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Review Article

DEVELOPMENT AND APPLICATIONS OF MICRO-AND NANOROBOTICS IN DRUG DELIVERY

ARCHANA DHYANI[1*], JYOTSNA BHATT[1], NARDEV SINGH[1], ASHISH DHYANI[2]

[1*]School of Pharmacy, Graphic Era Hill University, Dehradun, India. [2]Department of Hotel Management and Hospitality, Graphic Era (Deemed to be) University, Dehradun, India
[*]Corresponding author: Archana Dhyani; [*]Email: archana.dhyani89@gmail.com

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ABSTRACT

Micro-and nanorobotics is a new field of research that emerged from the fusion of micro/nanotechnology and robotics and has since acquired enormous importance. The advantages of micro-and nanorobots include their small dimension, lightweight, high flexibility, and high sensitivity. Micro-and nanorobots have sparked the scientific community's interest in research and opened up a broad variety of application areas, including medication delivery and disease diagnostics, due to their differences from macroscopic robots. Over the past 30 y, research on micro-and nanorobots has made major strides. This manuscript provides a detailed explanation of the development of these robots. Then, each of the primary robot components including their actuation, design, production, and control is discussed separately. Additionally, potential challenges in developing such robots are explored from the perspectives of intelligence and sensing, therapeutic applications, materials, and performance.

Keywords: Micro or nanorobots, Targeted delivery, Actuation, Design, Development

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INTRODUCTION

Therapeutic drug delivery plays an important role in the treatment or management of diseases. The treatment of any disease depends how efficiently the absorption, distribution, metabolism and elimination occurs from the body. When the drug is administered and it enters the body, there are various constraints or barriers like blood brain barrier, capillary endothelium barrier, blood placental barrier, blood retinal barrier, cerebrospinal fluid barrier and blood testis barrier. After passing through these barriers the drug has to be reached to its target site. Sometimes, there are medicines which are not able to cross these physiological barriers and the drug may get deteriorated in the body due to which the pharmacokinetic and pharmacodynamic property of the drug gets lost [1].

There are also certain side effects of the drug due to the accumulation of drug into the non-target organs and tissues. Therefore, it becomes important goal to target the drug to the desired site [2]. With the development in science and technology, the use of micro/nano robotics has gained importance in society. In today's era the, robots plays a significant role in almost each and every field. The macroscale robots can be used in industries for transportation of cargo and in manufacturing applications like welding, fitting and assembling or other similar types of operations. The macroscale robotics can be used in farms, service industry and even in hospitals. However for *in vivo* diagnosis and treatment the macroscale robotics cannot utilized because of their large size. Since the macroscale robots cannot be used due to their large size so these robots cannot be easily enters the extremely small spaces. That is why there is a need of developing micro or nano robots so that they can be utilized for targeting the specific site of the body [3]. In order to avoid all these problems, the field of micro robotics and nanorobotics opens the door for advancement in medical diagnosis and treatment. The micro or nanorobotics has unique ability to move inside the body. Similarly because of its small size it can easily perform the complex task even at small scales. Apart from this micro or nanorobotics have great flexibility, robustness, adaptability and accuracy [4, 5].

Microrobotics or nanorobotics are the small tiny devices having the capability to move, operate, sense and perform at micro or nanoscale. The size of micro or nanorobots in which the size of one dimension is at least one dimension (1000 μm=1 mm) or nanometer range (1000 nm=1 μm). Robotic approaches at micro/nanoscale offers various merits over traditional dosage form in targeting the drug to the specific site [5]. The robotic particles are driven by biomoleules (enzymes), chemical (H_2O_2), light or electromagnetic energy [6]. The mobile nature of micro/nanorobotics helps in targeting the drug to specific tissues like tumors, microcapillaries or viscous fluids such as retinovitreous chamber [7].

In recent years, micro-or nanorobotics have found usage in biomedical applications. One example is the efficient delivery of medications to certain target organs using micro or nanorobots. Since these nano or microrobots are new carriers, they can be directed to the desired location by certain inputs [8, 9]. Chang *et al.* 2017 created wire-shaped magnetoelastic nanorobots that could deliver drugs with magnetoelectric assistance and target a place using wireless magnetic fields [10].

In a different work, Douglas and his team created a DNA nanorobot that can carry compounds to cells and is controlled by an aptamer-encoded logic gate, allowing the robot to respond to a variety of signals, including cell surface markers [11]. In an another study, Ullrich and his co-workers conducted an experiment in rabbit eyes and evaluated the mobility of microrobots in various mediums. This demonstrates that invasive intraocular surgery can be performed using microrobots [12]. Due to the flexible performance and surface functionalization, micro or nanorobots can be employed for illness diagnosis. Micro or nanorobots can be used to treat cancer because they have more precise localization in tumors and cellular absorption. The capacity of these tiny particles to target cancer and tumors has improved efficacy without causing any negative effects, advancing the era of micro or nanorobots. These micro or nnorobots are used in dentistry and in the management of diabetes in addition to targeting cancer cells [13-15]. Therefore, it can be said that using micro or nanorobots has many applications in the biomedical field. Additionally, its application in the biomedical sphere fosters the expansion of the healthcare industry and advances medical technology [16]. This review consists of detailed explanation of the development of the micro or nanorobots. Then, each of the primary robot components including their actuation, design, production, and control is discussed separately. Additionally, potential challenges in developing such robots are explored from the perspectives of intelligence and sensing, therapeutic applications, materials, and performance. For literature search the data of past 15 y were reviewed from Pubmed, Science direct, Bentahm Sciences etc.

Design strategies

A crucial area of study in the field of micro-and nanorobotics is design strategy. Different varieties of micro and nanorobots have undergone extensive design effort in order to achieve a variety of goals. Typically, the design of micro and nanorobots is inspired by the modeling of mechanical structures, bionics, and bio-syncretic designs. Macroscale mechanical structures are shrunk down to the micro-or nanoscale scale to produce micro/nanomachines. For instance, numerous nanoscale motors have been developed utilizing the macroscopic motor as a prototype. Schalley and his associates hypothesize drotaxane-based molecular motors at the molecular level; in this instance, the natural system prototypically exhibits all the characteristics of a macroscopic motor [17].

Mechanical devices based on molecules or nanocomponents can aid in the study of microscopic or nanoscopic signal transmission, which has a lot of potential for use in the biomedical field. Designing micro- and nanorobots using biomimetics, or the imitation of biology or nature, is becoming increasingly common. The use of bionics to the study of diverse robot kinds has produced outstanding outcomes [18-20]. For biomedical applications, numerous micro and nanorobots navigate in viscous fluidic environments. Many eukaryotic cells, including bacteria, and other microorganisms with flagella have the ability to propulsion themselves to swim. Researchers have looked into a range of bionic swimmers based on this potential. These reconfigurable helical microswimmers exhibit desirable propulsive performance at low Reynolds numbers and can even be constructed from soft materials [21, 22].

A new class of robots called biohybrid or biosyncretic robots can be created by fusing electromechanical components and biological materials with useful functions, combining the benefits of both living and non-living systems. The study of these types of robots has recently attracted a lot of interest. The publishing trend on biohybrid actuation, in particular, shows how swiftly technology has developed in recent years [23]. In addition, bacteria or cells with flagella can be employed to create biohybrid micro and nanorobots. Two types of microrobotswere suggested. The first involved a sperm's incorporation of a microtubule for movement, and the second involved a sperm's incorporation of a helical structure. For the direction and transportation of motile and immotile sperm, tubular and helical spermbots have been utilized [24].

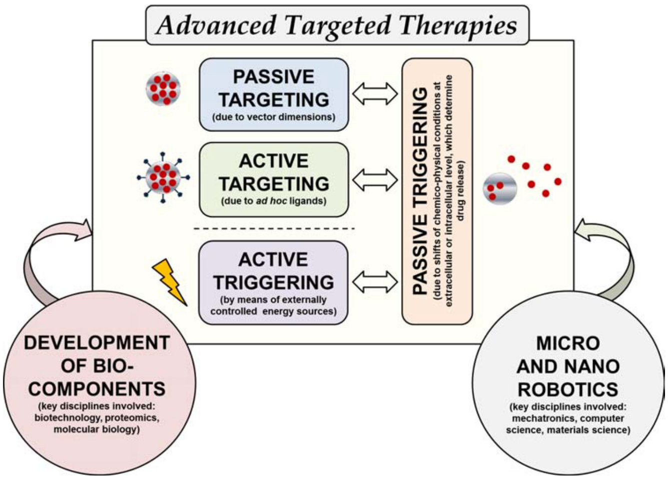

Fig. 1: Advanced targeted strategies [81]

Fabrication techniques

Normally, instruments like computer numerical control (CNC) machines are used to process ordinary robots, but when the scale of the robot is shrunk to the microscale or even the nanoscale, these normal processing techniques are no longer applicable. New fabrication techniques for micro-and nanorobots must therefore be developed. As a result, we look at the main processes used to make micro and nanorobots, such as lithography, material deposition, material assembly, and other processes [25].

Photolithography, a non-conventional 3D printing technique, is frequently utilized to create micro and nanorobots. Horiguchi and team created a microcasting mould using lithography technology and cultivated rebuilt heart tissue inside the mould to create a bioactuated microdevice [26, 27]. Porous micro and nanostructures were also created through lithography in the work of Hu and his co-workers, which may be more advantageous for targeted drug delivery [28].

A new sort of microfabrication technology called microstereolithography was also created on the basis of stereolithography (SL). In comparison to the conventional SL method, microstereolithography employs a smaller laser spot (a few micrometres), resulting in a much smaller photocuring reaction in the photoresist. The bulk of currently employed micro stereolithography techniques are restricted to the use of a single material, despite the fact that many applications (such as tissue engineering, biological organs and composites) require for micro/nanostructures comprised of many materials [29]. In order to accomplish multi-material micro/nanoscale, Choi created surface projection microstereolithography based on a syringe pump. To transport and distribute multiple materials, a microstereolithography system was integrated with 3D printing and a syringe pump. Using the developed tools and procedures, that group also created multi-material (3 different resin materials) microstructured 3D printing. Microstereolithography and surface biomimetic alteration work together to create scaffolds that are more biocompatible and perform better in bone tissue engineering [30, 31].

An additional method for building micro and nanorobots is material deposition. Physical vapor deposition is often employed. For instance, to improve adhesion and magnetic actuation, Gao and his team produced a large number of helical vessels and successively deposited thin coatings of Ti and Ni on the extensive spiral channels [32, 33]. For instance, He and his group used glancing-angle deposition to produce L-shaped Si/Pt nanorods. The force generated by the catalytic reaction on the surface of the Pt layer propels the nanorod from the Pt side [34].

A large degree of material assembly is also required for the construction of micro-and nanorobots. To put the components of the micro-and nanorobots together in the appropriate configuration for the desired function is the basic notion behind material assembly. No matter what kind of material is used as the actuator, it is possible to combine different inorganic materials, biological materials, and non-biological materials. Alternatively, live things themselves can be combined directly [35].

As the number of functions and performance rise, it is projected that the structure of micro and nanorobots will become highly complex, making it doubtful that a single assembly procedure will be sufficient. As a result, it is frequently utilized to realize the assembly of micro and nanorobots with intricate architectures by integrating multiple manufacturing techniques. Microtubes and magnetosperm, for example, can be made using photolithography and electron beam evaporation techniques, whereas helical micromachines like capsules and syringes can be made using 3-D direct laser writing (DLW) and physical vapor deposition processes [36]. The manufacturing of micro-and nanorobots can be carried out via a variety of alternative techniques, including template-based wetting operations, focused ion beams, and micro-molding [37-39].

Control of motion

Another problem that built, formed micro and nanorobots must address is motion control. Motion control is the process of adjusting a micro-or nanorobot's position and speed in real-time so that it maintains the desired motion parameters and follows the anticipated trajectory. The actuation techniques used by micro and nanorobots play a major role in how they control their motion [40].

As an illustration of how the driving mechanism and the directing technique interact, Hong and colleagues combined chemotaxis and phototaxis to accomplish global directionality control in artificial micro/nanomotors [41]. Visible light is used as the micromotor's power source and controller by Zhou and his team. By swiftly turning on and off the light and adjusting the brightness, you can start and stop the micromotor. The micromotor was controlled by an external magnetic field in their future work [40, 41].

The most popular type of driving is magnetic. Regardless of how a micro or nanorobot is propelled, researchers frequently employ magnetism to control the robot's movements. Magnetic fields; for instance, can be used to drive both chemically and acoustically powered nanowire motors and microsphere vehicles. In addition, time-varying magnetic fields are frequently used to control the mobility of micro and a nanorobots [42]. Using a time-varying magnetic field, a microrobot's surface was moved in a regulated stick-slip motion. The modification of the magnetic field's properties is relatively significant when it comes to controlling the mobility of micro-and nanorobots [42].

Without the use of magnetic fields, the concentration and distribution of the chemical fuels used to power micro-and nanorobots can be changed to control their speed and direction [43]. The microbots will move more quickly by increasing the fuel and surfactant amounts. Because catalytic motors are relatively sensitive to the fuel gradient imposed in the system, Pt-Au rods are used to move in the direction of regions with high fuel concentrations [44, 45].

Real-time placement of these robots is essential because they are mostly employed in biomedical applications for micro and nanorobots. Force feedback and vision are frequently used by modern micro-and nanorobots for feedback control. Li and his group created a closed-loop visual feedback control system for microvehicles. Real-time visual input was provided by a CCD camera attached to a microscope. In their research, they combined artificial intelligence (AI) with microrobot control, presenting a novel approach to manipulating microstructures. The intelligent microrobot can instantly distinguish between target objects, such as cancer cells and healthy red blood cells, and can autonomously select the best route to follow cancer cells [43].

Challenges in micro-and nanorobots

As micro/nano technology, robotics, biomedicine, and electromechanical science have developed, so has research on micro and nanorobots. Existing micro and nanorobots can only perform one function due to their small size, and it is difficult to combine many functions (such as actuation, perception, assessment, and intelligence) into a single robot. For usage in practical applications, intelligent micro-and nanorobots must combine signal perception, acquisition, processing, and transmission [44]. A stronger feedback mechanism is needed to comprehend the robot's position in real time and the outcomes of lesion therapy. This keeps the nano and microrobots in contact with their external controllers [45].

Second, micro and nanorobots should close the gap between scientific research findings and market need by resolving issues encountered in clinical applications. Although a wide variety of micro-and nanorobot prototypes have been developed, the usage of these devices in clinical settings has not yet been generally adopted in the field of medicine. Applications requiring *in vivo* use of micro-and nanorobots should consider their biodegradability, reliability, and compatibility [46].

Third, improved fabrication techniques for micro-and nanorobots, as well as novel energy conversion mechanisms that are more reliant on wireless control and drive techniques. The driving methods used now fall short in each of these areas. For example, the electric drive needs external electrodes, the light drive needs light to reach the tissue, and the magnetic drive needs an external magnetic field. Additionally, the majority of currently employed systems can only control the movement of micro and nano robots in two dimensions, or the plane [47].

Fourth, new materials are required for micro and nanorobots. Biosyncretic micro and nanorobots have been a significant part on the field of micro and nanorobots because they offer benefits over both living and nonliving components. Additionally, some living microorganisms can be used directly in the construction of micro and nanorobots. These kinds of robots can use living things as sensing or driving components [48].

Mechanism of actuation

Actuation methods of nanorobotics can be physical, chemical, biological methods and hybrid actuation methods.

Physical actuation

The physical actuation method involves the use of electrical signal, magnestism piezoelectricity, light, thermotics and acoustics. As per the source of power, micro or nanorobots can be classified as magnetically driven, light-driven, ultrasound-driven, and electrically driven.

Magnetic actuation

This method offers the benefits of good penetration and it can be used for incorporating biological materials easily in human body without causing any harmful effects. The other advantages of using magnetic actuation are that the method is non-invasive and it allows the micro/nanorobotics to move freely in the body without disturbing the internal environment.

Steager and his team created an electromagnetic coil-actuated, magnetically actuated U-shaped device. The magnetic robot was created by photolithographically combining magnetic nanoparticles and photoresist. The robot could accommodate and transport microbeads with chemicals to the desired site in neurons and thus can be used in site specific targeting [49].

Li and co-workers proposed the design of a fish-like magnetic nanorobot. The nanorobot was prepared by using gold segment as a head, nickel segments as body and one gold segment as caudal fin. All the parts are connected by a flexible structure which is made up of silver. The robot has same propulsive activity as that of propulsive activity of fish. The propulsive activity of the robot can be obtained by oscillating magnetic field having a frequency of 11 Hz [50].

Electric field

The second most favored method for nano or microrobotics propulsion. Since the magnetic and electrical fields cannot be separated, they can combine into one another under certain circumstances. Magnetic fields and electric fields are typically inseparable, yet under some situations, they can change into one another. An study was conducted by Fan et al., 2010, in which they shows that the gold nanowires conjugated with cytokines such as TNF-α(tumor necrosis factor α) which can be transported using electrophoretic and dielectrophoretic forces to a desired location [51].

A colloidal system driven by electric and magnetic energy has been reported by Demirörs and his team. High-frequency electric field (0.5-2.5 Hz) is used for the pickup ability of colloidal system. The colloidal system is basically coated with a layer of nickel, and thus its motion is controlled by the magnetic field. Thus both the mechanism electric and magnetism are responsible for the movement of nanorobotics/microrobotics in the body [52].

In a study proposed by Jeong *et al.,* 2020 they used two actuation schemes for the working of microrobot. The first actuation scheme was based on electromagnetic actuation while the second scheme was based on acoustics. Electromagnetic actuation was based on pair of electric coils while acoustic bubble actuation was responsible for drug release. When two different bubbles of varying length are exposed to sound waves, the bubble whose natural frequency corresponds to the applied frequency causes vibration and causes flow. Thus the study shows that micro robot can be used to target desired or targeted site, carry and releases the drug effectively to the desired location [53].

In another study by Liang and his co-workers designed a rotational carbon nanotube (rotational motor). The motor shows fast response and high-speed movement under electric field. The motion was originated from electric induced water dipole orientation. The motor shows good characteristics in water and in simulating body fluids. Similarly, nanoparticles can perform directional movement under the effect of electrical energy [54]. Si and his co-worker proposed a study of nanorobot which consists of nanoparticle and four single stranded DNA which is placed in a nanopore device for controlling the motion. On applying the electric field, four single-stranded DNA can be captured one by one by nanopores. The results reveal that electrophoresis and electroosmosis are responsible for the actuation of robotic movements. The direction and strength of electrososmosiscan be controlled by altering the charges on nanopores [55].

Light actuation

Another mechanism responsible for the actuation of nano or microrobots is light actuation. The propulsive activity of the nanoswimmer can be actuated by thermophoresis which is generated by the temperature gradient. Wang and his team designed a nanoswimmer fabricated of liquid metal gallium which is needle shaped. Additionally, it was discovered that the light's intensity can be used to modify the activity of nanoswimmer. The nanoswimmer can swim at a pace of 31.22 m/s when exposed to a laser with 5 W. cm^2 intensity. The nanoswimmer can be used in biomedical uses and as active support materials for future generation [56].

Acoustic field actuation

Ultrasonic field is another source for the actuation of micro or nanorobots. Wang *et al.*, 2009 designed micro or nanorobots, which is metal rod shaped by electrodeposition method. The robot when placed in ultrasonic field, it can achieve velocities upto 200 µm/s. The research studies has shown that ultrasonic waves in the frequency of megahertz can suspend, advance, arrange, rotate and assemble the robots in higher ionic strength solutions and in water [57].

In another study conducted by Lee and his co-workers proposed a novel mechanism of ultrasonic actuation The mechanism is based on generation of acoustic radiation in a standing wave which is responsible for movement of particles. The speed and motion of the particles were controlled by a transducer and an electric platform [20].

Chemical self-actuation method

The chemical self-actuation approach relies on the creation of an asymmetric field that can be caused by concentration gradients or bubble recoil, which upsets the equilibrium of a micro or nanorobot and causes it to move. For the first time Whitesides *et al.* in 2000 designed a micro or nanorobot. The terminal of the micro or nanorobot consists of porous glass plated with platinum. It can generates a large amount of oxygen by decomposition of H_20_2 on the surface of platinum, which causes generation of an actuation force between H_20_2 and air which cause robot to push. The whole process causes conversion of chemical energy into kinetic energy through oxidation–reduction reaction.

In a study conducted by Chen and his co-workers designed micro/nanorobot of Au/Pt hybrid for targeted drug delivery and for management of cancer. The mechanism of actuation is based on self-electrophoresis. The maximum speed of micro/nanorobot is 4µm/s [39].

Biological self-actuation

In the past few years scientists uses biological materials as an actuator of micro or nanorobots. A study conducted by Magdanz and his team in which they proposed the use of flagella containing spermatozoa as a force of actuation for the fabrication of micro or nanorobot. When combining sperm cells with nanotubes, the flagella of the sperm interacts with the microtubes, which causes actuation of the micro or nanorobot. Since the use of spermatozoa is safe and highly mobile, therefore, sperm-driven micro or nanorbots are promising device in case of artificial insemination and reproductive disorders [58].

Table 1: Different types of actuation methods

Type of actuation	Actuation method	Advantages	Disadvantages	Reference
External field	Magnetic field	High penetration, no harm to biological systems that are alive	Application of high-intensity magnetic fields in biomedicine: safety issues	[49, 50]
	Electric field	Powerful penetration, variable electric field strength	Limits on the use of electrodes in biomedicine	[51]
	Light field	exact targeting	UV light is dangerous because it easily causes irreparable damage to biological materials.	[56]
	Acoustic field	Strong actuation force and piercing force, changeable height, and biocompatibility within a specific frequency range	Easily causes biological tissues harm	[57]
Self-actuation	Chemical	Excellent biocompatibility	Concerns with fuel safety, hazardous H_2O_2, nontoxic urea, a quick response time, and a lack of feedback	[39]
	Biological	Highly safe	need to continue acting, restricted range	[58]

Applications of micro/Nanorobotics

With the help of technology, we can now alter the world around us on a smaller and smaller scale. Nanomedicine is a subfield of nanotechnology that is quickly expanding in the field of medicine. Nanoparticle technology is now widely known and used frequently, particularly in the pharmaceutical industry. Building nanorobots, which are machines with components made at the nanoscale, is an intriguing and promising area of nanotechnological research. Many of the potential applications in this field of study are actively being investigated and developed.

Hematology

In the discipline of hematology, there is a strong foundation of research and prospective uses for nanomedicine and nanorobotic applications. There are numerous possibilities for nanorobotics in haematology that are currently being researched, from primary hemostasis restoration to emergency non-blood oxygen-carrying chemical transfusions [59].

A nanorobot known as a respirocyte is one of these technologies that are currently being developed. As it moves through the bloodstream, this robot can do three different tasks. As oxygen enters the respiratory system, it must first be captured and distributed throughout the bloodstream. Secondly, it gathers carbon dioxide from tissues for discharge into the lungs. Finally, it fuels its own processes by metabolizing circulating glucose [60]. The robot would have a total size of around one micron, or 1,000 nanometers. The built-in parts, however, would be made at the nanoscale. The onboard computer has a diameter of 58 nm, while the oxygen and carbon dioxide loading rotors have a maximum diameter of 14 nm in any one dimension. The respirocyte is made to carry 236 times more oxygen per unit than other cells [61].

Another area where nanorobotics may be useful is the hemostasis process. Hemostasis is a complex process with multiple phases that balances thrombosis and fibrinolysis via a variety of promoters and inhibitors. Hemostasis can be quite successful at stopping bleeding and encouraging vessel repair when it functions properly. However, physiologic hemostasis has inherent constraints, such as an average bleeding duration of five minutes, which can be overcome by nanorobotics. Additionally, our existing ways of treating this impairment carry inherent hazards when our physiologic hemostatic processes are compromised, such as when thrombocytopenia is present. Patients receiving platelet transfusions run the risk of contracting infections and possibly inciting an immunological reaction. The nanorobot for this termed as an artificial mechanical platelet or “clottocyte [62].

Finally, the utilization of nanorobots as phagocytic agents is another prospective use in this field. These nanorobotsare referred to as "microbivores." These robots' exterior surfaces would be constructed with a vast array of programmable binding sites for pathogens or antigens, ranging from HIV to E. coli. According to some hypotheses, microbivores could be employed to cure septicemia within hours of administration and could be up to 80 times more effective than our natural phagocytic systems. Given the alarming rise in antibacterial resistance, the development of nanorobotical capacities to fight illness may open up new avenues for the treatment of infection [63].

Neurosurgery

Since its inception as a theoretical concept, nanotechnology has developed into a vibrant field of suggestions and ideas and is currently the subject of ongoing study and technological advancements. Neurosurgery is especially poised to benefit from many of the improvements in nanotechnology as it typically operates at the microscopic level. These advantages include, among many others, increased pathology detection, minimally invasive intracranial monitoring, and drug delivery.

Spinal cord injuries and nerve damage are significant life-altering events for patients and a significant area of concern in the discipline of neurosurgery. Since more than a century ago, reconnecting transected nerves has been a common procedure thanks to improvements in both technique and technology. The goal of optimizing and increasing nerve reconnection outcomes is currently being explored through a variety of different avenues, one of which is encouraging axon regeneration using growth factors and enriched scaffolds. To restore function, transected axons must first have their connectivity restored. This can't be done because to technical restrictions on large-scale surgery. Technology advancements have resulted in the creation of nanoscale tools that enable the manipulation of individual axons. A 40-nanometer-diameter nano knife has been created and shown useful for axon surgery [64].

Dielectrophoresis, which involves manipulating polarizable particles in space using electrical fields, has been proven to be useful for producing controlled axon movement inside a surgical field [65]. Axon fusion between the two ends can be produced using a variety of techniques, including electrofusion, polyethylene glycol, and laser-induced cell fusion, after carefully cutting the axons in half and positioning them using dielectrophoresis. With the reconnecting of neurons, nanodevices are offering a new level of precision and control. Treatment of cerebral aneurysms prior to rupture is one of the best approaches to reduce morbidity and mortality in the field of neurosurgery. A brain aneurysm rupture carries a high fatality rate. 10% of patients pass away before they reach the hospital, 25% of patients pass away within 24 h of an aneurysm rupturing, and nearly 50% pass away within 30 d [66]. There are no cost-effective recommendations for diagnosing cerebral aneurysms in patients. Nanorobotics may offer a potential method for identifying new aneurysms or for closely monitoring those that have already been found.

Cacalcanti *et al.* 2009 developed an intravascular nanorobot that may recognize aneurysm development by spotting increased nitric oxide synthase protein levels inside the injured blood artery. These nanorobots might be equipped with the ability to wirelessly transmit data to healthcare professionals regarding relevant vascular changes, potentially cutting down on screening expenditures for imaging and frequent follow-up visits. The creation of the platform needed for this device is crucial since it will allow for the horizontal development of the concept for numerous additional applications, such as tumor detection or ischemia alterations [67].

Oncology

Lowering the mortality and morbidity associated with oncological diseases and their treatment, as well as raising the standard of care and clinical outcomes for cancer patients, is all objectives set forth by the Institute of Medicine. The community's increasing senior population and the rise in cancer diagnoses that comes with an ageing population serve to highlight the urgency of this need. The treatment of cancer has already showed great promise thanks to nanotechnology. Examples of the expanding role of nanoparticle technology include improving the treatment of metastasis, overcoming medication resistance, and raising the sensitivity of cancer imaging tools [68].

It has been successfully created to create a nanorobot that can recognize diseased cells on its own and release therapeutic medicines where the cancerous cells are located. This nanorobot can be customized to release a variety of payloads when activated and can be designed to engage with a variety of various cell surface receptors. This nanorobot was built by manipulating synthetic DNA strands to fold into a desirable tertiary shape. When the DNA nanorobot touches the intended target, its conformation structurally reorganises and switches from a closed to an open state, releasing the held therapy. Freitas suggests creating a nanorobot he refers to as a pharmacyte, which also includes a medicinal payload for the treatment of malignancies. This nanorobot would have locomotory capabilities to move through tissue walls and cell membranes, surface binding sites to bind chosen targets, and self-sufficient energy generation [69].

Studies have also looked into how nanorobots might be used during tumor excision procedures to help with intraoperative tumor margin detection and mapping. An analogous strategy without the use of nanorobots has been investigated, and its effectiveness has been proven. The research demonstrated that when a radioactive colloid injection into the prostate was given the day before tumour excision, radioisotope guided sentinel lymph node dissection, as opposed to open lymph node dissection, was more sensitive in identifying early metastasis [70].

By removing the necessity for the patient to be admitted a day before the treatment and the danger of prostatitis connected with the injection, the use of nanorobots can improve this surgery. During the process, nanorobots would be injected intravenously to look for tumour tissue margins and metastatic sites [71].

Numerous advancements in nanotechnology have made it possible to better cancer treatment, and it is conceivable that many more applications will be envisioned as nanorobotic technology develops. The suggested designs may set new standards for cancer screening, detection, and prevention with further technological advancement.

Dentistry

Dentistry is one industry where nanorobotscan be used both routinely and specifically. Nanorobots have the potential to be used in virtually every aspect of dental care and treatment, improving patient care. These applications include routine cleanings, aesthetic procedures like teeth whitening, treatment of hypersensitivity, and even orthodontics. Almost every aspect of dental care, including the initial analgesics a dentist might administer at the beginning of a session, can be enhanced by nanorobots. The patient receives an oral administration of a solution comprising millions of nanorobots. These robots can fit inside the gingival sulcus and finally pass via tooth tubules that are only a few microns in diameter to reach the pulp. The ability to activate analgesic activity in very specific locations close to the dentist's point of care would be made possible by central control of these nanorobots [72].

One use for nanorobots in dentistry is the initial analgesia a dentist might give patients at the start of a visit. A suspension comprising millions of nanorobotsis administered orally to the patient. These robots are small enough to fit inside the gingival sulcus and eventually travel through pulp-accessing tooth tubules with a diameter of just a few microns. These nanorobots might be controlled from a central location, enabling the activation of analgesic activity in much-targeted locations near the dentist's treatment area [73]. In order to bind the targeted pathogens for the therapy of infection; nanorobots can be covered in highly specialized proteins. A tiny camera can be used to visualize the root during a surgery like a root canal, which eliminates any guesswork. Root canal procedures may have a higher success rate thanks to nanorobots. Root canal treatments performed by the National Health Service in 2011 had a success rate of 70%, therefore, there is still opportunity for improvement [74].

Additionally, nanorobotics may be used to treat dental disorders, including dentine hypersensitivity. According to studies, hypersensitive teeth can contain significantly more dentinal tubules than healthy teeth, and the dentinal tubules can also be larger than usual. It might be possible to prevent stimuli from penetrating and eliciting a pain response by inserting nanorobots into these dentinal tubules and selectively ablating or occluding tubules inside the hypersensitive teeth [75].

Other potential uses for nanorobots in dentistry include tooth repositioning through the direct replacement of enamel layers, dental aesthetic surgery, and even the incorporation of nanorobots into mouthwash and toothpaste to improve routine dental care [76].

Vascular

Intravascular therapy has only recently cemented itself as a mainstay of treatment for conditions like aneurysms, tumors, and atherosclerosis, despite the fact that the concept has been debated for a variety of conditions since more than a century ago. Nanotechnology's development has increased the effectiveness of already existing technologies and is inspiring the development of brand-new methods for the prognosis, treatment, and prevention of illness by means of the vascular system [77].

The intravascular use of nanorobots significantly increases the possibility for screening and monitoring for life-threatening medical conditions as well as for tracking the beginning and progress of chronic diseases. Aneurysms in the brain, cancers for which there are no screening protocols at the moment, such as lung cancer, and unstable atherosclerotic lesions are a few examples of life-threatening illnesses that could be checked for. Intravascular nanorobots would move continuously and deliver up-to-date information as needed. Additionally, integration with current technologies would enable wireless continual syncing and prompt alerts for changes in health conditions. The ability to manage chronic diseases optimally is improved by monitoring chronic health disorders like diabetes. Our society's increased life expectancy and quality of life are largely due to advancements in primary prevention techniques [78].

Nanorobotscan be created to perform direct intravascular therapy in addition to screening and monitoring tasks. Nanorobots, for instance, could deliver mechanical or pharmaceutical therapy directly to the target location in the case of coronary artery stenosis. Nanorobotsare also used in the acute treatment and prevention of aneurysm rupture. A nanorobot's intravascular navigational capability can enable localized drug distribution to lessen bleeding as well as a localization tool as an imaging adjunct. Nanorobotscan also be employed for the early diagnosis and treatment of cancer [79-83]. Intravascular nanorobots' capacity for continuous circulation can offer ongoing tumour monitoring. Using a nanorobot for direct local treatment delivery can increase the effectiveness of a treatment by enabling the delivery of a larger treatment dose with a lower risk of toxicity due to a more constrained volume of distribution. A potential area of modern nanotechnology development is intravascular nanorobotics. Although the technology is there for these designs, it will be some time before nanorobotics is widely used in clinical settings. This is because the current concepts are still undergoing research and proof of concept tests [80, 82, 84].

CONCLUSION

Scientists are currently making strides towards creating technology on a scale that is orders of magnitude smaller than ever before. In the past, the scientific community and the society at large underwent profound transformations as we learned to alter the planet on a smaller scale. Nanotechnology is poised to transform many of the paradigms with which we think about illness, diagnosis, treatment, prevention, and screening, just like the age of microscopes brought about the field of bacteriology. Micro-or nanorobotics is growing in potential applications across all medical specialties, increasing the range of therapeutic alternatives, and enhancing the effectiveness of current therapies. Within a generation, it is most likely probable those medical applications of nanorobotic technology will proliferate.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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