transfection by human embryo kidney cells when in targeted contact with helical microrobots loaded with plasmid DNA. (E) Released drugs from hydrogel-based microswimmer for active labeling.

be employed to manipulate nanorobots using electrophoresis or dielectrophoresis. Photons are used in light-driven actuation to create movements, offering excellent temporal and spatial resolution. External field actuation is critical in applications like targeted medication delivery, microsurgery, and sophisticated diagnostic procedures requiring precise control and low invasiveness.

3.1.1. Magnetic Field Actuation. In an electromagnetic system, the electric field is mainly used to produce an external magnetic field, which is then used to actuate the nanorobot/microrobot. This external magnetic field can regulate the nano robot's movement and function, facilitating accurate navigation and task performance in a biological setting. This mechanism is essential to the efficient functioning of magnetic field-actuated nanorobots/microrobots because it permits targeted and responsive actuation depending on the characteristics of the magnetic field.[120]

The field of developing micro/nanorobots that are actuated by magnetic fields has advanced during the past few years. In 2005, Dreyfus and colleagues developed a micro/nanorobot powered by a different magnetic field.[121] The robot may move like cilia in microorganisms by applying a steady magnetic field along its horizontal axis and an oscillating magnetic field perpendicular to it. The success of this study provided the groundwork for additional research. Steager et al. constructed a magnetic U-shaped robot that was actuated using five electromagnetic coil controllers to generate a gradient magnetic field. They also presented a magnetically actuated robotic system that can automatically manipulate cells and microbeads. A U-shaped pattern is created by photolithography when magnetic nanoparticles and photoresists are combined uniformly to create a magnetic U-shaped robot. Using a gradient magnetic field, the robot might autonomously pick up and move chemically injected microbeads to particular areas within neurons, perhaps serving a purpose in targeted medication administration.[122] With one passive gold segment serving as the caudal fin, two active Ni segments serving as the body, and one passive gold segment serving as the head, Li et al. created a fish-shaped magnetic actuation micro/nanorobot that was coupled via a flexible porous Ag structure. How the robot swims in response to a plane oscillating magnetic field is remarkably similar to how fish move. As a result, the robot can travel at relatively high speeds and has good propulsion efficiency. It has proven possible to achieve a maximum speed of 30.9 μm/s, or a dimensionless speed of 0.6, by employing an 11 Hz oscillating magnetic field.[49] Figure 3 depicts the Magnetically powered micromotors for targeted cargo delivery.

After completing the design, Li et al. focused on creating a symmetric multilinked two-arm nano swimmer, or freestyle swimmer-type, of magnetically actuated micro/nanorobots. This type of nano swimmer comprises two Ni arm segments and a central Au body segment joined by flexible porous Ag

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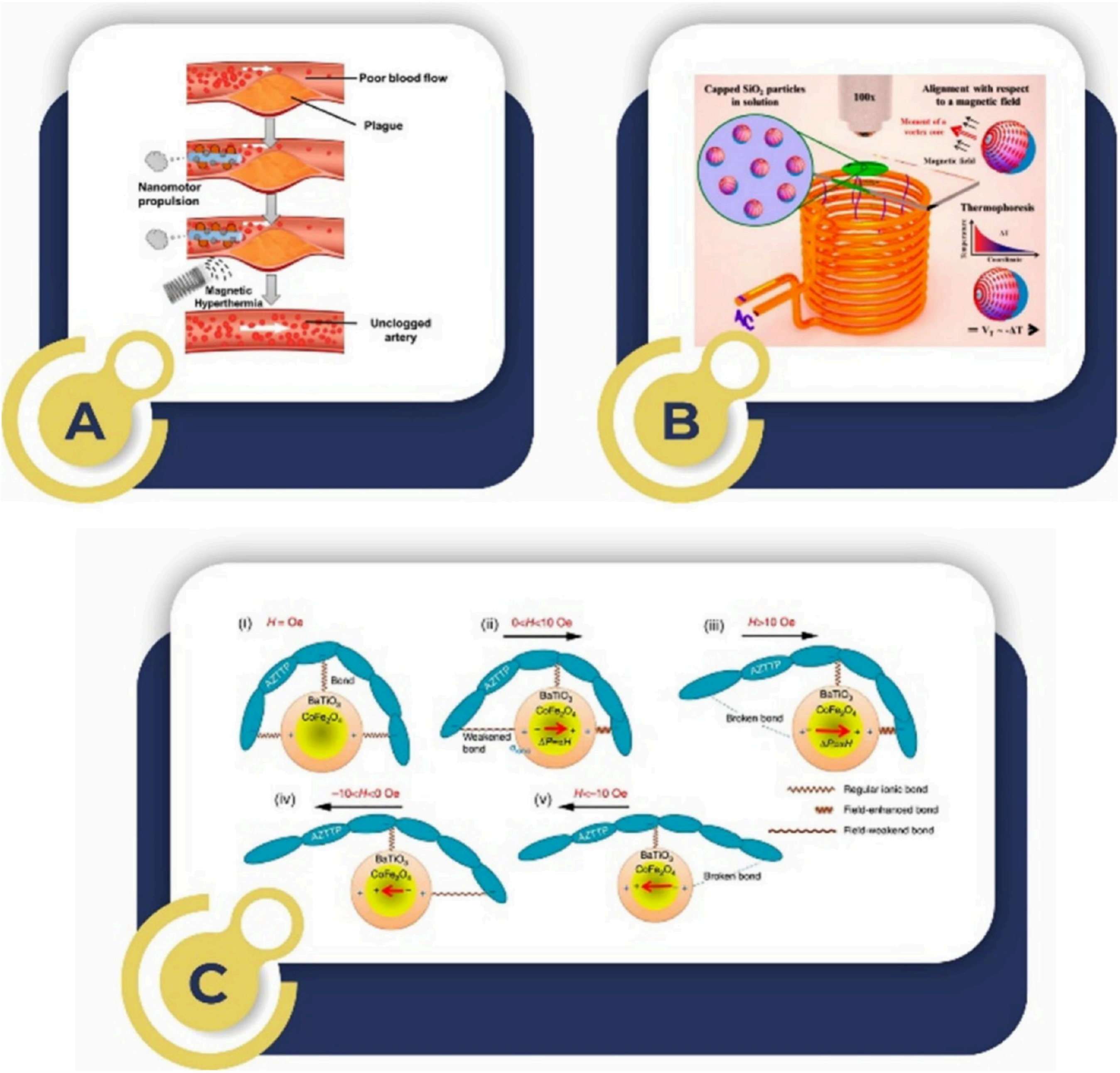

Figure 4. (A) Schematic process of removing cholesterol plaque in the blood artery via the magnetic hyperthermia of nanorobots. (B) Experimental setup of Janus nanorobots for magnetically induced thermophoresis. Thermophoretic force, triggered by the temperature difference, causes the self-propulsion of a Janus particle. (C) Underlying physics of the magnetoelectrically triggered drug (i.e., AZTTP) release process.

hinges. The robot swings symmetrically thanks to the flexible porous Ag part. The robot's two arms may swing in different directions under the influence of an oscillating magnetic field by magnetizing the Ni piece, enabling a freestyle swimming mode. The robot's speed and orientation may be changed remotely by altering the magnetic field. At 59.6 μm/s, the most incredible speed is comparable to a relative speed of almost 12 body lengths per second. A nonplanar swinging swimming mode was created for the first time using oscillating magnetic fields. Regarding maximal movement speed and propulsion efficiency, the freestyle swimmer micro/nanorobot and the fish-like micro/nanorobot both have clear benefits, with the latter robot outperforming the former.[50]

The nano eel is a soft hybrid nanorobot created by Mushtaq et al. that resembles an electric eel. It is equipped with a polyvinylidene fluoride copolymer tail that is flexible and intelligent, attached to the head of a polypyrrole nanowire. A Ni ring for magnetic actuation decorates the head. The magnetic head module (Ni−polypyrrole) oscillates in response to an applied alternating magnetic field. The ferroelectric tail bends, and the electric polarization shifts because of the piezoelectric effect. The results of experimental research demonstrate that the nano eel can move from surface walking to three-dimensional swinging and spiralling by varying the strength and frequency of the magnetic field. In addition, the nanoeel may be precisely guided to a particular site for medication release by adding an appropriate magnetic field.

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Delivering drugs to cancer cells with a magnetic field of 10 mT and 7 Hz is possible. In the drug release mode, the efficiency of killing cancer cells is 35%, whereas in the swimming mode, it is 10%. The research findings statistically validated the feasibility of employing nanorobots for precise medication administration. This will encourage the application of nanorobots in medical settings and lay a strong basis for upcoming studies.[123] Figure 4 shows the magnetic stimulation of micro/nanorobots for hyperthermia, thermophoresis, and magnetoelectric applications.

Wang et al. created a novel kind of micro/nanorobot that can monitor cancer's condition to treat it. This robot manipulates living cells with precision using multistage magnetic tweezers. The multistage magnetic tweezers have six magnetic poles and six coils positioned at the top and bottom. The high permeability foil used to make the tip ensures a large magnetic gradient. To make sure the robot is subjected to the force of a three-dimensional magnetic field when entering cells put on the glass slide, the device was mounted on a microscope glass slide. Early cancer detection may be possible with robots that monitor the force between cells. This discovery has new hope for cancer treatment.[124]

A micro/nanorobot with three-dimensional magnetic actuation was created by Kim et al.[125] That can precisely move grown nerve cells to join separated nerve clusters. It can selectively reconstruct neuronal networks in vitro and direct the growth of axons. With its repeatability, selectivity, and exact connection, the micro/nanorobot can serve as a foundation for the targeted transport of nerve cells and the development of active neural networks in vitro, thereby increasing the study of neural networks and neural connectivity. This offers a possible basis for sophisticated artificial neural network programmable models in vitro. Zheng et al. created a sea star-like microrobot whose flexible tentacles can efficiently conform to the outer outlines of any target with autonomous deformation in a liquid environment for gripping and releasing. The design was inspired by the movement process of starfish preying on shellfish. The robot can be operated in a variety of ways, such as by encasing magnetic nanoparticles inside its body or by capturing magnetic microspheres.[126]

3.1.2. Electric Field Actuation. Robots that are micro- or nanoscale can be activated by external electric fields. In general, magnetic and electric fields are inseparable, yet there are situations in which they can change into one another. An innovative kind of micro robot without intricate mechanical components was created by Jeong et al. There were two suggested actuation systems. The first uses a pair of Helmholtz and Maxwell electric coils to power microrobots electromagnetically. The second is medication release by acoustic bubble actuation. This suggests the new microrobot will find applications in other biomedical domains and targeted drug delivery.[127] A theoretical proposal of a nanorobot with four single-stranded DNAs and a nanoparticle positioned atop a quad-nanopore device for motion control was presented by Si et al.[128] When an electric field is applied, the nanopores may sequentially pick up each of the robot's four single-stranded DNAs.

To more efficiently actuate micro/nanorobots, Qu et al., who also wished to research electromagnetic fields in the application of micro/nanorobots, employed finite element methods to mimic the magnetic field generated by a coil assembly. The study's findings offer benchmarks for the use of electromagnetically powered micro- and nanorobots.[129] Actuation can also be produced by adding conductive materials to a micro or nanorobot and then modifying the robot's surface charge or the electrochemical reaction at the interface using electric fields. A microelectrode device with interdigitation was proposed by Zhang et al.[130] Also, Guo et al.'s technique involved applying alternating current (AC) and direct current (DC) electric fields to a three-dimensional orthogonal microelectrode device to control nanomotors.[131] Figure 5 depicts the electrically stimulated artificial muscles using electrically controlled magnetic nanorobots (MNRs).

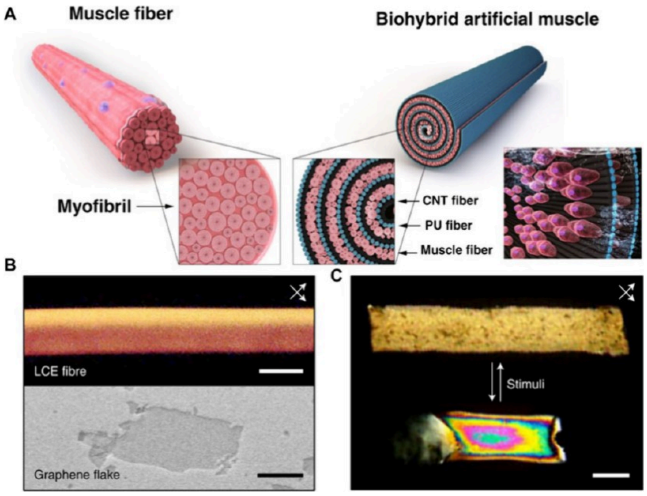

Figure 5. (A) The structural similarities and differences between natural and artificial muscles. (Adapted with permission from ref 132. Copyright 2021, Microsystems and Nanoengineering.) (B) Polarized optical microscope of liquid crystal formation observed at 45° angles concerning cross-polarizers (top) and scanning electron microscope image of an electrographite flake (bottom). (C) The shape deformation of artificial muscles during relaxation and contraction. (Adapted with permission from ref 133. Copyright 2022, Springer Nature.)

3.1.3. Light Field Actuation. The discipline of micro and nanorobotics has seen a notable increase in the use of light as an actuator, indicating its extraordinary potential for various applications, such as drug release mechanisms and theranostics. Light actuation uses the unique qualities of light, namely its high accuracy, noncontact nature, and small-scale object manipulation capabilities, to provide precise control over micro and nanorobots. These capacities have sparked innovative methods in other fields, including biomedical research.[134]

Micro/nanorobot movement and functionality are controlled by light field actuation, which uses several different concepts. One such idea is the photocatalytic reaction, in which light energy causes chemical reactions on the nanorobots' surface that propel them forward or activate particular functionalities.[120] Another necessary process is the photothermal effect, which produces localized thermal gradients that can propel the nanorobots by light absorption and subsequent conversion to heat. In biomedical applications, these effects are used to enable precise control and targeted actions.[135] In recent years, notable progress has been made in creating light-field-actuated micro/nanorobots. Researchers have investigated a variety of light-responsive materials and techniques

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to enable controlled actuation and navigation of these microscopic robots in biological contexts.

A liquid metal gallium nano swimmer in the shape of a needle that can move in a controlled manner when exposed to near-infrared laser light was created by Wang et al.[136] (Figure 6). Ingeniously, Sato et al.[32] created a molecular robot that resembles an amoeba and uses particular photoresponsive DNA signaling molecules to regulate the robot's movement. Unlike previous nanorobots, this robot is made solely of chemical and biological materials. This work effectively replicated the motion of cells and offered a strong foundation for the advancement of molecular robotics.[137] A novel kind of electrochemical actuator was studied by Miskin et al.[138] It has a controlled voltage, works with current silicon electrical devices, and can cause a robot to move.

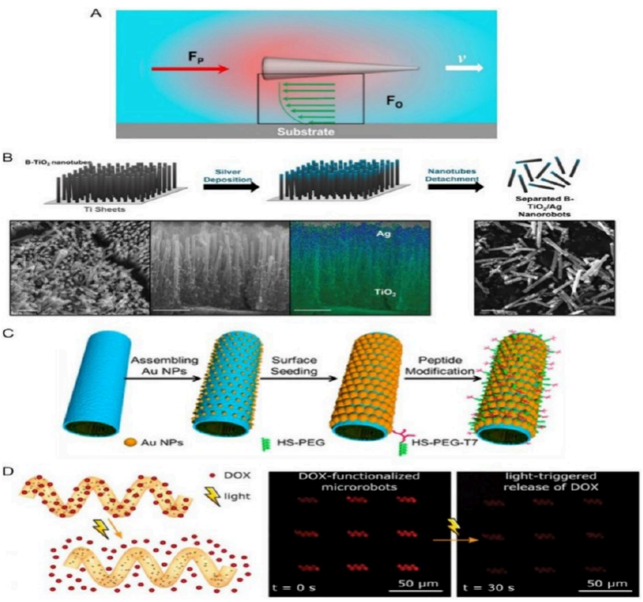

Figure 6. A) A controlled, needle-like LMGNS that moves when exposed to NIR laser. Reproduced with permission.[136] Copyright 2021, Elsevier. B) B-TiO_2/Ag nanorobot fabrication and characterization. Reproduced with permission.[139] Copyright 2022, Wiley-VCH. C) Schematic of The Pt NP-modified polyelectrolyte multilayer manufacturing process of micro engines. Reproduced with permission.[140] Copyright 2014, American Chemical Society. D) Schematic illustration of DOX-functionalized carboxy betaine microrobots for UV-light-triggered drug release and an example for the drug release demonstration. Reproduced with permission.[141] Copyright 2020, Wiley-VCH.

3.1.4. Acoustic Field Actuation. Sound at a frequency higher than the upper threshold of human hearing is known as ultrasound. Robots can move due to the pressure difference created by an asymmetric robot body structure in an ultrasonic field or the ultrasonic bubble-gathering effect produced by external ultrasonic fields. By using template electrodeposition, Wang et al. produced metal rod-shaped micro/nanorobots in batches. With the ultrasonic field's help, the robots could reach speeds of up to 200 μm/s.[142] Another novel ultrasonic actuation mechanism was proposed by Lee et al.[143] Drug particle/cell manipulation and micro/nanorobot actuation in clinical biology and medicine were made possible by creating an acoustic radiation force in a standing wave to trap and move particles. A novel technique was presented by Valdez-Garduño et al. that fixes the direction of a micromotor using an external magnetic field and transforms the ultrasound-induced oscillation motion of an asymmetrically dense Janus microstructure into a translational motion. This work offers a fresh approach to developing and using micro/nanomotors with ultrasonic propulsion.[144]

Focused ultrasound (FU) has been utilized to power and operate a variety of micro/nano robots. To create a focused ultrasonic field, researchers have developed transducers, such as concave, cylindrical, or organized ones, that concentrate MHz waves with high pressure onto a focal point.[134] This pressure can evaporate a liquid fuel or trigger a bubble trapped inside a specially built structure. For example, when exposed to a high-intensity FU beam, perfluorocarbon (PFC) emulsions can be caused to evaporate quickly. This procedure is called vaporization of acoustic droplets (Figure 7).

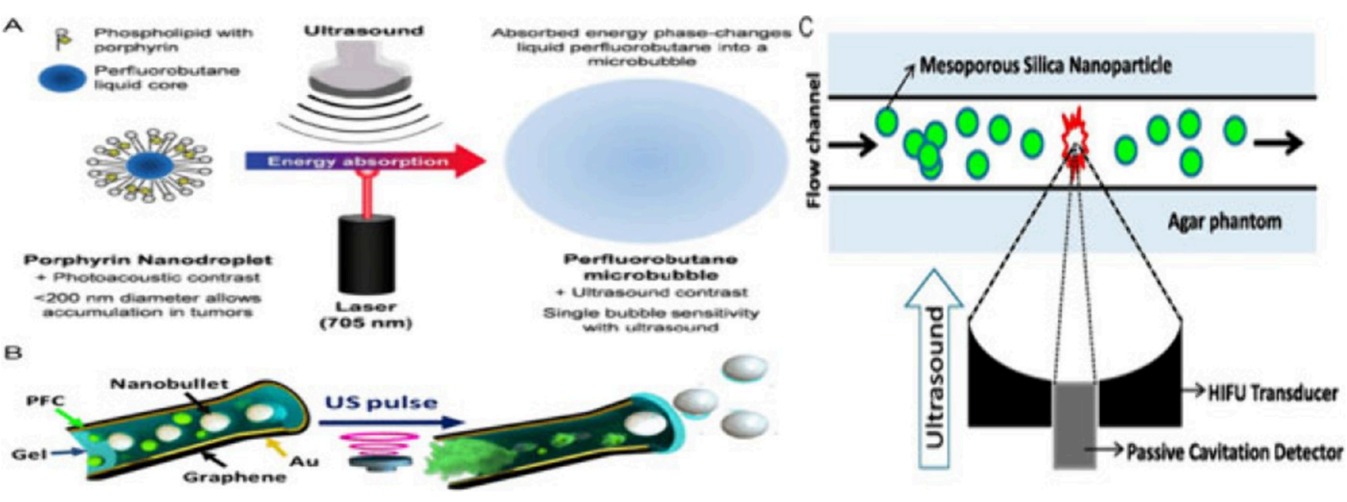

Figure 7. A) Convert porphyrin nanodroplets into PFC microbubbles by phase transition. Used by permission.[145] Copyright Wiley-VCH, 2016. B) A PFC-powered microcannon that fires NBs. Used by permission.[146] Copyright The American Chemical Society. All rights reserved. C) Experimental design of fluorescein isothiocyanate-labeled mesoporous silica nanoparticle delivery via ultrasound-mediated cavitation-enhanced extravasation in the agarose phantom model. Used by permission.[147] Copyright Elsevier 2018.

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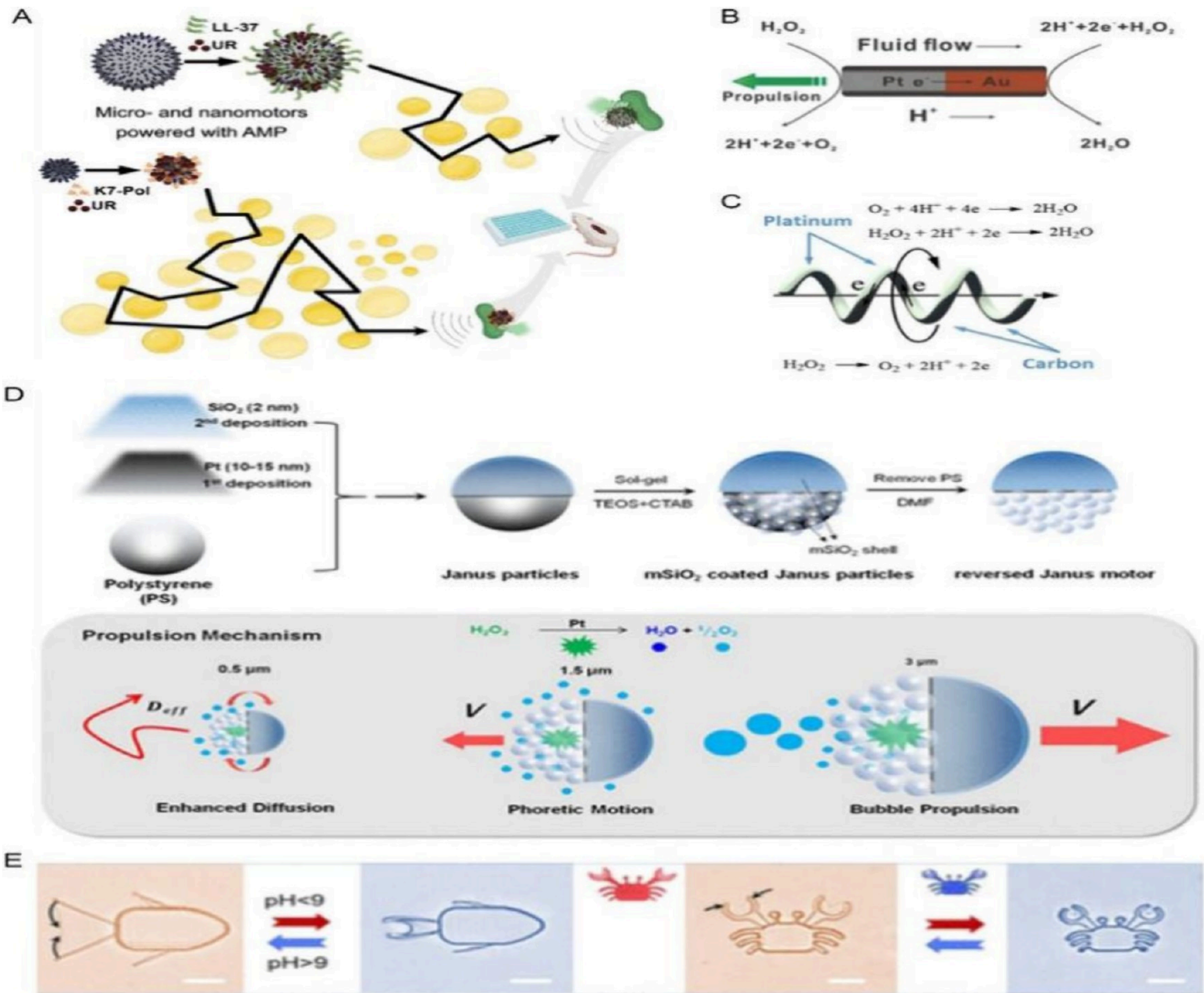

Figure 8. A). The urease micro- and nanomotors' AMP-coating technique allows for independent propulsion of the motors, which can target pathogenic infections in vivo and in vitro. Used by permission.[154] The American Chemical Society. Copyright 2022. B) Au−Pt bimetallic nanorod in an aqueous H_2O_2 solution driven by a self-electrophoresis process. Used by permission.[155] All rights reserved by Wiley-VCH, 2018. C) Diagram showing the catalytic helical carbon motor system's propulsion. Used by permission.[156] D) Diagrammatic representation of the production processes for reversed Janus motors and the different mobility scenarios. Copyright 2019, Wiley-VCH. Used by permission.[157] The American Chemical Society. All rights reserved. E) SMMC and SMMF optical pictures show how pH variations cause the fins and claws to open and close. Reproduced with permission.[158] Copyright 2021, American Chemical Society.

3.2. Self-Actuation.

Nanorobots that are self-actuating move and operate independently at the nanoscale using internal mechanics. These small robots use a variety of energy sources, including light, magnetic fields, and chemical reactions, to propel themselves and carry out specified activities without the need for outside control. This capacity is critical for applications requiring precise and controlled movements at the nanoscale, such as targeted medication administration, medical diagnostics, and environmental monitoring. A significant achievement in nanotechnology is the creation of self-actuating nanorobots, which allow for more complex and effective molecular interactions.

3.2.1. Chemical Self-Actuation. Creating an asymmetric field, such as bubble recoil or concentration gradients, is the fundamental component of chemical self-actuation, which allows a micro- or nanorobot to break its static equilibrium and begin to move. In 2002, Whitesides et al.[148] created the first micro/nanoscale self-actuation robot. This micro/nano robot's terminal was fitted with a Pt-plated porous glass filter, which can produce a lot of O_2 through the breakdown of H_2O_2 on the Pt surface and create an actuation force to push the robot at the point where the H_2O_2 solution and air meet. Through an oxidation−reduction reaction, this mechanism transforms the chemical energy in the surrounding environment into kinetic energy. As the first self-actuation micro/nanorobot, despite its limitations, its design served as a source of inspiration and ideas for further study.

Based on prior studies, Bao et al. creatively created a V-shaped micro/nanorobot composed entirely of Pt. The nanorobot can sustain rotation and follow a stable course because it is powered by oxygen molecules produced during the breakdown of H_2O_2.[149] A z-shaped Au/Pt hybrid self-actuation micro/nanorobot for cancer treatment and targeted drug delivery systems was proposed by Chen et al.[150] Self-

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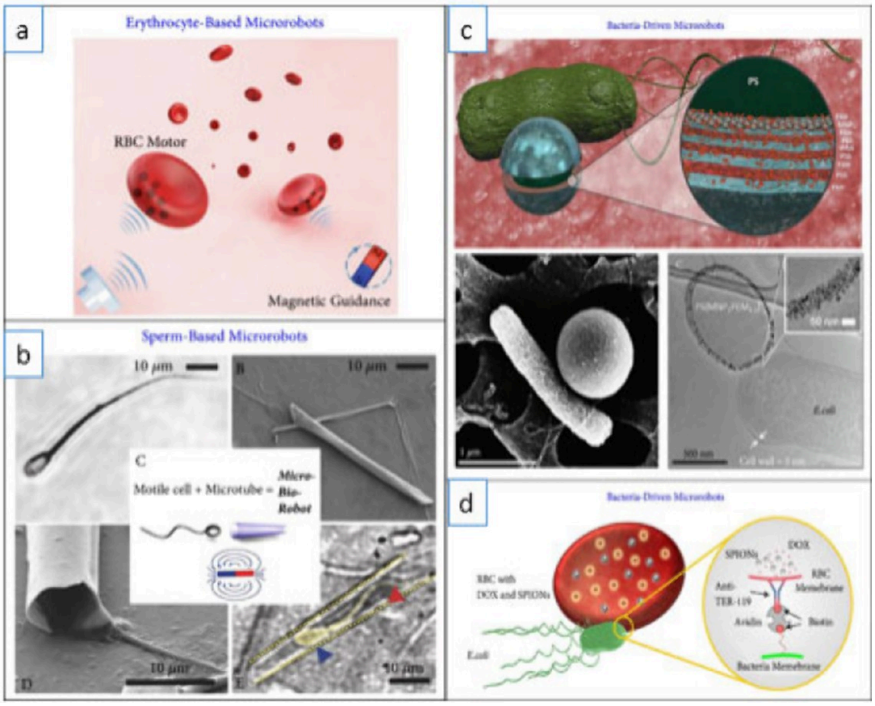

Figure 9. (a) Schematic illustration of magnetically navigated, ultrasonically propelled RBC micromotors in the whole blood. Reproduced with permission from reference 165. Copyright 2014, American Chemical Society. (b) Sperm flagella-driven microbiorobots. Reproduced with permission from reference 162. Copyright 2013, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (c) Bacteria-driven microswimmers based on PEM-MNP microparticles attached to *E. coli* MG1655 bacteria. Reproduced with permission from reference 166. Copyright 2017, American Chemical Society. (d) Magnetically guided, bacterially driven RBC microswimmers for active drug delivery. Reproduced with permission from reference 167. Copyright 2018, Science Robotics.

electrophoretic actuation serves as its foundation. Subsequently, Chen et al. created a z-shaped Pt hybrid nanorobot to satisfy the biomedical industry's increasing need for micro/nanorobots. Focused ion beam and plasma sputtering were employed in its production, and the robot's actuation system is self-electrophoretic.[151]

A micro/nanorobot based on Pt catalysis was created by Xu et al. (Figure 7c). It can be controlled by an electric mechanism that breaks down H_2O_2. Xu investigated the motion behavior of the number of rotations by using a chemical vapor deposition technique to create a large number of helical molecule chains.[152] To combat dental plaque and other oral health issues, Villa et al. developed a self-actuated tubular microrobot that combines reactive chemicals that grow on the surface of the biofilm with microbubbles.[153] How proteins move molecularly in animal cells inspired scientists to use enzymes as catalytic engines, utilizing chemical reactions to power micro/nanorobots. Enzyme actuation provides a superior development possibility and uses biocompatible fuels compared to conventional chemical self-actuation techniques. Antimicrobial Peptides (AMP)-coated bioactive micro- and nanomotors for autonomous infection therapy are schematically illustrated in Figure 8.

DNA nano switches and urease-powered micromotors were paired by Patino et al. to accomplish swimming and pH value sensing.[159] Wang and colleagues[44] developed a lipase-based nanomotor. Lipase serves two purposes in this instance. First, it can be used as a power engine by utilizing triacetin as fuel and a catalytic reaction to achieve particle diffusion. Within 50 min, the second feature, an active cleaning function, can break down triglyceride droplets by almost 98%. This has much promise for use in biomedicine and can be utilized to treat disorders linked to triglycerides.[160]

3.2.2. Biological Self-Actuation. Suitable biological materials, such as the flagella or cilia of swimming microorganisms, are actuators of micro/nanorobots, drawing inspiration from nature. In a solution of water and glucose, Behkam and Sitti[161] suspended droplets of bacteria, including *E. coli* and polystyrene. To prepare micro/nanorobots, Magdanz et al.[162] suggested using spermatozoa-bearing flagella as an actuation force. Researchers have made magnetically navigated, ultrasonically propelled red blood cell (RBC) micromotors in the whole blood (Figure 9a). The robot moves when sperm cells and nanotubes are combined because the sperm flagella's swing interacts with the microtubes. Sperm-driven micro/nanorobots (Figure 9b) are anticipated to emerge as a potential tool in artificial insemination and other reproductive technologies because of the spermatozoa's superior motility and safety benefits over bacteria (Figure 9c) and other microorganisms.

Martel[47] discovered that no information regarding the use of MC-1 magnetotactic bacteria (MTB) in cancer treatment, particularly as an additional strategy to spread into tiny capillaries, had been included in earlier research. Therefore, Martel devised a novel method for pushing medicinal chemicals and microbeads together for targeted therapy by combining ferromagnetic materials with the magneto tactic bacteria MC-1 and magnetically guided, bacterially driven RBC microswimmers for active drug delivery (Figure 14d). This study's findings suggest that using magnetotactic bacteria to treat cancer is a successful strategy.[163] Xing et al. developed an intelligent micro/nanorobot known as an AI microrobot using

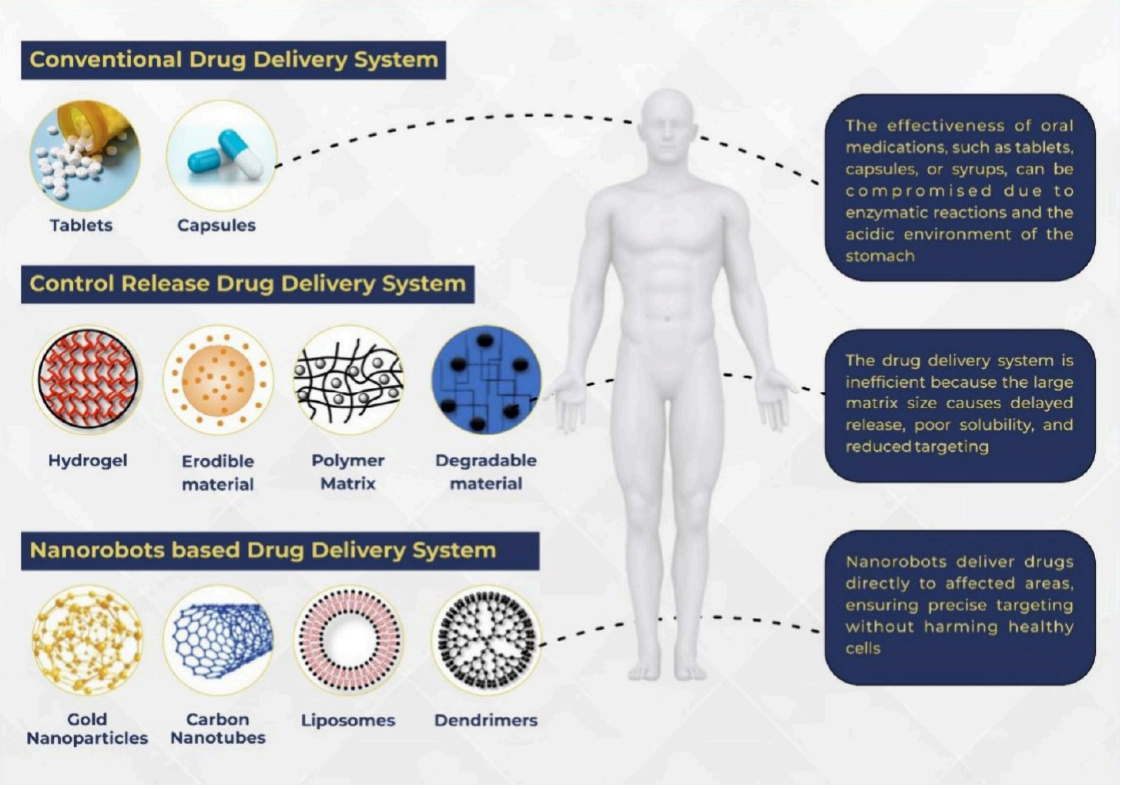

Figure 10. Diagram showing how conventional drugs were supplied without using nanocarriers, causing damage to cells or organs that were considered healthy. By contrast, current techniques use nanorobots to deliver drugs to targeted body areas.

marine-derived magnetotactic bacteria (AMB-1) as a template.[164]

4. USE OF NANOROBOTS IN MEDICAL APPLICATIONS

Due to their precise and varied capabilities, nanorobots are transforming medical applications. Nanorobots can deliver drugs directly to damaged cells through targeted drug delivery, reducing side effects and increasing therapy effectiveness. These tiny devices navigate through the body to conduct complex tasks with less harm and faster recovery times during minimally invasive surgery. By serving as contrast agents, nanorobots in biomedical imaging increase the resolution and precision of diagnostic scans, facilitating the early and precise diagnosis of disease. Furthermore, nanorobots can detect biomarkers and other molecular signals with great sensitivity in biosensing, making it easier to diagnose diseases early and monitor physiological states in real time. In addition to cancer therapy and tissue engineering applications, nano and microrobots hold a significant place. These uses demonstrate how revolutionary nanorobots may improve patient care and medical research.

4.1. Target Drug Delivery. Targeted cargo delivery is one of the most significant medical uses for nanorobots that can transform what is considered the pinnacle of medical practice. Systemic pathways and local diffusion provide limited delivery and distribution efficiency; however, active navigation of immensely concentrated diagnostic and therapeutic substances to the site of action may overcome them. Thus, it could limit systemic toxicity's impact by maximizing the cumulative effectiveness of single-dose delivery. A nanorobot must have these abilities to succeed and efficiently implement targeted drug delivery strategies. Positional control: The nanorobot must be capable of actively moving and directing concentrated products, e.g. drugs, imaging contrast compounds, siRNA, cells, vaccines, etc., and reduce the inaccurate distribution by maintaining the cargo throughout its journey up until getting to the designated site; (3) Temporal control: The therapeutic discharge need to be configurable and activated via environmental or outwardly regulated stimulation to ensure the nanorobot can offer a refined and maintained therapeutic window. About these needs, actuation and manipulation techniques, the nanorobot's material design, cargo unloading plan, and biodegradable qualities become crucial ideas in a delivery nanorobot.[168] The correct body form with porousness in the material may accomplish focused cargo loading. Porous hydrogel networks in a nanorobot may very efficiently store significant volumes of diagnostic and therapeutic products.[66] After achieving the objective, the nanorobot should disintegrate in a suitable period in its specific physiological milieu to avoid a foreign body response.[66,169] Autodelivery of diagnostic and therapeutic product varieties with customizable kinetics using environmental detection of local signals, e.g. disease indicators, may allow nanorobotic diagnostics and therapies in a meticulously performed and configurable operation.[66] Also, nanorobots may be externally actuated by employing light to deliver products in specified temporal patterns[170]—translational prospects. To extend life expectancy through the advancement of medication delivery systems, drug development and delivery have shifted from the micro to the nano level during the previous few decades (Figure 10).

In stomach tissue, acidic conditions are frequently employed to promote medication administration, such as encouraging the propulsion of nanorobots via hydrogen generated by the

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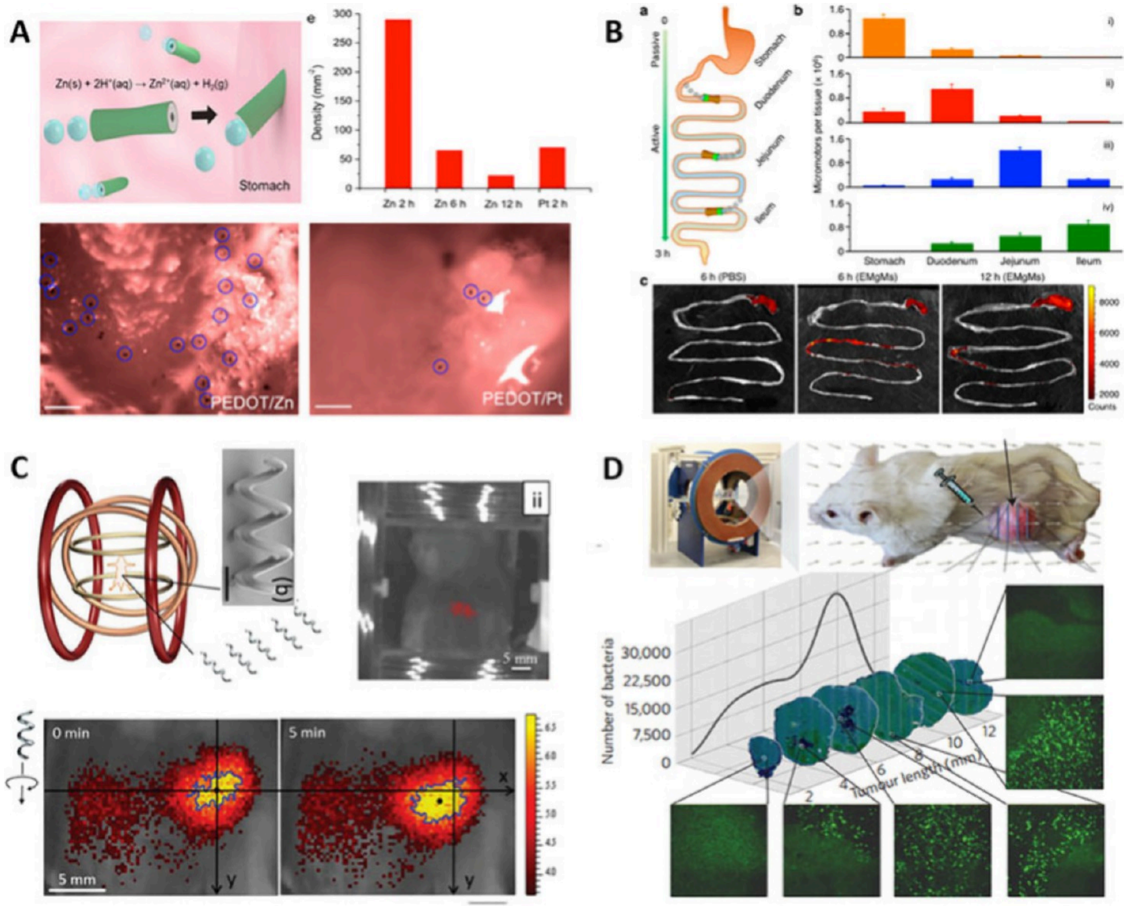

Figure 11. (A) Zinc-based micromotors driven by acid for improved retention in the mouse stomach. (Adapted with permission from ref 172. Copyright 2015, American Chemical Society.) (B) To avoid the acidic stomach environment and instead selectively position and propel spontaneously within the gastrointestinal tract, an enteric micromotor coated with a pH-sensitive polymer barrier (enteric coating) is used. (Adapted with permission from ref 173. Copyright 2016, American Chemical Society.) (C) Regulated swimming of a swarm of microrobotic flagella that resemble bacteria in vivo (Adapted with permission from ref 174. Copyright 2015, John and Wiley.) (D) Drug-containing nanoliposomes are delivered to tumor-hypoxic areas by magneto-aerotactic motor-like bacteria. (Adapted with permission from ref 175. Copyright 2016, Springer Nature.)

interaction of metals with hydrogen ions. Esteban-Fernández de Ávila et al. devised a Mg-based micro robot filled with clarithromycin (CLR) for treating mice having stomach infection.[171] *H. pylori*-infected mice were orally treated with nanorobots to cure stomach infections. The findings indicated that the CLR-loaded nanorobots group decreased about 1.8 times the magnitudes of the *H. pylori* load over the negative control group (treated using deionized water or microrobot with no CLR). The scientists established this approach's safety and nontoxic properties in mice along with the therapeutic efficacy. A comparable Zn-based microrobot was similarly constructed by Gao al (Figure 11).[172] Utilizing gold nanoparticles (AuNPs) as a model medication, microrobots could effectively administer and maintain the drug in the mice's stomachs at a rate more than three times higher than that of the oral NPs group. Mice injected with nanorobots had their stomach tissue sections examined to verify the devices' safety. Figure 11 shows the motile drug delivery by biocompatible fuel-powered MNR, and Figure 12 depicts the motile drug delivery by biocompatible fuel-powered MNRs.

Wu et al. achieved deep imaging of the microrobotic system in the intestines using photoacoustic computed tomography (PACT) technology.[181] To create a micromotor capsule, the outside of the magnesium-based micromotors was coated with enteric coating. As the capsule entered the gut, near-infrared red (NIR) caused it to undergo a phase change, which allowed the capsule shell to break and release the micromotors. The chemical interaction between magnesium and H_2O powers the micromotor. The medications were released gradually as the nanorobots disintegrated. Dox was successfully transferred to the mice's gut via the micromotors' alginate layer.

Blood presents more significant mobility barriers for micro/nanorobots than other bodily fluids since it contains many free-moving cells and other materials. By using the chemical interaction between tranexamic acid and carbonate, Baylis et al.[182] developed self-propelled particles. In mice and pigs, blood vessel bleeding was stopped using thrombin adsorbed on porous particles. The studies demonstrated that this device could supply thrombin for hemostatic therapy and flow steadily through the circulation. For intravascular medication administration, novel model microrobots, such as sperm micromotors[183] and multifunctional surface micro rollers[184] have also been developed recently. Studies on medication delivery to tumors, the eyes, and other locations are also being conducted.

Because of problems with undesirable drug buildup and nanoparticle biodistribution, finding a balance between therapeutic efficacy and negative effects on healthy tissues is

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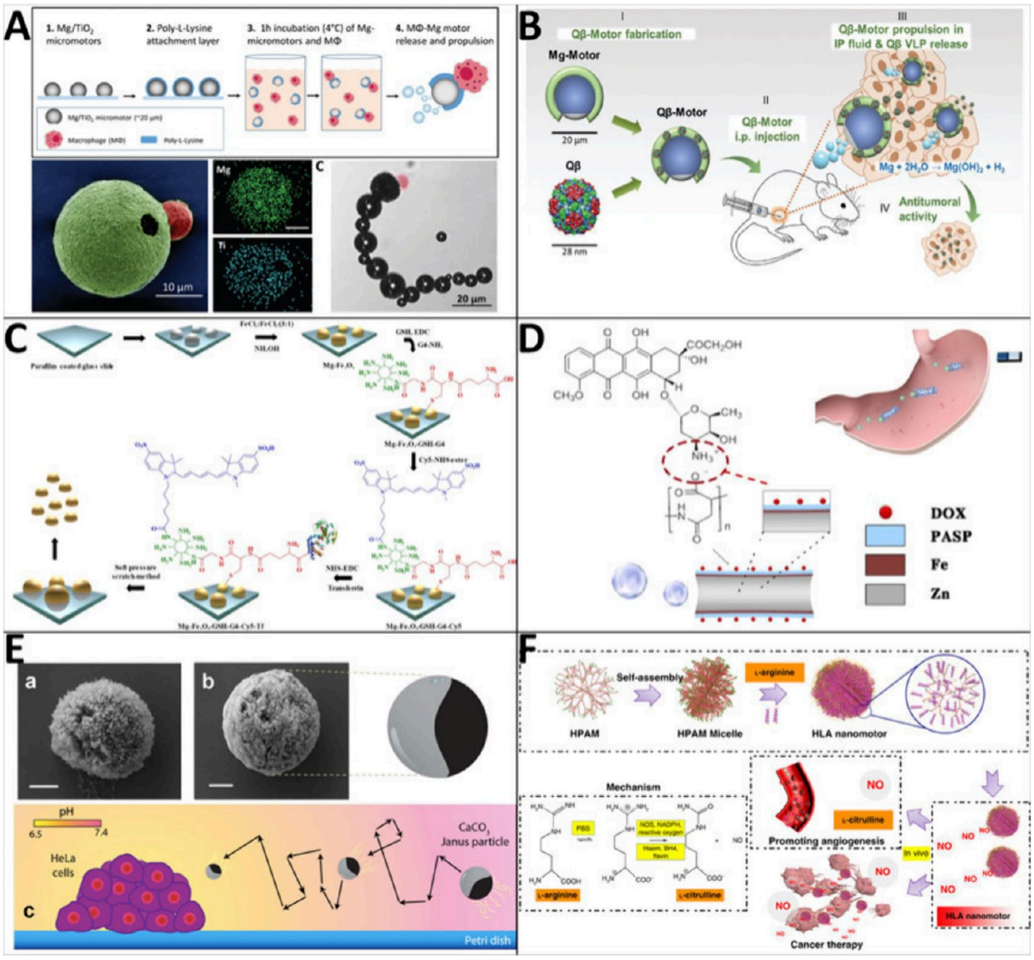

Figure 12. (A) Macrophage-magnesium biohybrid micromotor. (Adapted with permission from ref 176. Copyright 2019 John Wiley and Sons.) (B) Bacteriophage virus-like nanoparticles (QβVLPs)-loaded Mg-based micromotors. (Adapted with permission from ref 177. Copyright 2020, John Wiley and Sons.) (C) Mg-Fe_3O_4-based magneto-fluorescent nanorobot. (Adapted with permission from ref 178. Copyright 2021, Springer Nature.) (D) Poly(aspartic acid)/iron−zinc microrockets. (Adapted with permission from ref 179. Copyright 2019, American Chemical Society.) (E) Calcium carbonate micromotors. (Adapted with permission from ref 180. Copyright 2016, Springer Nature.) (F) NO-driven nanomotors (Adapted with permission from ref 119. Copyright 2019, Springer Nature.)

a barrier to the clinical adoption of nanoscale agents for targeted therapy—an intravascular catheter developed by Iacovacciet al.[185] is suggested because it may effectively remove magnetic nanocarriers that are not helpful to therapy from the bloodstream, reducing their uncontrollably dispersed dispersion and potential side effects. The device is a tiny module fitted into a 12-French catheter used in therapeutic settings. It is based on 27 permanent magnets grouped in two coaxial series. When 500 and 250 nm nominal diameter superparamagnetic iron oxide nanoparticles are utilized as carriers, this device can catch approximately 94% and 78% of the unused agents, respectively. Table 3 shows the different types of nanomaterials used in target drug delivery.

4.2. Minimally Invasive Surgery. The field of robotics-assisted surgery, defined as “the use of a mechanical device to assist surgery in place of a human-being or in a human-like way”[191] is gaining ground on several standard general surgical procedures, particularly minimally invasive surgery.[16] Currently, the surgical field uses three primary kinds of robotic systems. Active, semiactive and master−slave systems. Active systems carry out preprogrammed duties and operate independently (under the supervision of the operating surgeon). The PROBOT and ROBODOC systems are notable instances of this. In addition to these robot systems’ preprogrammed components, semiactive systems provide a surgeon-driven component. Formal master-slave systems, of which the ZEUS and da Vinci platforms were the predecessors, do not have any setup or succinct reviews of how robotics may improve autonomous surgery components of other systems. They are entirely reliant on surgical action. Surgeon hand motions are relayed to laparoscopic surgical equipment, which accurately duplicates surgeon hand activity but intracorporeally. Since they traded world records and advanced the boundaries of minimally invasive surgery, these two competing systems, da Vinci and ZEUS have dominated the area of robotic surgery for some time.

The three-armed ZEUS platform used the speech-activated Automated Endoscopic System for Optimal Positioning (AESOP) camera system. Its three arms were divided into two for holding surgical equipment and one for holding the camera. A three-to-four-armed system was depicted by the da Vinci platform, with a binocular lens (for three-dimensional vision) held by the center arm. More important, however, could be the ability of the surgical tools attached to the cart’s remaining arms to be moved in seven different ways at the wrist. It was a unique marketing factor and an invention that

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Table 3. Different Types of Nanomaterials, Fabrication Method, Target Drug Name, and Location of Target Site

S. no	Nanomaterial	Fabrication Method	Target Drug	Location of targeted site	Refs
1	Urease-powered nanomotors (nano robots)	4D printing	DOX	Bladder cancer cells	105
2	Bacteri robot	Biohybrid fabrication	Paclitaxel	Breast cancer	107
3	Light-responsive polymers	Photoinitiated polymerization	Curcumin	Inflammatory sites	186
4	Drug-loaded NIR-driven nano robots	Magnetic field-assisted synthesis	Paclitaxel	Blood vessels	187
5	PEDOT/Au micro robots	Electrodeposition, enteric polymer coating	Magnesium	Intestine	108
6	Mg/TiO_2/ PLGA microrobots	Asymmetric coating	Clarithromycin	Stomach	171
7	TiO_2/PLGA/Fe-Se@chitosan-coated Mg microspheres	Ionic gelation	Iron and selenium	Intestine	111
8	Pt-coated mesoporous silica	Asymmetric coating	Cisplatin	colorectal cancer	109
9	Mg microrobots	Asymmetric coating	PLGA and hyaluronic acid	Bone	188
10	DHM	Magnetic field-assisted synthesis	5-FU	Cancer cells	112
11	Superparamagnetic/catalytic microrobots (PM/Pt microrobots)	Magnetic field-assisted synthesis	DOX	Breast cancer cells	113
12	Mg-based micro robots	Asymmetric coating	Dexamethasone	Bone	188
13	Biomimetic micromotor toxoid	Atomic layer deposition (ALD)	Staphylococcal α-toxin	Small intestine	114
14	Microcapsules (encapsulated micro robots)	Embedding method with layer-by-layer deposition	DOX	Colon cancer cells	181
15	Silica nanobottle (Si NB) robots	Asymmetric chemical synthesis method	Clarithromycin	Stomach	110
16	Retrievable intraocular bilayer hydrogel microrobot	Photocuring of PDMS mold through UV exposure	DOX	Eye	115
17	Porous hollow helical microswimmers	Biotemplated synthesis	Spirulina	Not specified	189
18	Soft erythrocyte-based bacterial microswimmers	Attachment of drug-loaded RBCs to *E. coli* MG1655 via biotin-avidin-biotin binding complex	DOX	Cancer cells	117
19	Poly(ethylene glycol)-*b*-polystyrene (PEG-PS) polymersome-based Janus nanomotors	Electron beam evaporation	Fluorescein sodium salt	Endothelium of cancer cells	118
20	Nitric oxide-nanomotors	Not specified	Nitric oxide	Various cells including joint muscle cells and cancer cells	190

eventually proved vital in the future supremacy of the da Vinci platform year Carpentier et al. (also employing the da Vinci platform) completed a mitral valve replacement—notably making use of the revolutionary "wristed" devices for the first time. In 1998, a Fallopian tube reanastomosis was carried out with the ZEUS technology. At the London Health Sciences Centre in Ontario, Douglas Boyd and associates performed the first closed-chest beating-heart cardiac bypass surgery the following year. The same team then executed a heart revascularization surgery, again utilizing the ZEUS platform. The year 2001 saw the use of the ZEUS system in a transatlantic cholecystectomy, with the patient residing in Strasbourg, France, but the operational surgeon doing the surgery in New York. The ZEUS and da Vinci systems were combined after the merger of Computer Motion and Intuitive Surgical in 2003. Consequently, the da Vinci platform became the focus of further advancements and modifications, and it has dominated the robotic surgery field for over ten years.[192−195]

With the use of endoscopy or robot-assisted surgery, the risks associated with radical procedures have been decreased, postoperative patient morbidity has been minimized, recuperating periods have been cut short, and centimeter-sized incisions have been reduced to millimeter-sized key holes.[196] The notion of minimally invasive surgery may be extended to highly tiny, targeted, and controlled physical harm as a curative therapy paradigm via remote microscopic manipulation.[197] Nanorobots can remove blockages in the ductal and urinary systems and drill through blood clots in the circulatory system to restore normal flow conditions.[198−200] Millimeter incisions or fenestrations may be performed by configured robots, going beyond luminal modifications. Malignant tumors in delicate areas, including the central nervous system (CNS), may be removed with great precision and mechanical force, which can have significant medical implications. The nano robots' soft carrier compartment may release drugs or disintegrate enzymes locally to remove any debris left behind after hard drilling. Additionally, nanorobots may be used in obstructive procedures to maintain lumen openings or as semi or permanent implants in the luminal organs. Certain obstructions might require the nanorobots to remain quiescent inside the body until a local corrective operation needs to be conducted. Figure 13 shows the nanorobots used in minimally invasive surgery.

The design and implantation of novel kinds of reconfigurable stents in the circulatory system and luminal organs may benefit significantly from remote control and steering. It is essential to thoroughly evaluate the robustness and biocompatibility of nanorobots in such long-term applications. The execution of such physical surgeries in tissues requires extremely accurate spatial navigation with great dexterity, as well as force and position regulation methods. Additionally, for remote actuation systems to be widely used in clinical settings, they should be affordable for hospitals and provide sufficient penetration force to carry out the intended purpose.[168] Miniaturised devices that can administer different drugs, including DNA intracellularly, and open cell membranes with precision to destroy aberrant cells offer exciting prospects for noninvasive surgery. Drilling can be done by nano/microrobots emitting sharp points or moving corkscrew-likely when a rotating magnetic field is applied. With its exceptional

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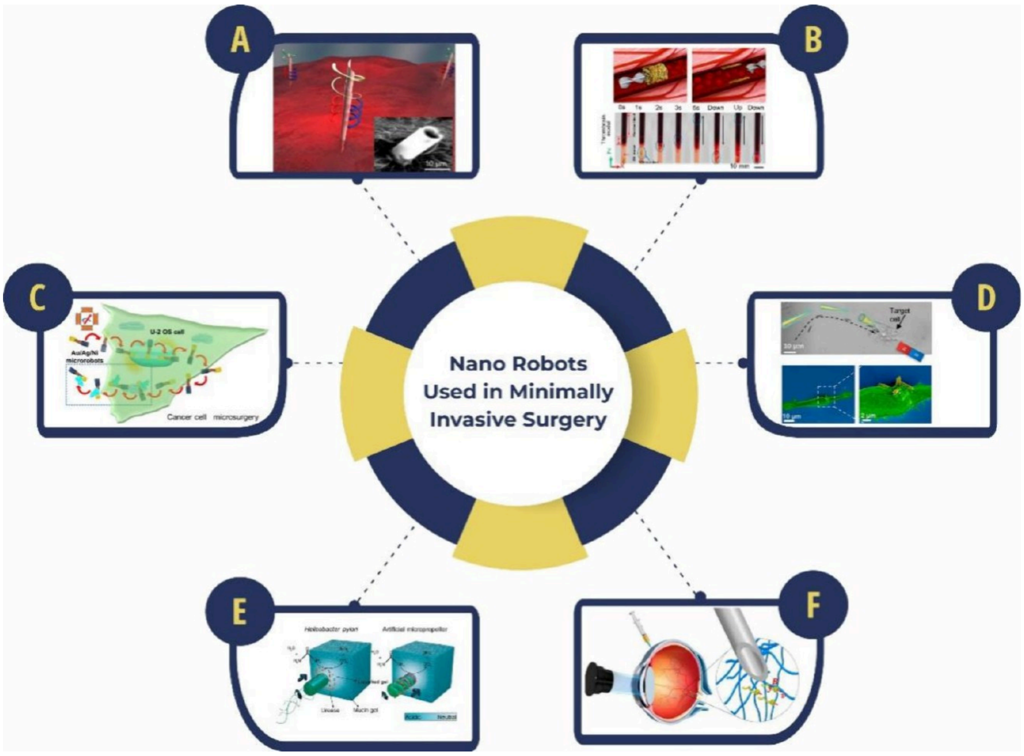

Figure 13. (A) Schematic and experimental images (inset) depict rolled-up magnetic microdrillers with a sharp end penetrating a pig liver postdrilling motion. (B) Schematic of a driller operating in a 3D vascular network and experimental results showing the driller dislodging a blood clot. (C) The movement of an Au/Ag/Ni surface walker under varying frequencies of a transversal rotating field shows the magnetic navigation of microrobots penetrating and removing a cell fragment. (D) Magnetic manipulation of Si/Ni/Au nanospheres for targeted intracellular transfection. (E) Penetration of *Helicobacter pylori*, a helical MagRobot, into mucin gels and mucus liquefaction via enzyme-catalyzed reaction. (F) Long-range propulsion of injected slippery MagRobots in the vitreous toward the retina, aided by a magnetic field and standard optical coherence tomography.

precision, the drilling feature holds enormous potential for performing untethered microsurgeries.

Mechanical drilling driven by magnetism allowed micro-drillers (tubular Ti/Cr/Fe microdrillers with sharp points) to pierce some pig liver tissue. Cardiovascular disorders may benefit from applying a millimeter-sized magnetic driller that can perforate a blood clot in a simulated thrombosis model environment and navigate through a 3D vascular channel. The surface walkers exhibit exceptional minimally invasive micro-surgery capabilities by acting as microscalpels that can penetrate cancer cells, seize a portion of the cytosol, and escape the cells without damaging the cytoplasmic membrane. Using revolving magnets, Au/Ni/Si nano spears functionalized with plasmid could enter U87 glioblastoma cells and distribute the gene (eGFP expression-plasmid) across the cells in a significant area. The locomotion behaviors and application performance of micro/nanorobots in biological environments are influenced by various factors, including crowded biological environments, complex rheology (such as viscoelastic-ity, shear-thinning), interactions with boundaries, hysico chemical and histological barriers (e.g., cell membrane, blood-brain barrier, intestinal mucosal barrier), and others. There have been attempts to take advantage of MagRobots' ability to actuate in complicated biofluids. For instance, Peer Fischer's group created a helical micro driller surface functionalized with urease to overcome the mucus barrier. The same group developed magnetic helical micro propellers that could swim inside the biopolymeric network of pig vitreous humor over a centimeter distance while being navigated by a rotating magnetic field and clinical optical coherence tomography to advance toward clinical application. Table 4 shows the different types of nanomaterials used in minimally invasive surgery.

4.3. Biomedical Imaging. Numerous applications exist in the medical area for integrating medical imaging modalities with micro/nano robots. Micro/nano robots are useful as carriers for accessing the lesion site and release medications since they may penetrate regions of the body that are not

Table 4. Different tYpes of Nanomaterials Used in Minimally Invasive Surgery, Fabrication Method, and Location of Targeted Site

S. no	Nanomaterial	Fabrication method	Location of targeted site	Refs
1	Gold nanoparticles	CVD	Tumors	201
2	Silver nanoparticles	Laser ablation	Blood vessels	202
3	Quantum dots	Molecular beam epitaxy	Brain	203
4	Carbon nanotubes	Arc discharge method	Lungs	204
5	Iron oxide	Coprecipitation	Liver	205
6	Silica nanoparticles	Sol−gel method	Kidney	206
7	Zinc oxide	Hydrothermal synthesis	Pancreas	207
8	Polymeric micelles	Self-assembly	Heart	208
9	Liposomes	Thin film hydration	Colon	209
10	Dendrimers	Divergent/convergent synthesis	Bladder	210

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accessible with catheters or other tools. Micro/nano robot placement, tracking, and guiding may be facilitated by medical imaging technology's reliable and timely pictures. Medical imaging technology may be of considerable assistance in precisely locating and controlling micro/nanorobots inserted into the body. Precision medicine is one of the many medical specialties where the two work well together.[211] Zhang's group reported on the in vivo medical resonance imaging (MRI) tracking of a swarm of microalgae-based helical robots inside the subcutaneous tissues of a mouse stomach, as one sample example depicted in Figure 14.[169]

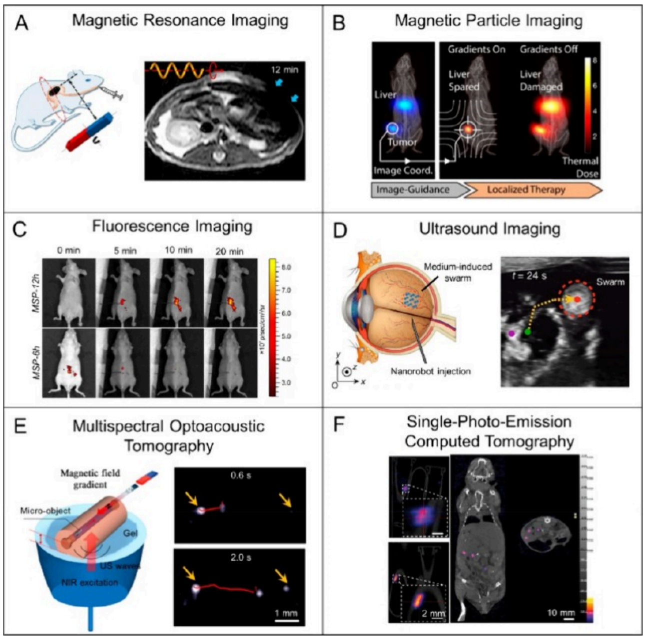

Figure 14. (A) MRI of microrobot swarms in rat stomach tissue after magnetic actuation over time. Reproduced with permission from ref 169. Copyright 2017, Science Robotics. (B) The image-guided theranostic platform combining magnetic particle imaging and localized hyperthermia in a U87MG xenograft mouse shows superparamagnetic nano robots in the liver and tumor. Reproduced with permission from ref 212. Copyright 2018 ACS. (C) In vivo fluorescence of spirulina-based MagRobots in mouse intraperitoneal cavity over time. Reproduced with permission from ref 169. Copyright 2017, Science Robotics. (D) Ultrasound tracking of MagRobot swarm generation in a bovine eyeball. Reproduced with permission from ref 213. Copyright 2019 Nature. (E) Real-time tracking of microrobots in phantoms using multispectral optoacoustic tomography actuated by a permanent magnet. Reproduced with permission from ref 214. Copyright 2019 ACS. (F) SPECT images of radiolabeled microrobots in an Eppendorf tube and mice. Reproduced with permission from ref 215. Copyright 2019 Wiley-VCH.

The ability to monitor individuals or groups is a crucial clinical advantage of medical micro/nano robots. They can be readily detected and directed throughout the body, and even transmit signals to promote trigger release, therefore their possibility for medical imaging is not to be discounted. For instance, at a penetration depth of 2 mm, the micro/nanorobot is readily discernible in the in vivo environment. Its real-time location in a mouse vein is tracked by optical coherence tomography imaging, which provides information on the micro/nano robot's movement in vivo.[216] An alternative approach involves creating live intestinal micro/nanorobots that are controlled drug carriers and imaging contrast agents using PACT guidance. The micro/nanorobot is equipped with a multilayer functional coating; the Au layer amplifies optical absorption and boosts conveyance rate; the gelatin hydrogel layer increases the load capacity of various operational components; and the polyethene layer preserves the robot's geometry during motion. Real-time observations of the movement of micro/nanorobot capsules to their designated location are possible due to their excellent space-time resolution, noninvasiveness, outstanding molecular contrast, and superior penetration.[181]

Furthermore, Iacovacci et al.[215] suggested a therapeutic microrobot powered by magnetism and composed of double-layer hydrogels that react thermally. Within the hydrogel frame of the little robot are radioactive chemicals and magnetic nanoparticles that serve as imaging agents. Whereas imaging agents can track micro/nanorobots inside the body, magnetic nanoparticles may be utilized to externally control and initiate shape modifications of microdevices. After the mouse underwent epithelial imaging, the micro/nanorobots were found in the belly of the animal using single-photon emission tomography scanning. The research laid the groundwork for the subsequent creation of single-robot closed-loop control by demonstrating a first: that hydrogel structures as small as 100 μm in diameter may be used to image a single micro/nanorobot. Micro/nanorobots can also use magnetic resonance imaging in addition to photoacoustic. Using a simple immersion method, the spiral microcones robot created from spirulina microalgae in magnetite suspension possesses super-smooth magnetism. Given the benefits of in vivo fluorescence imaging, the spiral robot demonstrated perfect cytotoxicity, natural deterioration, inherent fluorescence, and magnetic resonance signals without modifying its surface. It can track noninvasively in deep organs or superficial tissues using autologous fluorescence and magnetic resonance imaging, and it can traverse steadily in a range of biological fluids. Mice were injected subcutaneously and abdominally, and magnetic resonance imaging revealed the presence of a micro/nanorobot group in their stomachs.[169] A particular kind of biohybrid magnetite microrobot that is image-able, biodegradable, and specifically cytotoxic to cancer cells has been reported by Yan et al. MNPs are used in a simple, one-step fabrication process that is economical and appropriate for large-scale production. According to their findings, the synthesized biohybrid microagent may be monitored noninvasively by autofluorescence/MR imaging in either deep organs or superficial tissues and can navigate robustly in various biofluids.[169] Table 5 shows the nanomaterials used in biomedical imaging.

In addition, numerous sophisticated tracking and imaging methods have shown their value in biomedical applications within the framework of micro/nanorobotics. Endoscopy provides a minimally invasive method for real-time tracking and visualization of nanorobots inside luminal structures and internal organs. Especially in gastrointestinal or vascular applications, it makes it easier to precisely track their movements and interactions with biological tissues.[242] Dynamic X-ray-based tracking made possible by fluoroscopic imaging allows the real-time visualization of nano robots moving through the body. This method works particularly well for interventional operations like minimally invasive surgery or focused drug distribution. Furthermore, by observing blood flow and tissue perfusion at the microvascular level, laser speckle imaging has been investigated for tracking nanorobots.[243] This technique is a promising tool for tracking the

Table 5. Different Types of Nanomaterials Used in Minimal Biomedical Imaging, Fabrication Method, Modality, and Application

S. no	Nanomaterial	Fabrication method	Name of modalities	Application	Refs
1	Carbon nanotubes	CVD	MRI	Target drug delivery	217, 218
2	Carbon nano tubes	CVD	MRI	Diagnostic imaging	219, 220
3	Gold nano particles	Self-assembly	Computer tomography (CT)	Photo thermal therapy	96, 220, 221, 222
4	Lipid based nano particles	Microfluidic assembly	Fluoroscopic imaging	Gene delivery	223, 224
5	Silicon nano wires	Electrochemical synthesis	Ultrasonography (USG)	Bio sensing	225, 226
6	Silicon, gold nano wires	Self-assembly, template assisted fabrication	PACT	Drug delivery and deep imaging	219, 227
7	Carbon nano materials	CVD	Positron emission tomography (PET scan)	Radiotherapeutics	228
8	Gold or bismuth nano particles	Citrate reduction method	CT scan	Contrast enhanced imaging	229, 230
9	Carbon nano wires	CVD	PET scan	Cancer diagnosis	231, 232
10	Porous gold nano wires	Electro chemical reduction	USG	Drug delivery	233, 234
11.	Iron oxide nano particles	Chemical precipitation	MRI	Therapeutics in cancer	235, 236
12	Single walled carbon nano tubes (SWNTS)	CVD	Near infrared fluorescence/positron emission tomography scan (PET/NIRF imaging)	Tumor target imaging	227, 237
13	Colloidal gold nanoparticles	Citrate reduction	CT	Nano diagnostics	238, 229
14	Meso porous silica nano materials	Electro chemical reduction	Fluoroscopy imaging	Drug delivery	237, 239
15	Gold nano particles	Chemical reduction	CT	Angiogenesis monitoring of tumors	240
16	CNT	CVD	MRI	Active therapy triggering	241

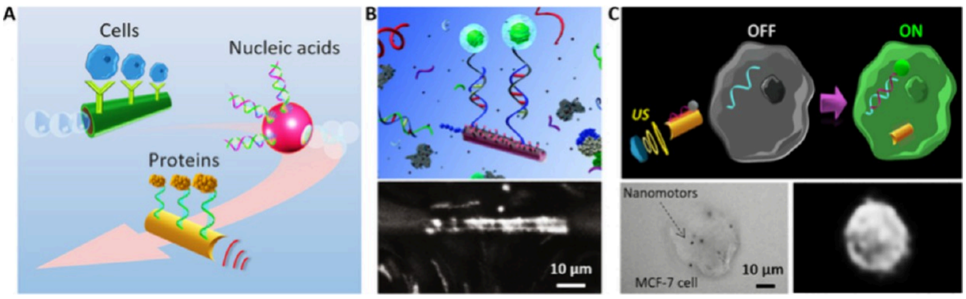

Figure 15. (A) Equipping micro/nano robots with various bioreceptors to enable them to sense target analytes, such as proteins, nucleic acids, and cells. (B) Microrockets functionalized with ssDNA for nucleic acid separation and selective hybridization. (Adapted with permission from ref 246. Copyright 2011 American Chemical Society.) (C) Ultrasound-propelled nanomotors for the specific intracellular detection of miRNA in intact cancer cells. (Adapted with permission from ref 247. Copyright 2015 American Chemical Society.)

therapeutic effects of nanorobotic therapies since it can record dynamic physiological changes in real-time. The potential for accurate tracking, superior control, and better clinical results in cutting-edge medical applications is increased when these imaging modalities are incorporated into micro/nanorobotics research.[244]

4.4. Biosensing. Medical diagnosis may be possible thanks to the ability of micro/nanorobots to engage with specific receptors when mixed with fluids. Micro/nano robots provide precise pretreatment analysis for the treatment of diseases by specifically identifying various entities such as proteins, cells, bacterial toxins, metal ions, etc. Excessive ion concentration may be avoided by accurately detecting metal ions in the blood to safeguard human health. For instance, a novel class of magnetic mesoporous silica/Au/tetra ethylene pentamidine/heparin/ZnS·Mn/MMS/ZM/Au/T/Hep) micromotors can identify and eliminate blood copper excess directly. Tetra methylene pentaamine (TEPA) was adsorbable on the micro/nanorobot, demonstrating strong adsorption capacity and a short processing time for Cu^{2+}. The solute was distributed more quickly and was thoroughly mixed with the target. The microtube made of magnetic meconium silica offered a rich load area for the adsorption of TEPA. A remarkable 74.1% of blood copper ions were removed because of the combined effects of the mesoporous structure, adsorption function group, and excellent mobility. Simultaneously, after being separated from the blood, the micro/nanorobot used variations in fluorescence signals to specifically monitor the blood's copper ion content. Micro/nanorobot motion may be accomplished autonomously without requiring ultrasound or stirring, completing the self-mixing process. Once Cu^{2+} is extracted from the blood, the magnetic Fe_3O_4 allows the micro/nanorobot to split apart fast. The findings of this study addressed issues with lengthy treatment cycles, high costs, diagnosing and treating patients separately, and the limited therapeutic efficacy of conventional treatment approaches. They also offered evidence for integrating toxin detection and elimination in the blood.[245] Figure 15 shows the Strategies and examples of micro/nanorobots for sensing.

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Table 6. Different Types of Nanomaterials, Fabrication Methods, and Biosensing Element

S. no	Nanomaterial	Fabrication method	Biosensing element	Refs
1	Gold nanoparticle	Photoelectrochemical	Glucose level	248
2	Quantum dots with gold nanoparticles	Top-down approach	DNA-modifying enzymes	249
3	Carbon nanotubes	Bottom up approach	Cancer biomarkers	250
4	Silicon nanowires	Chemical etching	Detect dopamine and serotonin (ST) neurotransmitters	251
5	Magnetic nanoparticle	Electrochemical	Analyze carcinoembryonic antigen (N/A)	252
6	ZnO nanostructure	Hydrothermal synthesis	Sensing biomolecules like glucose, cholesterol, urea, and uric acid	253
7	Silver nanowires	Electrochemical	Glucose level	254
8	Palladium nanoparticles	Ultrasonic method	Determination of glucose	255
9	Lipid nanoparticles	Thin film hydration	Cholesterol level	
10	Chitosan (CHIT)-based nanofibers	Electrochemical	Detection of monosodium glutamate	256
11	AuNp	Physical freeze-drying technology	Virus particles detection	257
12	Ag nanoclusters (AgNCs)	Fluorescent method	Viral nucleic acids of SARS-CoV-2, HIV-1, and influenza virus	258
13	Fe_3O_4@SiO_2 core−shell nanorods	Chemical colorimetry	Biochemical detection technique is the enzyme-linked immunosorbent assay (ELISA)	259
14	Gold nanowires	Origami technique	Detection of cancer cells	260
15	Ag−AuNRs microrobots	Magnetic	SARS-CoV-2 virus	261

When used as an implanted mobile sensor, a micro robot may track certain biochemical markers and wirelessly communicate this spatiotemporal data to external sources. This data may be assessed via medical imaging techniques or biochemical signals generated as nano robot byproducts. This may provide ongoing health monitoring and prompt detection of developing diseases. It has been shown that featured surfaces, nanoparticles, and shape-changing polymers are viable options for implanted biosensors that react to intrinsic signals. In vivo, nucleic acid detection, for instance, is made easier by long-term durability and near contact with the targeted tissue as opposed to laborious traditional procedures.[168] Yang et al. use the specific fluorescence responses that the fluorescent magnetic spore-based micro robot (FMSM), a microscale mobile sensing instrument, has to effectively detect C. diff toxins.[226] Table 6 shows the nanomaterials used in biosensing.

4.5. Tissue Generation and Cancer Therapy. The goal of tissue regeneration, a dynamic and complex process in regenerative medicine, is to restore the structure and functions of tissues through a sequence of cellular and molecular events. With the ultimate goal of enhancing patient outcomes and quality of life, the developments in tissue regeneration show great promise for treating various medical ailments, from degenerative diseases to severe injuries. Nevertheless, it has certain drawbacks, such as the need for invasive surgical procedures, imprecise targeting, and adverse consequences such as local tissue damage. These problems might cause discomfort, hinder postoperative recovery, and affect how well a treatment works. Researchers have proposed using miniature synthetic micro/nanomotors to achieve precise therapeutic interventions with less invasiveness and no unfavorable side effects. These tools are intended to provide a minimally invasive platform for transforming external energy into regeneration signals or accurately distribute stem cells to the injured tissues. In this regard, nano/microrobots have special qualities that make them suitable for tissue regeneration applications, such as their small size, high precision, and efficiency.[262]

To treat osteoarthritis (OA), Li et al. utilized decellularised cartilage extracellular matrix (ECM) functionalized with Fe_3O_4 nanoparticles (by dip coating) as a scaffold for the transport of human bone marrow mesenchymal stem cells (MSCs). The scaffold's porous structure offered a suitable area for cell seeding. Within 12 h of arriving at their intended location, MSCs were freed from the scaffold and began to proliferate. Additionally, the scaffold deteriorated 20 days after cultivation. In vivo test results demonstrated that this formulation efficiently restored knee joint function in 3 weeks, emphasizing the significance of functional cells and microenvironments.[263]

A porous chrysanthemum pollen shell was coated on iron nanoparticles to create CDBMRs by Liu et al. In an external magnetic field with magnetic velocity and input frequency dependency, they showed targeting ability by increasing magnetic frequency until critical frequency velocity increased while passing this critical point decreased velocity. This magnetic characteristic allowed an external magnetic field to convey this microrobot to its objective. The target site used time-varying magnetic fields to enter cells with microrobots. Cell perforation caused by burr-like micro spikes on this microrobot caused cell death. Its hollow shape facilitated therapeutic chemical loading and release at the target spot. The porous, burr-like microstructure makes it suited for cell adhesion and transport. An external magnetic field electrically stimulated cells to induce osteogenic differentiation and increase bone formation, proving tissue regeneration.[264] In Choi et al. research, a biohybrid microrobot was built by integrating chitosan-heparin nano complex (NC) into the *Chlamydomonas reinhardtii* (*C. reinhardtii*) microalgae for speeding wound healing. It can permeate through the blood clots and produce oxygen in the microenvironment of diabetic wounds via photosynthesis that alleviates hypoxic conditions of wound.[265]

The high death rate and the dearth of efficient diagnostic and therapeutic techniques make cancer one of the most untreatable diseases. There are previously unheard-of possibilities to create MNR-based cancer diagnostic platforms thanks to micro- and nanorobot-assisted sensing, imaging, and therapy developments. In contrast to regular nanoparticles, which move in biofluids in a Brownian motion, MNRs effectively self-propel to overcome viscous resistance in an ultralow Reynolds number ($Re \ll 1$) environment. This special motility ability has driven the advanced design and functionalization of MNRs

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as a foundation for next-generation cancer therapy platforms, which holds promise for better therapeutic drug penetration and accurate distribution. Additional research is being done to enable the promising cancer-related uses of MNRs through enhanced barrier penetration, imaging-guided operation, and biosensing.[266] Researchers have established strict requirements for the core components of nanorobots' designs to guarantee that they can successfully eradicate cancer cells from the human body. Notably, medical nanorobots are still in their early phases of development and have not yet been extensively used in therapeutic procedures. These devices ' precise composition and structure can vary significantly depending on their intended use and the safety, effectiveness, and scalability requirements.[244]

As nanotechnology advances, drug delivery has emerged as one of the most common uses of nanorobots in cancer treatment. Small sizes, high specific surface area/internal void volumes, and exceptional physicochemical properties are some of the obvious characteristics of the nanodrug carriers that have been produced. Generally speaking, an ideal nanorobot has certain unique abilities like propulsion, tissue penetration, controlled navigation, cargo transportation, and release.[267,268] The majority of drug delivery nanocarriers currently on the market rely on systemic circulation in addition to the constraints of passive mass transport. They also lack the self-driving force and navigational capabilities necessary for targeted distribution and tissue penetration. According to reports, several antitumor treatments employing nanorobots allow for accurate therapeutic drug delivery to specific tumor regions.[269]

Using a biological template approach, Xie et al. converted pine pollen into a magnetic microrobot, vacuum-loaded doxorubicin into the robot's natural cavity, and then utilized the microrobot's cooperative behavior to transfer medications through the PDMS narrow channels. The seminatural magnetic microrobot employs its magnetic rotor inside the cavity to create fluid and release the payload drug molecules to kill cancer cells once they reach their internal space.[270] Felfoul et al. discovered that drug-loaded nanoliposomes may be effectively delivered to hypoxic areas of the tumor utilizing biohybrid microrobots (based on Magnetococcus marinus strain MC-1) powered by an external magnetic field.[271] Garcia et al. demonstrated that near-infrared light-triggered medication release may be achieved using ultrasound-driven nanowire motors to deliver drugs quickly to HeLa cancer cells. In this instance, it was discovered that within 15 min of exposure to NIR light, 38% of the DOX payload medication was released inside cancer cells. He et al. used layer-by-layer self-assembly technology to construct a tubular multilayer microrobot. These microrobots can deliver doxorubicin to cancer cells at up to 68 μm/second thanks to a combination of bubble driving and magnetic field guidance.[272] When subjected to NIR light, Xuan et al. demonstrated that a nanorobot system could move in a certain direction. Au half-nanoshells could create a thermal gradient under NIR irradiation, supplying self-heating energy to overcome Brownian motion. The immunological ability of the nanorobots to preferentially engage cancer cells was conferred by the wrapping of the Janus mesoporous silica nanomotor (MPCM@JMSNMs), which was powered by NIR light and cloaked in macrophage cell membranes.[273]

4.6. Biohybrid Microrobots. The concept of "biohybrid micro and nanorobots" describes functional micro- and nanorobots that combine artificial (such as inorganic or polymer particles) and biological (such as DNA, enzymes, cytomembranes, and cells) components.[93] Micro- and nanorobots that combine biological and artificial components are known as biohybrids. The benefits of onboard actuation, sensing, control, and execution of various medicinal activities, including single-cell manipulation, cell microsurgery, and targeted drug delivery, can be possessed by them.[274] A study by Maier et al. noted that by hybridizing complementary DNA strands, the DNA flagella were affixed to magnetic iron oxide microparticles (1 μm), creating biohybrid magnetic microrobots that rotated perpendicular to the direction of swimming.[275]

DNA nanorobots have demonstrated significant promise for precision cancer (immuno) treatment, vaccination, and tumor-targeted medication delivery.[276,277] Leukocytes have been designed into biohybrid microrobots because of their inherent qualities and functions, such as chemotaxis and secretion activity. Immunocyte-based microrobots can target diseased tissues on their own, actively deliver therapeutic drugs, and release the drugs locally.[278] To achieve NIR-responsive precision medication release at tumor locations in a spatiotemporally regulated way, Dogan et al. study reported that dual-targeting macrophage-based microrobots were created with controllability by innate chemotaxis and external magnetic field.[279] Tubular and helical sperm robots, which have emerged from the combination of synthetic micro- and nanomaterials with spermatozoa, have enormous potential for use in biomedical and engineering domains, including aiding artificial insemination and delivering drugs or genes.[280]

It has been shown that attaching folate ligands to the surface of RBC vesicles through the FR interaction improves the effectiveness of tumor magnetic targeting and makes it easier to deliver specific medications to ovarian cancer cells.[281,282] Multiple peritrichous flagella seen in *Escherichia coli* can be bioengineered into microrobots for noninvasive, targeted distribution in physiological settings.[283,284] According to a study by Ouajdi, oxygen-depleted hypoxic areas of the tumor are typically resistant to treatment. This suggests that drug-loaded nanoliposomes can be delivered into hypoxic areas of the tumor using the magneto-aerotactic migration behavior of magnetotactic bacteria, specifically Magnetococcus marinus strain MC-14.[285] In a revolutionary development, Sylvain Martel and associates have used magnetically directed nanorobotic agents derived from Magnetococcus marinus MC-1 cells to help deliver drug-loaded nanoliposomes into hypoxic tumor areas. A biohybrid microrobot was created in a study by Choi et al. by introducing chitosan-heparin nano complex (NC) into *Chlamydomonas reinhardtii* (*C. reinhardtii*) microalgae to speed up wound healing.[286] The results of a study by Gundersen et al. showed that the creation of biohybrid microrobots based on guidable mesenchymal stem cells (MSCs) is compatible with their biological and therapeutic roles. Therefore, MSC-based biohybrid microrobots offer a new approach to delivering gene treatments to tumors and other disorders.[287] A study by Gong et al. showed the enormous potential of magnetic biohybrid microrobot multimers (BMMs) based on Chlorella (Ch.) for targeted medicine administration and suggested a unique approach.[288]

A study by Wang et al. suggested a simple method for producing magnetic microrobots with several uses in large quantities by employing Spirulina (Sp.) as a biotemplate and depositing Fe_3O_4 and Au nanoparticles. The microrobots are a promising and effective platform for drug loading, targeted

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Table 7. Biohybrid Microrobot Materials, Size, and Applications

S. no.	Material	Size	Application	Refs
1	DNA flagella + magnetic iron oxide	1 μm	Tumor-targeted drug delivery, vaccination for precision cancer (immune) therapy	275−277
2	Macrophages + silica particles	60−500 μm	Enhances the ability to target tumors and fight them by magnetically activating and gathering many macrophages.	279
3	Neutrophils + silica particles	5−20 μm	Active drug delivery of drugs and slow release into malignant gliomas	291, 292
4	Sperm cell + iron oxide	50−100 μm	Artificial insemination, drug and gene delivery	280
5	Erythrocytes + gold nanowires/magnetic mesoporous silica nanoparticles	6−8 μm	Tumor cell-specific drug delivery and prolonged drug circulation in the bloodstream	281, 282
6	*Escherichia coli* + gold particles	1−10 μm	Transportation of drug-loaded nanoliposomes into hypoxic tumor lesions	283, 284
7.	Magnetococcus various strains + magnetic iron oxide crystals	1−2 μm	Transportation of drug-loaded nanoliposomes into hypoxic tumor regions	285
8	*Chlamydomonas reinhardtii* + chitosan heparin nanocomplex	5−15 μm	Acceleration wound healing, especially chronic wounds	286
9	Mesenchymal stem cells + magnetic nanoparticles	1−5 μm	Anticancer therapy (target chemotherapeutic drug delivery)	287
10	Chlorella + iron oxide nanoparticles	3−5 μm	Target drug delivery (targeted anticancer therapy)	288
11	Spirulina species + iron oxide, gold nanoparticles	5−20 μm	Drug loading, targeted delivery, chemo photothermal therapy	289
12	Thalassiosira weissflagii diatom + Fe_3O_4	20 nm−2 μm	Combination therapy of glioblastoma	293
13	Spirulina microalgae + Fe_3O_4 nanoparticles	5−20 μm	Image-guided treatment (fluorescence compound and contrast agent for MRI)	284
14	Spirulina plantesis + Fe3O4 nanoparticles	5−20 μm	Cancer multimodal imaging and therapy	294
15	Motile algae + red cell membrane-coated nanoparticles	100 μm	Transportation of anticancer drugs to the targeted lung metastases	295

delivery, and chemo-photo thermal therapy because of their fascinating characteristics.[289] Even though these robots have a lot of potential, issues, including biocompatibility, power supply, manufacturing processes, and control mechanisms, still need to be resolved. A major challenge is ensuring these biohybrid systems coexist peacefully with biological beings without eliciting negative reactions or rejections.[290] Table 7 describes the biohybrid micro robots with materials, size and their applications used.

5. CHALLENGES AND OPPORTUNITIES

In the last ten years, micro/nanorobots have become a unique and adaptable framework for combining the benefits of robotic sciences with nanotechnologies. Thus, various design concepts and propulsion systems have been used to create extremely powerful and specialized micro/nanorobots. We are only beginning to explore the potential of micro/nanorobots in addressing healthcare challenges. Filling in the knowledge gaps in nanorobotics could significantly influence various medical fields. Enough efforts and developments are needed to fully realize the potential of these tiny robots for sophisticated surgeries in hitherto inaccessible body areas. With their high mobility, deformable structure, adaptive and sustainable operation, precise control, group behavior with swarm intelligence, sophisticated functions, and even the ability to self-evolve and self-replicate, future micro/nanorobots must emulate the natural intelligence of their biological counterparts.[173]

A major challenge is finding novel energy sources for biocompatible, long-term, autonomous in vivo functioning. New alternative fuels and propulsion mechanisms are required for safe and sustainable operation in the human body, even though many chemical fuels and external stimuli have been investigated for nanoscale locomotion in aqueous conditions.[296] Due to their reliance on hydrogen peroxide fuel, most catalytic micromotors are limited to in vitro applications. The short lifespan of micromotors that run on active material propellants (such as magnesium, zinc, aluminum, or calcium carbonate) is caused by the propellant being used up quickly during propulsion. According to recent research, body fluid components like blood glucose or urea may be used to power enzyme-functionalized nanomotors.[297,298] These enzyme-based motors' power and stability still need to be improved for practical use. While fuel-free and on-demand speed regulation is a great feature for nanoscale surgery, magnetic and acoustic nanomotors may impede autonomous therapeutic interventions.[299]

Transferring nanorobots from test tubes to living things will take a lot of work. Viscous biological fluids like stomach fluid or entire blood have already been used to illustrate the potent performance of micro/nanorobots.[300,301] Scrutiny is necessary when operating these tiny devices in human tissues and organs, which impose larger impediments to motion.[302] Because the functioning and intelligence of small robots mostly depend on their materials and surface qualities, designing robots to accomplish tasks at the nanoscale scale is effectively a materials science or surface science problem. Biomedical nanorobots are made for delicate tissues, fluctuating physiological circumstances, and unexpected biological events. Thus, various smart materials, biological, responsive, or soft, are highly wanted to offer the actuation and multifunctionality required while preventing permanent robotic faults in intricate bodily systems relevant to human physiology. According to a recent publication, the rotational trap stiffness of a revolving magnetic microrobot can be adjusted to prevent macrophage absorption.[303]

On the other hand, combining artificial nanomachines with organic biological materials can reduce the negative impacts of immune evasion and biofouling in complicated biological fluids, improving mobility and longevity in these environments.[304] Responsive materials are greatly desired to build reconfigurable nanorobots that can operate adaptively under quickly changing settings. To ensure mobility and mechanical compliance with the human body and tissues, nanorobots must

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also be soft and malleable.[305,306] They ought to eventually be composed of temporary, biodegradable components that vanish after serving their purpose.[307] The development of novel techniques for synthesis and fabrication, including three-dimensional nano printing, is necessary to produce biomedical nanorobots on a large scale, with excellent quality and at a reasonable cost. It will therefore be possible to advance nano robots to a new level through innovative materials and construction methods. Biomedical nano robots are anticipated to collaborate, with thousands of units moving simultaneously and autonomously to target the illness site. Multiple nano robots working in unison could be utilized to carry out tasks that are not feasible for a single robot, like large-scale detoxification procedures or the efficient distribution of medicinal payloads. While individual navigation and group behavior of nano robots have been studied, it is a difficult problem to duplicate the group communication and synchronized coordination of natural intelligence, from one to many. Enhancing the precision treatment capability of nano robots requires advancing their swarm intelligence toward machine learning and group motion planning at the nanoscale. The authors have discussed challenges and opportunities related biocompatibility, control and navigation, delivery and targeting, safety and ethical consideration separately.

5.1. Biocompatibility. Since the complexity of the interactions between biological matter and the materials used to build nano robots varies and can cause the nano robots' surface characteristics to change depending on their environment, researchers have not fully understood the mechanisms underlying the interactions between nano robots and living systems.[308] In a brief post, Kostarelos discussed the necessity for nano robots to be toxicologically inert, biodegradable, or able to be evacuated from the body. It should be noted that this mostly discusses human toxicity rather than potential environmental consequences that might arise after the nano robots have been ejected from the body.[309] The application of nano robots for environmental sensing, monitoring, and cleanup was discussed by Gao and Wang. "To prevent potential adverse environmental impacts, the potential toxicity of micro/nanoscale motors needs to be evaluated," they remark. Though they anticipate a broad application of nanorobots in the environment, they do not offer any concrete suggestions on achieving that.

A study on DNA nano robots and their compatibility with higher organisms' immune systems was conducted by Surana et al. they observe that although DNA is a naturally occurring biopolymer, when it is present in the wrong location at the wrong time, it can cause a severe inflammatory response. As a result, alien, "nonself" DNA from other organisms can be damaging and immunogenic. They claimed, therefore, that it is critical to consider the different cellular and systemic reactions that such DNA designs can provoke, reactions that are probably specie specific. These factors serve two purposes: they protect the organism in question from the DNA nano robot while also ensuring that the nano robot performs its intended medicinal function in cells. Once more, human toxicological reactions are the main focus instead of environmental toxicity.[310] The safety of the nano robot was evaluated in the work by Li et al.[311] concerning the DNA nanosheet/tubular nano robot. At relevant concentrations, it was shown that the nanorobots did not cause any thrombi or enhanced blood coagulation in nontumor-bearing animals. Furthermore, no cytotoxic or immunological reactions were seen. Additionally, they did not affect blood coagulation or thrombi in Bama miniature pigs, an animal whose anatomy and physiology are similar to that of humans. These studies are restricted to effects on human toxicity, even though they offer a preliminary hint that such nano robots might be safe.

In addition, numerous other factors need to be considered when working with nano robots, including as the material, size, form, surface coating, actuation and sensing mechanisms employed, and the working environment in which the nano robot is operating.[312] Although efforts have been made to identify potential targets such as the lung, liver, heart, and brain as well as key entrance channels such as the lung, gut, and maybe skin, the discovery of hazards associated with the usage of nano robots in the human body is still in its early stages.[313]

The degree of toxicity may vary in severity depending on the mechanism's design, the material employed, the driving and sensing systems put in place, and the location of deposition within the human body.[314] As a result, to preserve clinical significance, toxicity data is displayed through a system-based methodology that centers on targets related to the liver, neurological system, lung, and skin that are thoroughly covered in.[315]

5.2. Control and Navigation. Control is the capacity to direct and govern the behaviors and actions of nano robots, including their contact with biological targets, propulsion, and directionality and the capacity to steer nano robots through intricate biological environments such as blood arteries, tissues, or organs to deliver them to specific target places is known as navigation. A nano robot's ability to move and function depends on its driving components; passive drive and active drive are the two types of driving modes available.[316] While active drive uses an onboard molecular motor, electric nanomotor, pumps, or a membrane to power the nano robot, the former is used at bodily entry and in nanorobot control.[317] Since energy is lost when moving, running, and transmitting data, the task requires a sufficient energy supply, which goes against the nano robot size constraint. Micro-chemical cells and its transformed versions, such as fuel cells, ATP motors, etc., are examples of internal energy sources. There are two sorts of external sources: one uses contact to dissipate energy in the form of light or current, and the other converts external energy using an onboard converter.[316]

Several attempts have been made to use motor proteins to create robotic robots that can move independently. However, the peculiarly unstable nature of proteins in various environments has limited their application.[59] Diverse forms of self-propelled micro/nanomachines, including motors, engines, robots, and swimmers, provide a wide range of applications in the medical domain. However, sensing, regulated release and administration, biocompatibility, and propulsion are regarded as major obstacles in biological applications.[318] When considering its fuel storage capacity, surface area-dependent factors like the energy dissipation rate become considerably relevant and limiting. Nano robots have been produced in a range of shapes (with spherical, helical, or asymmetric geometries) since they need to be able to harvest energy from the external environment to move. Fuel-based and fuel-free propulsion are the two categories into which propulsion mechanisms can be classified based on the driving force needed. Making these nano robots commercially viable will depend heavily on cost, scale-up, and fabrication.[318]

It is important to understand that for nano robots to perform difficult medical tasks, their complex in vivo

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environment requires precise and sophisticated control and navigation skills. Thus, another urgent problem is to investigate robust control and autonomous navigation of nano robots. Jiang et al. assert that sophisticated control techniques including path planning, localization, and mapping are crucial.[319] Nano robots can travel across complicated biological settings using efficient path planning algorithms that identify the best paths while avoiding obstacles. Nano robots can precisely navigate and carry out tasks using mapping and localization techniques, allowing them to precisely determine their position and construct detailed maps of their environment. Incorporating real-time feedback systems and machine learning algorithms further enhances these capabilities, enabling nano robots to execute tasks with extreme accuracy and adjust to dynamic changes in their surroundings. Thus, to increase the effectiveness and dependability of nano robots in biomedical applications, future research should concentrate on creating these sophisticated control systems.[320]

Inspired by the way the skeleton of the cell moves the motor protein, Henry Hess et al. used motor protein to demonstrate a nanoscale train.[321] Research by Yurke et al.[322] showed that fuels and DNA components might be used to open and close an actuator. Using DNA strands, the NC Seeman group created the first biped nano robot with a spinning motor.[323] The rotor rotates eight times per second as the ATP hydrolyzes and provides driving power and motion, thanks to the work of the Carlo Montemagno group at the University of Cornell, who used a unique substance to bind nickel ions to the ATP molecule.[324] The Alex Zettl nano robot group, which constructed the smallest synthesis engine with a diameter of 500 nm in 2003,[64] was a logical fit for cilia and flagellum. By combining sensors and imaging modalities, it is possible to monitor biological reactions and nano robot behavior in real-time, which improves navigation and control skills.

5.3. Scalability and Manufacturing. Scaling down the fabrication process of biohybrid robots while preserving their functionality and complexity can be problematic. Developing scalable manufacturing procedures is vital for practical application. One of the key issues in scalability is the translation of laboratory-scale fabrication technologies to mass-production approaches. Many biohybrid micro/nanorobots are initially produced utilizing specialized equipment and hand assembly methods which may not be suitable for large-scale manufacture. Adapting these technologies to high-throughput manufacturing environments without compromising the performance or biocompatibility of the devices is a critical problem. Moreover, integrating numerous components, including biological entities and synthetic materials, in biohybrid micro/nanorobots adds another degree of complexity to the production process.[325] Coordinating the assembly of these varied components in a controlled and reproducible manner while maintaining the functionality and biocompatibility of the final product poses a considerable challenge. Research should focus on establishing scalable, high-throughput manufacturing processes that enable for mass production without losing quality or precision. Advancements in 3D and 4D printing technologies, which allow for the precise layering of materials at the nanoscale, could alter how biohybrid robots are made. 4D printing, in particular, can produce dynamic structures that change their shape over time in response to external stimuli. This allows for developing more sophisticated robots that evolve with their surroundings.[326] Additionally promising are nanomanufacturing methods that make use of self-assembly processes. Developing biohybrid robots that can self-assemble complex nanostructures could result from self-assembling nanostructures, significantly reducing production time and costs. Another approach that might expedite the production process is investigating biofabrication methods that use biological systems such as bacterial or yeast-based systems to construct components.[327]

5.4. Delivery and Targeting. Nanorobotics in pharmaceuticals requires a thorough consideration of potential dangers and advantages before development and implementation. To protect patient safety, researchers and regulatory bodies must evaluate and control any hazards related to using nanorobots for interventions. This entails addressing issues with immunological reactions, long-term consequences, biocompatibility, and possible inadvertent interactions with biological systems. However, it is important to acknowledge the revolutionary potential of nanorobotics in the pharmaceutical industry. Precision medication administration increases therapeutic efficacy, and personalized treatment is made possible by nanorobots, and these developments have the potential to greatly benefit patient outcomes and quality of life. Thorough preclinical research and carefully planned clinical trials are necessary to minimize risks and maximize benefits. Clear communication of the capabilities and constraints of the technology is essential to establishing public confidence and encouraging moral decision-making.

It is anticipated that nano robots would advance in sophistication, gaining better medication loading capabilities and more precise drug delivery. This may result in the creation of cutting-edge treatments for a variety of illnesses, such as infectious diseases, neurological conditions, and cancer.[328] Combining nano robots with cutting-edge imaging methods and customized medicine strategies may result in highly individualized treatments that are catered to the unique illness profiles of individual patients,[329,330]. Researchers are delving into the notion of nano robot swarms, in which numerous nano robots cooperate to accomplish intricate tasks. These swarms have the potential to improve medication delivery effectiveness and facilitate the simultaneous targeting of many bodily sites.[331] Ghada Al-Hudhud has created a model and researched swarm nano robots. The experiment's outcomes demonstrate how well the swarm is coordinated when it arrives, preventing overcrowding around the target concentration emitters. Furthermore, the grouping would encompass a larger region surrounding the target site.[332]

Combining biological elements with artificial nano robots, biohybrids have the potential to provide novel capabilities by combining the advantages of both naturally occurring and artificially created systems. In addition, scientists are using biological systems as inspiration to create nano robots that are more versatile and mobile.[333] Technological developments in nanorobotics could lead to remote sensing and actuation, allowing external energy sources like light or magnetic fields to drive nanorobots. Micro/nanomotors must pass immune system clearance for in vivo applications like cargo transport and medication delivery, otherwise they risk being rejected as foreign objects. Therefore, defeating the host's immune system is essential, in addition to improving medication delivery and therapeutic efficacy.[334]

Tissue penetration is one of challenges, due to size restrictions and physiological barriers, it is still difficult for nano robots to penetrate deeply into tissues or through

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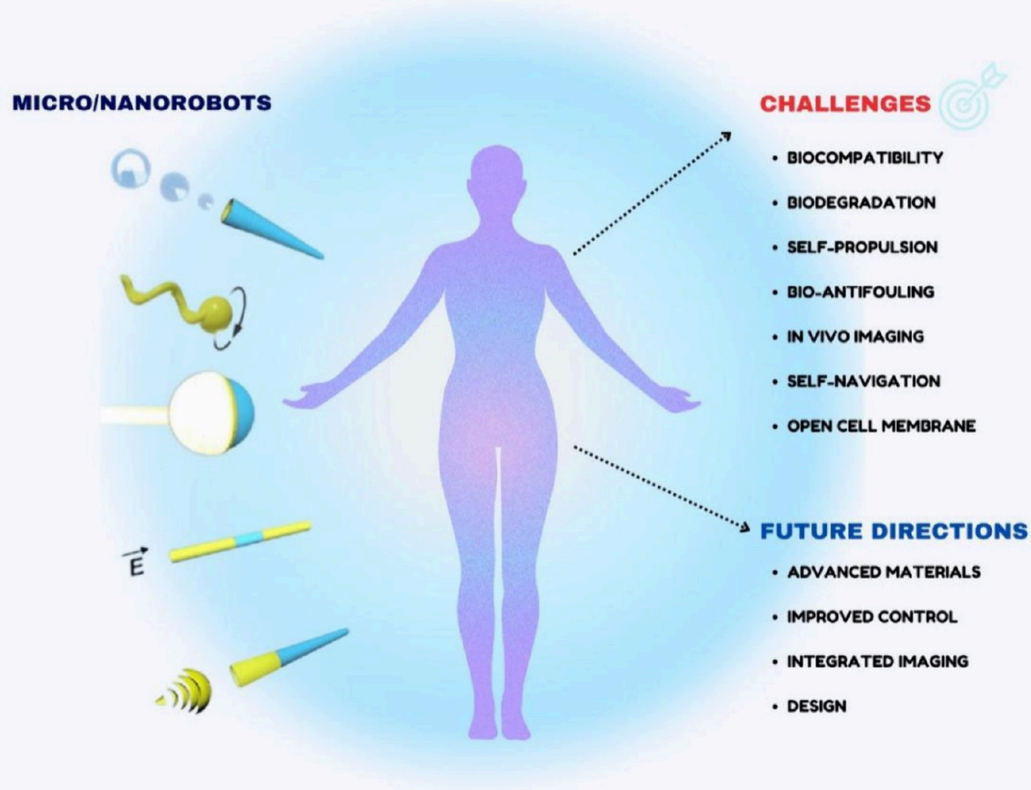

Figure 16. Limitations and future directions of micro/nanorobots

biological barriers. Wang and associates presented the first example of delivering and releasing medication by an artificially catalytic micromotor; they were able to move the drug molecule and release it to the necessary locations.[335] Controlled Release also can be difficult to maintain the appropriate medication concentrations at target areas by controlling the release kinetics of therapeutic payloads from nano robots. Clearance and Elimination: to reduce potential long-term consequences, it is important to ensure that nanorobots are cleared or degraded from the body promptly following medication administration.

5.5. Safety and Ethical Consideration.

Like any new technology, nanorobots have ethical issues that must be carefully considered. The medical field's ethical problems regarding nano robots include informed consent, privacy and autonomy, unexpected effects, equity, and access. Patients' informed consent may be needed before using nano robots in medical procedures.[336] Patients must receive sufficient information regarding the type of treatment, hazards, and advantages linked to interventions with nano robots. Patient autonomy and privacy concerns are brought up by using nanorobots in medical procedures. It should be the right of patients to make knowledgeable decisions regarding the employment of nano robotic technology in their treatment.[20]

Unintended effects or any potential unanticipated risks related to nano robot interventions must also be considered in nano robotics research. Important factors could include long-term environmental or inadvertent off-target effects on healthy cells. Also ensuring fair access to treatments utilizing nano robots is crucial. As with any new medical technology, questions concerning the accessibility and cost of medications based on nano robots may surface, possibly leading to inequities in healthcare access. Biocompatible nano robots have the potential to enhance safety profiles over traditional medicines by decreasing systemic toxicity and off-target effects.[308] Ethical standards: guidelines for developing and using nanorobots in biomedical applications should be defined to address societal concerns and ensure ethical processes. Additionally, nanorobots could facilitate patient empowerment, giving people greater control over their health and well-being by offering customized treatment options and improved illness management.[337]

Medical nano robots offer a wide range of prospective applications that are still being investigated, whereas traditional nanomaterials have previously been used in many medical and biomedical applications. To reduce side effects and increase treatment effectiveness, these applications include targeted drug delivery, in which nanorobots can precisely administer treatments to particular tissues, cells, or even subcellular sites.[338] Another possible use is in vivo diagnostics, where nanorobots are employed to monitor many physiological indicators in real time, potentially assisting in the early identification and detection of illnesses.[339] Additionally, nanorobots can completely transform regenerative medicine by aiding in tissue regeneration and repair and modifying the immune system by either boosting its antitumor activity in cancer treatments or decreasing it in autoimmune illnesses. Additionally, medical nanorobots could be used for less invasive microsurgical operations, which would enable more targeted and accurate interventions, less trauma, and quicker recovery periods.[340] It is projected that as medical nanorobots research and development progresses, their potential uses will grow even further, revolutionizing healthcare and offering novel treatment alternatives for a variety of illnesses.[341]

In conclusion, there are substantial differences between medical nanorobots and regular nanomaterials in their design

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components, targeting capabilities, power systems, biocompatibility, safety considerations, and possible uses. The development of medical nanorobots holds great promise for various innovative biomedical applications, such as cancer treatment, diagnostics, tissue repair, immune system modulation, and microsurgery, even though traditional nanomaterials have been effectively used in drug delivery applications.[342] Medical nanorobots have the potential to revolutionize medicine and offer novel treatment approaches for a range of illnesses, improving patient outcomes and the standard of healthcare as research and development in this area advance.[343] Certain nations have acknowledged the potential hazards linked with nanomaterials and have implemented legislative policies for advancing and investigating relevant nanotechnology. Marchant et al., for instance, put forth a framework centered on incremental international cooperation, in which programs about nanoresearch and development are carried out by established safety norms and where shared objectives can be decided upon and outlined as an international convention. These safety procedures provide suitable courses of action and significant safeguards against the possible harm of nanomedical technology if potential harm is discovered.[344] Figure 16 illustrates the challenges and future directions of micro/nanorobots.

6. CONCLUSIONS

This paper thoroughly overviews the outstanding advancements in using micro/nanorobots in medicine, specifically in targeted drug delivery, minimally invasive procedures, image diagnosis, and biosensors. It also covers the design, manufacture, and actuation of nanorobots. The creation and use of nanorobots in medicine will grow into a significant subject of study in the upcoming years. Researchers must investigate nano robots' biocompatibility, retention, toxicity, biodistribution, and therapeutic efficacy to fully understand their potential in this sector. Our interventions will become more effective and proactive with the advent of surgical nanorobots, targeted drug delivery, and gene therapy, enabling the treatment of diseases in currently unfeasible ways. The advantages of micro/nanorobots over traditional therapy methods are as follows: they can penetrate deep tissues, reduce trauma, and improve treatment efficiency. Research in this area is still in its early stages now, and there are still a lot of obstacles to be solved before clinical transformation occurs. Robot clusters may be able to move autonomously in the future thanks to developments in domains like artificial intelligence, and individual robot cooperation may even be made easier. These advancements are promising, particularly in complex treatments like large-scale medicine and tumor immune environment therapy. The ultimate objective is to create a micro/nanorobot system that is both safe and broadly available so that more people can receive accurate and effective medical care. In conclusion, there is still a long way to go before the full promise of micro- and nanorobots in treating human diseases is realized. There are a lot of aspects that need to be investigated, including moral issues. Over the next ten years, research into the micro/nanorobot platform will increase rapidly. Micro/nano robots could transform the medical profession if certain safety and controllability requirements are fulfilled.

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Notes

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ABBREVIATIONS

AFM Atomic Force Microscopy
SEM Scanning Electron Microscopy
CNTs Carbon Nanotubes
FIB Focused Ion Beam
MEMS Micro-Electro-Mechanical Systems
HMDS Hexamethyldisilane
CVD Chemical Vapor Deposition
PVD Physical Vapor Deposition
SiO_2 Silicon Dioxide
Si_3N_4 Silicon Nitride
TAED Template-Assisted Electrochemical Deposition
H_2O_2 Hydrogen Peroxide
Ag Silver
Au Gold
Al Aluminum
Cu Copper
Ni Nickel
O_2 Oxygen
H_2O Water
TPP Two-Photon Polymerization
PMMA Poly(methyl methacrylate)
PDMS Polymethyldisiloxane

DOX	Doxorubicin
PLGA	Poly(lactic-*co*-glycolic acid)
H_2	Hydrogen
DHM	Degradable Hyperthermia Microrobot
CMC	Carboxymethyl Cellulose
PEG	Polyethylene Glycol
MSNs	Mesoporous Silica Nanoparticles
MnO_2	Manganese Dioxide
AC	Alternating Current
DC	Direct Current
MNRs	Magnetic Nano Robots
FU	Focused Ultrasound
PFC	Perfluorocarbon
AMP	Antimicrobial Peptides
MTB	Magneto Tactic Bacteria
CLR	Clarithromycin
AuNPs	Gold Nanoparticles
PACT	Photoacoustic Computed Tomography
NIR	Near Infrared Red
ALD	Atomic Layer Deposition
PEG−PS	Poly(ethylene glycol)-*b*-polystyrene
AESOP	Automated Endoscopic System for Optimal Positioning
CNS	Central Nervous System
MRI	Medical Resonance Imaging
TEPA	Tetra Methylene Pentaamine
FMSM	Fluorescent Magnetic Spore-Based Micro Robot
OA	Osteoarthritis
ECM	Extracellular Matrix
MSCs	Mesenchymal Stem Cells

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