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Review

# Nanorobots in drug delivery systems and treatment of cancer

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**Abstract:** Cancer is the 3rd leading cause of death globally, and the countries with low-to-middle income account for most cancer cases. The current diagnostic tools, including imaging, molecular detection, and immune histochemistry (IHC), have intrinsic limitations, such as poor accuracy. However, researchers have been working to improve anti-cancer treatment using different drug delivery systems (DDS) to target tumor cells more precisely. Current advances, however, are enough to meet the growing call for more efficient drug delivery systems, but the adverse effects of these systems are a major problem. Nanorobots are typically controlled devices made up of nanometric component assemblies that can interact with and even diffuse the cellular membrane due to their small size, offering a direct channel to the cellular level. The nanorobots improve treatment efficiency by performing advanced biomedical therapies using minimally invasive operations. Chemotherapy's harsh side effects and untargeted drug distribution necessitate new cancer treatment trials. The nanorobots are currently designed to recognize 12 different types of cancer cells. Nanorobots are an emerging field of nanotechnology with nanoscale dimensions and are predictable to work at an atomic, molecular, and cellular level. Nanorobots to date are under the line of investigation, but some primary molecular models of these medically programmable machines have been tested. This review on nanorobots presents the various aspects allied, i.e., introduction, history, ideal characteristics, approaches in nanorobots, basis for the development, tool kit recognition and retrieval from the body, and application considering diagnosis and treatment.

**Keywords:** nanorobots; atherosclerosis; cancer; nano sensors; nanoscale

## 1. Introduction

Cancer is the 3rd leading cause of death globally, as almost every six deaths is caused by it. By 2030, it's expected to be 26 million new cases of cancer, with almost 17 million deaths per year. The countries with low-to-middle income account for most cancer cases that are expected to be 61% by 2050. In 1965, the International Agency for Research on Cancer (IARC) was established with the mission of conducting multidisciplinary investigations into the causes of human cancers. After conducting several studies, particularly on the structure of genes, experts have concluded that changes in human lifestyle, diet, and environmental factors have resulted in an increased number of cancer cases. The current diagnostic tools, including imaging, molecular detection, and immune histochemistry (IHC), have intrinsic limitations, such as poor accuracy. However, researchers have been working to improve anti-cancer medication delivery systems so that they can target tumor cells more precisely and create fewer adverse effects than chemotherapy. Current advances, however, will not be enough to meet the growing demand for more efficient drug delivery systems.

Nanorobots, an emerging technology, are nano-devices developed to perform specific tasks with precision at the nanoscale (1–100 nm). To perform these specific tasks, nanorobots are designed to work at cellular levels in medical fields. These are machines with nanoscale intelligence and information that can sense, signal, respond, and process. For the synthesis of nanorobots, the mainly used element is carbon due to its inertness, high thermal conductivity, and strength. Moreover, the externally passive diamond coating is performed to elude host immune system attack.

Recent advancement in this field leads to the development of nanorobotic drug delivery systems, including surgical and cellular repair nanorobots. First of all, in 1986, Eric Drexler presented the idea of inserting medical nanorobots into the human body. In these nanorobots, artificial mechanical RBCs (respirocytes), WBCs (microbivores), and platelets (clottocytes) were used. A group of scientists in Korea led by designed a nanorobot that can diffuse a cancer cell's outer surface and then destroy the cell from the inside. These machine nanoparticles are gold-made and frequently fold and unfold to destroy a cell without any anti-cancer drug. DNA-based cancer-fighting nanobots are being utilized to cure tumors. Similarly, in another study, a new cancer treatment idea is proposed in which nanorobots formed from fragments of DNA (deoxyribonucleic acid) can not only eradicate cancer cells in the body but also kill them. Nanorobots, however, have certain drawbacks, including expensive design and development, high complexity, and invisibility. It becomes harder for drug-loaded nanorobots to travel through blood arteries due to the high blood viscosity; however, researchers are working to address this issue.

The use of nanodevices with higher complexity and possible uses in cancer treatment is the most current challenge in nanotechnology. These nanorobots can support or improve treatment efficiency by performing advanced biomedical therapies using minimally invasive operations. Chemotherapy's harsh side effects and untargeted drug distribution necessitate new cancer treatment trials. The nanorobots are currently designed to recognize 12 different types of cancer cells. Furthermore, the molecular motors in this equipment can alter their response to UV light and pass through cellular layers to cause necrosis and medications to target specific areas.

The nanorobots, or nanoparticles, are made with a mixture of a polymer and a protein called transferring, which has the capacity of detecting tumor cells because of its molecular particularities. Once they are in the cells, the chemical sensor gives the order to dissolve, and when nanoparticles are dissolved, they let loose some substances that act on the RNA of each cell, disabling the gene responsible for the cancer. Specifically, what the nanoparticles deactivate is the ribonucleic redacts, the protein associated with the cancer growth that is fabricated by the disabled gene. Cancer can be successfully treated with current stages of medical technologies and therapy tools. However, a decisive factor to determine the chances for a patient with cancer to survive is: how earlier it was diagnosed; what means, if possible, a cancer should be detected at least before the metastasis has begun. Another important aspect of achieving a successful treatment for patients is the development of efficient targeted drug delivery to decrease the side effects from chemotherapy. Considering the properties of nanorobots to navigate as bloodborne devices, they can help on such extremely important aspects of cancer therapy. Nanorobots with embedded chemical biosensors can be used to perform detection of tumor cells in early stages of development inside the patient's body. Integrated nano sensors can be utilized for such a task in order to find the intensity of E-adhering signals. Therefore, a hardware architecture based on nano-bioelectronics is described for the application of nanorobots for cancer therapy [1–4].

## 2. History of nanorobots

1980's by Nobel Prize laureate Richard Smalley. Smalley has extended his vision to carbon nanotubes, discovered by Sumio Iijima, which he envisions as the next super interconnection for ultra-small electronics. The term nanotechnology has evolved to mean the manipulation of the elements to create unique and hopefully useful structures [4].

**Beginnings:** 1981: Gerd Binnig and Heinrich Rohrer of IBM Zürich invented the Scanning Tunneling Microscope (STM). Used for imaging surfaces at the atomic level and identifying some properties (i.e., energy). 1985: Discovery of fullerenes (molecules composed entirely of carbon). They have many applications in materials science, electronics, and nanotechnology. 1991: discovering carbon nanotubes (cylindrical fullerenes) as a direct result of the fullerenes. Exhibit high tensile strength, unique electrical properties, and efficient thermal conductivity. Their electrical properties make them ideal circuit components (i.e., transistors or sand ultra-capacitors). Recently, research in chemical and biomedical engineering has used carbon nanotubes as a vessel for delivering drugs into the body [5].

**Contents:** 1991: Invention of the Atomic Force Microscope (AFM). One of the foremost tools for imaging, measuring, and manipulating matter at the nanoscale. It performs sit functions by feeling the surface with a mechanical probe. Since it allows for precision interaction with materials on the nanoscale, it is considered a nanorobot. 2000: The United States National Nanotechnology Initiative is founded to coordinate federal research and development in nanotechnology. Marks the start of a serious effort in nanotechnology research. 2000: The company Nano Factory Collaboration is founded. Developing a research agenda for building a nano factory capable of building nanorobots for medical purposes. Currently, DNA machines (nucleic acid robots) are being developed. Performs mechanical-like movements, such as switching, in response to certain stimuli (inputs). Molecular-sized robots and machines paved the way for nanotechnology by creating smaller and smaller machines and robots.

## 3. Ideal characteristics

It will communicate with the doctor by encoding messages to acoustic signals at carrier wave frequencies of 1–100 MHz. It might produce multiple copies of it to replace worn-out units, a process called self-replication. After the completion of the task, it can be retrieved by allowing it to excuse itself via the usual human excretory channel, so it can also be removed by active scavenger systems. Nanorobots must have a size between 0.5 and 3 microns large with 1–100 nm parts. It will prevent itself from being attacked by the immune system by having a passive, diamond exterior [6].

### 3.1. Advantages of nanorobots

Nanotechnology enables us to create functional materials, devices, and systems by controlling matter at the atomic and molecular scales, and exploiting novel properties and phenomena.

- Cost benefit ration is great.
- Environmentally friendly.
- Little pollution from production.
- No wasted materials.
- Very durable.
- Can complete work faster than larger robots.
- Nanorobots can be programmed to self-replicate.
- As the nanorobot does not generate any harmful activities there is no side effect. It operates at specific sites only.
- It has no side effect.

### 3.2. Disadvantages of nanorobots

- The initial design cost is very high [7].
- The design of the nanorobot is a very complicated one.
- Electrical systems can create stray fields, which may activate bioelectric-based molecular recognition systems in biology.
- Electrical nanorobots are susceptible to electrical interference from external sources such as RF or electric fields, EMP pulses, and stray fields from other in vivo electrical devices.
- Hard to interface, customize, and design; complex.
- Nanorobots can cause a brutal risk in the field of terrorism. Terrorism and anti-groups can make use of nanorobots as a new form of torturing the communities, as nanotechnology also has the capability of destructing the human body at the molecular level.
- Privacy is the other potential risk involved with nanorobots. As nanorobots deal with the design of compact and minute devices, there are chances for more eavesdropping than that already exists in nanorobots.
- The nanorobot should be very accurate; otherwise, harmful effects may occur.

## 4. Nanorobots and drug delivery systems

Predictions about the use of nanorobots considered applications in the Central Nervous System (CNS), cancer treatment, body surveillance, delicate surgeries, and endoscopy, among others. Challenges such as limitations of nanotechnology and few studies focused on the fundamental understanding of behavior in the nanoworld, difficult handling, and construction of these nanomachines. In nanomedicine, it has been explored in DDS, which acts directly on target points of the human body. Researchers develop systems able to deliver drugs in specific locations, also controlling the dosage and frequency of this release. Drug delivery systems can be applied in the treatment of articular diseases, dental, diabetes, cancer, and others. Diseases such as neoplasms, hepatitis, diabetes, pulmonary, dentistry, and cancer can be used nanorobot technology as a means of implementing the DDS. One of the advantages of this technology is the diagnosis and treatment of diseases with minimum prejudice to the healthy cells, lowering the risk of unfavorable effects, and directing healing and reconstructive treatment at the cellular and subcellular levels [8–21].

## 5. Technology applied in nanorobots for use as DDS

Recent improvements in drug delivery turn up higher quality in targeted drug delivery that identifies the specific cells with the self of nano sensors and regulates the discharge by use of smart drugs. Some researchers classify nanorobots in drug delivery and therapeutics according to their application, which is described below: Pharmacy: Classified as medical nanorobots with a size of 1–2 μm able to carry up to 1 μm3 of a given drug in the tanks. They are controlled using mechanical systems for sorting pumps. Depending on the situation, the weight is discharged into the extracellular fluid or cytosol (the aqueous component of the cytoplasm of a cell). They are provided with molecular markers or chemotactic sensors that guarantee full targeting accuracy. Glucose and oxygen extracted from the local environment, such as blood, intestinal fluid, and cytosol, are the onboard power supplies. After the nanorobot completes tasks, they can be removed or recovered by centrifuge nan apheresis [22–28].

**Diagnosis and imaging**: The authors cite microchips that are overlaid with human molecules. The chip is projected to send an electrical signal when the molecules detect disease. Gives an example of special sensor nanorobots that can be introduced into the blood under the skin, where they verify blood contents and notify of any possible diseases. They can also be used to monitor the sugar level in the blood. The advantages are the low price to produce and ease of manipulation [26–32].

**Reciprocates:** It's about an artificial red blood cell, which is a blood-borne spherical 1 μm diamondoid 1000 atmosphere pressure vessel with reversible molecules and selective pumps. The power is obtained by endogenous serum glucose. This artificial cell can give 236 times more oxygen to the tissues per unit volume than RBCs (Red Blood Cells) and to administer acidity. The nanomachine is constructed with 18 billion atoms justly organized in a diamondoid pressure tank that is pumped full of up to 3 billion oxygen ($O_2$) and carbon dioxide ($CO_2$) molecules. It is impossible to release these gases from the tank. Gas concentration sensors on the outside will signal when it is time to discharge $O_2$ and unload $CO_2$ [26,27].

**Clottocytes:** This nanorobot is classified with a unique biological capability: "instant" hemostasis using clottocytes, or artificial mechanical platelets. It is known that platelets are roughly spheroidal nucleus-free blood cells measuring approximately 2 μm in diameter. Platelets join at a place of bleeding. There they are activated, becoming tacky and lumping together to form a tampon that aids in stamping the blood vessel and stopping the bleeding. They also deliver substances that help promote coagulation. Another interesting feature is its ability to perform phagocytosis of foreign particles and killing of microfilariae larval parasites. A complete functional design is elaborate, but the work of Freitas focuses on the purely mechanical aspects of the hemostatic function of platelets and reports the function in a small in vivo population of medical nanorobotic devices [33].

**Microbivores:** It is an oblate spheroidal device for biomedical applications with 3.4 μm in diameter along its major axis and 2.0 μm in diameter along its minor axis.

Composed precisely organized of 610 billion atoms in a 12.1 μm 3 geometric volume. The nanobot can continuously consume up to 200 PW. This power is used to digest trapped microbes. Microbivores have different characteristics of natural or antibiotic-assisted biological phagocytic defenses, acting approximately up to 1000 times faster. Another distinctive feature is related to the ability to phagocyte approximately 80 times more efficiently than macrophage agents in terms of volume/sec digested per unit volume of phagocytic agent. Thus, according to the existing technological proposals, nanorobots are an efficient and innovative way for applications in nanomedicine, including DDS and therapeutics (diagnostic and therapeutic) [34]. Searching keywords "drug delivery systems" in the database Periodic CAPES, it was obtained 176,511 publications. Only 0.21% is related to nanorobots, and in this amount of work, only 8% have a relationship between "drug delivery systems and nanorobots". Another database searched was Web of Science [35,36].

The results were 113,896 publications with the keyword "drug delivery" and 201 for nanorobots. The survey also showed that only 0.02% was published with the correlation "drug delivery and nanorobots". Before the number of published papers, it is noted that much more should be done so that nanomedicine can grow apace with the help of nanorobots in treating diseases, in particular cancer.

## 6. Drug delivery systems for anticancer drugs

The therapeutic index of most anticancer drugs is narrow, causing toxicity to normal stem cells, hematological adverse effects, and gastrointestinal effects, among others. Doxorubicin is used in several types of cancer, such as HD (Hodgkin's disease), in which treatment is administered in combination with other antineoplastic agents in order to reduce their toxicity [37]. Paclitaxel is administered by intravenous infusion and plays a role in the treatment of breast cancer.

Among the adverse effects encountered, some serious, are bone marrow suppression and cumulative neurotoxicity [38]. Cisplatin is an alkylating agent that causes intra-DNA-binding filaments. Some of its side effects are nausea and severe vomiting, as well as being nephrotoxic. Camptothecin is used in the treatment of neoplasias due to the inhibition of type I topoisomerases, an essential enzyme for the cellular replication of genetic material. Several efforts have been implemented to use nanotechnology to develop DDS that can minimize the harmful effects of conventional therapies. Clinical trials are studies in humans to measure the parameters of safety and efficacy of new drugs; they are essential for the arrival of new therapeutic alternatives in the market [39]. Anyway, just a few DDS reached more advanced stages of clinical evaluation, such as those consisting of doxorubicin, paclitaxel, camptothecin, and platinum complexes [40]. Doxorubicin was stacked on the surface of Single-Walled Carbon Nanotubes (SWNTs) [41]. Doxorubicin was employed as a polymer prodrug/collagen hybrid in metastatic tumor cells. The use of polymeric prodrug nanotechnology applied to the treatment of neoplasia shows up as a new development in this area boundary [42]. Super Paramagnetic Nanoparticles of Iron Oxide (SPIONs) loaded with doxorubicin were coated with modified inulin and evaluated for potential use in anti-neoplastic therapy [43].

This arch for biocompatible materials that can serve as a drug delivery system is always the focus of nanotechnology. Nanoparticles HA (hydroxyapatite)—a major constituent of bone and teeth—were used to carry Paclitaxel (tax), an antineoplastic agent, and the results suggest good expectations with treatment starting from hydrophobic drugs [44]. Searching carbon materials, nanoscale graphene oxide was tested as a drug carrier of anti-cancer [45].

Another possible application area of the drug delivery system is especially important in the intrathecal route of administration for the relief of pain related to certain types of cancer. The application drug delivery system intrathecal may be useful in refractory pain to others of administration or even in cases of persistent pain [46]. Again, observing the research with the themes "drug delivery systems and cancer" found a total of 31,134 publications. As noted in recent years, the interest increases in DDS have been directly associated with the need for alternative conventional chemotherapeutics, which possess some serious side effects for the patient [47].

### 6.1. Limitations of chemotherapy

Conventional chemotherapeutic agents work by destroying rapidly dividing cells, which is the main property of neoplastic cells. This is why chemotherapy also damages normal healthy cells that divide rapidly, such as cells in the bone marrow, macrophages, digestive tract, and hair follicles [48]. Conventional chemotherapy is that it cannot give selective action only to the cancerous cells. This results in common side effects of most chemotherapeutic agents, which include myelosuppression (decreased production of white blood cells causing immunosuppression), mucositis (inflammation of the lining of the digestive tract), alopecia (hair loss), organ dysfunction, and even anemia or thrombocytopenia. These side effects sometimes impose dose reduction, treatment delay, or discontinuance of the given therapy [49]. Furthermore, chemotherapeutic agents often cannot penetrate and reach the core of solid tumors, failing to kill the cancerous cells [50]. Traditional chemotherapeutic agents often get washed out from the circulation being engulfed by macrophages. Thus, they remain in circulation for a very short time and cannot interact with the cancerous cells, making the chemotherapy completely ineffective. The poor solubility of the drugs is also a major problem in conventional chemotherapy, making them unable to penetrate the biological membranes [51]. Another problem is associated with P-glycoprotein, a multidrug resistance protein that is overexpressed on the surface of cancerous cells, which prevents drug accumulation inside the tumor, acts as the efflux pump, and often mediates the development of resistance to anticancer drugs. Thus, the administered drugs remain unsuccessful or cannot bring the desired output [52–60].

### 6.2. Drug delivery and nanorobots in cancer treatment

The clinical use of nanorobots for diagnosis, therapeutic, and surgical purposes should be done with intravenous injection. Therefore, the nanorobots can be released directly into the patient's bloodstream. The major cancer treatment cycle for chemotherapy pharmacokinetics includes absorption and metabolism, plus a break for the body's re-establishment before the next chemotherapy session. Patients are normally treated in cycles of every 2 weeks for small tumors. As an initial time threshold for medical purposes, nanorobots should be able to analyze and provide a body diagnosis within one week through the use of proteomic-based sensors. The uptake kinetics of a low molecular weight using a magnetic resonance contrast agent can predict the delivery of protein drugs to solid tumors. Hence, a similar approach is useful to verify in vivo nanorobot biosensor activation through targeted detection.

The test and diagnosis are an important part of the research on nanorobots. It enables rapid testing and diagnosis at the first visit, so without the need for a follow-up visit after the lab test, and the detection of diseases at an earlier stage. The limitation in vivo use of nanorobots is the need for energy for propulsion. Higher levels of energy are required since "low inertia and high viscous forces are coupled with low efficiency and low convective motion". The fuels of chemically powered nanomotors were toxic. The availability of alternative sources of energy, such as sound waves and light, has led to an increase in the research on in vivo use of nanorobots, which resulted in more patent applications. One study of nanomotors is the acoustic propulsion of nanorod motors inside living cells" [61–67].

Which was a result of the development of ultrasonic-wave-powered minerals, which are safe for living systems. 65 reported an in vivo model of artificial micromotors in a living organism. The model examines the distribution, retention, cargo delivery, and acute toxicity role of synthetic motors in mouse stomachs via oral administration. This work is anticipated to significantly advance the emerging field of nano/micromotors and to open the door to in vivo evaluation and clinical applications of these synthetic motors. This development may be an important step for the possibility of in vivo applications of drug delivery for cancer treatment with decreasing the side effects of chemotherapy. Juul et al. published a paper on their research into nanorobots that contain medicine that can be opened and closed based on the surrounding temperatures. Recently, reported bacteria-based microrobots (bacteriology) as a new type of active drug delivery system. In the study, genetically modified non-toxic Salmonella typhi-murium (flagellar bacteria), which is attracted to chemicals released by cancer cells, is used. Perault and Shih from the Wyss Institute for Biologically Inspired Engineering at Harvard University introduced virus-inspired enveloped DNA nanostructures as a design strategy for biomedical applications. Recent studies revealed that nanotechnology, DNA engineering of molecular-scale devices with superb control over geometry, and site-specific functionalization promise fascinating advantages in advancing nanomedicine. However, instability in biological environments and innate immune activation remain obstacles for in vivo application. After nanorobots cross cellular membranes for targeted delivery, drug retention in the tumor will determine the therapeutic efficiency.

The chemotherapy is influenced by drug transfer processes from plasma to tissue in achieving more effective tumor chemotherapy based on its composition. Thus, the major advantage of nanorobots for cancer drug delivery is to minimize chemotherapy side effects. As the best approach, the nanorobot architecture incorporates CNT (carbon nanotubes) and DNA, which are recent candidates for new forms of nanoelectronics.

ACMOS (Complementary Metal Oxide Semiconductor) for constructing circuits with features in the tens of nanometers as a hybrid biosensor with single-chain antigen-binding proteins. This process uses activation based on proteomics and bioelectronics signals for formation release. Therefore, each time the nanorobot detects predefined changes in protein gradients, nanoactuators are activated to manipulate drug delivery. Changes to chemical and thermal signals are applicable conditions directly related to major medical target identification. Some examples of changing protein concentrations inside the body near a medical target under pathological circumstances are NOS (Nitric Oxide Synthase), E-cadherin, and BCL-2 [68,69].

## 7. Approaches in nanorobots

**Biochip:** The joint use of nanoelectronics, photolithography, and new biomaterials provides a possible approach to manufacturing nanorobots for common medical applications, such as surgical instrumentation, diagnosis, and drug delivery [69]. Biochips not only consist of immobilized molecules spatially addressed on planar surfaces but also contain biomolecules fixed in microchannels or microcells or on an array of beads or sensors. Nanotechnology has made biochips more applicable for commercialization purposes where biochips could be implanted inside the body to dynamically transmit information and monitor any biological changes in vivo [70].

**Nubot:** Nubot is an abbreviation for "nucleic acid robot". They are organic molecular machines [71]. DNA structure can provide means to assemble 2D and 3D nanomechanical devices. DNA-based machines can be activated using small molecules, proteins, and other molecules of DNA [72]. Nubots have DNA structures used for targeting drug delivery as a carrier.

**Bacteria-based:** This approach proposes the use of biological microorganisms, like the bacterium Escherichia coli. Thus, the model uses a flagellum for propulsion purposes. Electromagnetic fields normally control the motion of this kind of biologically integrated device.

**Open technology:** A document with a proposal for nanobiotech development using open technology approaches has been addressed to the United Nations General Assembly. According to the document sent to the UN, in the same way that open source has in recent years accelerated the development of computer systems, a similar approach should benefit society at large and accelerate nanorobots development.

**Nanobearing and nanogears:** To establish the feasibility of molecular manufacturing, it is first necessary to create and analyze possible designs for nanoscale mechanical parts that could, in principle, be manufactured [73]. "Ability to model molecular machines (systems and devices) of specific kinds, designed in part for ease of modeling, has far out run our ability to make them. Design calculations and computational experiments enable the theoretical studies of these devices, independent of the technologies needed to implement them." The simple structure and operation of molecular bearings make it the most convenient class of components to be designed. One of the simplest examples is Drexler's overlap-repulsion bearing design.

**Medical nanorobot architecture:** The main parameters used for the medical nanorobot architecture and its control activation, as well as the required technological background that may lead to manufacturing hardware for molecular machines, are described next.

**Manufacturing technology:** The ability to manufacture nanorobots may result from current trends and new methodologies in fabrication, computation, transducers, and manipulation. Depending on the case, different gradients on temperature, the concentration of chemicals in the bloodstream, and electromagnetic signature are some of the relevant parameters for diagnostic purposes [74].

CMOS VLSI (Very Large Scale Integration) systems designed using deep ultraviolet lithography provide high precision and a commercial way of manufacturing early nanodevices and nanoelectronics systems. The CMOS industry may successfully drive the pathway for the assembly processes needed to manufacture nanorobots, where the joint use of nano photonics and nanotubes may even accelerate further the actual levels of resolution ranging from 248 nm to 157 nm devices [75]. To validate designs and achieve a successful implementation, the use of VHDL (Verification Hardware Description Language) has become the most common methodology utilized in the integrated circuit manufacturing industry [76].

**Chemical sensor:** Manufacturing silicon-based chemical- and motion-sensor arrays using a two-level system architecture hierarchy has been successfully conducted in the last 15 years. Applications range from the automotive and chemical industry with detection of air to water element pattern recognition through embedded software programming to biomedical uses. Through the use of nanowires, the existing significant costs of energy demand for data transfer and circuit operation can be decreased by up to 60%. CMOS-based biosensors using nanowires as materials for circuit assembly can achieve maximal efficiency for applications regarding chemical changes, enabling new medical treatments [77]. Chemical nano sensors can be embedded in the nanorobot to monitor E-cadherin gradients. Thus, nanorobots programmed for such tasks can make a detailed screening of the patient's whole body. In our medical nanorobotic architecture, the mobile phone is applied to retrieve information about the patient's conditions [78,79]. For that, it uses electromagnetic waves to command and detect the current status of nanorobots inside the patient. New materials, such as strained channels with relaxed Si Gelayer scan, reduce self-heating and improve performance. Recent developments in 3D circuits and FinFET double-gates have achieved astonishing results, and according to the semiconductor roadmap, they should improve even more [80]. To further advance manufacturing techniques, Silicon-On-Insulator (SOI) technology has been used to assemble high-performance logic sub90nm circuits. Circuit design approaches to solve problems with bipolar effects and hysteretic variations based on SOI structure have been demonstrated successfully [81]. Thus, already-feasible 90nm and 45nm CMOS devices represent breakthrough technology devices that are already being utilized in products.

**Power supply:** The use of CMOS for active telemetry and power supply is the most effective and secure way to ensure energy as long as necessary to keep the nanorobot in operation. The same technique is also appropriate for other purposes, like digital bit-encoded data transfer from inside a human body [82]. Thus, nanocircuits with resonant electric properties can operate as a chip, providing electro-magnetic energy supplying 1.7 mA at 3.3 V for power, allowing the operation of many tasks with few or no significant losses during transmission [83]. Radio frequency-based telemetry procedures have demonstrated good results in patient monitoring and power transmission with the use of inductive coupling [84] using well-established techniques already widely used in commercial applications of RFID (Radio Frequency Identification Device). The energy received can also be saved in ranges of 1 μW while the nanorobot stays in inactive modes, just becoming active when signal patterns require it to do so. Some typical nanorobotic tasks may require the device only to spend low power amounts once it has been strategically activated. For communication, sending RF signals 1 mW is required. A practical way to achieve easy implementation of this architecture will obtain both energy and data transfer capabilities for nanorobots by employing mobile phones in such a process [85]. The mobile phone should be uploaded with the control software that includes the communication and energy transfer protocols.

**Data transmission:** The application of devices and sensors implanted inside the human body to transmit data about the health of patients can provide great advantages in continuous medical monitoring [86]. Most recently, the use of RFID for in vivo data collection and transmission was successfully tested for electroencephalograms. For communication in liquid workspaces, depending on the application, acoustic, light, RF, and chemical signals may be considered as possible choices for communication and data transmission. Chemical signaling is quite useful for nearby communication among nanorobots for some teamwork coordination [87]. Work with RFID has been developed as an integrated circuit device for medicine [88,89]. Using integrated sensors for data transfer is the better answer to reading and writing data in implanted devices. Teams of nanorobots may be equipped with single-chip RFID CMOS-based sensors. CMOS with a submicron system-on-chip design could be used for extremely low power and longer distances through acoustic sensors. For the nanorobot, active sonar communication frequencies may reach up to 20 µW @ 8 Hz at resonance rates with a 3V supply [90]. In our molecular machine architecture, to successfully set an embedded antenna with a 200 nm size for the nanorobot RF communication, a small loop planar device is adopted as an electromagnetic pick-up having a good matching on low noise amplifier; it is based on gold nanocrystal with 1.4 nm, CMOS, and nano electronic circuit technologies [91]. Frequencies ranging from 1 to 20 MHz can be successfully used for biomedical applications without any damage.

**Targets it and their communication with the machines [92]:** The nanorobot design includes integrated nano electronics which involves the use of mobile phones. It uses an RFID (CMOS transponder system) for in vivo positioning, using a well-established communication protocol that allows tracking information about its positioning. There are three approaches to recognizing the target site: first, as a point of comparison, the scientists use nanorobots with small Brownian motions to find the target by random search. In a second method, it monitors for chemical concentration significantly above the background level.

After detecting the signal, it estimates the concentration gradient and moves toward higher concentrations until it reaches the target. In the third approach, nanorobots at the target release another chemical, which others use as an additional guiding signal to the target. With these signal concentrations, only it passes within a few microns of the target is likely to detect the signal. Most recently, the use of RFID for in vivo data collection and transmission was successfully tested for electroencephalograms. For communication in liquid workspaces, depending on the application, acoustic, light, RF, and chemical signals may be considered as possible choices for communication and data transmission. One of the simplest ways to send broadcast-type messages into the body, to be received by in vivo nanorobots, is aural messaging. A device similar to an ultrasound probe would encode messages on aural carrier waves at frequencies between 1–10 MHz. Thus, the supervising physician can easily send new commands or parameters to nanorobots already at work inside the body. Each nanorobot has its own power supply, computer, and sensorium; thus, it can receive the physician's messages via aural sensors, then compute and implement the appropriate response. The other half of the process is getting messages back out of the body, from the working nanodevices out to the physician [93].

**Applications-diagnosis and treatment [92–94]:** Medical nanorobots can perform a vast array of diagnostic, testing, and monitoring functions, both in tissues and in the blood stream. These devices could continuously record and report all vital signs, including temperature, pressure, chemical composition, and immune system activity, from all different parts of the body.

**Cancer therapy:** Nanorobots with embedded chemical biosensors can be used to perform the detection of tumor cells in the early stages of development inside the patient's body. These nanorobots would search out and identify the cancer-affected cells using certain molecules as they could be introduced into the bloodstream. Medical nanorobots would then destroy these cells.

Nanorobots with chemical nano biosensors can be programmed to detect different levels of E-cadherin and beta-catenin as medical targets in primary and metastatic phases, helping target identification and drug delivery. Integrated nano sensors can be utilized for such a job to find the intensity of E-cadherin signals. Nanorobots could also carry the chemicals used in chemotherapy to treat cancer directly at the site.

**Diabetes:** The protein sodium-dependent glucose co-transporter system has an important influence in maintaining proper gastrointestinal cholinergic nerve and skeletal muscle function activities, regulating extracellular glucose concentration. The hSGLT3 molecule can serve to define glucose levels and serves as a sensor to identify glucose for diabetes patients. For glucose monitoring, the nanorobot uses an embedded chemo sensor that involves the modulation of hSGLT3 protein glucose sensor activity. Through its onboard chemical sensor, the nanorobot can thus effectively determine if the patient needs to inject insulin or take any further action, such as any medication clinically prescribed. They flow with the RBCs through the blood stream, detecting the glucose levels. In the medical nanorobot architecture, the significant measured data can be then transferred automatically through the RF signals to the mobile phone carried by the patient. At any time, if the glucose achieves critical levels, the nanorobot emits an alarm through the mobile phone.

## 8. Surgery

Surgical nanorobots could be introduced into the body through the vascular system or at the ends of catheters into various vessels and other cavities in the human body. A surgical nanorobot, programmed or guided by a human surgeon, could act as a semiautonomous on-site surgeon inside the human body. It performs various functions, such as searching for pathology and then diagnosing and correcting lesions by nanomanipulation, coordinated by an onboard computer while maintaining contact with the supervising surgeon via coded ultrasound signals. The earliest forms of cellular nano surgery are already being explored today.

## 8.1. As an artificial oxygen carrier

The artificial mechanical red cell, the respirocyte, is an imaginary nanorobot that floats all along in the bloodstream. The respirocyte is a tiny pressure tank that can be pumped full of oxygen ($O_2$) and carbon dioxide ($CO_2$) molecules. These gases can be released from the tiny tank in a controlled manner. When the nanorobot passes through the lung capillaries, $O_2$ partial pressure is high and $CO_2$ partial pressure is low, so the onboard computer tells the sorting rotors to load the tanks with oxygen and dump the $CO_2$. When the device later finds itself in the oxygen-starved peripheral tissues, the sensor readings are reversed. $CO_2$ partial pressure is relatively high and $O_2$ partial pressure is relatively low, so the onboard computer commands the sorting rotors to release $O_2$ and absorb $CO_2$. Respirocytes mimic the action of the natural hemoglobin-filled red blood cells and can deliver 236 times more oxygen per unit than a natural red cell.

## 8.2. As artificial phagocyte(microbivore)

Microbivore is an artificial mechanical phagocyte of microscopic size whose primary function is to destroy microbiological pathogens found in the human bloodstream using the “digest and discharge” protocol. The chief function of microbes is to wipe out microbiological pathogens found in the human bloodstream using the “digest and discharge” procedure. Microbivores, upon given intravenously (I.V.), would achieve complete clearance of the most severe septicemic infections in hours or less, far better than the weeks or months needed for antibiotic-assisted natural phagocytic defenses. The nanorobots do not boost the risk of sepsis or septic shock because the pathogens are completely digested into harmless simple sugars, mono-residue amino acids, mononucleotides, free fatty acids, and glycerol, which are the biologically inactive effluents from the nanorobot.

## 8.3. As artificial neurons

Nanorobots can be employed in replacing every neuron in one’s brain with a nanorobot that is designed to function just like normal, natural neurons. The nanotech neurons are functionally equivalent. They connect to the same synapse of the original neuron, and they perform the same functional roles.

**Atherosclerosis:** Medical nanorobots can locate atherosclerotic lesions in blood vessels, mainly in the coronary circulation, and treat them either mechanically, chemically, or pharmacologically.

**Cell repair and lysis:** An interesting utilization of nanorobots may be their attachment to transmigrating inflammatory cells or white blood cells to reach swollen tissues and assist in their healing process. Mobile cell-repair nanorobot is capable of limited vascular surface travel into the capillary bed of the targeted tissue or organ, followed by extravasations, histation, cyto-penetration, and complete chromatin replacement in the nucleus of one target cell, and ending with a return to the bloodstream and subsequent extraction of the device from the body, completing the cell repair mission.

**Hemophilia:** One particular kind of nanorobot is the choanocyte or artificial platelet. The choanocyte carries a small mesh net that dissolves into a sticky membrane upon contact with blood plasma. According to Freitas RA, the man who designed the choanocyte, clotting could be up to 1000 times faster than the body's natural clotting mechanism.

**Gout:** Gout is a situation where the kidneys lose the ability to remove waste from the breakdown of fats from the bloodstream. This waste sometimes crystallizes at points near joints like the knees and ankles. A nanorobot could break up the crystalline structures at the joints, providing relief from the symptoms, though it wouldn't be able to reverse the state permanently.

**Kidney stones:** Kidney stones can be intensely painful; the larger the stone, the more difficult it is to pass. An nanorobot could break up kidney stones using a small laser.

**Cleaning wounds:** Nanorobots could help remove debris from wounds, decreasing the likelihood of infection. They would be particularly useful in cases of puncture wounds, which can be difficult to treat using more conventional methods.

**Gene therapy:** Medical nanorobots can readily treat genetic diseases by comparing the molecular structures of both DNA and proteins found in the cell to known or desired reference structures. Any irregularities can then be corrected, or desired modifications can be edited in place. In some cases, chromosomal replacement therapy is more efficient than cyto repair.

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