Nano Robots in drug delivery systems and the treatment of cancer

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ABSTRACT:
Nan robotics is an emerging field of nanotechnology having nanoscale dimensions and is predictable to work at an atomic, molecular, and cellular level. The Nan robot skeleton is made up of carbon and its toolkit contains components like a medicine cavity containing medicine, a micro camera, a payload, a capacitor and a swimming tail. As nanorobots have special sensors i.e. physical or chemical which detect the target molecules in the human body can be used for the diagnosis and treatment of various vital diseases i.e. cancer, diabetes, atherosclerosis, haemophilia, kidney stones, etc. Nan robots 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 Nan robotics, basis for the development, tool kit recognition, and retrieval from the body, application considering diagnosis and treatment.

KEYWORDS: nanorobots, atherosclerosis, cancer, nanosensors, nanoscale.

Introduction

Nanotechnology provides a wide range of new technologies for optimizing the drug delivery of pharmaceutical products. Nanotechnology raises hopes for the patients that suffer from chronic diseases like cancer, multiple sclerosis, cardiovascular diseases etc.

Nanotechnology is a part of applied science whose theme is to control the matter on atomic and molecular scale. Nan medicine is a subfield of nanotechnology referred to the repair, construction and control of human biological systems using devices built upon nanotechnology standards.[1] the full potential of nanomedicine is unlikely to arrive until after complex, high-sophisticated, medically programmable nanomachines and nanorobots are developed. Nan medicine would make use of these nanorobots introduced into the body, to repair or detect damages and infections.[2]

Nanotechnology is a field of applied science focused on the design, synthesis, characterization and application of materials and devices on the nanoscale. The application of nanotechnology within medicine has the ability to revolutionize the cure, alleviation and prevention of disease drastically, and ultimately reinforce the restoration and preservation of health through the design, characterization, production and application of nano sized, intelligent materials. 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 free some substances which actuate on the RNA of each cell disabling the gene responsible of the cancer. Specifically, what the nanoparticles deactivate is the ribonucleic redacts, the protein associated with the cancer growth which 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 began. Another important aspect to achieve 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 blood borne devices, they can help on such extremely important aspects of cancer therapy. Nan robots with embedded chemical biosensors can be used to perform detection of tumor cells in early stages of development inside the patient's body. Integrated nanosensors can be utilized for such a task in order to find intensity of E-cadherin signals. Therefore a hardware architecture based on nanobioelectronics is described for the application of nanorobots for cancer therapy. Analyses and conclusions for the proposed model is obtained through real time 3D simulation.

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]
December 29, 1959: Richard Feynman gives the famous “There’s Plenty of Room at the Bottom” talk. - First use of the concepts of nanotechnology. Describes individual atoms and molecules that can be manipulated. 1974: Professor Norio Taniguchi defines nanotechnology as “the processing of, separation, consolidation, and deformation of materials by atom/molecule.”1980’s: Dr. Eric Drexler publishes several scientific articles promoting nanoscale phenomena and devices.1986: The book Engines of Creation: The Coming Era of

Nanotechnology by Dr. Eric Drexler is published. He envisioned nanorobots as self-replicating. A first book on nanotechnology.
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 and ultra-capacitors). Recently, research in chemical and biomedical engineering have 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 its 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: 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 size robots and machines paved the way for nanotechnology by creating smaller and smaller machines and robots.

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 channels or can also be removed by active scavenger systems Nan robots must have a size between 0.5 to 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].

ADVANTAGES OF NANOROBOT: 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
- Nan robots 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

DISADVANTAGES:

- 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 deals with the designing 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.

Nanorobotics and drug delivery systems[8-21]

Predictions about the use of nanorobotics 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 nanorobotics 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 stances .

Technology Applied in Nanorobotics for Use as DDS[22-28]

Recent improvements in drug delivery turn up higher quality in targeted drug delivery that identifies the specific cells with the self of nanosensors 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 size of 1-2 μm able to carry up to 1 μm3 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 environments such as blood, intestinal fluid, and cytosol are the onboard power supply. After the nanorobot completes tasks, they can be removed or recovered by centrifuge nan apheresis .

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 a disease. Gives an example of special sensor nanobots 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 easily of manipulation[26-32].

Respirocytes: It's about an artificial red blood cell which is a blood-borne spherical 1 μm diamondoid1,000-atmosphere pressure vessel with reversible molecules-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 (O2) and carbon dioxide (CO2) molecules. It is possible to release these gasses from the tank. Gas concentrationsensors on the outside will signal when it is time to discharge O2 and unload CO2 [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 2μm in diameter. Platelets join at a place of bleeding. There they are activated, becoming tacky, and lumping together to form a tampon that aids stamp 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 (2016) 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. Thenanobot can continually 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 1,000 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 theranostic[34](diagnostic and therapeutic). Searching keywords "drug delivery systems" in the database Periódicos CAPES [48], it was obtained 176,511 publications. Only 0.21% is related to nanorobotics, and in this amount of work only 8% have a relationship between "drug delivery systems and nanorobotics". Another database searched was WebOf Science [35-36]. The results were 113,896 publications with the keyword "drug delivery" and201 for nanorobotics. The survey also showed that only 0.02% was published with the correlation "drug delivery and nanorobotics". 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 nanorobotics in treating diseases, in particular cancer.

Drug Delivery Systems for Anticancer Drugs

The therapeutic index of most anticancer drugs is narrow, causing toxicity to normal stem cells, hematological adverse effects, gastrointestinal 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 which causes intra-DNA binding filaments. Some of its side effects are nausea and severe vomiting as well as can be nephrotoxic . Camptothecin is used in thetreatment 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, it is essential for the arrival of new therapeutic alternatives in the market [39]. Anyway, just a few Drug DeliverySystems reached more advanced stages of clinical evaluation such as consisting of doxorubicin, paclitaxel, camptothecin, and platinum complexes Anyway just a few DDS reached more advanced stages of clinical evaluation such as consisting of doxorubicin, paclitaxel, camptothecin, and platinum complexes[40]. Doxorubicin was stacked on the surface of Single-Walled Carbon Nanotubes (SWNTs)[41]. TheDoxorubicin 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]. Superparamagnetic Nanoparticles of Iron OxideSPIONs) loaded with doxorubicin were coated with modified inulin and evaluated when the potential use in antineoplastic therapy [43].

The search for biocompatible materials that can serve as a DrugDelivery System is always the focus of nanotechnology. Nanoparticle HA (Hydroxyapatite) – a major constituent of bone and teeth - were used to carryPaclitaxel (Tax), an antineoplastic agent - and the results suggest good expectation 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 of31134 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].

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 the cancerous cells, which prevents drug accumulation inside the tumor, acting 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 [52-55].

Nanorobots in Cancer Treatment Cancer could be defined as a group of diseases characterized by the uncontrolled growth and spread of abnormal cells in the body is what defines cancer, and the number of individuals affected each year continues to climb[56]. Cancer takes the first place in their search due to its effect of human life and its cost to the economy. Conforming to the Global OncologyTrend Report, by the IMS Institute for HealthcareInformatics, global spending on cancer medications reached $100 billion in 2014 . Cancer treatment is probably the main reason for the development of nanorobotics, it can be successfully treated with current stages of medical technologies and therapy tools with the help of nanorobotics. To determine the prognosis and chances for a patient with cancer to survive it could be considered: the time of disease evolution considering the diagnosis time if earlier have a better prognosis; another important aspect to achieve successful treatment for patients is the development of efficiently targeted drug delivery to decrease the side effects of chemotherapy [56]. Considering the properties of nanorobots to navigate as bloodborne devices, they can help important treatment processes of complex diseases in early diagnosis and smart drug delivery . A nanorobot can provide an efficient early diagnosis of cancer and help with smart chemotherapy for drug delivery.

Nanorobots as drug carriers for timely dosage regimens allow maintaining the chemical compounds for a longer time as necessary into the bloodstream circulation, providing predicted pharmacokinetic parameters for chemotherapy in anti-cancer treatments. It avoids the current resulting extravasations towards non-reticuloendothelial-located cancers with high degenerative side effects during the chemotherapeutic process. 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[57,58,59,60].

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 antigen detection . The test and diagnosis are an important part of the research on nanorobotics. It enables rapid testing 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 nanorobotics 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 "AcousticPropulsion 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. Gao et al. 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 *invivo* evaluation and clinical applications of these synthetic motors". This development may be an important step for the possibility of *in viv*o 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, Park et al. (2014) reported bacteria-based microrobot (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 are used. Perrault and Shih from Wyss Institute for Biologically Inspired Engineering at HarvardUniversity 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(Deoxyribonucleic acid) which are recent candidates for new forms of nanoelectronics .A CMOS (Complementary metal oxide semiconductor) for constructing circuits with feature sizes 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 medicament 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 .

Approaches in Nanorobotics:

Biochip:

The joint use of nanoelectronics, photolithography, and new biomaterials provides a possible approach to manufacturing nanorobots for common medical applications, such as for surgical instrumentation, diagnosis, and drug delivery[69]. Biochips not only consist of immobilized biomolecules 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].

Nubots:

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 biological integrated device.

Open Technology:
A document with a proposal on nano biotech 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 nanorobotics 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 outrun 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 technology background that may lead to manufacturing hardware for molecular machines, are described next.

1. **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 (Complementary Metal Oxide Semiconductor) industry may successfully drive the pathway for the assembly processes needed to manufacture nanorobots, where the joint use of nanophotonic and nanotubes may even accelerate further the actual levels of resolution ranging from 248nm to 157nm 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].

2. **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 auto motive and chemical industry with detection of air to water element pattern recognition through embedded software programming, and 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 material for circuit assembly can achieve maximal efficiency for applications regarding chemical changes, enabling new medical treatments[77]. Chemical nanosensors 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 SiGe layers can reduce self-heating and improve performance. Recent developments

in 3D circuits and FinFETs double-gates have achieved astonishing results and according to the semiconductor roadmap should improve even more[80]. To further advance manufacturing techniques, Silicon-On-Insulator (SOI) technology has been used to assemble high-performance logic sub 90nm circuits. Circuit design approaches to solve problems with bipolar effect and hysteretic variations based on SOI structures have been demonstrated successfully[81]. Thus, already-feasible 90nm and 45nm CMOS devices represent breakthrough technology devices that are already being utilized in products.

3. **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 electromagnetic energy supplying 1.7 mAat 3.3V for power, allowing the operation of many tasks with few or no significant losses during transmission[83]. RF-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[85]. The energy received can be also saved in ranges of ~1μW 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 ~1mW 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 process[86]. The mobile phone should be uploaded with the control software that includes the communication and energy transfer protocols.

4. **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[87]. Most recently, the use of RFID for in vivo data collecting 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[88]. Work with RFID (Radio Frequency Identification Device) has been developed as an integrated circuit device for medicine[89,90]. 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 submicron SoC design could be used for extremely low power longer distances through acoustic sensors. For the nanorobot active sonar communication frequencies may reach up to 20μW@8Hz at resonance rates with 3V supply[91]. In our molecular machine architecture, to successfully set an embedded antenna with 200nm 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 1.4nm, CMOS and nanoelectronic circuit technologies[92]. Frequencies ranging from 1 to 20MHz can be successfully used for biomedical applications without any damage.

Target Site and Their Communication with the Machines[93] :
The nanorobot design includes integrated nanoelectronics which involves the use of mobile phones. It uses RFID (radio frequency identification device) CMOS (complementary metal oxide semiconductor) 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 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 collecting 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 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[94].

Applications- Diagnosis and Treatment[95]
Medical nanorobots can perform a vast array of diagnostic, testing, and monitoring functions, both in tissues and in the bloodstream. 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 nanosensors 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[96].

Diabetes:
The protein hSGLT3 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 chemosensor 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 bloodstream 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[97].

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 nanosurgery are already being explored today [98].

As an Artificial Oxygen Carrier:
The artificial mechanical red cell, "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 (O2) and carbon dioxide (CO2) molecules. These gases can be released from the tiny tank in a controlled manner. When the nanorobot passes through the lung capillaries, O2 partial pressure is high and CO2 partial pressure is low, so the onboard computer tells the sorting rotors to load the tanks with oxygen and dump the CO2. When the device later finds itself in the oxygen-starved peripheral tissues, the sensor readings are reversed. CO2 partial pressure is relatively high and O2 partial pressure relatively low, so the onboard computer commands the sorting rotors to release O2 and absorb CO2. Respirocytes mimic the action of the natural hemoglobin-filled red blood cells and can deliver 236 times more oxygen per unit volume than a natural red cell[99].

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 microbivore 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[100].

As Artificial Neurons:
Nanorobots can be employed in replacing every neuron in one’s brain with a nanorobot which is designed to function just like normal, natural neurons. The nanotech neurons are functionally equivalent. They connect to the same synapses of the original neuron, and they perform the same functional roles[101].

Atherosclerosis:
Medical nanorobots can locate atherosclerotic lesions in blood vessels, mainly in the coronary circulation, and treat them either mechanically, chemically, or pharmacologically[102].

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, his natation, 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[103].

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 Robert A. Freitas, Jr., the man who designed the choanocyte, clotting could be up to 1,000 times faster than the body's natural clotting mechanism[104].

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. A 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 in cyto repair.

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