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Smart Drug Delivery Using Nanorobots

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Abstract

In recent years, the field of micro/nanorobot research has gained popularity. Because it can be used in targeted medication distribution, surgical procedures, disease detection, etc., it has enormous promise in medical therapy. Different from conventional medication delivery, which depends on blood flow to drug delivery to difficult-to-reach locations is made possible by the planned micro/nanorobots' ability to move independently. Micro/nanorobots were powered by either endogenous power (chemical reaction energy) or exogenous power (magnetic fields, light energy, auditory fields, electric fields, etc.). Additionally, DNA origami and cell-based micro/nanorobots lacking the capacity for independent movement were shown in this piece. Important safety and biocompatibility concerns are brought up using micro/nanorobots in drug delivery. Biomedical imaging, biosensing, minimally invasive surgery, and targeted drug delivery are some of the key nanorobot medical applications that use cutting-edge actuation technologies to improve accuracy. The study also looks at current developments in micro/nanorobot actuation and discusses key issues for the future such as biocompatibility, control, navigation, and distribution.

Keywords: Micro/nanorobot, targeted drug delivery, exogenous power, endogenous power, cell-based micro/nanorobot, DNA origami, bio imaging; biocompatibility

INTRODUCTION

One of the biggest obstacles in pharmaceutical development is still accurate drug delivery. Effective dosages of medications should ideally reach the target tissues or cells, something that conventional techniques frequently fall short. By boosting targeting medication, providing sustained or controlled release, altering tissue distribution, and improving solubility, nanotechnology provides answers. Drug delivery mainly relies upon blood circulation to guarantee efficient systemic distribution and therapeutic action when using passive or active-targeted nanocarriers [1]. One of the biggest obstacles in pharmaceutical development is still accurate drug delivery. By improving targeting, solubility, release control, and distribution all of which depend on blood circulation for efficient delivery nanotechnology provides answers [2]. With the use of external energy for mobility, micro and nanorobots allow for accurate drug administration. In contrast to conventional bloodstream dependent techniques, their autonomous movement enables access to difficult to reach locations [3].

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Precision medicine, a major area of focus in contemporary biomedicine, is advanced by the development of micro/nanorobots. These robots, developed by Professor Toshio Fukuda, allow for the manipulation and analysis of single cells. With continuous material advancements, they hold enormous promises for cellular and DNA level diagnosis and treatment, tackling illnesses at their source [4].

Richard Feynman first proposed the idea of nanorobots in 1959, emphasizing their potential for treating heart disorders. Later, Robert Freitas' studies on respirocytes made significant contributions to discipline. Numerous nanorobots for drug administration and treatment have been made possible by recent advancements in bioinformatics, robotics, nanostructuring, and medical imaging [5]. Robots, active particles, and intelligent nano/micromotors all have a lot of promises for challenging biomedical activities and lab-on-a-chip applications. With successful applications in ovarian cancer and eye treatment, designs – such as helices, walkers, cilia, and biohybrids – allow for pathogen isolation, biosensing, targeted cell transport, and minimally invasive surgery [6]. Biohybrid micro and nanorobots blend synthetic materials like inorganic or polymer particles with biological elements like DNA, enzymes, and cells. Nanorobots, an interdisciplinary technology, put together useful nanoscale devices that are frequently utilized in the diagnosis and treatment of cancer. These tiny devices, which are driven by blood flow or external sources, target illness locations and deliver medications, genes, and sensing molecules. More advanced nanorobots that can carry out a variety of medical duties are the goal of future developments, which will eventually turn them into bloodstream nanosubmarines [7].

TYPES OF NANOROBOTS

Based on Therapeutic Action

Respirocytes

Respirocytes are synthetic nanorobots that resemble red blood cells and have a diameter of about 1.4 μm. Compared to normal red blood cells, respirocytes provide 2–6 times more oxygen to bodily tissues and have the capacity to store up to 3 billion oxygen and carbon dioxide molecules. Anemia, lung disorders, hypoxia, and other respiratory disorders may be treated with these synthetic nano medical erythrocytes, which could act as universal blood substitutes [8]. To stay buoyant, a respirocyte has capillaries for carbon dioxide, oxygen, and water. To generate energy for operation, it uses specialized rotors for gas exchange and glucose intake, which combine with stored oxygen via an internal fuel cell [9].

Microbivores

Microbivores, also known as nanorobotic phagocytes, are nanorobots that mimic human white blood cells. Through phagocytosis, they capture and break down pathogens in the bloodstream, reducing them to tiny molecules. Reversible binding sites, telescoping grapples, a morcellation chamber, and a digesting chamber for waste processing are the four parts of every microbivore [10]. Like how food is digested, the primary function driving microbivore design is the digestion of organic materials. Reversible binding sites are used to capture microorganisms, telescoping grapples are used for manipulation, a morcellation chamber is used to mince the germs, and a digestion chamber breaks down the particles chemically [11].

Clottocytes

Instant hemostasis is made possible by clottocytes, which are nanorobots that act as artificial platelets. They help coagulation and are roughly 2 μm in size, just like normal platelets. Freitas (2016) described their mechanical hemostatic capabilities and showed that they worked well in a small population of medical nanorobots in vivo [12].

Pharmacytes

Pharmacytes are envisioned as active medicinal nanorobots with precision drug delivery capabilities that are 1–2 microns in size. They carry up to ~1 m^3 of pharmacological payload in onboard tanks, unlike passive nanoparticles. Molecular sorting pumps that are managed by an onboard computer are used to unload this payload. Drugs can be delivered into extracellular fluids or straight into the cytosol by a transmembrane injector, depending on the intended therapeutic outcome. Pharmacytes are eliminated from the body by natural excretory channels or nanoapheresis once their purpose is accomplished [13]. To destroy a small number of cancer cells, current chemotherapy delivers enormous doses of drugs, which can have detrimental side effects. Pharmacytes could increase treatment precision by directly administering cytocidal drugs and labeling target cells with molecular markers, which would activate the body's defense mechanisms through a process known as "phagocytic flagging" [14].

Based on Material Composition

Inorganic Nanorobots

Diamondoid Materials in Nanorobotic: Because of their great mechanical stiffness, density, and binding strength, many scientists predict that diamondoid materials like pure diamond will be used to create the most dependable and efficient medical nanorobots. Simple self-assembly techniques cannot produce complex diamondoid nanorobots. Rather, it is crucial to use positionally controlled techniques, in which the position and movement of each component are carefully regulated during production. Mechanosynthesis, which use mechanical forces to create covalent bonds and precisely construct diamondoid structures at the molecular level, is a crucial technique in this area. Gaining proficiency in mechanosynthesis is essential for mass-producing sophisticated nanorobots [15]. Diamondoid mechanosynthesis nanorobots are constructed with full positional control from the beginning to the end, claims Robert A. Freitas. Mechanosynthesis is the process of controlling covalent bonding using mechanical forces to create precise nano and microscale structures. It uses atomic-precision positioning technologies, including scanning probe microscopes (SPM), to achieve site-specific chemical synthesis by:

- applying an electric field to activate reactions in small surface areas,
- using the tip as a catalyst, or delivering mechanical energy to trigger surface reactions, the scanning tunneling microscope (STM) can manipulate atoms individually and enable chemical reactions, achieving controlled mechanosynthesis [16].

Organic Nanorobots

DNA Nanorobots: DNA nanorobots are made to deliver medications precisely to the right cells, minimizing side effects and preventing harm to healthy cells. They are dynamic DNA nanostructures that use controlled state transitions to carry out tasks. Using this method, numerous smaller complimentary staple strands are folded with huge single stranded DNA, usually the 7.3 kilobase genome of the M13 bacteriophage. Accurately moving nanoscale objects along programmable routes is a major issue. DNA is a great material for creating massive nanomechanical devices and structures. The development of one-dimensional arrays and two-dimensional DNA lattices successfully lays the groundwork for targeted DNA nanorobot delivery systems [17]. DNA icosahedra were made for imaging cells and loading payloads. Through the attachment of endocytic ligands, such as folic acid, galectin-3, and Shiga toxin B-subunit to icosahedra loaded with quantum dots, scientists were able to monitor the dynamics of endocytic pathways at the single particle level. Furthermore, loading photoresponsive polymers allowed for the targeted spatiotemporal imaging of individual endosomes in particular “Caenorhabditis elegans” cells, demonstrating their potential for precise imaging applications and real time cellular route mapping [18].

PARTS AND DESIGN OF NANOROBOTS

- *Chemical Sensor:* E-cadherin gradients can be monitored by chemical nanosensors built into nanorobots, allowing for thorough whole body patient screening. To retrieve patient data, mobile phones use electromagnetic waves to communicate with these nanorobots. Instead of floating freely in blood flow, nanorobots place themselves close to vessel walls to improve sensing. The measurement duration and detection threshold are crucial elements in chemical signaling because they establish when signals are deemed received, enhancing the responsiveness of nanorobots and the precision of biosensing inside the body [19].
- *Power Supply:* The fabrication of circuits at nanoscale scales is made possible by significant advancements in nanoelectronics employing CMOS technology, which also provide active telemetry and an efficient power supply for nanorobots. CMOS facilitates digital data flow within the body and provides dependable energy to keep nanorobots functioning. A safe and useful way to power and communicate with nanorobots is radio frequency (RF)-based telemetry, which uses an inductive coupling like RFID technology and has demonstrated successful results for patient monitoring and power transmission [20].

- *Nanocomputers:* The body's nanobots are guided and controlled by nanobot sensors, which can be electrical, biological, organic, or quantum. Gene expression is controlled by molecular-level DNA computers that are coded with four DNA bases. Obstacle detection by sensors allows for fresh trajectory planning based on tasks and the environment. Chemical contact sensors and transducers are the foundation of nanobots, and sensor interactions are assessed based on particular biomedical applications [17].
- *Data Transmission:* Continuous medical monitoring can benefit greatly from the use of sensors and devices that are implanted inside the human body to convey data about the health of patients. Depending on the use, acoustic, light, radio frequency, and chemical signals may be considered as viable options for data transfer and communication in liquid workspaces [19, 21].

MICRO/NANOROBOTS WITH AUTONOMOUS MOVEMENT ABILITY

Endogenous Power Driven Nanorobots

Chemically Driven Nanorobots

In this instance, the power source for the nanorobots will be biological fuels. Adenosine 5-triphosphate (ATP), glucose, urea, and hydrogen peroxide are a few examples of biological fuels. Endogenous power allows nanorobots to navigate autonomously by using their own fuel [22].

- *Self-Electrophoretic Nanowires:* The first self-propelling nanorobots used noble metals, like silver or platinum, to catalyze the breakdown of hydrogen peroxide. The water and oxygen created by this reaction create bubbles that move the nanorobot ahead. Bimetallic nanorobots composed of platinum and gold, on the other hand, move via self-electrophoresis as opposed to bubble propulsion. Gold serves as the cathode and platinum as the anode in these. Protons are created when hydrogen peroxide is oxidized at the platinum end and subsequently consumed at the gold end. The motion of the nanorobot is propelled by an internal electric field produced by this redox reaction, which eliminates the requirement for external forces or obvious bubble formation [23].

Understanding the motion of catalytic nanomotors at micro and nanoscale is crucial for designing new devices. There is still no consensus on their energy transduction mechanisms. We initially proposed an interfacial tension model, where oxygen from the Pt-Au nanorod's reaction with H_2O_2 disrupts local hydrogen bonding, reducing interfacial tension and generating motion toward the Pt end. In contrast, Fournier proposed a bubble-driven mechanism for nanorotors, suggesting propulsion arises from bubble formation during catalytic reactions [24].

- *Bubble Propelled Tubular Nanomotors:* Bubble-propelled chemically powered tubular microengines ("microrockets") were introduced in 2008 by Mei and Schmidt to address the limitation of catalytic nanowire robots in low ionic strength environments [25]. An L-shaped Si/Pt particle in hydrogen peroxide moves with the catalytic Pt side at the rear. Similarly, Janus particles (e.g., silica or polymer spheres half-coated with Pt) exhibit propulsion away from the Pt side. The catalytic decomposition of H_2O_2 into H_2O and O_2 creates a higher oxygen concentration on the Pt surface. Oxygen forms bubbles once it exceeds a critical nucleation radius (R_0), growing until reaching a detachment radius (Rd). Bubble detachment induces a momentum change, producing a driving force (Fdrive) that propels the particle. As long as H_2O_2 remains, bubbles continuously form and detach, maintaining motion via repeated momentum transfer [26].
- *Enzyme Powered Motors:* Enzyme-powered MNRs rely on biocatalytic reactions of widely available biocompatible fuel substrates. Therefore, they can also be powered by biocompatible bioavailable fuels, such as urease, glucose, and lipase, and are considered to be promising drug delivery platforms for tumor therapy [27].
- *Urease Powered EMNMs:* Urease-powered Janus platelet micromotors (JPL-motors) are created by asymmetrically immobilizing urease on natural platelets, enabling directional motion via asymmetric urea decomposition into ammonia and carbon dioxide, leveraging platelets' multifunctionality and biological targeting capabilities. JPL-motors generate a concentration gradient and directional flow from urea decomposition, enabling self-diffusiophoretic

propulsion. Optical tracking shows enhanced motion with increasing urea concentrations (0–200 mM) in PBS solution [28].

- *Catalase Powered EMNMs:* Catalase was encapsulated within the inner compartments of stomatocytes by adding it to extruded polymersomes, followed by PEG addition. During the polymersome shape transformation, catalase becomes trapped in the "stomach" of the stomatocytes, enabling nanomotor assembly. In the presence of H_2O_2, catalase decomposes it into water and oxygen, generating propulsion via a bubble-driven mechanism. The first use of catalase alone to power micromotors was reported by Sanchez et al., employing a roll-up technique with thin Au/Ti films and covalently bound catalase. These micromotors achieved speeds up to 8 body-lengths per second surpassing traditional Pt-based designs in efficiency and performance [29].
- *Glucose Oxidase (GOx) Based EMNM:* The liver regulates blood glucose levels through glycogenesis, glycogenolysis, and gluconeogenesis. β-cells function as glucose sensors, secreting insulin to maintain glucose homeostasis by balancing uptake, storage, and release. In 2005, Mano and Heller demonstrated the first GOx BOD powered system. GOx oxidized glucose on one fiber side, while BOD reduced oxygen on the other, generating proton flow that dragged water molecules, propelling the nanomotor in the opposite direction [30].

Exogenously Powered Driven Nanorobots

External-field-powered MNRs are fuel-free microrobots driven by light, ultrasound, electric, or magnetic fields. They offer enhanced controllability, longer operational lifespan, and reduced toxicity compared to chemical MNRs. Magnetic MNRs typically utilize alternating fields like rotating or oscillating modes for propulsion [31].

Magnetically Driven Nanorobots

For accurate non-contact manipulation, magnetic actuators can pierce tissue. Moreover, it has been proved by medical experiments that the method is harmless and without pollution to the human body under the magnetic field of low intensity.

- *Basic Propulsion Mechanisms:* The magnetic gradient and magnetic torque are always necessary for micro/nanorobots to be propelled by magnetic fields. Micro/nanorobots and other magnetic dipoles do not feel any magnetic force in a uniform magnetic field. Their magnetic dipole moment will also not produce any torque if it is in line with the field. Nevertheless, a magnetic torque acts to align the dipole moment when it is not co-linear with the field, resulting in rotation. Motion keeps going until alignment is reached. By modifying the magnetic field, this phenomenon allows for control over the robot's movement. Therefore, a spatiotemporally variable magnetic field is necessary to achieve continuous motion. Using this method, researchers may dynamically modify the external magnetic field to precisely start, halt, and guide magnetic micro/nanorobots [32].
- *Propulsion Mechanisms of Single Nanorobots:* The design of propulsion microsystems, including the architecture and form of micro and nanorobots and the magnetic field configuration, is based on a thorough understanding of the various propulsion mechanisms. Three general categories could be used to classify the translational processes of magnetic miniature machines:
  - Corkscrew motion.
  - Undulatory motion (i.e., traveling-wave motion).
  - Surface-assisted propulsion (i.e., surface walker) [33].
- *Magnetic Drive Structures Used in NRs:*
  - *Helical NRs:* Honda et al. developed a centimeter-scale magnetic helical robot in 1996 and presented a helical swimming mechanism for microrobots in low Reynolds number (Re) settings. It was able to swim effectively in viscous silicon oil when wirelessly activated by a revolving magnetic field. Later, scientists created spiral-tailed, magnetic-headed microrobots modeled after bacterial flagella. The robot rotates due to magnetic torque when it is subjected to a low-intensity rotating magnetic field. This rotating motion is converted into linear

propulsion by the helical structure, allowing for effective mobility in low-Re situations. Many contemporary magnetic microrobot designs for biomedical applications are based on this idea [34].

- *Biohybrid NRs:* Magnetic particles and biological microorganisms, such as bacterial and plant cells, are combined in biohybrid microrobots. Because of their availability, mechanical flexibility, immunosuppressive surfaces, and potent drug-carrying capabilities, red blood cells (RBCs) hold great promise as cell-based transporters. Targeted medication delivery is hampered by their micron-scale size, which restricts their capacity to travel outside blood arteries and directly reach tumor cells. Incorporating magnetic carriers can help address this difficulty by enabling external magnetic fields to direct and concentrate therapeutic chemicals to tumor locations, increasing the efficacy of solid tumor imaging and treatment [35]. Recent developments have combined synthetic micro- and nanomaterials with spermatozoa to create tubular and helical sperm robots for biomedical applications such as drug or gene delivery and artificial insemination. One study created a robotic sperm with a flexible polystyrene tail and magnetic head via electrospinning; activated by oscillating magnetic fields, it was able to move forward at a speed of up to 0.9 body lengths per second. However, the nonuniform charge distribution in sperm membranes affects their behavior and interactions [36].

- *Other Structures:* Janus particles are frequently used in spherical magnetic microrobots, which combine functional portions for targeted medication administration with magnetic components that respond to external fields. Usually, template-assisted electrochemical deposition (TAED) with anodic polycarbonate or aluminum oxide membranes is used to create rod-like MagRobots. Electrodeposition time controls the length of the nanostructure. Ferro or ferrimagnetic nanowires orient their long axis parallel to the applied magnetic field for efficient actuation after dissolving the template [33].

Electric Field Propelled Micro/Nanorobot

Through a phonon imbalance brought on by a temperature differential, coaxial carbon nanotubes (CNTs) can produce motion. This makes room temperature linear nanomotor operation possible. Furthermore, when a static electric field is generated, nanoparticles in water align with it [34].

- *Motion Modes of Electrically Controlled MNRs:* Magnetic nanorobots (MNRs) can be precisely and predictably controlled since their mobility is usually controlled by the strength and direction of the applied electric field. Common motion modes include:
  - Rolling, which is perfect for targeted drug delivery in the bloodstream because rolling MNRs can navigate vessels to reach specific sites.
  - Swimming, which is helpful for unclogging arteries or delivering drugs to specific organs or tissues.
  - Crawling, which is appropriate for wound healing or tissue exploration because it allows MNRs to move through complex structures, like the digestive tract or damaged tissue, for therapeutic or diagnostic purposes [37].

Mechanism of electric field propulsion: Alternating current (AC) electric fields are more frequently utilized to circumvent electrophoresis, even if direct current (DC) electric fields have some benefits. In AC fields, self-rectified electroosmosis and induced-charge electrophoresis (ICEP) drive diode motors and asymmetric micro/nanodevices, respectively. Asymmetric micro/nanomotors are polarized by the AC field, which causes an unequal counter-charge in the electric double layer (EDL). This produces electro-osmotic flow, which propels the motors in a direction dictated by the orientation of the AC field and the motor's design [38].

Light Energy Propelled Micro/Nanorobots

Light is perfect for microscale actuation because it is an electromagnetic wave that provides precise space-time control and customizable energy through different wavelengths and intensities. The five

primary categories of light-powered microrobots include optical tweezers-driven, photothermal, photomechanical, photochemical, and those powered by other light-based methods. A metal-semiconductor Schottky heterojunction is formed in the Au/TiO_2 structure. Electrons migrate into TiO_2 when Au absorbs light, separating holes in the valence band from electrons in the conduction band. The proton gradient produced by electrons converting H^+ in water to H_2 powers the nanomotor. In the meantime, photocatalytic treatment is aided by holes in TiO_2 that oxidize harmful tumor chemicals like glutathione. Through light-driven catalytic reactions, this dual function allows the Au nanorod/TiO_2 nanomotor to move and aid in tumor treatment [39].

Ultrasound Energy Propelled Micro/Nanorobots

Because of their dependability and biocompatibility, ultrasonic-powered nanorobots which are frequently composed of gold hold considerable potential for active targeted medication delivery. Usually, gold nanowires made via template electrodeposition are used to convey these nanomotors. The nanomotor is propelled forward by a pressure gradient created by incoming ultrasonic waves in a concave cavity created by the deposition of a copper sacrificial layer at one end [40]. Solid Au, Ni, solid Au, and nanoporous Au (PAu) segments with relative diameters of 0.45, 0.2, 0.45, and 0.63 μm comprise one design of Au nanowire motors. The PAu segment is created by selectively eliminating Ag after co-depositing Au and Ag alloy. To match length, control nanomotors lacking the PAu segment use longer Au segments. When modified with coatings, such as negatively charged poly (sodium 4-styrenesulfonate) (PSS), poly(acrylic) acid (PAA), or methyl thioglycolate (MTG), the PAu segment improves doxorubicin (DOX) loading and controlled release, hence increasing drug confinement and delivery efficiency [41].

TARGETING DRUG DELIVERY SYSTEMS

For a few years now, nanobots have been employed in cancer treatment in a variety of methods. One application of nanobots that is frequently seen is the targeted distribution of pharmaceuticals. The best treatment outcomes come from this delivery method since the drugs are superloaded into the tumor locations [42].

Passively Targeted Drug Delivery Systems

By taking advantage of tumor-induced circulatory obstacles, passive targeting improves drug delivery; nevertheless, it cannot guarantee accurate delivery to disease areas. Despite numerous systems, EPR based passive targeting frequently leads to poor drug accumulation at the target, which limits its ability to effectively treat malignancies and causes serious side effects [43].

Active Targeted Drug Delivery System

The recognition range (<0.5 nm) limits an active targeted delivery system that primarily relies on ligand-receptor mediated interaction. There are three forms of active targeting. First order targeting targets organs. Cells are the focus of second order targeting. Targeting inside the cells is known as third order targeting [44].

MICRO/NANOROBOTS FOR PRECISION SURGERY

Robotic devices increase the capabilities of surgeons and assist them overcome obstacles in complex surgeries. Robot-assisted surgery allows for very precise, flexible, and controlled minimally invasive operations. Nanodrillers, micro-grippers, and microbullets are examples of untethered micro/nanorobotic instruments that provide special surgical benefits. These devices usually consist of two robotic arms that a surgeon controls remotely from a console that has computer support and video-assisted visualization. Tetherless microgrippers improve surgical results by enabling micro and nanorobots to collect and retrieve tissue samples from difficult-to-reach body parts [45].

Micro/Nanorobot in Eye Surgery

They showed that propulsion in biological media should satisfy two primary criteria: (1) particle size and shape could be effectively passed through the macromolecular network; (2) Reduce the interaction

between propellers and biopolymer networks. The first micro-nano robot to penetrate the vitreous to reach the retina used a perfluorocarbon surface coating that reduced the interaction of the propeller with biopolymers such as collagen bundles present in the vitreous [46].

Micro/Nanorobot in Dentistry

In the field of dentistry, robotic technology provides more accurate, better, and faster treatments. Numerous robotic applications have been created such as drilling robots, orthodontic archwire-bending robots, tooth arrangement robots, and automatic tooth crown preparation robots. With the release of the LaserBot microrobot in 2013, a femtosecond laser could be precisely controlled in three dimensions for clinical tooth-crown production. Additionally, by converting trapped organic debris into innocuous vapors, nanorobotic dentifrices included in toothpaste or mouthwash can clean subgingival surfaces. These tiny gadgets are affordable, have a crawl speed of 1 to 10 microns per second, and are designed to deactivate if eaten, guaranteeing safety [47].

MICRO/NANOROBOTS IN BIOSENSING

To achieve "on-the-fly" precise biomolecular interactions, the micro/nanorobot sensing technique depends on the motility of artificial nanomotors functionalized with various bioreceptors across the sample. In unprocessed bodily fluids, these receptor-functionalized micro/nanomotors provide strong binding and targets, including proteins, nucleic acids, and cancer cells [48].

Motion-Based Sensing

One of the most important aspects of micro/nanorobot design is the ability to move in a controlled, independent manner. Motion based sensing was the first to be created and the most investigated because motion in an aquatic environment can depend on several factors (such as the concentration of chemical species). Any changes in these factors will immediately affect the motion [49].

Optical Sensing

Micro/Nanorobots for Colorimetric Sensing

Colorimetric sensing is the term for sensors that provide visual readouts, frequently with the use of fluorescent labels such as dyes, proteins, and quantum dots, or plasmonic nanoparticles (Au, Ag). There are established protocols for the widespread usage of fluorescent markers. Popularized during COVID-19, lateral flow immunoassay (LFIA) is useful for clinical diagnostics and field applications because it makes biomolecule and nucleic acid detection easy, quick, and portable [50].

Micro/Nanorobots for Surface-Enhanced Raman Spectroscopy Sensing

One effective method for detecting molecules is Raman spectroscopy (RS), especially Surface-Enhanced Raman Spectroscopy (SERS). SERS uses nanostructured metals, like Au or Ag, to increase Raman signals by several orders of magnitude [51]. Using MoS_2 flakes embellished with Au nanoparticles (10–30 nm), a microrobot was created. MoS_2 produced electron-hole pairs under 785 nm laser irradiation, which resulted in heat that drove the microrobot in the direction of light. Au nanoparticles made SERS detection possible at the same time. By acting as both propulsion and SERS substrates, the gold-modified micromotors concentrated the detection zone and raised SERS sensitivity by improving target molecule signals and building up at the irradiation site [52].

Electrochemical Sensing

Compared to other detection methods, electrochemical biosensors have several benefits, such as high sensitivity, low power consumption, compatibility with portable devices, and the capacity to evaluate complicated environmental samples. Electrochemical reactions at the contact between an electrode and an electrolyte are the basis for electrochemical sensors operation. In addition to promising novel methods, like biosensing based on nanowires or magnetic nanoparticles, electrochemical biosensors also include conventional techniques like potentiometry, voltammetry, amperometry, impedance spectroscopy, and other field effect transistor-based applications [53].

IN VIVO MICRO/NANOROBOTIC APPLICATIONS

Delivery of Therapeutic and Imaging Agents for Cancer Therapy

In contrast to passive diffusion, medical micro/nanorobotics allow for accurate and quick medication delivery, which encourages in vivo applications. Fluorouracil has been administered using magnetically guided nanorobots to inhibit the growth of tumors in mice, with external triggers guaranteeing targeted release. Like this, Listeria monocytogenes carried gene- and protein-loaded nanoparticles that allowed for the tracking of gene expression by changes in luminescence in different mouse organs [54].

Transport and Release of Cells

HeLa cells have been effectively discharged and multiplied in mice using nanorobots to transfer stem cells for tissue healing. Enteric-coated magnesium-based microrobots allow for delayed activation that is depending on thickness or pH. Biohybrid microrobots, like helical structures that guide sperm for assisted fertilization, are another intriguing in vitro use [55].

Retention of Payloads in the Gastrointestinal Tract

Mg-based drug-loaded micromotors with chitosan coating improved stomach wall binding and retention in a mouse model of *H. pylori*. According to toxicity studies, their magnesium cores dissolved when propelled in gastrointestinal fluid, allowing for self-destruction without leaving any dangerous residues. To eradicate *H. pylori*, antibiotic medication must be carefully chosen while taking resistance patterns into account [56].

Wound Healing

Compared to traditional biomaterials, which have been used for decades, nanoparticle-based wound care therapies are relatively new. Silver has been utilized in biomedical equipment since the time of the ancient Romans. Treatments based on silver nanoparticles are cheap, have no systemic toxicity, and work well against bacterial and viral infections, but they do not do much to speed up the healing process in chronic wound environments [57].

Biopsy

Because they provide for exact tissue access, nanorobotics hold potential for biopsies and surgery, complementing fewer invasive techniques. Using residual stress powered actuators within nickel rigid areas and chromium gold hinges, microgrippers (also known as μ-grippers) are smaller than traditional biopsy forceps. They may be magnetically guided and respond to thermal stimuli, providing controlled grabbing for medical and diagnostic uses [58].

CONCLUSION

The use of micro/nanorobots in pharmaceutical drug delivery is expected to revolutionize the field. Medical treatments are administered and beneficial to us. These tiny devices, which are made to function at the nanoscale, have the potential to completely transform healthcare in several ways, spurring more study and development in the area. According to reports, tailored media is made possible by micro/nanorobots. They can optimize treatment regimens, minimize side effects, and improve therapeutic outcomes by customizing drug delivery to each patient's needs. These obstacles can be overcome by micro/nanorobots, creating new opportunities for the treatment of ailments that were previously thought to be incurable. By administering several medications or therapeutic substances at once, micro/nanorobots enable multimodal therapies. To completely comprehend the biocompatibility, retention, toxicity, biodistribution, and therapeutic efficacy of nanorobots, researchers must find their potential in this field. With the development of surgical nanorobots, targeted medication delivery, and gene therapy, our interventions will become more proactive and successful, making it possible to treat diseases in ways that are today impractical. Micro/nanorobots have the following advantages over conventional therapy techniques: they can enter deep tissues, lessen trauma, and increase treatment effectiveness. Research in this field is still in its early phases, and many challenges need to be overcome before clinical change takes place. Future advancements in fields like artificial intelligence may enable robot clusters to move independently, and individual robot collaboration may even become simpler.

These developments are encouraging, especially in complicated therapies like tumor immune environment therapy and large-scale medicine. The goal is to develop a safe and widely accessible micro/nanorobot system so that more people can obtain precise and efficient medical care. In conclusion, much work needs to be done before the full potential of micro and nanorobots in the treatment of human diseases is realized. Numerous topics, including moral difficulties, require investigation.

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