Review Article

NANOROBOTS: THE FUTURE TREND OF DRUG DELIVERY AND THERAPEUTICS

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ABSTRACT

Nanorobotics an advanced submicron device generally made of bio-nanocomponents. The present research work targets in diagnosing, treating and preventing disease improving the human health. The nanorobotics has an eminence future in the drug delivery technology. This review sums up the various possibilities in which they can turn up to be the important device for ultrafine targeted drug delivery. The works shows various trial of using molecular components to produce bio nanodevice. With the aid of biotechnology, molecular biology (as engineered organism) and molecular medicine can develop fully self sufficient nanorobots. In long term, perhaps 10-20 years from today, the earliest molecular machine system may join the medical and pharmaceutical armamentarium. In the pharmaceutical field it has an immense future as a drug delivery system at a ultrafine level. Various new approaches as pharmacyte, nanocar, microbevores, reperocytes are discussed in this review.

Keywords: Nanorobotics, Molecular medicine, Nanodevices.

INTRODUCTION

Nanotechnology can best be defined as a description of activities at the level of atoms and molecules that have applications in the real world. A nanometer is a billionth of a meter, that is, about 1/80,000 of the diameter of a human hair, or 10 times the diameter of a hydrogen atom. The size-related challenge is the ability to measure, manipulate, and assemble matter with features on the scale of 1-100nm. In order to achieve cost-effectiveness in nanotechnology it will be necessary to automate molecular manufacturing. The engineering of molecular products needs to be carried out by robotic devices, which have been termed nanorobots. A nanorobot is essentially a controllable machine at the nano meter or molecular scale that is composed of nano-scale components. The field of nanorobotics studies the design, manufacturing, programming and control of the nano-scale robots[1].

To start with, it would be targetable not just to specific tissues or organs, but to individual cellular addresses within a tissue or organ. Alternatively, it would be targetable to all individual cells within a given tissue or organ that possessed a particular characteristic (e.g., all cancer cells, or all bacterial cells of a definite species, etc.). This ideal vehicle would be biocompatible and virtually 100% reliable, with all drug molecules being delivered only to the desired target cells and none being delivered elsewhere so that unwanted side effects are eliminated. The ideal vehicle would remain under the continuous control of the supervising physician, including post-administration. Even after the vehicles had been injected into the body, the doctor would still be able to activate or inactivate them remotely, or alter their mode of action or operational parameters. Once treatment was completed, all of the vehicles could be removed intact from the body, leaving no trace of their presence. This hypothetical ideal drug delivery vehicle a "pharmacyte."[1] The application of advanced nanotechnology to medicine, or nanomedicine in particular, the future engineering discipline of medical nanorobotics will eventually make possible the design, fabrication, and therapeutic deployment of pharmacytes. Drug molecules could be purposely delivered to one cell, but not to an adjacent cell, in the same tissue. To fully appreciate the scope of this future development it is helpful to briefly review some of the background and recent history of medical nanorobotics. There is a development in this field which opens up other technology using micro/nano electronic mechanical system (MEMS,NEMS) using artificial tiny chips to assembled bionanorobotics. Just like pace maker there is a growth of replacing body cellular parts with artificial nanocompoments in near future.

A Brief History of Nanomedicine and nanorobotics: Nanomedicine and nanorobotics has been an important part of nanotechnology from the very beginning. And since nanotechnology began as a visionary enterprise, nanomedicine started by applying mainly nanomechanical concepts to the body. In 1999 book on Nanomedicine, Robert Freitas assembled an impressive array of ingenious ideas that derive from ongoing developments and inevitably lead to extravagant speculations [2]. Freitas's conflation of the short-term with the long-term and even with technical impossibilities remains characteristic even of the far more restrained technical papers of today. The 2004 presentation of the cancer nanotechnology initiative in the United States revolves around the goal of "eliminating death and suffering from cancer by 2015"[3]. The 2006 European Technology Platform on Nanomedicine is more subtle than this. It speaks of a "revolution in molecular imaging in the foreseeable future, leading to the detection of a single molecule or a

single cell in a complex biological environment"[4] .This statement elegantly glosses over the fact that the problems of detecting molecules and cells are magnitudes apart: Cells are a hundred to a thousand times larger than molecules and it is certainly much easier to imagine a contrast agent or marker attached to or inside a cell. In the same report, the speculative spirit of Eric Drexler and Robert Freitas informs a vision of cell-monitoring and repair: The detection of disease will happen as early as possible and "ultimately this will occur at the level of a single cell, combined with monitoring the effectiveness of therapy."

The most balanced overview of nanomedicine to date is the European Science Foundation's 2006 Forward Look on Nanomedicine. It is firmly grounded in current research. As it distances itself from speculation and hype, it seeks to give shape to a nanomedical research agenda that is clearly set apart from the grab-bag of nanotechnologies.9 In effect, the report drives a wedge between scientific nanomedicine and something lesser that might be called medical nanotechnology. Nanomedicine is based on molecular knowledge of the human body and it involves molecular tools for the diagnosis and treatment of disease. Medical nanotechnology encompasses all the other ways in which nanotechnology affects health care, especially all that comes from the miniaturisation of devices and the integration of information and communication technologies in diagnostic tools and health monitoring – including a radical transformation of the present day.

What is a nanorobot

Nanorobots are nanodevices with a diameter of about 0.5 to 3 microns and will be constructed within a dimensions in the range of 1 to 100 nanometers. The main element used will be carbon in the form of *diamond / fullerene nanocomposites* for the strength and chemical inertness of these forms to avoid being attacked by the host's immune system. Such devices have been designed in recent years but no working model has been built so far. The mobilizing of nanorobotsis an essential area for interest powering of the nanorobots can be done by metabolizing local glucose and oxygen for energy. In a clinical environment, another option would be externally supplied acoustic energy. Other sources of energy within the body can also be used to supply the necessary energy for the devices. They will have simple onboard computers capable of performing around 1000 or fewer computations per second. This is because their computing needs are simple. Communication with the device can be achieved by *broadcast-type acoustic signalling*.

Nanorobots would constitute any passive or active structure (nano scale) capable of actuation, sensing, signaling, information processing, intelligence, swarm behavior at nano scale. These functionalities could be illustrated individually or in combinations by a nano robot (swarm intelligence and co-operative behavior). So, there could be a whole genre of actuation and sensing or information processing nano robots having ability to interact and influence matter at the nano scale. Some of the characteristic abilities that are desirable for a nanorobot to function are:

i. Swarm Intelligence – decentralization and distributive intelligence

ii. Cooperative behavior – emergent and evolutionary behavior

iii. Self assembly and replication – assemblage at nano scale and 'nano maintenance'

iv. Nano Information processing and programmability – for programming and controlling nanorobots (autonomous nanorobots)

v. Nano to macro world interface architecture – an architecture enabling instant access to the nanorobots and its control and maintenance

There are many differences between macro and nano-scale robots. However, they occur mainly in the basic laws that govern their dynamics. Macro scaled robots are essentially in the Newtonian mechanics domain whereas the laws governing nanorobots are in the molecular quantum mechanics domain. Furthermore, uncertainty plays a crucial role in nanorobotic systems. The fundamental barrier for dealing with uncertainty at the nano scale is imposed by the quantum and the statistical mechanics and thermal excitations. For a certain nano system at some particular temperature, there are positional uncertainties, which cannot be modified or further reduced [2].

The nanorobots are not to naked eye, which makes it hard to manipulate and work with. Techniques like Scanning Electron Microscopy (SEM) and Atomic Force Microscopy (AFM) are employed to establish a visual interface to enable to sense the molecular structure of nano scaled devices. Virtual Reality (VR) techniques are currently being explored in nano-science and bio-technology research as a way to enhance the operator's perception by approaching more or less a state of 'full immersion' or 'telepresence'. The development of nanorobots or nano machine components presents difficult fabrication and control challenges. Such devices will operate in microenvironments whose physical properties differ from those encountered by conventional parts. Since these nano scale devices have not yet been fabricated, evaluating possible designs and control algorithms requires using theoretical estimates and virtual interfaces/ environments. Such interfaces/ simulations can operate at various levels of detail to trade-off physical accuracy, computational cost, number of components and the time over which the simulation follows the nano-object behaviors. They can enable nano-scientists to extend their eyes and hands into the nano-world and also enable new types of exploration and whole new classes of experiments in the biological and physical sciences. VR simulations can also be used to develop virtual assemblies of nano and bio-nano

components into mobile linkages and predict their performance. Nanorobots with completely artificial components have not been realized yet. The active area of research in this field is focused more on molecular robots, which are thoroughly inspired by nature's way of doing things at nano scale. Mother Nature has her own set of molecular machines that have been working for centuries, and have been optimized for performance and design over the ages. As our knowledge and understanding of these numerous machines continues to increase, we now see a possibility of using the natural machines, or creating synthetic ones from scratch, using nature's components. This chapter focuses more on molecular machines and explores various designs and research prevalent in this field. The main goal in the field of molecular machines is to use various biological elements — whose function at the cellular level creates motion, force or a signal — as machine components. These components perform their preprogrammed biological function in response to the specific physiochemical stimuli but in an artificial setting. In this way proteins and DNA could act as motors, mechanical joints, transmission elements, or sensors. If all these different components were assembled together in the proper proportion and orientation they would form nano devices with multiple degrees of freedom, able to apply forces and manipulate objects in the nanoscale world. The advantage of using nature's machine components is that they are highly efficient and reliable.

Nanorobotics is a field which calls for collaborative efforts of physicists, chemists, biologists, computer scientists, engineers and other specialists to work towards this common objective. Fig. 1 details the various fields which come under the field of bio nanorobotics (this is just a representative figure and not exhaustive in nature). Currently this field is still evolving, but several substantial steps have been taken by great researchers all over the world and are contributing to this ever challenging and exciting field.

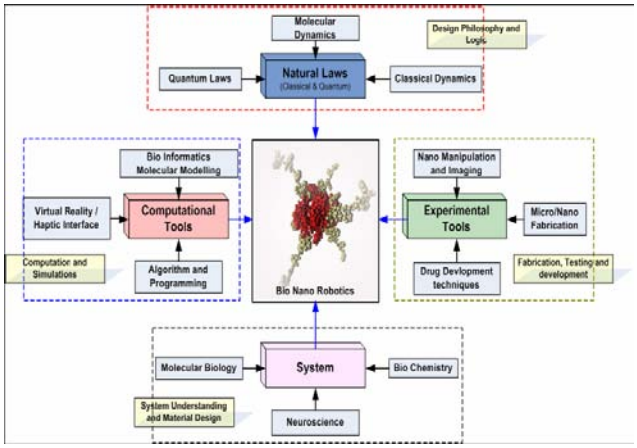

Figure 1: Bio nanorobotics – a field needs cooperation

The ability to manipulate matter at the nano scale is one core application for which nanorobots could be the technological solution. A lot has been written in the literature about the significance and motivation behind constructing a nanorobot. The applications range from medical to environmental sensing to space and military applications. Molecular construction of complex devices could be possible by nanorobots of the future. From precise drug delivery to repairing cells and fighting tumor cells; nanorobots are expected to revolutionize the medical industry.

Current status of bionanocomponents and nanodevice

1. Nanopores

They are considered as the earliest and simple medical active nanodevice generally comprising of nanosize perforations. In 1997 Desai and Ferrari created what could be considered one of the earliest therapeutically useful nanomedical devices[5] employing bulk micromachining to fabricate tiny cell-containing chambers within single crystalline silicon wafers. The pore size of 20 nm large enough to allow small molecules such as oxygen, glucose, and insulin to pass, but are small enough to impede the passage of much larger immune system molecules such as immunoglobulins and graft-borne virus particles. Safely ensconced behind this artificial barrier, immunoisolated encapsulated rat pancreatic cells may receive nutrients and remain healthy for weeks, secreting insulin back out through the pores while the immune system remains unaware of the foreign cells which it would normally attack and reject. Microcapsules containing replacement islets of Langerhans cells. The flow of materials through nanopores can also be externally regulated[6], t of the charge he nature is the driving force. Current research is directed toward reliably fabricating pores with specific diameters and repeatable geometries at high precision,[7] understanding the unzipping of double-stranded DNA as one strand is pulled through the pore[8] and the recognition of folded DNA molecules passing through the pore[9]

2. Molecular imprinting

Molecular imprinting[20-21] is an existing technique in which a mixture of functionalized monomers interacts reversibly with a target molecule using only noncovalent forces. The complex is then cross-linked and polymerized in a casting procedure, leaving behind a polymer with recognition sites complementary to the target molecule in both shape and functionality. Each such site constitutes an induced molecular "memory," capable of selectively binding the target species. Chiral separations, enzymatic transition state activity, and high receptor affinities have been demonstrated. Molecularly imprinted polymers could be medically useful in clinical applications such as controlled drug release, drug monitoring devices, quick biochemical separations and assays,[22] recognition elements in biosensors and chemosensors,[23] and biological and receptor mimics including artificial antibodies (plastibodies) or biomimicking enzymes (plastizymes)[23].

3. Quantum dots

Quantum dot are tiny particles measuring only a few nanometers across, about the same size as a protein

molecule or a short sequence of DNA. They come in a nearly unlimited palette of sharply-defined colors which can be customized by changing particle size or composition. P articles can be excited to fluorescence with white light, can be linked to biomolecules to form long-lived sensitive probes to identify specific compounds up to a thousand times brighter than conventional dyes used in many biological tests, and can track biological events by simultaneously tagging each biological component (e.g., different proteins or DNA sequences) with nanodots of specific color.

Quantum Dot Corp. (www.qdots.com), the manufacturer, believes this kind of flexibility could offer a cheap and easy way to screen a blood sample for the presence of a number of different viruses at the same time. It could also give physicians a fast diagnostic tool to detect, say, the presence of a particular set of proteins that strongly indicates a person is having a heart attack or to detect known cellular cancer markers[24]. On the research front, the ability to simultaneously tag multiple biomolecules both on and inside cells could allow scientists to watch the complex cellular changes and events associated with disease, providing valuable clues for the development of future pharmaceuticals and therapeutics.

4. Fullerenes and Nanotubes

Soluble derivatives of fullerenes such as C60 have shown great utility as pharmaceutical agents. These derivatives, many already in clinical trials (www.csixty.com), have good biocompatibility and low toxicity even at relatively high dosages. Fullerene compounds may serve as antiviral agents (most notably against HIV, where they have also been investigated computationally[25]), antibacterial agents (*E. coli*,[26] *Streptococcus*,[27] *Mycobacterium tuberculosis*,[28] etc.), photodynamic antitumor[29] and anticancer[30] therapies, antioxidants and anti-apoptosis agents which may include treatments for amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease)68 and Parkinson's disease. Single-w alled and multi-walled[31] carbon nanotubes are being investigated as biosensors, for example to detect glucose,[34] ethanol, hydrogen peroxide, selected proteins such as immunoglobulins,[33] and as an electrochemical DNA hybridization biosensor[32].

5. Targeted Nanoparticles and Smart Drugs

Drug targeting to the site specific is the growing demand in drug delivery superficially for the treatment of the diseases with minimum damage to the healthy cells lowering the risk of adverse effect. Recent development in drug delivery turns up for the ultra fine targeted drug delivery that sense the specific cells with the self of nanosensors and control the release by use of smart drugs. Research has been reported on the use of nanotubes of gold and sliver for the medium of gene delivery[35]. The use of the" smart bombs" for the treatment of cancer has received FDA approval comprising of radio therapeutic agents like yttrium and iodine to kill cancer cells [36]. Major work undertaken is in the field of enzyme activated drug delivery systems which depends on the interaction bio substrate with the enzyme in drug delivery to archive a site specific drug delivery. Works on an antibody directed enzyme-triggered prodrug cancer therapy is being developed by researchers at the University of Gottingen in Germany[37]. On the other hand Yoshihisa Suzuki at Kyoto University has designed a novel drug molecule that releases antibiotic only in the presence of an infection[38]. Nanoparticles with an even greater range of action are being developed by Raoul Kopelman's group at the University of Michigan. Their current goal is the development of novel molecular nanodevices for the early detection and therapy of brain cancer, using silica-coated iron oxide nanoparticles with a biocompatible polyethylene glycol coating.[39] Fei Yan, in Kopelman's lab, is working on these nanodevices, called the Dynamic Nano-Platform, now being commercialized as therapeutic "nanosomes" under license to Molecular Therapeutics (www.moleculartherapeutics.com).

6. Dendrimers

Dendrimers[40] represent yet another nanostructured material that are having a branched neural look. Starburst dendrimers are tree-shaped synthetic molecules with a regular branching structure emanating outward from a core that form nanometer by nanometer, with the number of synthetic steps or "generations" dictating the exact size of the particles, typically a few nanometers in spheroidal diameter. The peripheral layer can be made to form a dense field of molecular groups that serve as hooks for attaching other useful molecules, such as DNA, which can enter cells while avoiding triggering an immune response, unlike viral vectors commonly employed today for transfection. Upon encountering a living cell, dendrimers of a certain size trigger a process called endocytosis in which the cell's outermost membrane deforms into a tiny bubble, or vesicle. The vesicle encloses the dendrimer which is then admitted into the cell's interior. When released to the specific site it becomes a part of the genome of the cell. The technique has been tested on a variety of mammalian cell types[41] and in animal models[42].

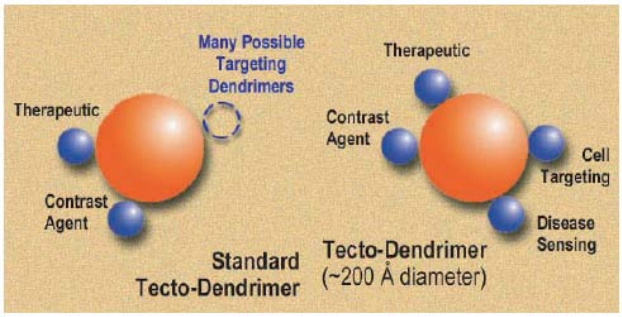

Figure 2: The standard tecto-dendrimer device, which may be composed of monitoring, sensing, therapeutic, and other useful functional modules. 106 Image courtesy of James Baker, University of Michigan.

At the University of Michigan is extending this work to the synthesis of multi-component nanodevices called tecto-dendrimers built up from a number of single-molecule

dendrimer components[43]. Tecto-dendrimers have a single core dendrimer surrounded by additional dendrimer modules of different types, each type designed to perform a function necessary to a smart therapeutic nanodevice (Fig.2). This device can help in (1) diseased cell recognition, (2) diagnosis of disease state, (3) drug delivery, (4) reporting location, and (5) reporting outcome of therapy.

7. Bionanorobotic devices

Here are the details of some of the man made and naturally occurring molecular machines. We divide the molecular machines into three broad categories – protein-based, DNA-based and chemical molecular motors. These motors in future trend binds with the other nanocomponets will act as the energy source for the nanorobots. Protein based molecular machines generally composed of i. ATP Synthase ii. The Kinesin, Myosin, Dynein and Flagella Molecular Motors. Walker et al. has worked to determine the rotation of at p synthatase and concluded that specific rotation occurs due to rotary motion between γ subunit and the alpha and beta hexamer[11] as in fig 3.

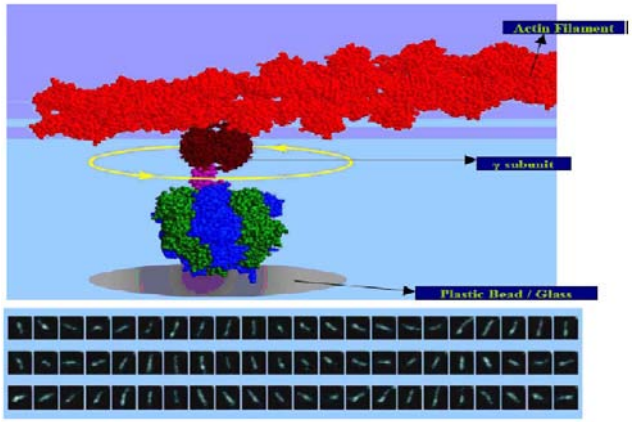

Figure 3: The given diagram (upper one) shows the effect of actin and other subunits in rotation. Lower photo graph as obtained from Kinosita labs shows the Images of a rotating actin filament (sequential image at 33ms intervals).

On the other hand DNA based machines are well accepted mechanoelectrical as well as electronic device[12-14]. Bernard Yurke and colleagues made an artificial DNA based molecular machine that also accepted DNA as a fuel[15]. The machine, called DNA tweezers, consisted of three strands of DNA labeled A, B and C. Strands B and C are partially hybridized on to the central strand A with overhangs on both ends.

Recent times chemists have been able to create modify and control many different types of molecular machines. Many of these machines have resemblance with everyday macro-scale machines such as gears, propellers, shuttles etc. Not only this, all of these machines are easy to synthesize artificially and are generally more robust than the natural molecular machines. Most of these machines are organic compounds of Carbon, Nitrogen and Hydrogen, with the presence of a metal ion being required occasionally. Electrostatic interactions, covalent and hydrogen bonding play essential role in the performance of these machines. Such artificial chemical machines are controllable in various ways – chemically, electrochemically and photochemically (through irradiation by light). Some of them are even controllable by more than one ways, rendering more flexibility and enhancing their utility. Rotaxanes[16-18] and Catenanes are the ideal examples. Rotaxane is characterized by a dumb-bell shaped compound with two heavy chemical groups at the ends and a light, cyclic component, called macrocycle, interlocked between the heads as shown in Fig. 4. It has been shown[19] that a reversible switch can be made with a rotaxane setup.

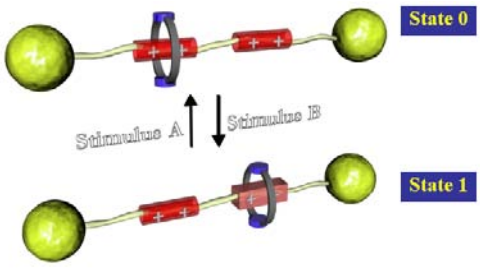

Figure 4: A typical rotaxane shuttle set-up. The macrocycle encircles the thread-like portion of the dumb-bell with heavy groups at its ends. The thread has two recognition sites which can be altered reversibly so as to make the macrocycle shuttle between the two sites.

The pathway of the development of nanorobots

The roadmap for the development of bio-nanorobotic systems for future applications is shown in Fig. 6. The roadmap progresses through the following main steps:

Step 1: Bio Nano Components

Development of bio-nano components from biological systems is the first step towards the design and development of an advanced bio-nanorobot, which could be used for future applications. Since the planned systems and devices will be composed of these components, we must have a sound understanding of how these behave and how could they be controlled. From the simple elements such as structural links to more advanced concepts such as motors, each component must be carefully studied and possibly manipulated to understand the functional limits of each one of them. DNA and carbon nanotubes are being fabricated into various shapes, enabling possibilities of constructing newer and complex devices. These nano-structures are potential candidates for integrating and housing the bio-nano components within them. Proteins such as ATP Synthase, kinase, etc could either be used as could be as the nano rotary moto that receives energy from photosensor proteins like rhodopsins. The initial work is intended to be on the bio-sensors, such as, heat shock factor. These sensors will form an integral part of the proposed bio-nano assemblies, where these will be integrated within a nano structure and will get activated, as programmed, for gathering the required information at

the nano scale as in (fig 5). Tools and techniques from molecular modeling and protein engineering will be used to design these modular components.

Step 2: Assembled Bio Nano Robots

The next step involves the assembly of functionally stable bio-nano components into complex assemblies. Some examples of such complex assemblies or bio-nanorobots (fig 5) . The modular organization defines the hierarchy rules and spatial arrangements of various modules of the bio-nano-robots such as: the inner core (the brain / energy source for the robot); the actuation unit; the sensory unit; and the signaling and information processing unit. By the beginning of this phase a "library of bio-nano components" will be developed, which will include various categories such as, actuation, energy source, sensory, signaling etc. Thereon, one will be able to design and develop such bio-nanosystems that will have enhanced mobile characteristics, and will be able to transport themselves as well as other objects to desired locations at nano scale. Furthermore, some bio-nanorobots will have the capability of assembling various bio-components and nano-structures from in situ resources to house fabrication sites and storage areas, while others will just manipulate existing structures by repairing damaged walls or making other renovations. There will also be robots that not only perform physical labor, but also sense the environment and react accordingly. There will be systems that will sense an oxygen deprivation and stimulate other components to generate oxygen, creating an environment with stable homoeostasis.

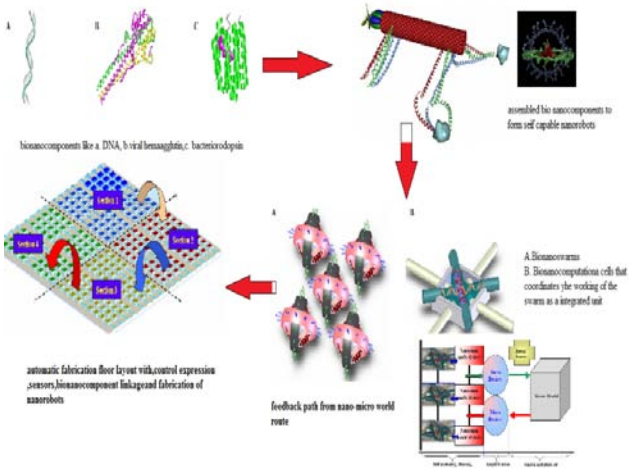

Figure 5: The gradual development of nanorobots in stepwise fashion as described.

Step 3: Distributive Intelligence, Programming and Control

With the individual bio-nanorobots in full function, they will now need to collaborate with one another to further develop systems and "colonies" of similar and diverse nanorobots. This design step will lay the foundation to the concept of bio-nano swarms (distributive bio-nanorobots) in fig 5. Here work has to be performed towards control and programming of bio-nano swarms. This will evolve concepts like distributive intelligence in the context of bio nanorobots. Designing swarms of bio-nano robots capable of carrying out complex tasks and capable of computing and collaborating amongst the group will be the focus. Therefore, the basic computational architectures needs to be developed and rules need to be evolved for the bio-nanorobots to make intelligent decisions at the nano scale.

Step 4: Automatic Fabrication and Information Processing Machines

For carrying out complex missions, such as sensing, signaling and storing, colonies of these bio-nanorobotic swarms needs to be created. The next step in nanorobotic designing would see the emergence of automatic fabrication methodologies of such bio-nano robots in vivo and in vitro. Capability of information processing, which will involve learning and decision making abilities, will be a key consideration of this step. This would enable bio-swarms to have capability of self-evolving based on the environment they will be subjected to. These swarms could be programmed to search for alternate energy sources and would have an ability to adapt as per that resource. Energy management, self-repairing, and evolving will be some of the characteristics of these swarms.

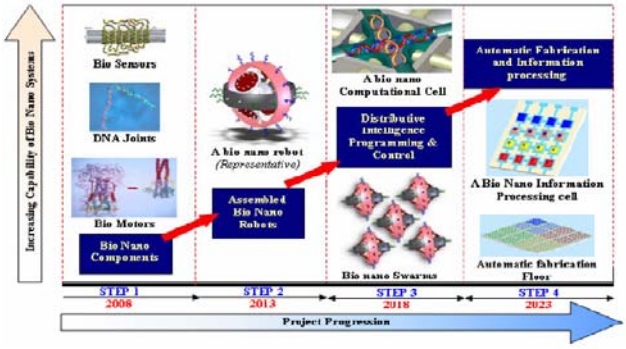

Figure 6: The path way of progress in the field of with the expected tenure.

Design Philosophy and Architecture for the Bio-Nanorobotic Systems[1]

a) Modular Organization: Modular organization defines the fundamental rule and hierarchy for constructing a bio-nanorobotic system. Such construction is performed through stable integration of the individual 'bio-modules or components', which constitute the bio-nanorobot. For example, if the entity **ABCD**, defines a bio-nanorobot having some functional specificity (as per the Capability Matrix defined in Table 1) then, A, B, C, and D are said to be the basic bio-modules defining it. The basic construction will be based on the techniques of molecular modeling with emphasis on principles such as Energy Minimization on the hyper surfaces of the bio-modules; Hybrid Quantum-Mechanical and Molecular Mechanical methods; Empirical Force field methods; and Maximum Entropy Production in least time.

Table 1: *Defining the Capability Matrix for the Bio-Modules*

Functionality	Bio Nano Code	Capabilities Targeted	General Applications
Energy Storage and Carrier	E	Ability to store energy from various sources such as, Solar, chemical for future usage and for its own working	Required for the working of all the bio-chemical mechanisms of the proposed bio-nano-robotic systems
Mechanical	M	Ability to precisely move and orient other molecules or modules at nano scale. This includes ability to mechanically bind to various target objects, and carry them at desired location.	1. Carry drugs and deliver it to the precise locations. 2. Move micro world objects with nano precision. For example, *Parallel platforms* for nano orientation and displacements.
Sensory	S	Sensing capabilities in various domains such as, chemical, mechanical, visual, auditory, electrical, magnetic	Evaluation and discovery of target locations based on either chemical properties, temperature or others characteristics.
Signaling	G	Ability to amplify the sensory data and communicate with bio-systems or with the micro controllers. Capability to identify their locations through various trigger mechanisms such as fluorescence	Imaging for Medical applications or for imaging changes in Nano Structures
Information storage	F	Ability to store information collected by the sensory element. Behave similar to a read - write mechanism in computer field	1. Store the sensory data for future signaling or usage 2. Read the stored data to carry out programmed functions. 3. Back bone for the sensory bio-module 4. Store nano world phenomenon currently not observed with ease
Swarm Behavior	W	Exhibit binding capabilities with "similar" bio-nano robots so as to perform distributive sensing, intelligence and action (energy storage) functions	All the tasks to be performed by the bio-nano robots will be planned and programmed keeping in mind the swarm behavior and capabilties
Bio Nano Intelligence	I	Capability of making decisions and performing Intelligent functions	Ability to make decision
Replication	R	Replicate themselves when required	1. Replicate at the target site and 2. Replication of a particular bio-module as per the demand of the situation

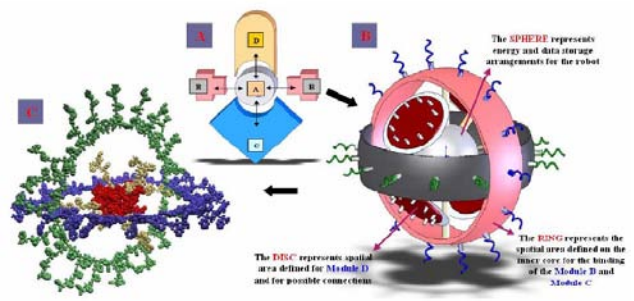

Figure 7: ***(A) A*** Bio-Nano-Robotic Entity 'ABCD', where A, B, C and D are the various Bio Modules constituting the bio-nano-robot. In our case these bio modules will be set of stable configurations of various proteins and DNAs. ***(B)*** A Bio-Nano-Robot (representative), as a result of the concept of Modular Organization. All the modules will be integrated in such a way so as to preserve the basic behavior (of self-assembly, self-replication and self organization) of the bio-components at all the hierarchies. The number of modules employed is not limited to four or any number. It's a function of the various capabilities required for a particular mission. ***(C)*** A molecular representation of the figure in part B. It shows the red core and green and blue sensory and actuation bio-modules.

Modular organization also enables the bio-nanorobots with capabilities such as, organizing into swarms, a feature, which is extremely desirable for various applications. Fig. 7A & B shows the conceptual representation of Modular Organization. Fig. 7C shows a more realistic scenario in which all the modules are defined in some particular spatial arrangements based on their functionality and structure. A particular module could consist of other group of modules, just like a fractal structure (defined as fractal modularity). The concept of Bio Nano Code has been devised, which basically describes the unique functionality of a bio nano component in terms of alphabetic codes. Each Bio Nano Code represents a particular module defining the structure of the bio nano robot. For instance, a code like **E-M-S** will describe a bio nano robot having capabilities of energy storage, mechanical actuation and signaling at the nano scale. Such representations will help in general classifications and representative mathematics of bio nanorobots and their swarms. Table 1 summarizes the proposed capabilities of the bio-modules along with their targeted general applications. The Bio Nano Code **EIWR || M || S || FG**

b) The Universal Template – Bio Nano STEM System: The modular construction concept involves designing a universal template for bio-nano systems, which could be 'programmed and grown' into any possible Bio Nano coded system. This concept mimics the embryonic stem cells found in the human beings, that are a kind of primitive human cells which give rise to all other specialized tissues found in a human foetus, and ultimately to all the three trillion cells in an adult human body. Our Bio Nano Stem system will act in a similar way. This universal growth template will be constituted of some basic Bio Nano Codes, which will define the Bio-

Nano-STEM system. This STEM system will be designed in a manner that could enable it to be programmed at run-time to any other required bio-module Bio-Nano STEM system, having the Bio Nano Code: EIWR || M || S || FG and having enhanced sensory abilities.

Applications of nanorobots in drug delivery and therapeutics:

1. Pharmacyte[44]

Pharmacyte are the medical nanorobots of size 1-2µm capable of carrying a drug load of $1\mu m^3$ in the tanks which are controlled by mechanically shorting pumps. Depending on the requirements the load is dumped in the extracellular fluid or cytosol. They are provided with a molecular markers or chemo tactic sensors that ensure 100% targeting accuracy. The on board power supply is provided with glucose and oxygen drawn from local environment such as blood, intestinal fluid and cytosol. After the task completion they can be removed or recovered via centrifuge nepheresis.

Pharamacyte can be used to –

- Deliver cytocidal agent targeting the cancer cells by cytopenetration or by nanoinjection.
- To enhance or upgrade cell signaling process in the body.
- It can serve as the source of hormonal replenishment from external source.
- Replacement of biochemical upon detection by markers and sensors for better cellular capacity.

2. Diagnosis and Imaging[45]

Nanobiotech scientists have successfully produced microchips that are coated with human molecules. The chip is designed to emit an electrical impulse signal when the molecules detect signs of a disease. Special sensor nanobots can be inserted into the blood under the skin where they check blood contents and warn of any possible diseases. They can also be used to monitor the sugar level in the blood. Advantages of using such nanobots are that they are very cheap to produce and easily.

3. Respirocytes[46]

This is a artificial mechanical red blood cell which is a bloodborne spherical 1-diamondoid 1000-atm pressure vessel (Fig. 8) it has active pumping powered by serum glucose, able to deliver 236 times more oxygen to the tissues per unit volume than natural red cells and to manage acidity. The nanorobot is made of 18 billion atoms precisely arranged in a diamondoid pressure tank that can be pumped full of up to 3 billion oxygen (O2) and carbon dioxide (CO2) molecules. Later, these gases can be released from the tank in a controlled manner, using the same molecular pumps. Respirocytes mimic the action of the natural hemoglobin-filled red blood cells. Gas concentration sensors on the outside of each device let the nanorobot know when it is time to load O2 and unload CO2 (at the lungs), or vice versa (at the tissues). An onboard nanocomputer and numerous chemical and pressure sensors enable complex device behaviors remotely reprogrammable by the physician via externally applied acoustic signals.

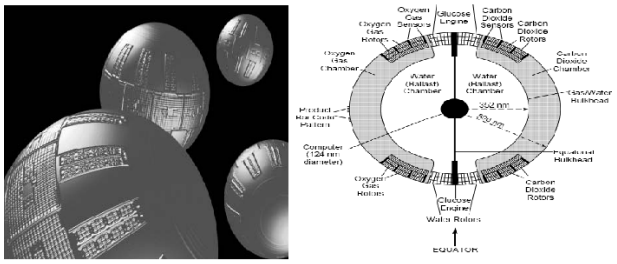

Figure 8: An artificial red cell: the respirocyte

Each respirocyte can store and transport 236 times as much gas per unit volume as a natural red cell, so the injection of a 5-cc therapeutic dose of 50% respirocyte saline suspension, a total of 5 trillion individual nanorobots, into the human bloodstream can exactly replace the gas carrying capacity of the patient's entire 5.4 L of blood. If up to 1 L of respirocyte suspension could safely be added to the human bloodstream this could keep a patient's tissues safely oxygenated for up to 4 h in the event a heart attack caused the heart to stop beating, or it would enable a healthy person to sit quietly at the bottom of a swimming pool for 4h, holding his breath, or to sprint at top speed for at least 15 min without breathing. Primary medical applications of respirocytes will include transfusable blood substitution; partial treatment for anemia, perinatal/neonatal, and lung disorders; enhancement of cardiovascular/ neurovascular procedures, tumor therapies, and diagnostics; prevention of asphyxia; artificial breathing; and a variety of sports, veterinary, battlefield, and other uses.

4. Microbivores[47-48]

An artificial mechanical white cell of microscopic size, called a "microbivore," has as its primary function destroying microbiological pathogens found in the human bloodstream, using a digest and discharge protocol. The microbivore is an oblate spheroidal nanomedical device (Fig. 10) measuring 3.4 μ in diameter along its major axis and 2.0 μ in diameter along its minor axis, consisting of 610 billion precisely arranged structural atoms in a gross geometric volume of 12.1 μ^3 and a dry mass of 12.2 pg. The device may consume up to 200 pW of continuous power while completely digesting trapped microbes at a maximum throughput of 2 μ^3 of organic material per 30-s cycle, which is large enough to internalize a single microbe from virtually any major bacteremic species in a single gulp. The nanorobots would be 80 times more efficient as phagocytic agents than macrophages in terms of volume/s digested per unit volume of phagocytic agent, and the nanorobots would have far larger maximum lifetime capacity for phagocytosis than natural white blood cells.

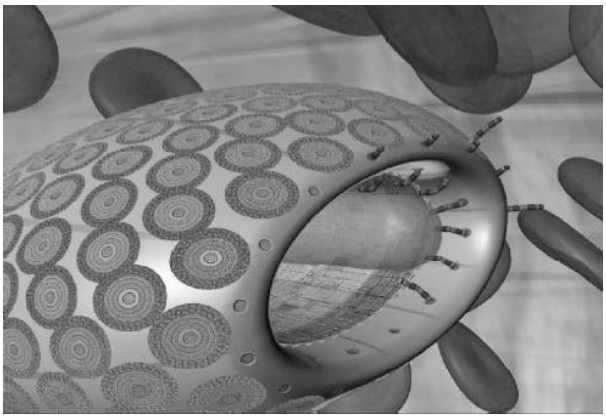

Figure 9: An artificial white cell: the microbivore

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