

In-Vivo NanoBot aided Cancerous Tissue Targeting And Therapy

**– A Paper on a conceptual NanoBot capable of In-Vivo Cancer
Sensing & Therapy**

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Abstract

Nanotechnology is playing a pivotal role in detection and therapy of Cancer. This paper tries to bring disparate technologies of the Nanotech arena involved in detection and treatment of cancer. A conceptual design of a futuristic NanoBot based on today's Nanotech capabilities is discussed. Such a NanoBot when injected into the blood stream would zoom into the target site, sense the cancerous tissue and deliver the requisite drug to the exact site. This would involve a *NanoCarrier* for In-Vivo locomotion, *NanoSensor* for sensing the Cancerous tissue/cells and finally the *DrugEncapsulate* for encapsulating the drug & controlled delivery to the exact location. The whole NanoBot would be controlled by a NanoComputer/brain. Technologies and approaches to design each of these units and how each of them fit into the final NanoBot unit is discussed.

Introduction:

Research on use of Nanotechnology in treatment and early detection of Cancer is going on in many universities across the world. Some of the possibilities of Nanotechnology in medicine has been inspiration for the Science Fiction classic film “Fantastic Voyage” where tiny submarine ships/nanobots were injected into the body and travelled through the bloodstream to eradicate foreign bodies. The reality is more prosaic, but the potential is nonetheless exciting.

Various breakthroughs have been achieved in disparate areas of Cancer treatment and management like effective detection of cancer, delivery of targeted therapeutics and monitoring of the effectiveness of cancer interventions. Still, a comprehensive approach to actual, real-world use of these techniques in Cancer detection and treatment is not in vogue, at least not yet.

This paper tries to bring together the disparate approaches that have been developed, to fit the pieces of jigsaws and suggest a conceptual idea of a Nanobot effective enough to selectively target and destroy malignant Cancerous tissue.

Existing Treatment Methods¹:

There are many ways to treat cancer ranging from Chemotherapy to immunotherapy, though each method has its own risks and side effects. The treatment method depends on the extent or stage of cancer and the extent to which it has spread. And in most cases a combination of methods are employed in therapy.

i. Chemotherapy

Chemotherapy is the an aggressive method of treatment which relies on anti-cancer medications (usually an assortment of drugs) to control cancer. The drugs are administered intravenously, in pill form or even applied directly to the skin. The drugs acts by interrupting the process of metastasis of the cancerous cells. Sometimes chemotherapy is given along with radiation therapy.

The worst part of Chemotherapy is its side-effects which include hair loss, severe nausea, rashes etc. This is because most often the drugs used start destroying the healthy cells along with the malignant ones.

ii. Radiation Therapy

Radiation therapy uses energy to shrink tumors and kill cancer cells. It has particularly been effective in treating cancers of the head and neck, and bladder and lung cancer. This technique relies on the use of certain types of energy radiations to kill cancer cells and shrink tumors. These could be in the form of waves or particles like protons, electrons, x-rays and gamma rays. It is basically of two types; Internal

radiation (Brachytherapy) which uses radiation that is placed very close to the tumor site in form of a small container, called an implant and External radiation (Systemic), in which a machine called linear accelerators is used to point radiation at the cancerous cells and surrounding tissues (like nearby lymph nodes). Like other treatment methods the side effects include fatigue, changes of the skin, loss of appetite. Also in certain cases radiation is found to have resulted in other forms of cancer in the patient on which the same was administered.

iii. **Surgery**

This is usually the first choice used by physicians. It also has an important role in diagnosing and staging of cancer. Prophylactic/Preventive surgery is used to remove tissues which are not malignant, but are liable to turn cancerous. Diagnostic surgery is used to obtain a tissue sample to analyze whether or not it is malignant or to determine the type of cancer it is. Curative surgery is the removal of a tumor when it appears to be confined to one area. It is done when it's possible by surgery to remove whole of the malignant tissue. It is a primary treatment of cancer and may be used alone or along with chemotherapy or radiation therapy.

However, it is not effective if the cancer has spread. Also there is the normal risks of complications, associated with most surgeries.

Why Nanotechnology for Cancer Therapy³

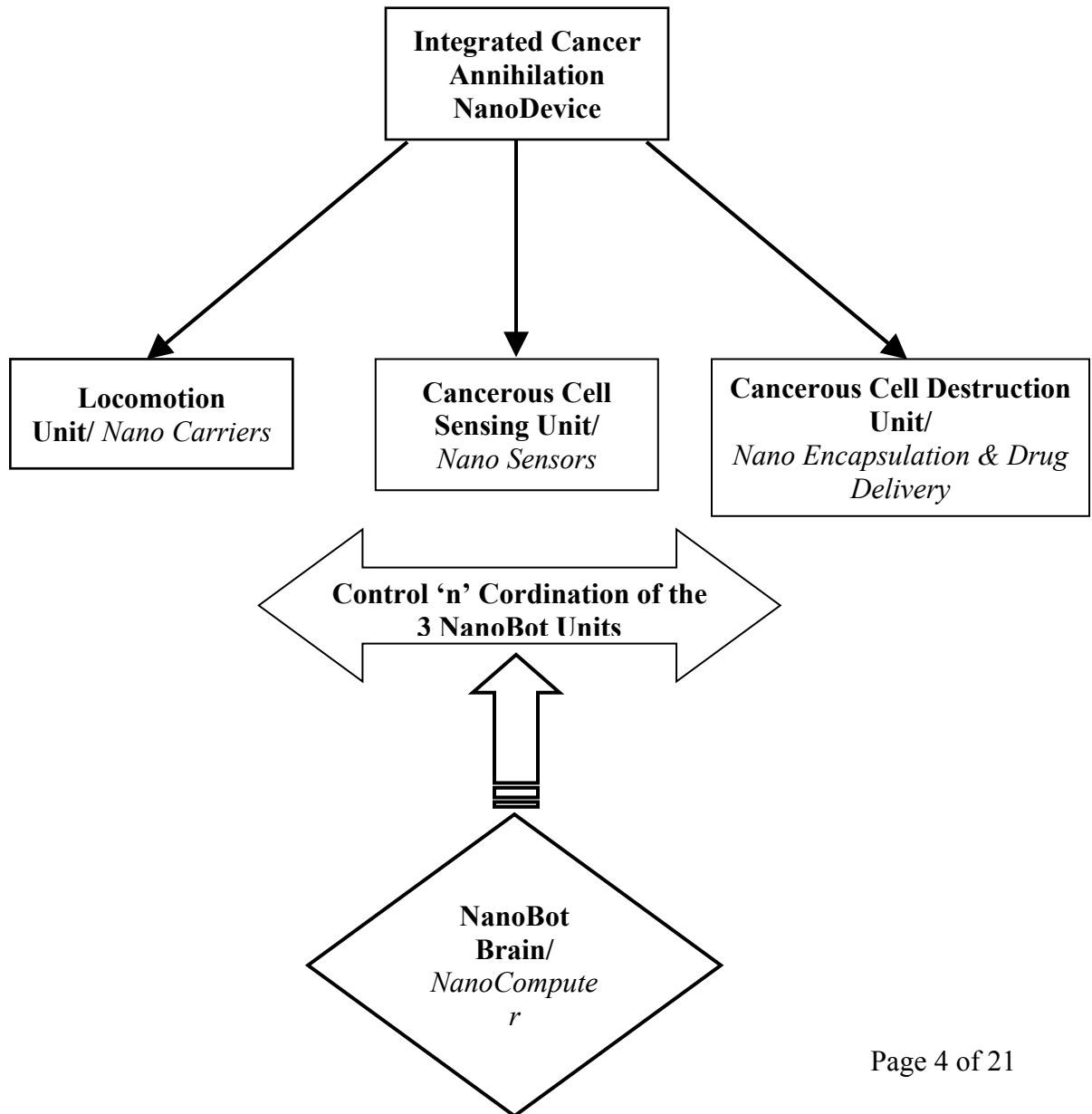
Nanotechnology could be used in both cancer diagnosis and therapy. It could overcome most of the shortcomings (like collateral damage to healthy cells) of the conventional methods of Cancer diagnosis/treatment. The key reasons that nanotechnology could help transform cancer research and clinical approaches to cancer care are :-

- Most biological processes, including those processes leading to cancer, occur at the nanoscale. For cancer researchers, the ability of nanoscale devices to easily access the interior of a living cell affords the opportunity for unprecedented gains on both clinical and basic research frontiers.
- The ability to simultaneously interact with multiple critical proteins and nucleic acids at the molecular level will provide a better understanding of the complex regulatory and signaling patterns that govern the behavior of cells in their normal state as well as the transformation into malignant cells.
- Nanotechnology provides a platform for integrating research in proteomics -- the study of the structure and function of proteins, including the way they work and interact with each other inside cells -- with other scientific investigations into the molecular nature of cancer.

Proposed NanoBot Design for In-Vivo Cancer Sensing And Therapy

In Cancer Therapy, targeting and localized delivery are the key challenges. To overcome the shortcomings of conventional methods, we have to selectively attack the cancer cells, while saving the non-malignant tissue from excessive burdens of drug toxicity. Theoretically, the proposed Bot should do the following :-

- Nano-Sensors to sense the presense of malignant cells in body
- Nano carriers to carry the combined NanoSensor-NanoDrugEncapsulate to vicinity of cancerous tissues
- Nano drug delivery particles to encapsulate drugs to be delivered at specific cancerous tissue sites and controlled drug-delivery at specific sites
- A Nano-Computer/Brain to integrate the above activities in a complex In-Vivo environment



NanoCarriers

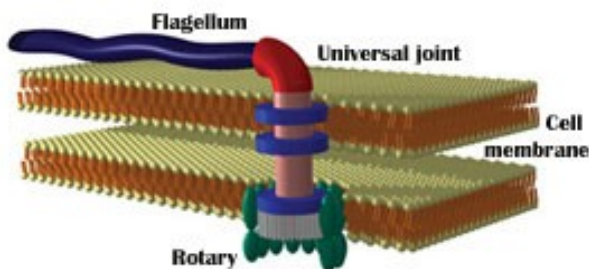
The primary purpose of NanoCarrier would be capability of automated navigation in the human body, to the vicinity of the organ/tissue where carcinogenic tissue is suspected. Understanding the motion of lower animal forms, such as bacterial Flagellar motion, can help to design and fabricate bio-inspired robots able to navigate in tortuous, slippery and difficult -to-access cavities of the human body. In general, such an approach is termed as *Biomimetics*.

A preliminary analysis of different approaches to development of an automated NanoCarrier including In-Vivo Navigation Strategies and Simulation as a tool for NanoBot prototype development is discussed here.

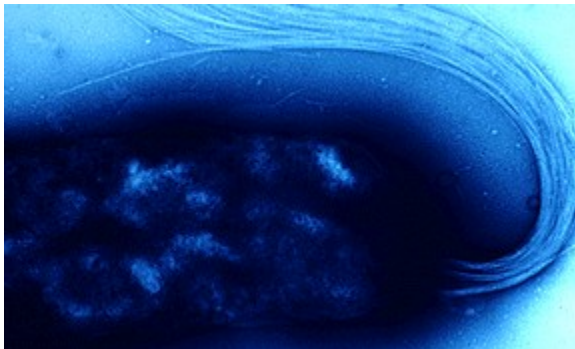
Bio-inspired Solutions/Biomimetics for NanoBot Locomotion

A: Modelling on Bacterial Flagellum

Organisms like Bacteria or worms (both harmful pathogens & useful) have long thrived in human body. The ease with which such organisms travel in the human body fluids point to the utility in studying them to design a similar automated nanobot locomotion system.



[Fig 1:](#) A bacterial flagellum about the size of 25 nanometres



[Fig 2:](#) An electron microscope image of bacterial

A study of engineering complexity of a bacterial flagellum reveals immense complexity. The bacterium moves about with a whip-like flagellum, driven by a bio-motor embedded in the outer shell. The flagellar motor is powered by proton flow, and closely resembles microscopic electric motors, powered by electron flow. The motor generates waves in the cord, which drive the germ forward.

A bacterial flagellar motor has the amazing quality of combining speed with efficiency. These are extremely efficient motors which can quickly stop, start, change speeds, and reach a top speed of about 100,000 rpm. The cell is propelled up to 15 body-lengths per second at top speed.

Also it is very versatile, as it has forward and reverse gears, enabling the germ to reverse direction within a quarter of a turn. In contrast most man-made electric motors are up to 75–95% efficient at larger sizes, but lose efficiency as they get smaller. The bacterial motor is almost 100% efficient at cruising speed. The bacterium uses only 2% of its total energy for swimming.

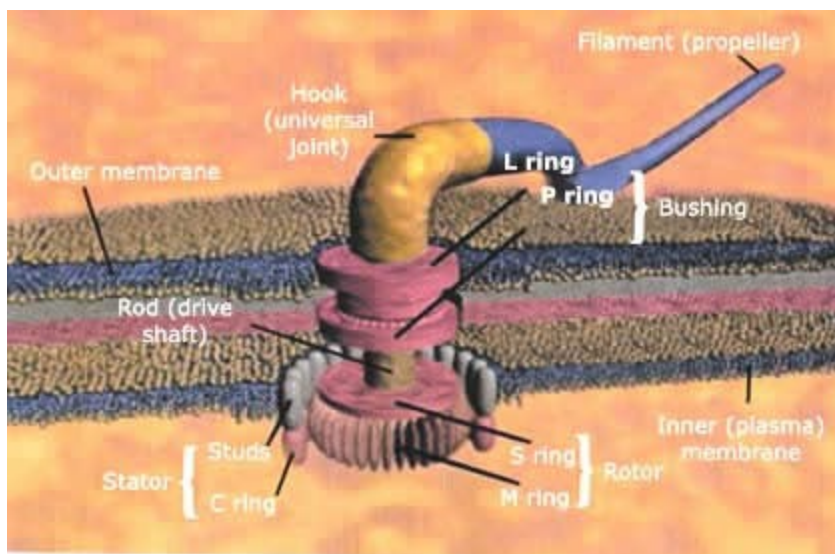


Fig 3: A schematic machine modelled on a flagellum

B: Modelling on Tapeworm Motion⁴

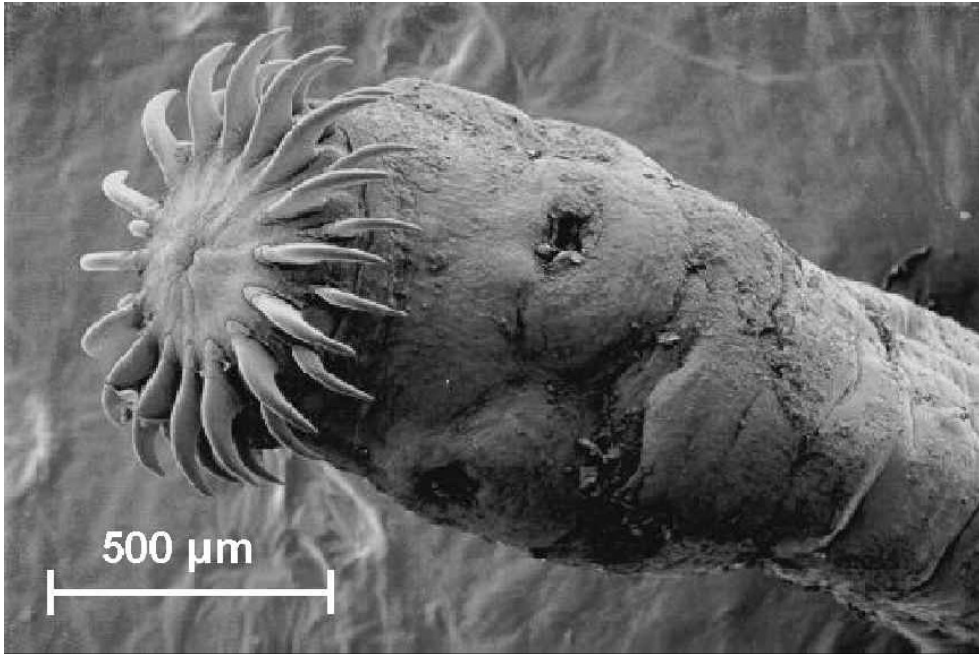


Fig 4. Head of a tapeworm with suckers and hooks.

A typical tapeworm is able to move effortlessly in the gastrointestinal tract without causing any damage to the tract during its typical grasping-elongation movement. This mechanism if modelled could be replicated for NanoBot locomotion especially on gastrointestinal tract.

During locomotion initially adhesion happens onto the substrate, where adhesion can mean friction, grasping, attachment, etc. Post adhesion, the locomotion is achieved by exploiting a simple periodic elongation. A sort of reactive behaviour, even if at low level, must be implemented in order to obtain such a 'bio-attachment' and a 'bio-locomotion'. For example, the simplest inchworm system is based on clamping modules (which attach to the substrate) and elongation modules (which produce a displacement when at least one clamping module is active). The locomotion system of worms is controlled by an action-perception-reaction architecture, which makes the mechanism effective.

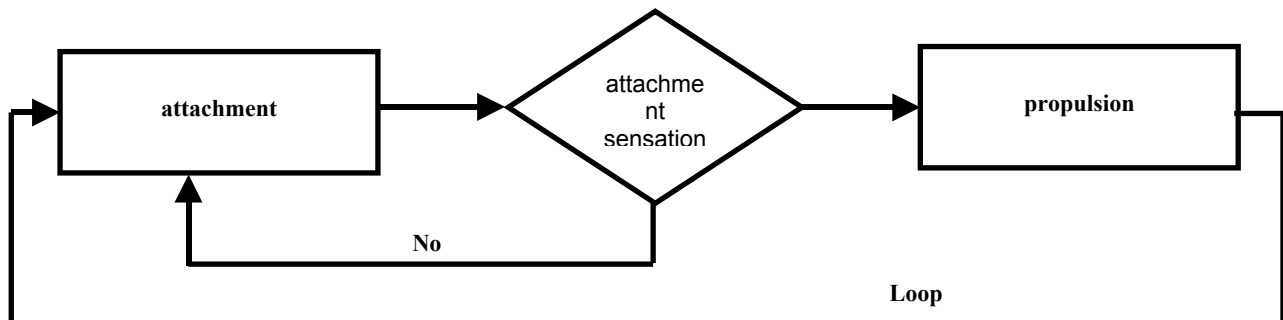


Fig 5. Perception-reaction loop for locomotion.

As in figure above, the locomotion unit possesses a low-level control (attachment sensation) that allows activation of the propulsion system only if clamping is effective. This simple perception-reaction loop is well known and it has been implemented in almost every robotic system and also in several toys mimicking animal behaviours (e.g. Sony's AIBO robotic dog). Most robots with a perception-reaction behaviour exploit a high-level control based on vision sensors.

Based on such a bio-model a typical NanoBot working on such a system will have basically two types of actuators:-clamper and extensor. The clamper is used to adhere or clamp the device securely onto the locomotion environment, while the extensor produces a positive displacement (known as the stroke, i.e. the difference in length of the extensor in its elongated and retracted phases). The simplest inchworm device consists of two clampers at its ends and one extensor in the middle is shown below.



Figure above shows the gait sequence of the forward propulsion (Dario *et al.* 1999).

In-Vivo Navigation Techniques⁵

NanoBots should be able to navigate In-Vivo to specific target sites needing treatment within the human body. Two alternative strategies have been suggested which most likely produce the best clinical results.

a) Positional Navigation -The first strategy is positional navigation, in which the nanorobot knows its position inside the human body to ~micron accuracy at all times in some clinic-centered or body-centered coordinate grid system. The nanodevice relies upon dead reckoning, cartotaxis, microtransponder network alignment, or triangulation on external beacon signals to establish its position continuously. This method requires some onboard computation, at least a basic set of sensors (e.g., acoustic), and probably also a good clock ([Nanochronometry](#)). However, if the target coordinates are poorly specified, the system might fail or lead to positional errors.

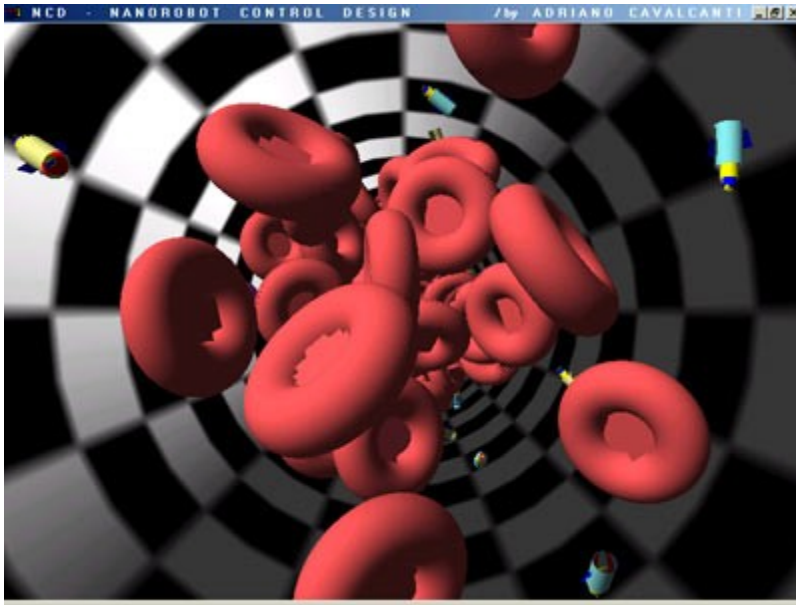
b) Functional Navigation - The second strategy is functional navigation, in which nanodevices seek to detect subtle variations in their environment, comparing diverse sensor readings with the profile of the target tissue or cell and congregating wherever this very precisely defined set of preconditions exists. These preconditions may be thermal, acoustic or barostatic, cytochemical or immunochemical, mechanical or topological, or even genetic. The crudest forms of functional navigation may be called demarcation, wherein the doctor manually creates detectable artificial conditions at or near the target site such as dermal hot spots, injected chemical plumes, or focused ultrasonic beam spots of appropriate magnitudes and frequencies. Demarcation strategies can be implemented using extremely simple onboard sensors and control devices, possibly not even requiring a nanorobot computer, thus may prove useful early NanoBot prototypes. More sophisticated forms of functional navigation can be extraordinarily flexible because targets may be specified without the physician having to know their exact physical location in the body -- e.g., nascent cancer tumors, T cells reactive to specific antigens, infected deep-thoracic lymph nodes, bacteria of a particular species, broken capillary vessels, or virus particles having a specified protein coat chemistry. The physician need not know the exact number of targets, nor even if any targets are present at all. These forms of functional navigation require onboard computation, a resident database of relevant parameters and operational details, and a wider assortment of sensors and control protocols. But they also offer the greatest benefit at lowest risk for the patient and thus must be regarded as the preferred approach once the technology is available.

Simulation for NanoBot Design⁶

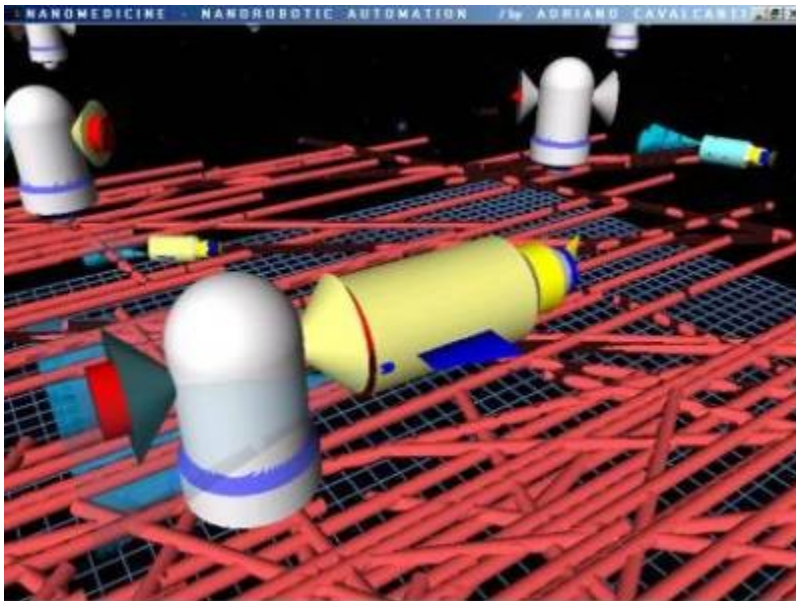
Simulation is an essential tool for exploring alternatives in the organization, configuration, motion planning, and control of nanomachines exploring the human body. The nanorobots require specific controls, sensors and actuators, basically in accordance with each kind of biomedical problem.

A tool called the **Nanorobot Control Design (NCD)** simulator has been developed Adriano Cavalcanti of the School of Electrical and Computer Engineering, University of Campinas, Brazil. The simulator consists of several modules that simulate the physical conditions, run the nanorobot control programs determining their actions, provide a visual display of the environment in 3-D, and record the history of nanorobot behaviors for later analysis.

Advanced simulations can include various levels of detail, giving a trade-off between physical accuracy and the ability to control large numbers of nanorobots over relevant time scales with reasonable computational effort. Another advantage is that simulation can be done in advance of direct experimentation. It is most efficient to develop the control technology in tandem with the fabrication technologies, so that when we are able to build these devices, we will already have a good background in how to control them. Given below are a few images of simulations run on NCD.



[Fig 6](#): View of the NCD simulator workspace showing the occlusion, red blood cells and nanorobots inside a blood vessel.



[Fig 7](#): NanoBot delivers a molecule to the organ inlet -- represented by the white cylinder.

NanoSensors

According to the Biotechnology Industry Organization, Washington D.C., "A biosensor is composed of a biological component, such as a cell, enzyme, or antibody, linked to a tiny transducer, a device powered by one system that then supplies power to a second system. Biosensors are detecting devices that rely on the specificity of cells and molecules to identify and measure substances at extremely low concentrations."

The NanoSensor of the NanoUnit should be able to detect tiny amounts of cancer marker proteins. Typical examples are PSA (prostate-specific antigen) or PSA- α 1-antichymotrypsin, which are indicators of prostate cancer or say telomerase, a ribonucleoprotein complex found to be active in at least 80% of all known human cancers. The different combinations of such cancer markers in the body fluids/blood would be indicators to presence of different carcinogenic tissue. Blood is a very complex mixture of proteins with an estimated million species of proteins. And it's constantly bathing over tissues, and proteins leaking into it if tissues are diseased, and dying. Hence proteins indicative of cancer in blood are at very low concentration, and there is need to sort through multiple species of proteins and find the carcinogenic ones at very low concentration, which would be a big challenge.

Hence the primary abilities of the NanoSensor would be:-

- Sensitivity to different Cancer markers, even in very low concentrations (<1 pg/ml)
- Ability to differentiate between different combinations of Cancer markers (different types of DNA or protein individually)
- To sense these different variations of concentration or/and combinations of different cancer marker proteins, by giving a suitable output signal for each combination/concentration.

To achieve these primary objectives the NanoSensor must have antibody probe molecules attached to the sensor surface which would be the binding site for the antigen (like PSA) . The NanoSensor will be able to convert the different Antigen-Antibody interactions at the chemical binding sites into distinguishable electric signals. There are different approaches to sense such chemical binding, some of which are described below:-

i. **Surface Stress BioSensors**¹¹

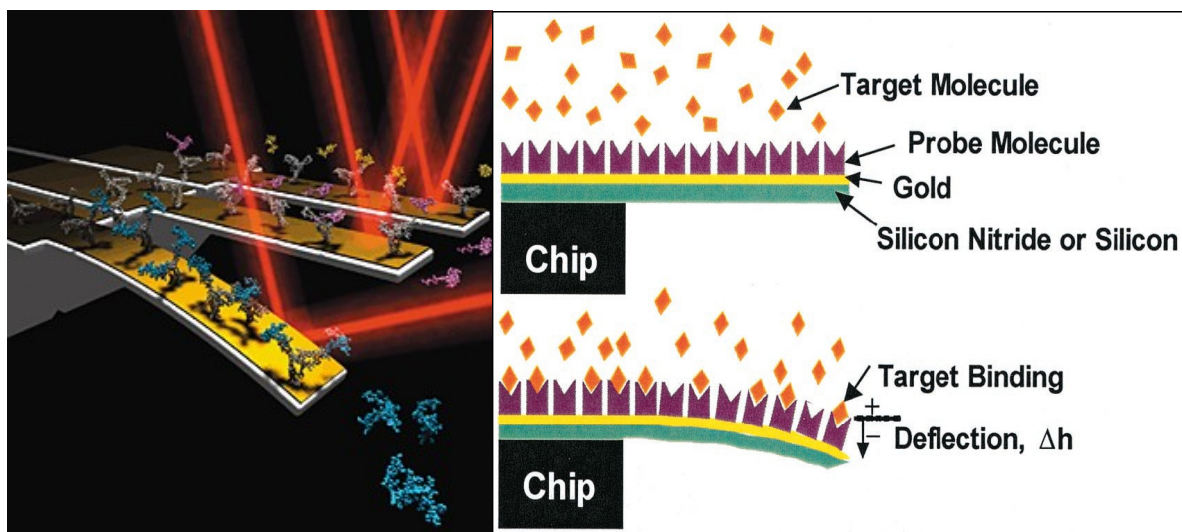


Fig 1: Specific biomolecular interactions between target and probe molecules alters the intermolecular interactions within a self-assembled monolayer on one side of a cantilever beam. This can produce a sufficiently large force to bend the cantilever beam and generate motion. The origin of this nanomechanical motion lies in the interplay between changes in configurational entropy and the intermolecular energetics.

Surface Stress BioSensors works on the principle that when a chemical binding reaction occurs on one surface a cantilever beam or a polymeric membrane, the curvature of the structure is modified due to changes in intermolecular forces upon binding. This forms a chemical-to-mechanical free energy transduction. The changes in deflection of the cantilever beam (bioactuation) due to changes in surface stress of cantilever beam is indicative of the different concentrations of cancer markers or such specific combinations indicative of different carcinogenic cells i.e. specific to each biomolecular reaction.

This value of the cantilever deflection, Δh , can be estimated from Stoney's formula³

$$\Delta h = 3\sigma(1 - \nu)/E \cdot (L/d)^2$$

where σ is the change in surface free-energy density (or surface stress) due to specific binding, E is the elastic modulus of the cantilever material, ν is its Poisson ratio, and L and d are the length and the thickness of the cantilever, respectively.

It is found that longer and thinner cantilevers would produce larger deflections for the same value of surface stress. Figure 2 shows the steady-state cantilever deflections as a function of PSA (prostate specific antigen) concentration for different lengths, L , and thicknesses, d , of cantilevers. The PSA concentration is indicative of prostate cancer.

Multiple such cantilevers can be integrated to detect different types of antigens.

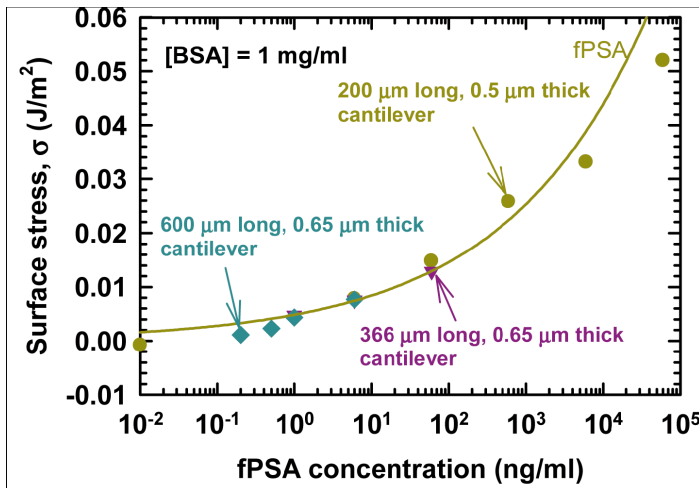


Fig 2: Surface stress as parameter for assaying PSA. The data for cantilever deflections for different cantilever geometries collapse onto a single curve for surface stress as a function of fPSA concentration.

ii. Surface Plasmon Resonance BioSensors¹³

Surface plasmon resonance (SPR) technology developed by Biacore International AB, Uppsala, Sweden, works on principle of change in refractive index of a gold coated chip due to biomolecular interactions at its surface.

Surface plasmon resonance (SPR) is a method for characterizing macromolecular interactions. It is an optical technique that uses the evanescent wave phenomenon to measure changes in refractive index very close to a sensor surface. The binding between an analyte in solution and its ligand immobilized on the sensor surface results in a change in the refractive index. The interaction is monitored in real time and the amount of bound ligand and rates of association and dissociation can be measured with high precision.

This biosensor has three key elements: a sensor chip, microfluidics, and the surface plasmon resonance (SPR) technology. SPR works by measuring the binding of an analyte to a ligand or receptor on the surface (see diagram below).

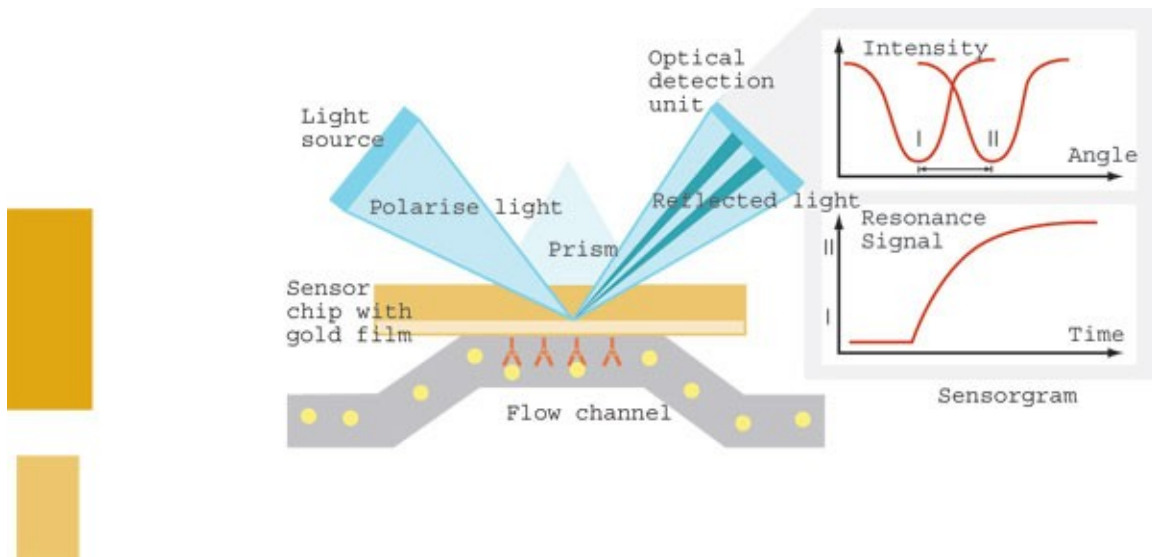


Fig 3: The gold layer in the sensor chip detects changes in mass of an aqueous layer that is close to the sensor chip surface by measuring changes in the refractive index

The SPR measures very precise changes in the mass on the surface. The sensor chip has a glass surface coated with a thin layer of gold that creates the physical conditions needed for SPR, which works by detecting changes in mass of an aqueous layer close to the chip's surface by measuring changes in the refractive index of light shown onto the reverse side of the chip. When molecules in the test solution bind to a target molecule, the mass increases. When they dissociate, it decreases. These increases and decreases can be monitored constantly.

Of the two above mentioned approaches to sensing, the former where the detection of change in curvature can be more easily detected by the chip in the proposed automated nanobot as compared to change in refractive index in case of latter. Though future developments in minaturisation (to nano-levels) of refractive index change detection could open doors to use of latter methodologies too in an automated setup.

Drug Encapsulation And Drug Delivery

Nano-enabled controlled drug delivery technology involves multidisciplinary scientific approach, and is very much essential in an effective Nano-enabled cancer therapy. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity and improved patient compliance and convenience.

Such systems use macromolecules as carriers for the drugs. Here drug is attached to a carrier molecule such as a synthetic polymer, antibody, hormone or liposome. As the absorption and distribution of the drug in such a system depend on the properties of the macromolecular carrier, parameters such as site specificity, protection from degradation and minimization of side effects can be altered by modifying the properties of the carrier.

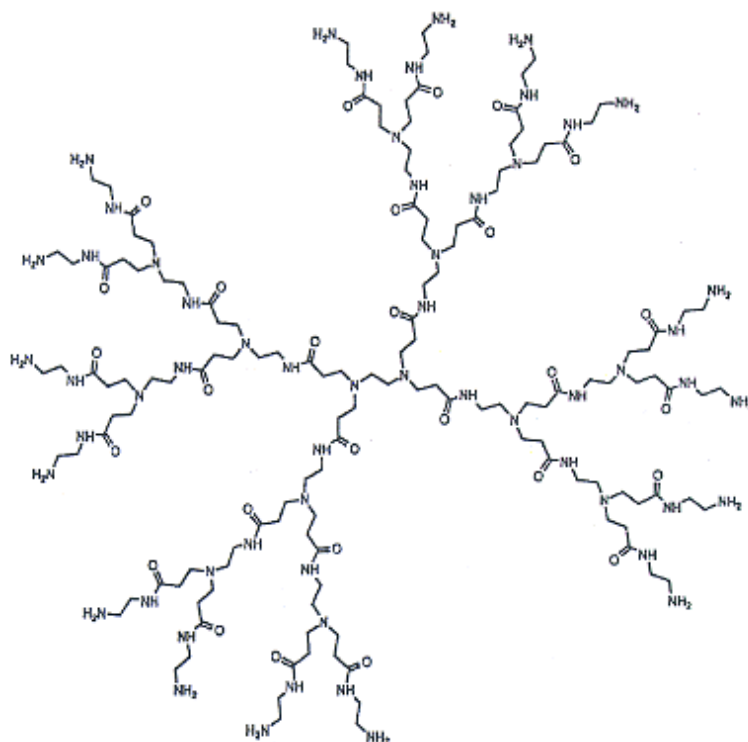
The typical requirements of an ideal drug carrier are:-

- It should be biochemically inert and non-toxic
- The carrier should protect the drug until it reaches the desired site of action
- Targeted & controlled delivery at desired site of action

Many polymeric drug-delivery systems like those based on polyethylene-oxide copolymers have been developed over the years and have been extensively reviewed¹⁶.

Currently the two common drug delivery systems are liposomes and polymeric systems. These both have limited applications, as liposome-based systems have poor stability and difficulty targeting specific tissues, and linear polymers are polydisperse¹⁷.

Of particular interest is the discovery of **Dendrimers**, a class of highly branched, monodisperse macromolecules which possess many of the above mentioned properties, as drug delivery systems.



Molecular structure of a Dendrimer

The properties of Dendrimers¹⁹ which make it suitable for Drug-Delivery are:-

- Globular shape and the presence of internal cavities
- Ability to encapsulate guest molecules in the macromolecule interior
- Presence of many chain-ends is due to which it has high water solubility and miscibility
- Lower [Polydispersity Index](#) (indicates the distribution of individual molecular weights in a batch of polymers)
- Multiple sites of attachment, and a controllable, well-defined size and structure that can be easily modified to change the chemical properties of the system
- Enhanced permeability and retention effect that allows them to target tumor cells more effectively than small molecules

Drug Encapsulation

Primarily, there are two modes of encapsulation of drugs to carriers:-

- **Encapsulation of drugs**, uses the steric bulk of the exterior of the dendrimer or interactions between the dendrimer and the drug to trap the drug inside the dendrimer.
- **Dendrimer-Drug Conjugates** have the drug attached to the exterior of the dendrimer. Most of these conjugates are inactive or have decreased activity relative to the free drug.

Controlled Drug Release

By combining the ideas of drug carriers and degradability, research has recently focused on controlled degradation of dendrimers and release of compounds. Some of the methods to initiate the release include light induced release, removal of protecting groups, and antibodies. Technically these modes of release are primarily⁴:-

- Linear Disassembly
- Geometric Disassembly
- Self-Immolative Disassembly
- Cascade Release

Basic Design And Requirement of the NanoComputer

NanoComputer would be the de facto CPU of the whole NanoBot. The crux of the In-Vivo operations of the whole NanoBot and it's constituent units described above would be controlled by the NanoComputer.

Many important medical nanorobotic tasks like acquisition and processing of sensor data, the control of sensors, manipulators, and mobility systems, navigation and communication, and the coordination of collective activities with neighboring nanorobots. Ex vivo computation has few theoretical limits, but computation by in vivo nanorobots will be subject to a number of constraints such as physical size, power consumption, onboard memory and processing speed.

The primary functionality of the NanoComputer with respect to each of the NanoBot units would be :-

- In-Vivo navigation processing** –Controlling the NanoCarrier to navigate the NanoBot unit to specific sites. This involves, navigation based on a grid-system in case of Positional Navigation or based on variations in the In-Vivo environment (See section *In-Vivo Navigation Techniques*). Along with this the NanoComputer would use a on-board sensor based anti-collision system to avoid obstacles. This

functionality would require in-built logic as well as advanced Artificial Intelligence circuitry to cope with the extremely un-predictable In-Vivo environment incl. diverse histological territories having markedly different mechanical and chemical characteristics.

- b) **Sensor Data processing**– This would primarily involve the control of sensors, dynamic acquisition and processing of sensor data. The NanoComputer would convert the signals of the NanoSensors (see section *NanoSensors*) to dynamically detect the presence of environmental chemicals or tissues. For example, in case of a Surface Stress BioSensor, the NanoComputer would compare the signals generated by the collection Stress Sensor to the inbuilt dataBase to arrive at the type of antigens and their concentration.
- c) **Drug Delivery decision processing** – The Drug Delivery decisions include, timing, quantity and rate of release of drug, based on the output of the *Sensor Data processing*.

Along with the above mentioned functionality, the NanoComputer would also sense the effectiveness of the whole drug delivery operation by analysing tissue samples over a prolonged periods if necessary.

Basic Design of such a NanoComputer: Memory & Computational Speed

The **Memory required** onboard such a medical nanorobot will be strongly mission dependent. A very simple mission might demand only the identification or handling of perhaps ~ 10 different molecules. Such an operation may need only a few bits, hence this memory requirement should be negligible.

On the other hand, a survey or assay mission might need to recognize $N = 100-1000$ distinct proteins. A spherical 1-micron nanorobot can have $>10^4$ fixed-shape receptors on its surface; if these will suffice, then it requires $N \log_2(N) \sim 10^4$ bits to identify each of $N = 1000$ different receptor types. A set of more advanced reconfigurable receptors might need $>10^4$ bits per receptor-pattern to specify each binding site geometry to the necessary atomic-scale resolution, thus imposing a total memory requirement of $>10^7$ bits for an onboard library of $N = 1000$ different receptor types. Consequently, simple missions involving basic process control with limited motility may require no more than $\sim 10^5-10^6$ bits of memory, comparable to an old Apple II computer (including RAM plus floppy disk drive). At the other extreme, a complex Cancer cell repair mission might require the onboard storage of a substantial fraction of the patient's genetic code, representing $\sim 10^9$ bits of memory including perhaps $\sim 0.2 \times 10^9$ bits of linear sequence data for all 100,000 protein types found in the human body, again assuming 300 amino acids per protein. An onboard

memory of 10^9 - 10^{10} bits would be in the same range as the 1985 Cray-2 (2×10^{10} bits) or the 1989 Cray-3 (6×10^8 bits) supercomputers.

Computational speed will also be strongly mission dependent. However, extremely simple process control systems in basic factory settings may only require speeds as slow as 10^4 bit/sec. Individual natural biocomputational devices (as opposed to multiple such biodevices operating in parallel) generally do not exceed this speed. At the extreme, a processing speed of 10^9 bits/sec allows a $\sim 10^9$ bit genomic information store to be processed in ~ 1 sec, the small-molecule diffusion time across an average 20-micron wide cell.

Based on the above requirements the final design objectives with an eye to minimizing energy dissipation would be:-

1. minimize onboard computation
2. maximize algorithmic efficiency (e.g. a super-Turing computer)
3. minimize power dissipation per computation operation (could be met using [reversible computing](#))

The various options available to design such a NanoComputer with the above requirements are would be Nanomechanical computers, Nanoelectronic computers and Biocomputers (incl. DNA based computing).

Issues to be tackled:

1. Immunoreactivity of the NanoBot which is a key measure of the biocompatibility and applicability of the device.
2. Danger of Phagocytosis of NanoBot by a phagocyte
3. Achieving positional accuracy on face of Thermal displacements at Nano-level to accurately direct NanoDevices on cells
4. In-Vivo testing to confirm non-toxicity of NanoBot materials
5. Unpredictability and complexity of the In-Vivo environment
6. Provision for safe ejection of the NanoBot after the operation or development of BioDegradable material for NanoBot parts
7. Ethical issues on use of invasive devices like NanoBots
8. Grey-Goo doom theory fears; chances of NanoBot going out of control in an In-Vivo environment and causing damage to vital organs

Conclusion:

The ultimate goal of research would be to integrate all the above units into a single nanoparticle that will circulate unhindered through the body, detect cancer-associated molecular changes, assist with imaging, release a therapeutic agent, and then monitor the effectiveness of the intervention. Such a nanoparticle would be able to act autonomously in the complex In-Vivo environment. Further advances in the field of Nano Sensors, Nano Computers and their testing in an In-Vivo environment will go a long way in actual development of the proposed NanoBot.

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