Review Article

Nanobot: Artificial Intelligence, Drug Delivery and Diagnostic Approach

Abstract

The design, construction, and programming of robots with overall dimensions of less than a few micrometres, as well as the programmable assembly of nanoscale items, are all part of nanorobotics. Nanobots are the next generation of medication delivery systems, as well as the ultimate nanoelectromechanical systems. Nano bioelectronics are used as the foundation for manufacturing integrated system devices with embedded nano biosensors and actuators in the nanorobot architectural paradigm, which aids in medical target identification and drug delivery. Nanotechnology advances have made it possible to create nanosensors and actuators using nano bioelectronics and biologically inspired devices. The creation of nanobots is fascinated by both top-down and bottom-up approaches. The qualities, method of synthesis, mechanism of action, element, and application of nanobots for the treatment of nervine disorders, wound healing, cancer diagnosis study, and congenital disease were highlighted in this review. This method gives you a lot of control over the situation and helps with sickness diagnosis.

Keywords: Nanobot, Artificial intelligence, Top-down, Bottom-up, Nanobot architecture, Drug delivery, Diagnosis.

1. INTRODUCTION

The Healthcare industry witnessed a significant revolt from developing the first vaccine to MRI but resulted in developing the cusp required scientist focuses on nanobot design. Nanobots are intelligent structures capable of actuation, sensing, signaling, information processing, intelligence, manipulation, and swarm behavior [1]. Nanobots are either biological-inspired or nano-electric mechanical systems. It enables and significantly promotes newer methodologies for diagnosis, medical therapies, and non-invasive surgeries through nano-technology [2-6]. In addition, it also promotes advances in genetics, biomolecular computing, a microbiological technique for the construction of digital circuits in living cells [7-9]. Bacteria have been used as physical system components and radio remote control for biological processes [10,11]. Feasible approaches for designing nanorobots include bottom-up and top-down approaches, involving assembling nanobots from small molecules and scaling the microelectromechanical system into a nanoelectromechanical system [12].

2. ARCHITECTURE OF NANOBOT

2.1 Sensor

The sensor is a device that detects changes in the physical environment and converts them into data interpreted by humans or machines. The sensor is an essential component of the nanobot. Without it, change in the background cannot be detected, and thus further sequential series of nanobot action ceased. Nanobot requires nanosensors that utilize the nanoscale phenomenon for its operation. Genuine sensors are considered devices that modify the conduciveness of nanowires or nanotubes, i.e., conductivity, when exposed to specific chemicals [13,14]. The sensitivity of the nanosensor changed by attaching the chemical groups to the sensing elements.

Chemical-based sensors possess microscopic cantilevers and are investigated by scientists as nanosensors in micron-scale size. The mechanism of the nanosensors is explained by detecting the cantilever deflection, resulting in creating chemical species due to surface tension and thus determining the shift in a vibrating cantilever's resonant frequency as its mass grows due to the deposition of the molecules [15,16].

Lithographic methods have produced cantilevers with a resonance frequency of 1GHz, but they are pretty massive to consider a nanoscopic [17]. Moreover, the lithographic fabricated sub-micrometer cantilever has an inelastic instability. Therefore, the scientist also uses the probe as a sensor, nanoscopic in size and such injected within the cell for reporting the chemical concentration within the cell [18-20]. But the limitation with such probes is they are not sensors, so they require a light source and fluorescence detector. Therefore, the most promising bio-sensor is the one that accounts for changes in the protein structure, resulting in detecting the active component [21].

2.2 Actuator

An actuator is a device that converts a control signal into mechanical motion using a source of electricity. The nanobot's actuator acts as a guide for the nanobot's progress towards the target.

2.2.1 Types of Actuators

2.2.1.1 Artificially designed molecular actuator

Artificially designed molecular actuators possess a single molecule or the network of the interlinked molecule where atoms are precisely placed concerning another atom. The energy source for its functioning is provided electrically, optically, and chemically. However, chemical energy sources are not helpful as they cannot deliberately switch on and off until machines run outs of fuel.

Light-driven actuators like linear shuttle [22], rotary motor [23] are considered the best actuator for the nanobot. When the suitable wavelength of the visible region falls over such light-driven actuators, a part of the molecule, i.e., the rotor, starts rotating continuously to a fixed part, known as the stator around the carbon-carbon double bond. The rotation proceeds in the following steps discussed below.

- *Cis-trans* isomerization through light.
- Isomerization brought by the light result in unstable conformation, so molecule changes spontaneously to more energetic advantageous conformation, allowing rotation to continue.

Light triggers another cis-trans isomerization in the final stage, this time with an unstable result that spontaneously decays to the original conformation, putting the cycle to a close [24].

2.2.1.2 Bio-motors

Bio-motors utilize the biological element whose action provides motion, jerk, or signal. Such components are engineered to perform pre-programmed biological functions in an artificial setting in response to specified physiochemical inputs. For example, proteins could act as motors, mechanical joints, transmission elements, sensors, and other biological structures [25]. With the exceptionally high efficiency (e.g., some approaching 100%), property of self-mimicking, and freely bioavailability in nature, bio motors gained a lot of traction. Motor proteins molecular cargo transporter transport organelles, lipids, and proteins within cells and are classified into three families: myosin, kinesins, and dynein's [26]. Myosin molecular motors move cargo 10 nm per step along actin filament tracks by hydrolyzing ATP. This causes the protein to change shape (i.e., conformational change), thus pushing itself along the actin filament that converts stored energy into mechanical energy. Both kinesin and dynein are engaged for transferring cellular material along microtubule tracks.

Microtubules are tubulin protein-formed tubules having a diameter of 25 nm and organized in cells. Different polarity is connected with opposite ends of microtubules. Kinesins go from the minus to the plus end of the molecule, whereas dyneins move from the plus to the minus end. Kinesin-based motors possess feet-like features for walking along the microtubules via ATP hydrolysis. Kinesins at a force of 5-6 pN and speed of 1000nm/sec take around 100 steps to detach themselves from the microtubule. Dyneins are involved in both cargo transport and the production of cilia and flagella bending motions.

2.2.1.3. Propellor

Propellors in nanobots provide the upthrust or push account for movement in the forward direction. Bacteria are considered as best Propellor as it shows phenomena of collision and diffusion due to their small size and absorption of thermal energy from the ambiance. Furthermore, bacteria use the cilia and flagella for bringing the propulsion in the low stokes medium, and its size is in the affordable range of nanobots [28].

2.2.1.4. Controller and Communicator of the nanobot

Depending on the application, acoustic, light, RF, and chemical signals can be used for communication and data transfer in liquid workspaces [6]. Chemical signalling and sensor-based behaviour are also useful for some collaborative coordination and biological instrumentation among nanobots [29-31].
Acoustic communication, as opposed to light communication methods, is better suited for long-distance transmission and detection with little energy use [32]. Optical communication, on the other hand, provides for faster data transmission, but it is inappropriate for nanobots due to its high energy cost [2].

3. TOP-DOWN APPROACH

Breaking bulk material into nanosized structures or particles is a top-down strategy. Top-down synthesis techniques are a variation on the technique used to make micron-sized particles. They are essentially simpler since they rely on bulk material division or bulk manufacturing process downsizing to build the correct structure with the desired characteristics. This method reduces a microscale electromechanical system to a nanoscale electromechanical system for nanobots.

3.1 Top-down Approach Challenges

- Moving from micro to nano-size, a complete change in fundamental physics and forces occurs, so it appears this approach could not scale down so quickly and effortlessly.
- Existed microelectromechanical system either possess sensor or actuator, not both, but the operation of nanobot require both to function, so here stands a limitation for this approach.
- Power generation becomes a significant issue as we go smaller. Alternative power generation methods have been proposed. However, even if we generate electricity, storing that energy becomes a much more severe difficulty. Getting smaller means increasing energy density to a level where downsizing storage batteries is no longer practical.
- Another issue that arises at the nanoscale is the dominance of viscous drag, so as a result, we'll need to generate a lot more power to overcome this resistance [12].

4. BOTTOM-UP APPROACH

The bottom-up nanofabrication approach combines simple units into more giant structures using chemical or physical forces operating at the nanoscale. Bottom-up tactics significantly complement top-down techniques in nanofabrication as component sizes shrink. Biological systems, where nature has harnessed chemical powers to generate practically all of the structures required for life, inspire bottom-up techniques.

4.1 Imaging tool for the nanofabrication of nanobot

Imaging tool in nanobot verifies soldering of an atom with another atom and their spatial arrangement in 3-D space that allows finally desired nanobot structure. The scanning electron microscope, transmission electron microscope, scanning tunneling microscope, and atomic force microscope are commonly used imaging tools in nanofabrication.

4.1.1 Electron microscopy

4.1.1.1. Scanning electron microscope (SEM)

SEM ability to resolve the image of nano-meter scale (less than 2 nm) and deep strength of field allows producing three-dimensional images of samples. The electron cannon in SEM is responsible for supplying the electrons that constitute the electron beam. Lenses usually magnetic curve the electron beam as it descends the electron column toward the specimen chamber and guides it to its surface. The electron beam strikes the sample placed above the specimen chamber and induces spills and scatter various radiation concentrations. The chamber containing the detector gathers the discharged radiations and produces findings. The output of the detector is determined by the amount of radiation received from the sample [33].

4.1.1.2. Transmission electron microscope (TEM)

An image was resolved through TEM using an atomic scale of magnitude of 0.1 nm. TEM has a similar operation as SEM. In contrast, the TEM detects electrons traveling through the sample's interior. The electron beam of TEM has high working energy ranging between 50 and 100 kV. For the electrons beam to flow through it and capture the picture of the sample, the sample must be exceedingly thin. TEM uses various detectors, standard fluorescent screens, and photographic films. Unlike the SEM, the TEM does not provide three-dimensional images but provides two-dimensional pictures [34].

4.1.2. Scanning Probe Microscopy

4.1.2.1 Scanning Tunneling Microscope (STM)

STM also can resolve specimens down to the atomic level [35,36]. The Nobel metal constitutes the scanning probe of the STM, which is sharpened or pointed to an atomic-sized tip and domed over a linear stage (x,y,z) driven by piezoelectricity [36,37]. The tunneling effect can be seen in the STM. This impact is apparent or obvious when a low electrically potential driven electron travels between the probe tip and the substance. In tunnelling procedures, the free distance between the probe tip and the observed sample is measured in angstroms. The tunnelling current has a nano-ampere order and is proportional to the distance between the probe tip and the sample. The probe tip and sample gap distance/space is maintained by using the feedback control method to keep the magnitude of tunneling current consistent (z). The probe tip is scanned across the entire surface of the sample in the x–y dimensions after the tunneling current is kept constant. The probe tip scans the material to generate a z(x,y) terrain map with sufficient resolution for detecting atomic-scale features, shown in Fig. 1 [38].

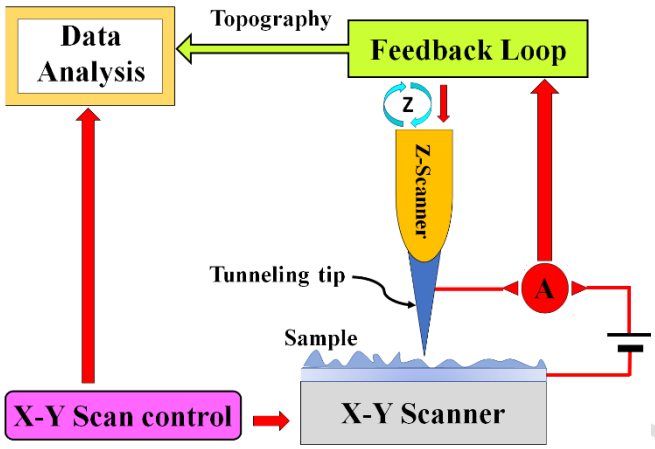

Fig. 1. Schematic diagram of STM

4.1.2.2. Atomic Force Microscope (AFM)

AFM discovery fascinated imaging of non-conductive material. Interatomic forces laid the foundation of AFM, and through it, an image of a liquid immersed sample was efficiently produced, which was impossible with SPM. The AFM probe tip is positioned on the microscale's cantilever beam edge. When the probe tip and sample atoms are relatively close together, the force generated between them causes the cantilever to deflect. Cantilever deflection is calculated by impacting a laser with the back of the cantilever. When a cantilever strikes a laser, the laser is reflected in the detector and decodes the cantilever's deflection, as depicted in Fir. 2 [39].

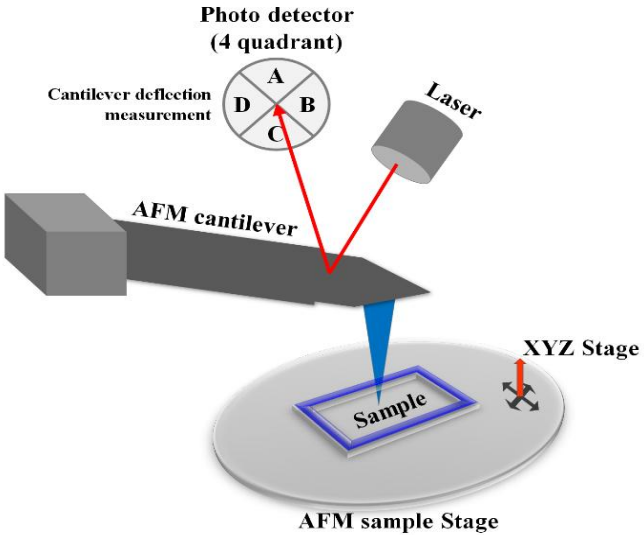

Fig. 2. Schematic diagram of AFM.

4.2 Manipulation tools

4.2.1. Atomic Force Microscope (AFM)

In 1980, Binnig and Rohrer devised SPM at IBM Zürich Laboratory and concealed Nobel Prize for it. SPMs ushered a new era for the nanoworld, providing a significant boost to the present progress in nanoscience engineering. First, SPMs are commonly used for imaging, but later, they discovered their capability to modify materials. The scanning tunneling microscope can manipulate atoms with low temperature (4 K) and ultra-high vacuum conditions. Samuelson's group at the University of Lund proved an AFM might

be used for nano assembly and manipulation by building blocks of comparatively larger molecular-sized and assembling them under ambient conditions.

4.2.1.1 AFM nano-manipulation protocols

Taking an initial sample picture to identify where the desired particle is and moving the desired particle against the parent particle by altering the AFM's operating parameter to a force stronger than utilised for imaging is the typical approach for manipulating nanobots with AFM.

4.3. Nano grippers

4.3.1. Optical tweezer

Optical tweezers produced both attractive or repulsive force based on differences in the refractive index of mediums and the utilized phenomenon of light to induce linear or angular momentum [40]. An optical tweezer uses a focused laser beam to hold and displace the microscopic and submicroscopic objects like atoms, nanoparticles and aids selective manipulation of nanoscale particles in the air as a substrate. Two laser beams illuminated substrate resulting in two counter-propagating evanescent waves, tungsten probe scatters two waves and generate a localized optical trap and probe finally selectively brought nanoscale into the trap [41].

4.3.2. Nano-tweezers

Pick-and-place manipulation and assembly require a solid grasping mechanism from the start. Gripping at the nanoscale is difficult due to the difficulty of balancing forces between the object, the surface, and the gripper, where van der Waals and electrostatic forces are more prominent [42]. In 2005, Kometani employed a focused ion beam chemical vapour deposition (FIB-CVD) on the 25 ends of a glass micropipette to create 3-D grippers with 2-4 fingers. The grippers are only a couple of microns thick. The grippers were electrostatically operated by applying enormous voltages ranging from 300 to 1200 volts. As voltages are applied, the space between fingers widens by around 0.1 to 2 m. A latex spherical with a diameter of 1 m was successfully grasped by the four-finger gripper. The writers, on the other hand, make no mention of a successful launch [43]. Wang detailed the construction and operation of a thermally actuated gripper inside a SEM in 2004. Three individually operated fingers make up the gripper. The thermal bimetallic strip actuates each finger. When a current is delivered, resistive heating occurs, causing the fingers to travel vertically. Traditional microlithography techniques and focused ion beam (FIB) milling are employed to create the fingertips. The thermal actuator can generate a vertical displacement of 1 m with an actuation power of only 0.14 mW, according to testing results. With a 3.8 mW actuation power, thermally induced displacements of up to 20 m have been obtained. Thermally actuated grippers were employed to selectively grab a 500 nm diameter and a 40 nm diameter multi-walled CNT from an unstructured cluster in this study [44].

4.3.3. Di-electrophoresis

It's an alternative approach for holding nanoscale things. Di electrophoresis manipulates polarizable materials using non-uniform electric fields. However, this method is still in its infancy [45].

4.4. Joining Nanostructures

4.4.1. Nano soldering

Nano soldering joins nanostructure by laying down carbonaceous material present in the electron microscope by the exposure of an electron beam [46]. Additive lithography is another name for electron beam-induced deposition [47].

EBID produced various three-dimensional nanoscale structures with a minimum size of 5 nm. The EBID method uses chemicals that result in different deposited materials, including tungsten, gold, copper oxide, and platinum compounds [47,48].

4.4.2. Nano welding

The process of nano-welding requires the electron beam at an elevated temperature. In nano-welding, the material deposition as in nano soldering does not require, but a high-temperature electron beam knocks the electron from the atoms. Striking of the electron causes the rearrangement and joining of the nanomaterial into welded molecular junction [49-52].

4.4.3. Sintering

In Sintering, substrate particles are localized near the desired location and allowed to heat. Heat melts the substrate materials to form a single nanostructure [28].

4.4.4. Chemical Bonding

Requicha describes the use of di-thiols to join gold nanoparticles using chemical bonding. Organic compounds having sulphur end groups are known as di-thiols. The di-thiols self-assemble and act as a chemical glue to hold the gold together. Two ways are demonstrated in the requicha. The particles are positioned and then immersed in the di-thiol solution to connect them in the first method. The di-thiols are applied first in the second technique, and then the particles are manoeuvred into contact, joining them [28]. Dong highlights experimental work involving the end-to-end joining of multi-walled CNTs. The authors demonstrate that the linking force is most likely due to chemical (i.e., covalent) bonds between the carbon atoms, rather than weaker forces like van der Waals [53], using model analysis and tests.

5. DIFFERENT TYPES OF NANOBOT

Based on the different modes of manufacturing from the bottom-up approach, the different types of nanobots are shown in Fig. 3.

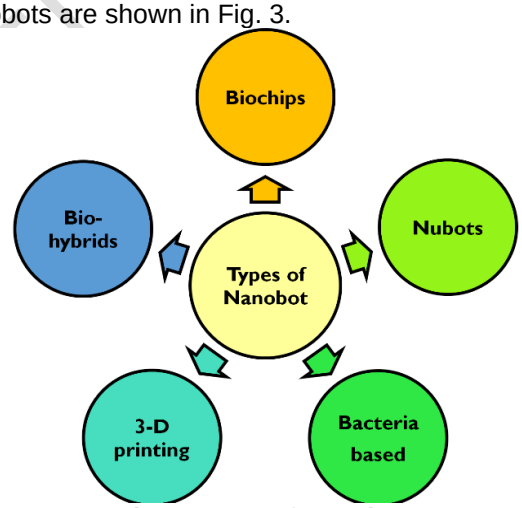

Fig. 3. Type of nanobot

5.1 Biochips

Amal gated use of photolithography, nanoelectronics, and biomaterial results in the formation of the nano biochips. The main types of biochips commonly used are Lab-on-

a-chip, DNA chips, and protein chips. The core component of biochips comprises a microarray (sensor), a transducer, signal processing unit, and readable output. For example, Digital microfluidic biochips were studied for biomedical purposes. A group of cells in a microfluidic array can be configured to operate as storage, functional operations, and dynamically conveying fluid droplets in a digital microfluidic biochip [54].

5.2. Nu-bots

Nu-bots are DNA-based nanobot that activates through small molecules, proteins, or other molecules of DNA [55-57]. The nubots contains several biological circuit gate. For example, DNA-based nanobot makes biological circuit gates and allow drug delivery at the target site within the body [58].

5.3. Bacteria based

In such nanobots, biological micro-organism like E. coli is commonly used. Such an approach uses the bacteria flagellum for propulsion purposes. The exposure of the electromagnetic field controls the motion of the integrated biological nanobot [59].
An intelligent DNA nanobot built a DNA framework enabling selective lysosomal degradation of tumor-specific proteins on cancer cells [60].

5.4. D printing

It is a technique of creating a three-dimensional structure using additive manufacturing processes. With a size range of 5-400 nm, the required precision of 3D printing must increase. Further, a two-step 3D printing procedure employed 3D printing, and laser-etched plates were integrated [61]. The 3D printing procedure promises the use of a laser etching machine to etch the features for the segmentation of nanobots into each plate, making it more accurate at the nanoscale. The plate is then delivered to a 3D printer, filling the carved areas with the nanoparticle of choice. The nanobot was built using the 3D printing method from the bottom up.

5.5. Biohybrid

Bio-hybrid systems employ the biomedical and robotic systems that Amal gates the biological and synthetic structural elements. Bio-nanoelectromechanical systems (Bio-NEMS) consist of nanoscale components like DNA, proteins, or nanoscale mechanical parts. The direct writing of nanoscale features using thiol-ene e-beams resist, followed by the functionalization of the natively reactive resist surface with biomolecules, allowed the writing of nanoscale features directly [62].

6. MECHANISM OF ACTION OF NANOBOT

Nanobot holds six degrees of freedom; they migrate around with fins, propellers and, translate, rotate in any direction. The unique sensory abilities permit the nanobot to identify target regions, barriers, and compounds sound in medical fields. The conduct of nanobot rely on random motions, chemical gradient detection and is functional in identifying therapeutic targets and drug delivery. The simulator allows multiple nanobots to function independently inside the body without interfering with the function of other nanobots [63].

6.1 Target identification

The capability of nanobots to move, sense, and manipulate objects is critical when interacting with target identification for disease therapy. Sensors and actuators can be controlled in various ways, depending on the medical application.

6.2 Sensor

Nanobots use their sensors to detect, identify the surrounding macroscale items in their environment, and target selective locations. External sensors on the nanobot alert it to collisions and detect a chemical signal or sudden temperature changes in specified areas. Chemical signals were used as a practical approach for medicine as a viable nanobot orientation. Every time the human body experiences an irregularity, a significant temperature rise may occur [64]. The temperature difference between the core temperature and the lesion site might be as high as 2 degrees Celsius [65]. As a result, scientists chose numerous organ-inlets as delivery targets to simulate nanobot intervention and contact with the workplace. These organ-inlets will produce chemical and thermal signals dependent on their protein requirement. Changes in chemical concentration will guide the nanobot. The nanobot can identify impediments across a distance of around 4 m, with an angular resolution corresponding to a 3 m diameter at that distance. The size of the biomolecule is so tiny that its accurate identification relies on chemical contact sensors. The sensing capabilities of nanobots enable it to assess the various sensing tasks it can perform. Chemical and thermal sensing are used to determine. How effectively may nanobot actuation be enhanced?

6.3 Actuation

The target of the nanobot includes identifying the chemical compound and reaching the target site to deliver the pre-set protein to the target organ site with a three-dimensional environment. The nanobot uses the control mechanisms incorporating movement throughout the environment to identify and reach the organ-inlets requiring protein medication delivery after identifying the biomolecules as proteins. Nanobot inside the body fluid Navigated through the two propellors that move with different velocities and adjust according to body fluid flow direction.

All objectives of nanobots in the task environment are listed in the simulator's position and orientation database. The simulator comprises many modules that imitate physical behavior, decide sensory information for each nanobot, control programs to determine nanobot actions, present the environment visually, and record the history of nanobot behaviour for later analysis. A multithreaded system is used in the computational technique to give dynamic updates for nanobot real-time sensing and activation (Fig. 4). The same concept and technique are used in respect to other nanobots and the workspace in general. Memory behaviour is based on pre-programmed actions and external stimuli trigger rules.

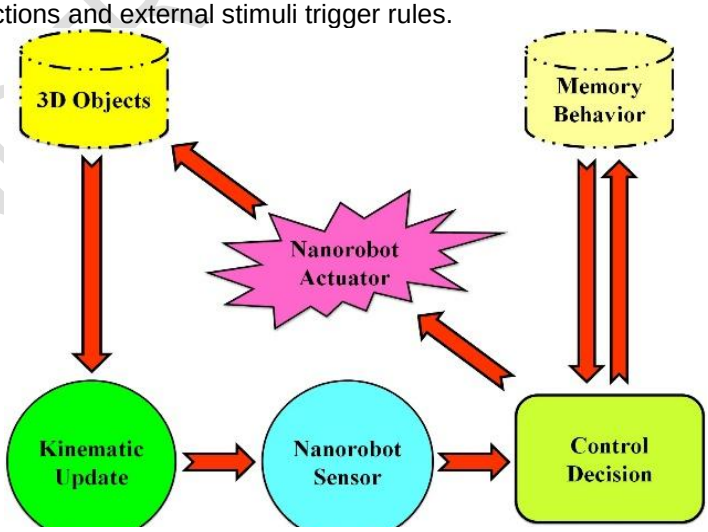

Fig. 4. Sensing and actuation of nanobot (*Nanobot simulation)*

7. IN-VIVO APPLICATIONS OF NANOBOT

Medical technology takes a long time to move from lab to clinical/commercialization. Still, exciting applications such as the ability to release the drug itself, sense the surrounding environment and act accordingly, and act as a neurotransmitter and many applications have grasped and convinced scientist attention to perform the in-vivo study. As a result, significant progress has been made in in-vivo research, from the initial proof of concept utilizing chemically propelled nanowires in peroxide to the recent explosion of in vivo investigations over the past three years; it took less than a decade. Table 1 describes the in-vivo studies performed and therapeutic outcomes of nanobots.

Table 1. *In-vivo* applications of nanobots.

Energy Source	Robotic Architect	In-Vivo Model	Purpose
Bio-hybrid	S. typhimurium functionalized mew particle (3 μm)	Mouse (Circulatory System, Thigh, Tail Veins).	Scanning of tumor site using fluorescene imaging [66]
	S. typhimurium engineered bacteria (1.2 μm)	Mouse (Colon)	Production and delivery of E-alpha emolysin against tumour in controlled manner [67]
Chemical	Zinc Micro rocket (15 μm)	Mouse (Stomach)	Holding of Cargo in stomach [68]
	Caco3 Janus NP (10μm)	Mouse (Tail, Liver) Pig (Femoral Artery)	Ceases bleeding [69]
	Mg Micro Rocket/Enteric Coating (15μm)	Mouse (GIT)	Targeted holding of cargo in different parts of GIT [70]
	Mg/Tio2/Chitosan Janus NP (20 μm)	Mouse (Stomach)	H. Pylori infection targeted therapy [71]
Physical	Polymer griper (300 μm)	Pig (Biliary Tree, Bile Duct)	Tissue biopsy [72]
	Magnetic microrod (300 μm Diameter)	Rabbit (Eye)	Intraocular navigation [73]
	Ni-Magnetic od (300*2 μm)	Mouse (Femoral Vessel, Brain)	Acceleration of thrombolysis [74]

8. THERAPEUTIC APPLICATIONS OF NANOBOT

8.1 Drug delivery for cancer diagnosis

Nanobot precision and speed for drug delivery within the body has forwarded its application towards in-vivo use [75]. The in-vitro evaluation of the nanobot showed chemotaxis and stimulus from the material subject activated the release of the drug towards the target [76,77]. For example, a magnetically controlled nanobot is used to administer fluorouracil medicine. That helped retard the tumor growth. The nanobot delivered a large volume of active drug in a targeted tumor area in the mice model by triggering the release of the drug from outside [78]. Transfer of nanoparticle attached with a payload of gene and protein within a mouse using listeria monocytogenes shows nanorobot also plays the role of releasing/distributing the payload within biotic species at the targeted sites. The luminescence produced after the payload delivery was used to measure gene expression [79]. A study over the application reveals the use of magnetotactic bacteria. Magnetotactic bacteria naturally created magnetic iron oxide particles and had shielded with the liposomes containing therapeutic payloads in-vitro [80]. These modified bacteria were employed to deliver drug-loaded liposomes in vivo to a mouse tumor site [81]. Recent breakthroughs in synthetic biology made it possible to deploy entirely bio-engineered biohybrid micro/nanobots that carry and deliver therapeutic payload without any inorganic/artificial components. *S. Typhimurium* has been discovered to create a therapeutic payload (-emolysin E, a pore-forming toxin) and release it when the bacteria are lysed using genetically modified bacteria [67].

8.2 Cell transportation and release

Nanobot simulated magnetically transported and delivered live cells to specific body locations. The HeLa cells were delivered and proliferated *in-vivo*. The transferred cells were released from the microrobot on their own and proliferated in the tissues [67]. These applications demonstrate, micro/nanobots could serve as a manifesto for regenerative medicine and cell-based therapy, potentially proving to be especially useful in the later stages of life, when organs and systems start to fail. Much more nanobot application in this context includes transporting and releasing cells by an in-vitro process such as guiding sperm toward an egg utilizing a helical structure for aided fertilization [82].

8.3 Retention of payloads in the gastrointestinal tract

Wang's with their colleague, developed a nanobot that used a gastric fluid as fuel and was driven by zinc and magnesium. Wang's nanobot increased payload retention of drug within the stomach [68,83] and accounted for the treatment of H. pylori bacterial illness and neutralization of gastric HCL [71,84]. The idea adopted for retention nanobot in the stomach by wang's is; 1) by the penetration of the nanobot within the surrounding tissue; 2) by improving the mass transport and nucleation caused by the gas bubble created as a means of movement for nanobot comparable to effervescences. Wang also used the polymer-coated magnesium-based nanobot to delay the activation and release of the drug or payload at the targeted site of the gastrointestinal tract. This polymer-coated magnesium dissolved at the neutral pH and triggered the release of the drug. The nanobot is selectively retained within the distinctive portion of the GIT according to the thickness of the coating [85].

8.4 Wound Healing

For detecting and mending wounds, the human body contains a variety of processes and biological triggers. However, when the damage is severe and bleeding profusely, or when there are insufficient localised coagulant factors in the target site, these biological mechanisms may fall short [85]. Medical micro/nanobots are working in this approach, aiming to simulate such systems by leveraging active delivery to promote fast and successful wound healing. The delivery of thrombin to stop the bleeding of wounds in the vasculature of mouse and pig models has been described using chemically propelled calcium carbonate-based microrobots. A combination of lateral propulsion, buoyant rise, and convection was used in the distribution mechanism [69].

8.5 Biopsy

Various in vitro systems for accurate micro/nanoscale surgery have been developed. But, their movement to in vivo models has yet to be done [86-89]. On the other hand, nanobots could be used synergistically to minimize invasive surgical procedures, enabling their use to suck tissues for use in biopsies or medicinal purposes. For example, remove the tissue from the bile duct of the pig via the using nanobot with a star-shaped gripper [72]—proof of using magnetic microrobots within a rabbit's eye for controlled navigation. The magnetized coil system allows the punctual wayfinding of the magnetic untethered microrobots in the posterior eye area [73,90]. The achievement of such applications shows the success of the chances of the robot's ability to affect its environment and the robot's controller's ability to retrieve the robots. The biopsy application of nanobots provides fertile ground for future nanobots research.

8.6 Local mixing for enhanced thrombolysis

In current medical treatments, the mixing effect is prominent for thrombus lysis. The scientist loaded the nanobot with the tissue plasminogen activator in the preclinical

stage. After administration in mouse (i.v.), nanobots were controlled magnetically. The vascular system blood brought the nanobot to the target site of the blood clot—the external magnetic field causes orientation in the nanobot resulting in the release of the tissue plasminogen. The factor is mixed with the blood and allows better tissue plasminogen activator molecule interaction with the blood clot interface results in a faster thrombolysis process [74]. The ability of nanobots to target blood clots in mice's brains was recently demonstrated [91].

8.7 Real-time imaging

Real-time imaging is not available for chemically propelled nanobots, posing a significant barrier to understanding their therapeutic effect. Real-time imaging is used by 75% of biohybrid robots, although fluorescence is the only technology used [66,67,79]. Imaging techniques of many kinds are used to support physical robots. Endoscopy and X-rays are two ways for detecting microgrippers inside the gastrointestinal system [72]. Fluorescence imaging techniques were employed to track the position of magnetically actuated helical microrobots inside the peritoneal cavity of a mouse [92] or subcutaneously [93], while optical cameras were used to see movement inside the eye [73,90].
In addition, biodegradable magnetic microhelix nanobots were detected in mice using a dual imaging method. The nanobots' position inside the subcutaneous tissue and intraperitoneal cavity was first determined using fluorescence imaging. The position of the nanobots inside the stomach of a mouse was determined using magnetic resonance imaging [94].

8.8 Toxicity

In animal models, most micro/nanobot studies only provide qualitative safety and toxicity assessments based on histology assays. Correct targeted administration requires understanding how foreign materials cluster throughout the body and how to reduce the dispersion of supplied micro/nanobots to non-target tissue while showing their specific effect on health. Each micro/nanobot design has its own set of safety issues. Biohybrids have the potential to invade and spread in unintended ways. Chemically driven micro/nanobots can alter the local chemical environment, perhaps affecting the microbiome of the gastrointestinal system. The majority of materials used in physical micro/nanobots are stiff and non-degradable, posing a threat. Despite these discrepancies, researchers might disclose more pertinent information to address toxicity even at this early stage.

The number of motors utilized for therapy (number or grams) indicates the escalation of units/dosage (the limit for toxicity and inefficacy). But most significantly, the dispersion and toxicity of the nanobot's constitutive components within the biological system are all potential parameters to consider.

8.9 Administration and retrieval

The most frequent administration and retrieval route for nanobots is injection (60 percent), followed by oral administration (30 percent), catheter (5 percent), and topical administration (5 percent) (5 percent). In terms of retrieval approach for micro/nanobots, biohybrid and chemical systems are biodegradable. Although the fate of their synthetic components was not always properly explained or demonstrated in some circumstances. The use of a magnetic catheter to enable both the deployment and recovery of microrobots in clinical practice [95] is a viable approach for retrieval. Recent in vitro research efforts have described totally biodegradable micro/nanobot systems [94,96-100].

9. PATENTS ON NANOBOT

Although significant work is currently pursuing nanobots, many nanobots and microbots structure paves their existence in the physical world. Nowadays, many patents are on the honor of scientists and perform the exotic application known worldwide. Some of the available patents on the nanobot are given in Table 2.

Table 2. Various patents on Nanobots.

Patent number	Publication date	Title
US 2008/0241065	02/10/2008	System and methods for the detection and analysis of in vivo circulating cells, entities and nanobot [100]
US 20110130325 A1	2/06/2011	Apoptosis- modulating protein therapy for proliferative disorders and nanoparticles containing the same [101]
US 20130224859 A1	29/08/2013	DNA origami devices [102]
WO 2014170899 A1	23/10/2014	Systems comprising nonimmunogenic and nuclease resistant nucleic acid origami devices for molecular computation [103]
US 20080269948 A1	30/10/2008	Hybrid control system for collectives of evolvable nanobot and microrobots [104]
US 8623638 B2	07/01/2014	Intelligent multifunctional medical device apparatus & Components [105]
20070225776A1	04/10/2007	Intracochlear nanotechnology and perfusion hearing aid device [106]

10. CONCLUSION

Nanorobots and NEMS are still in their early stages of development. Using biological motors and building artificial nanomachines, however, tremendous progress has been made. Nanodevice testing and coupling to create integrated systems that connect with the micro/macro world remain key problems. In modest numbers, AFMS successfully fabricates nanodevice and nanosystem prototypes and products. Chemical and physical procedures such as nano welding, chemical deposition, and simple heating can be used to link and assemble nanoscale objects. The field of medical nanorobotics has made significant progress. The in-vivo model's purpose is to assess the platforms' therapeutic efficacy and identify clinical risk, as analysing off-target consequences of nanorobots is just as important as assessing efficacy. The production of micro/nanostructure engines must take into account material biocompatibility and degradation, as well as in-vivo safety considerations. We should keep in mind that the plans and ambitions of a tiny number of scientists and engineers could soon have a direct and significant impact on the lives of millions of people. As a result, it's critical to think about the financial, societal, and ethical ramifications of using medical nanorobotics. These ramifications are anticipated to be comparable to those of major technical revolutions.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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