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Nanorobot architecture for medical target identification

Adriano Cavalcanti[1,2], Bijan Shirinzadeh[2], Robert A Freitas Jr[3] and Tad Hogg[4]

[1] CAN Center for Automation in Nanobiotech, Melbourne VIC 3168, Australia
[2] Robotics and Mechatronics Research Laboratory, Department of Mechanical Engineering, Monash University, Clayton, Melbourne VIC 3800, Australia
[3] Institute for Molecular Manufacturing, Pilot Hill, CA 95664, USA
[4] Hewlett-Packard Laboratories, Palo Alto, CA 94304, USA

E-mail: adrianocavalcanti@canbiotechnems.com

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Abstract

This work has an innovative approach for the development of nanorobots with sensors for medicine. The nanorobots operate in a virtual environment comparing random, thermal and chemical control techniques. The nanorobot architecture model has nanobioelectronics as the basis for manufacturing integrated system devices with embedded nanobiosensors and actuators, which facilitates its application for medical target identification and drug delivery. The nanorobot interaction with the described workspace shows how time actuation is improved based on sensor capabilities. Therefore, our work addresses the control and the architecture design for developing practical molecular machines. Advances in nanotechnology are enabling manufacturing nanosensors and actuators through nanobioelectronics and biologically inspired devices. Analysis of integrated system modeling is one important aspect for supporting nanotechnology in the fast development towards one of the most challenging new fields of science: molecular machines. The use of 3D simulation can provide interactive tools for addressing nanorobot choices on sensing, hardware architecture design, manufacturing approaches, and control methodology investigation.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

This paper presents the architecture and the simulation of nanorobots using sensor capability for medical target identification. Nanorobots are expected to enable significant new methodologies in diagnosis, medical therapies, and minimally invasive surgery [1–4]. In our work we demonstrate a computational and analytical new approach to help in the research and development of nanorobots [5, 6].

A first series of nanotechnology prototypes for molecular machines are being investigated in different ways [2, 7–12], and some interesting device propulsion and sensing approaches have been presented [13–16]. Some work has been done in 2D on cellular automata with the examination of collective behaviors of large numbers of robots to locate specific types of tissue [17]. More complex molecular machines, or nanorobots, having embedded nanoscopic features may provide broad advances on health care sector [18–23]. Through the use of nanotechnology techniques [24], advances on genetics and biomolecular computing [25], biological nanorobots can be applied to advance medicine [26]. For example, in microbiology engineering the construction of digital circuits in living cells has been demonstrated [27]. Bacteria have been used as physical system components [28], and radio remote control of biological processes has been demonstrated experimentally [29]. Some proposals on rigid materials with positional mechanosynthesis [30, 31], and manufacturing nanodevices were presented [7, 13, 32]. Recent developments in biomolecular computing have demonstrated the feasibility of biocomputers [33], a promising first step toward future nanoprocessors. Other examples include studies of building biosensors and nanokinetic devices [7, 8, 13, 19, 34].

Real time three-dimensional (3D) prototyping and simulation are important tools for nanotechnology development.

Such tools have significantly helped the semiconductor industry to achieve faster VLSI (very large scale integration) development [35]. It should similarly have a direct impact on the implementation of nanomanufacturing techniques and also on nanoelectronics progress [36]. Simulation can anticipate performance and help in new device design and manufacturing [37, 38], nanomechatronics control design and hardware implementation [8, 39]. The use of scientific visualization is a powerful tool for the purpose of designing devices at nanoscale [40]. In our work, the focus of interaction and sensing with nanorobots is addressed giving details on the workspace chemical and thermal signals dispersion through a 3D environment as a testbed for prototyping and analysis. The nanorobots must search proteins in a dynamic virtual environment and use different strategies to identify and bring those proteins for medical delivery.

2. Motivation

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 [41]. A nanorobot can provide efficient early diagnosis of cancer and help with smart chemotherapy for drug delivery. Nanorobots as drug carriers for timely dosage regimens allows maintaining the chemical compounds for a longer time as necessary into the bloodstream circulation, providing predicted pharmacokinetic parameters for chemotherapy in anti-cancer treatments [42]. It avoids the current resulting extravasations towards non-reticuloendothelial-located cancers with the high degenerative side-effects during chemotherapeutic process [43]. Nanorobots with chemical nanobiosensors can be programmed to detect different levels of *E-cadherin* and beta-catenin as medical targets in primary and metastatic phases [44–46], helping target identification and drug delivery.

In terms of diagnosis, a critical issue in cerebral aneurysm is to detect and locate vessel dilation, if possible before a subarachnoid hemorrhage occurs. Similarly, nanorobots using chemical sensors as embedded nanoelectronics can be programmed to detect different levels of nitric oxide synthase (NOS) pattern signals as medical targets in early stages of aneurysm development [47]. Integrated nanobiosensors and radio frequency (RF) wireless communication [8] can be utilized for such a task in order to find changes of gradients for NOS concentrations [48]. Chemical signals can also be useful for nanorobot medical target identification and actuation in another cerebral treatment. The amyloid-β protein deposits show changes on gradients as a symptom of Alzheimer disease [49, 50]. This information serves for the early diagnosis of Alzheimer disease and to guide possible immunotherapy treatments, with more efficient neurotransmitters delivery, like dopamine and amino acids such as g-aminobutyrate (GABA), with better medical administration. Nanorobots can use such signals to delivery genomic improved myelin basic protein [51], avoiding neurons to be attacked by the immune system providing better electric pulses between the nervous system and the muscles.

3. Medical nanorobotics

The feasibility of advancing techniques for control [5] and manufacturing molecular machines should be understood as emergent results from actual and upcoming stages of nanotechnology, based on nanoelectronics [8, 52], new materials [53–55] and genomics research [56]. New possibilities are coming from these developments which will enable new medical procedures [1, 18, 21, 26, 53, 57].

The nanorobot proposed prototyping must be equipped with the necessary devices for monitoring the most important aspects of its operational workspace. For biomedical application the temperature, concentration of chemicals in the blood, and electromagnetic signatures are some of the relevant parameters when monitoring the human body to detect some diseases [58, 59]. The application of new materials has demonstrated a large range of possibilities for use in manufacturing better sensors and actuators with nanoscale sizes [14, 35]. This downscaling will continue, according to the Semiconductor Industry Association's roadmap. By 2016, high performance ICs will contain more than 8.8 billion transistors in a 280 mm^2 area—more than 25 times as many as on today's chips built with 130 nm (nanometers) feature sizes [60]. Those developments allied with 3D simulation should facilitate the manufacturing design of nanorobots with integrated embedded nanoelectronics and circuits.

4. Background

Current developments in nanoelectronics [36] and nanobiotechnology [61] is providing feasible development pathways to enable molecular machine manufacturing, including embedded and integrated devices which can comprise the main sensing, actuation, data transmission, remote control uploading, and coupling power supply subsystems addressing the basics for operation of medical nanorobots.

A recent actuator with biologically-based components has been proposed [62]. This actuator has a mobile member that moves substantially linearly as a result of a biomolecular interaction between biologically-based components within the actuator. Such actuators can be utilized in nanoscale mechanical devices to pump fluids, open and close valves, or to provide translational movement.

To help control the nanorobot's position, a system for tracking an object in space can comprise a transponder device connectable to the object. The transponder device has one or several transponder antennas through which a transponder circuit receives an RF signal. The transponder device adds a known delay to the RF signal thereby producing an RF response for transmitting through the transponder antenna [63]. A series of several transmitters and antennas allow a position calculator associated with the transmitters and receivers to calculate the position of the object as a function of the known delay and the time period between the emission of the RF signal and the reception of the RF response from the first, second and third antennas.

Nanotechnology is moving fast towards nanoelectronics fabrication. Chemically assembled electronic nanotechnology

provides an alternative to using a complementary metal oxide semiconductor (CMOS) for constructing circuits with feature sizes in the tens of nanometers [64]. A CMOS component can be configured in a semiconductor substrate as part of the circuit assembly [65]. An insulating layer is configured on the semiconductor substrate, which covers the CMOS component. A nanoelectronic component is configured above the insulating layer. If several nanoelectronic components are provided, they are preferably grouped in nanocircuit blocks.

Biosensors are used to incorporate living components, including tissues or cells which are electrically excitable or are capable of differentiating into electrically excitable cells, and which can be used to monitor the presence or level of a molecule in a physiological fluid [66]. CNTs (carbon nanotubes) and DNA (deoxyribonucleic acid) are recent candidates for new forms of nanoelectronics [67]. These are combined to create new genetically programmed self-assembling materials for facilitating the selective placement of CNTs on a substrate by functionalizing CNTs with DNA. Through recombinant DNA technology, targets labeled with distinct detectable biomarkers can be defined, such as fluorescent labels, enzyme labels, and radioactive patterns, and employed in suitable biomolecular transducers [56].

5. Medical nanorobot architecture

The main parameters used for the medical nanorobot architecture and its control activation, as well as the required technology and current developments that can lead to manufacturing hardware for molecular machines, are described next.

5.1. Manufacturing technology

The ability to manufacture nanorobots can be understood as the result of current trends and new methodologies in fabrication, computation, transducers and manipulation. The hardware architecture for a medical nanorobot must include the necessary devices for monitoring the most important aspects of its operational workspace: the human body. To reach this aim, data processing, energy supply, and data transmission capabilities should be addressed through embedded integrated circuits, using advances in technologies derived from nanotechnology and VLSI design [35]. CMOS VLSI design using extreme ultraviolet lithography provides high precision and a commercial way for manufacturing early nanodevices and nanoelectronics systems [68]. To validate designs and to achieve a successful implementation, the use of VHDL (very high speed integrated circuit hardware description language) has become the most common methodology utilized in the integrated circuit manufacturing industry [69].

A large set of different chemical and biological sensors has been achieved with distinct sequences of peptides through combinatorial chemistry for selective detection of various medical targets. For example, nanobiosensors and fabrication processes on nanoelectronics have been investigated and established to achieve electrochemical activation at nanoscale environment [70, 71]. A post-integrated-circuit assembly of the nanostructures was also implemented [72], presenting a layout for analog digital readout, signal processing, and communications circuitry. It used a CMOS nanowire integrated circuit with low voltage for biological sensing. Another recent study has also demonstrated that IC CMOS-based nanobiosensor with an architecture using nanogaps of 200 nm length is efficiently used to detect biomolecules by means of voltage changes [73]. To achieve a higher sensitivity, biomolecules are immobilized in the electrically operated gate with flow of charge through the semiconducting channel. Similarly, following principles of integrated nanoelectronics and molecular organic compounds, a medical diagnostic nanosensor was recently presented [74]. The device can be used under *in vivo* as well as *in vitro* conditions. It achieves nanometer scale spatial resolution and provides accurate real time information regarding not only the concentration of a specific analyte of organic or inorganic nature but also its spatial distribution.

5.2. 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 [75]. Applications range from automotive and chemical industry with detection of air to water element pattern recognition through embedded software programming, and biomedical uses. Through the use of nanowires, existing significant costs of energy demand for data transfer and circuit operation can be decreased by up to 60% [76]. CMOS-based sensors with nanowires as material for circuit assembly can achieve maximal efficiency for applications regarding chemical changes, enabling new medical applications [25, 57].

Sensors with suspended arrays of nanowires assembled into silicon circuits can drastically decrease self-heating and thermal coupling for CMOS functionality [77]. Factors like low energy consumption and high sensitivity are among some of the advantages of nanosensors. Nanosensor manufacturing array processes can use electrofluidic alignment to achieve integrated CMOS circuit assembly as multi-element systems [76]. Passive and buried electrodes can be used to enable cross-section drive transistors for signal processing circuitry readout. The passive and buried aligned electrodes must be electrically isolated to avoid the loss of processed signals.

Some limitations to improving BiCMOS, CMOS and MOSFET actuators methodologies include quantum-mechanical tunneling for operation of thin oxide gates, and subthreshold slope [78]. Surpassing expectations, the semiconductor branch nevertheless has moved forward to keep circuit capabilities advancing. Smaller channel length and lower voltage circuitry for higher performance are being achieved with new materials aimed to attend the growing demand for high complex VLSIs. New materials such as a strained channel with a relaxed SiGe (silicon–germanium) layer can reduce self-heating and improve performance [79]. Recent developments in 3D circuits and FinFETs (fin-shaped field effect transistor) double-gates have achieved astonishing results. To further

advance manufacturing techniques, silicon-on-insulator (SOI) technology has been used to assemble high performance logic sub 90 nm circuits [80, 81]. Circuit design approaches to solve problems with bipolar effect and hysteretic variations based on SOI structures have been demonstrated successfully [79]. Currently feasible 90 and 45 nm CMOS devices represent breakthrough technology devices that are already being utilized in products. By 2016 these devices are expected to achieve 22 nm functionality.

5.3. Temperature sensor

Integrated nanothermoelectric sensors can be implemented as CMOS devices with promising uses for pattern identification [21]. Such an approach should permit a large production of infrared thermal sensors applied to different ranges of wavelength [82]. Nanorobots using temperature sensors open new medical possibilities for clinical diagnosis, as well as for ubiquitous data collection, with pervasive patient monitoring. CMOS as a thermoelectric sensor has the advantage of linear self-generated response with system integration without requiring bias or temperature stabilization [83]. Thus the infrared array could be integrated on a single chip within amplifiers and signal processing capabilities. Such an approach also allows a fast pace towards miniaturization with no loss of efficiency due to electromagnetic noise [82, 84]. CMOS can be operated at very low voltage levels, which is also a positive aspect, presenting good functionality and requiring little energy for nanorobots. Cantilever and bridge types are also valid techniques for possible different ways to implement CMOS thermoelectric sensors.

Nanowires are suitable for fabricating CMOS integrated devices [85]. CNTs are able to improve performance with low power consumption for nanosensors. Its particular high precision makes it quite useful for applications in infrared supersensitive biosensors, with applications such as target oriented temperature detection, and measurement in changes of body temperature. Nanosensors present important electrical properties, high thermal conductance and fast frequency response [14, 86]. The power consumption with NEMS (nano electro-mechanical systems) is three times lower if compared with traditional MEMS (micro electro-mechanical systems) thermal sensors, where for MEMS the operating values range in terms of mW [83]. Nanowires can be configured as two-terminal devices electrically designed to work as high or low resistance diodes. Crossed nanowire p–n junctions can function successfully as logic gates from crossed nanowire field effect transistors [85]. Therefore, microwire pitch incorporated in actual CMOS integrated designs can be reduced to the nanowire pitch by using on–off masks aligned diagonally to produce a one-to-one microwire to nanowire correspondence.

5.4. Actuator

There are different kinds of actuators, such as electromagnetic, piezoelectric, electrostatic, electrothermal, where they should be utilized depending on the aim and the workspaces where they will be applied [87]. A flagella motor has been quoted quite frequently as an example for a kind of biologically inspired actuator for molecular machine propulsion [88]. Adenosine triphosphate, also known in short as ATP, is equally used as an alternative for nanomotors [7]. DNA and RNA (ribonucleic acid) prototypes were also proposed for designing different types of devices.

A set of fullerene structures were presented for nanoactuators [89]. The use of CNTs as conductive structures permits electrostatically driven motions providing the forces necessary for nanomanipulation. CNTs can be used as materials for commercial applications on building devices and nanoelectronics such as nanotweezers and memory systems. SOI technology has been used for transistors with high performance, low heating and energy consumption for VLSI devices. CNT self-assembly and SOI properties can be combined to address CMOS high performance on design and manufacturing nanoelectronics and nanoactuators [90]. Owing to the maturity of silicon CMOS technology, as well as the unique properties of CNTs, the integration of CNT and CMOS technology makes use of the advantages of both [91].

For a medical nanorobot, the use of CMOS as an actuator based on biological patterns and CNTs should be considered a natural choice. In the same way DNA can be used for coupling energy transfer [29, 92], and proteins may serve as basis for ionic flux with electrical discharge ranges from 50 to 70 mV dc voltage gradients in the cell membrane [93]; an array format based on CNTs and CMOS techniques could be used to achieve nanomanipulators as an embedded system for integrating the future architecture of molecular machines [36, 94]. Ion channels can interface electrochemical signals using sodium for the energy generation which is necessary for mechanical actuators operation [93]. Actuators built as nanodevices can be programmed to perform different manipulations, enabling the nanorobot to directly interact with the molecular operating environment.

5.5. Energy supply

The most effective way to keep the nanorobot operating successfully is to establish the use of a continuous available source of power. The energy must be available and delivered to the nanorobot while it is performing predefined tasks in the operational environment. For a medical nanorobot, this means that the device has to keep working inside the human body, sometimes for long periods, and requires easy access to clean and controllable energy to maintain efficient operation.

Some possibilities to power the nanorobot can be provided from ambient energy [1]. Temperature displacements could likewise generate useful voltage differentials. Cold and hot fields from conductors connected in series can also produce energy using the well-established Seebeck effect. Electromagnetic radiation from light is another option for energy generation in determined open environments [95] but not for *in vivo* medical nanorobotics. Kinetic energy can be generated from the bloodstream due to motion interaction with designed devices embedded with the nanorobot [96], but this kinetic process would demand costly room within the nanorobot hardware architecture.

Most recently, remote inductive powering has been used both for RFID (radio frequency identification device) and biomedical implanted devices to supply power on the order of milliwatts [97–99]. A low frequency energy source can be sufficient to operate nanorobots. This functional approach presents the possibility of supplying energy in a wireless manner [97]. Thus, it enables one to operate sensors and actuators necessary for the controlled operation of nanorobots inside the human body.

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 [100]. Therefore nanocircuits with resonant electric properties can operate as a chip providing electromagnetic energy supplying 1.7 mA at 3.3 V for power, allowing the operation of many tasks with few or no significant losses during transmission [101]. RF-based telemetry procedures have demonstrated good results in patient monitoring and power transmission through inductive coupling [97, 98, 102, 103], using well-established techniques already widely present in commercial applications of RFID [104]. The energy received can also be saved in the range of $\sim$1 μW while the nanorobot stays in inactive modes, just becoming active when signal patterns require it to do so. Some typical nanorobotic tasks may require the device only to spend low power amounts, once it has been strategically activated. For communication, sending RF signals $\sim$1 mW is required. Allied with the power source devices, the nanorobots need to perform precisely defined actions in the workspace using available energy resources as efficiently as possible.

A practical way to achieve easy implementation of this architecture will be to obtain both energy and data transfer capabilities for nanorobots by employing a mobile phone in such process [105]. The cellular phone should be uploaded with the control software that includes the communication and energy transfer protocols.

5.6. 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 for biomedical problems [106, 107]. Most recently, the use of RFID for *in vivo* data collecting and transmission was successfully tested for electroencephalograms [101]. For communication in liquid workspaces, depending on the application, acoustic, light, RF, and chemical signals can be considered as possible choices for communication and data transmission [2]. Chemical signaling and sensor-based behaviour are quite useful for nearby communication among nanorobots for some teamwork coordination and biomedical instrumentation [5, 6, 108]. Acoustic communication is more appropriate for long distance communication and detection with low energy consumption as compared to light communication approaches [109]. Although optical communication permits faster rates of data transmission, its energy demand makes it not ideal for nanorobots [1].

Work with RFID has been developed as an integrated circuit device for medicine [99, 101, 104]. Using integrated sensors for data transfer is the best answer to read and write data in implanted devices. Teams of nanorobots should be equipped with single-chip RFID CMOS-based sensors [110]. CMOS with submicron SoC (System-on-Chip) design could be used for extremely low power consumption with nanorobots communicating collectively for longer distances through acoustic sensors [111]. For the nanorobot, active sonar communication frequencies may reach up to 20 μW @ 8 Hz at resonance rates with 3 V supply [109]. Cell phones are more widely accepted and usual than a RF CMOS transponders and can be extremely practical and useful as sensors for acquiring wireless data transmission from medical nanorobots injected inside the patient's body. Such phones can be a good choice for monitoring predefined patterns for many health problems. Electromagnetic radio waves are used to command and detect the current status of nanorobots inside the patient. This occurs as a transponder device emits a magnetic signature to the passive CMOS sensors embedded in the nanorobot, which enables sending and receiving data through electromagnetic fields [103]. The nanorobot data communication converts the wave propagation generated by the emitting signal through a well defined protocol. From the last set of events recorded in pattern arrays, information can be reflected back by wave resonance [112]. For nanorobot data transferring $\sim$4.5 kHz frequency with approximate 22 μs delays are possible ranges for data communication.

Frequencies ranging from 1 to 20 MHz can be successfully used for biomedical applications without any damage [101]. A small loop planar antenna working as an electromagnetic pick-up with a good matching to the low noise amplifier is used with the nanorobot.

6. System implementation

Research efforts have recently been directed towards molecular manufacturing and minimally invasive surgery [9, 15, 113, 114]. While the assembly of nanodevices is advancing continuously [53, 57, 115], further investigation on nanorobots for application in medicine enables significant insights on various aspects such as their operation and hardware architecture, with sensor and actuator designs. The software NCD (nanorobot control design) was implemented for nanorobot modeling. It is a 3D real time virtual environment useful for architecture analysis, system control design, and interactive simulation. Figure 1 describes the simulated microenvironment consisting of a long fluid-filled pipe, with a diameter of some tens of microns.

6.1. Drug delivery and diagnosis

The clinical use of nanorobots for diagnosis, therapeutic and surgical purposes should be done with intravenous injection. Therefore, the nanorobots can be released directly inside 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

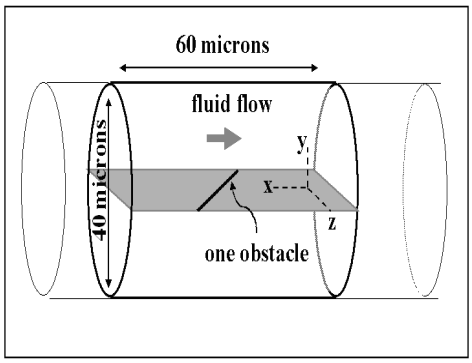

Figure 1. Schematic illustration of the simulated workspace as a section of a longer pipe. The x–z plane contains the obstacles.

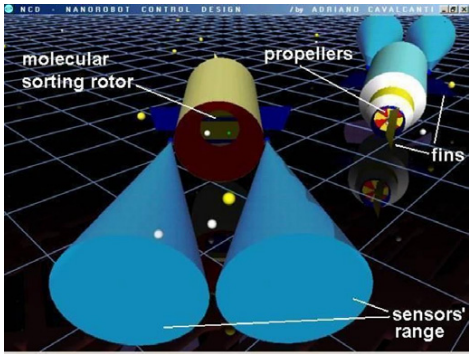

Figure 2. Nanorobots' design-sensors, molecular sorting rotors, fins and propellers. The depicted blue cones shows the sensors 'touching' areas.

before the next chemotherapy session. Patients are normally treated in cycles of every 2 weeks for small tumors [116]. As an initial time threshold for medical purpose, 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 [117]. Hence, a similar approach is useful to verify *in vivo* nanorobot's biosensor activation through targeted antigen detection.

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 [117]. Thus, the major advantage of nanorobots for cancer drug delivery is to minimize chemotherapy side effects. As the best approach, the nanorobot architecture incorporates DNA-CNT CMOS as a hybrid biosensor with single-chain antigen-binding proteins [73, 74, 118]. This process uses activation based on proteomics and bioelectronics signals for medicament release. Therefore, each time the nanorobot detects predefined changes of 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 on changing protein concentrations inside body near a medical target under pathological circumstances are NOS [47], *E-cadherin* [44] and Bcl-2 [119]. Moreover, a change of temperature normally occurs for inflamed tissues [120]. The model incorporates chemical and thermal parameters as clinically and therapeutically the most important guidelines on nanorobot prototyping analysis. The simulation in a 3D real time environment aims to establish a useful framework as a testbed for nanorobot foraging inside the body. Then, the considered therapeutic use of nanorobots includes cancer and intracranial treatments. This study provides a methodological approach that helps in the development of nanorobotics for medical target identification. Hence, chemical and thermal signals are paramount in this regard.

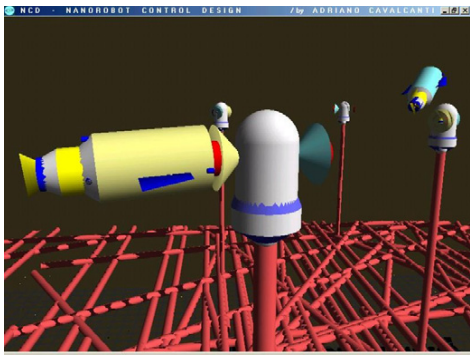

Figure 3. Organ-inlet is being assisted by the nanorobot with delivery of proteins.

6.2. Nanorobot interaction

Nanorobots can move with six-degrees-of-freedom, i.e., arbitrary translation and rotation fins and propellers (figure 2). They also have specific sensory capabilities to detect the target regions, obstacles and chemicals relevant for their medical application. We studied a prototypical task for nanorobots: moving through a fluid-filled vessel to locate target regions through thermal and chemical signals. The simulator allows the examination of a variety of control algorithms. Nanorobot behavior based on random motion and detection of chemical gradients is useful for medical target identification and drug delivery [121].

The simulator does allow multiple nanorobots to operate independently and in a cooperative mode. As one use for this capability, it is possible to investigate the robustness of control techniques by observing the mean time required for the interaction with the environment for the drug targets (figure 3). The nanorobot has to detect and locate any medical target, represented as organ-inlets, demanding protein injection in a period of time for the simulated dynamic scenery.

6.3. Diffusing signals

The 3D environment contains nanorobots, obstacles, biomolecules and specific medical targets. The medical

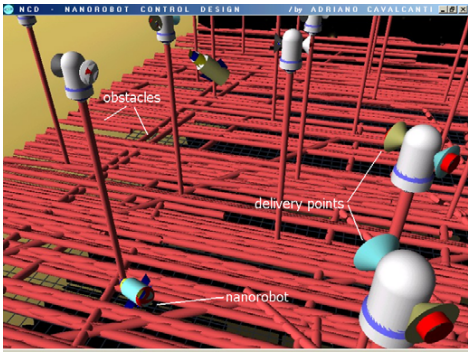

Figure 4. Virtual environment, top camera view.

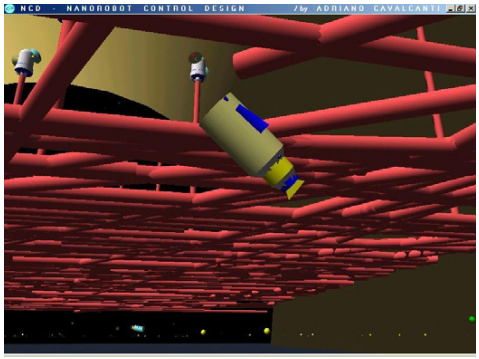

Figure 5. Sensing obstacles to avoid collisions.

targets represent organ-inlets, displaced stochastically as target locations or drug delivery points for medical applications (figure 4). These organ-inlets are closed when the chemical concentrations are near the desired levels. Otherwise, it will open diffusing chemical and thermal signals to show the required injection of protein drugs. A key choice in chemical signaling is the measurement time and detection threshold at which the signal is considered to be received [122]. Due to background concentration, some detection occurs even without the target signal. As a threshold, we use the diffusive capture rate ϕ for a sphere of radius R in a region with concentration as:

$$\phi = 4\pi DRC \tag{1}$$

where the concentration for other shapes such as cylinders are about the same [121]. All moving objects (i.e., the nanorobots and biomolecules) in the workspace have neutral buoyancy. In regard to the circulatory system about vessels geometries and the nanorobot sizes for medical purposes, the lumen diameters ranges from the vena cava with ∼3 cm in the heart, to ∼10 μm of capillary vessels. The simulated nanorobot has a size of 3 μm^3, which comprises 2 μm^3 with embedded nanobioelectronics as described in the nanorobot architecture [8], and 1 μm^3 as inside space for transporting substances for medical delivery. In the present study the nanorobot is transporting proteins.

The virtual environment as testbed includes a randomized network of obstacles. This construction creates a random network of obstacles in the plane bisecting the pipe (figure 5), which is quite appropriate as a basis for nanorobot control feedback purposes of motion analyzes and obstacle avoidance. The environment also presents spheres with 10 nm diameter as biomolecules that the nanorobots can use to supply medical targets with proteins. These spheres move with the fluid, and follow the laminar flow considered to be additional Brownian motions. In a typical molecular dynamics simulation, a set of molecules is introduced initially with a random velocity for each molecule and the intermolecular interactions can be expressed [123], using the Lennard-Jones potential:

$$V(r) = 4\varepsilon\left[\left(\frac{r}{\sigma}\right)^{-12} - \left(\frac{r}{\sigma}\right)^{-6}\right]. \tag{2}$$

Except for coronary artery blood flow, in typical biomedical applications the blood flow is laminar, especially for smaller vessels where the fluid velocity is typically lower [124, 125].

6.4. Fluid dynamics

The fluid in the workspace moves through the vessel with a velocity 1 mm s^{-1}, as is typical of flow in small blood vessels [1, 123, 126]. The fluid is described by the classical continuum equations [40, 123]. The continuity condition $\nabla \cdot v = 0$ and the Navier–Stokes equation are applied for the velocity v of the fluid:

$$\frac{\partial v}{\partial t} + (v \cdot \nabla)v = f - \frac{1}{\rho}\nabla P + \frac{\eta}{\rho}\nabla^2 v, \tag{3}$$

where η is the fluid's viscosity, ρ its density, P is the pressure and f is the external force, per unit mass, imposed on the fluid. The three components of the Navier–Stokes equation and the continuity condition give four equations for the three components of the velocity and the pressure. In contrast to the conventional and large scale robots, the nanorobot's world is dominated by viscosity while inertial and gravitational forces are negligible [1, 40]. The Reynolds number, defined as:

$$Re = L\rho v/\eta, \tag{4}$$

for objects of size L with velocity v, characterizes this behavior by giving the ratio of inertial to viscous forces. The Re is low for nanoscale robots operating in fluids of ordinary viscosities [1, 123]. The surrounding liquid has a density of 1 g cm^{-3} and viscosity of 1 cP, or 10^{-2} g cm^{-1} s^{-1}. As an example, if a nanorobot of size 1 μm moving at 1 mm s^{-1} in liquid flow has $Re = 10^{-3}$, much less than 1 and hence viscous forces dominate. As boundary conditions, the flow velocity v matches the velocity of each object in the fluid at the object's surface. We also impose a constant input velocity along the pipe as a boundary condition to maintain the fluid flow. This condition is maintained by a pressure gradient imposed on the fluid.

6.5. Interaction in viscous flow

Our environment contains two types of moving objects: the nanorobots and the small spheres representing biomolecules.

These objects are subject to both deterministic and random forces. The deterministic forces arise from the fluid motion and, in the case of the nanorobots, from their powered locomotion.

The inertial force on the object of size L moving with velocity v with respect to the fluid is of the order $F_{\text{inertial}} \cong \rho v^2 L^2$ and the viscous drag force is of the order $F_{\text{viscous}} \cong \eta v L$. Thus to keep moving, a nanorobot of size $L \cong 1\ \mu$m and velocity $v \cong 1$ mm s^{-1} with respect to the fluid must apply $F_{\text{inertial}} \cong 1$ fN (femtonewtons, 1 fN $= 10^{-15}$ N) and a much larger $F_{\text{viscous}} \cong 10^3$ fN of motive force. As a consequence of this dominance of viscosity, when a force F is applied to an object, it quickly reaches a terminal velocity where that force is canceled by the drag from the fluid. As an illustration of this behavior, if motive power to a swimming spherical nanorobot with radius $L = 1\ \mu$m, and the velocity $v = 1$ cm s^{-1} with respect to the fluid, is suddenly stopped, then the nanorobot will 'coast' to a halt with respect to the fluid in a time t_{coast} as:

$$t_{\text{coast}} = \frac{\rho L^2}{15\eta} = 0.1\ \mu\text{s} \tag{5}$$

and in distance $x_{\text{coast}} \cong v t_{\text{coast}} = 1$ nm. A comparable result applies to other shapes, e.g., the nanorobot and the smaller sized biomolecules. Thus an applied force quickly results in motion with constant velocity. It contrasts with the behavior when inertial forces dominate: an applied force produces a constant acceleration. A similar observation applies to rotations: a given torque rapidly produces a constant angular velocity rather than a constant angular acceleration.

Two main forces act on a nanorobot while it is not in contact with other objects. First is the force F_{r} produced by the robot itself, which is taken to be directed along the axis of the cylinder. Second is the drag from the fluid given by:

$$F_{\text{drag}} = -A_{\text{drag}} \eta L v, \tag{6}$$

where v is the velocity vector of the nanorobot with respect to the fluid, $v = v_{\text{robot}} - v_{\text{fluid}}$. The quantity A_{drag} is a geometric factor depending on the orientation of the nanorobot with respect to the fluid and is typically of order 1, e.g., for a sphere of diameter L, A_{drag} is 3π when no other objects are nearby. For other situations, A_{drag} has roughly the same magnitude, but the exact value must be determined numerically. To see how this is done, consider a small area dA on the surface of an object, treated as a vector oriented perpendicular to the surface. The fluid imposes a force vector $-T\,\text{d}A$ on that area, where T is a matrix representing the stress tensor for the fluid motion at the surface of the object. For incompressible fluids, its components are expressed:

$$T_{k,l} = P\delta_{k,l} - \eta\left(\frac{\partial v_k}{\partial x_l} + \frac{\partial v_l}{\partial x k}\right), \tag{7}$$

where is $\delta_{k,l} = 1$ when $k = l$ and is 0 otherwise.

In general, the velocity gradient and pressure vary over the surface of the object. The total drag force requires integrating the force on each part of the object. The difference in forces around the object can also give rise to a torque, causing the object to rotate as it moves through the fluid. The total force acting on the robot is $F_{\text{r}} + F_{\text{drag}}$, which is zero when the nanorobot velocity equals to:

$$v_{\text{robot}} = v_{\text{fluid}} + F_{\text{r}}/(A_{\text{drag}} \eta L). \tag{8}$$

The biomolecules move passively along with the fluid, i.e., their velocity is equal to v_{fluid}. Both the passive obstacles and other nanorobot are potential sources of collision and additional force. In particular, a collision with the wall of the pipe or one of the obstacles sets to zero the component of the object's velocity perpendicular to the wall or obstacle. When a biomolecule collides with a nanorobot, the biomolecule velocity perpendicular to the robot is set to zero; it may also be absorbed by the robot if it was identified as a protein. In addition to these deterministic forces, stochastic forces due to thermal motion of molecules in the fluid give rise to additional random motions, i.e., Brownian motion. As an indication of the size of these motions, the average displacement of a particle of radius L over a time t when the fluid has temperature T is:

$$b = \left(\frac{kTt}{3\pi\eta L}\right)^{1/2}, \tag{9}$$

where k is Boltzmann's constant and b is displacement. Operating at typical body temperature, this gives displacement for the nanorobot of about $\sqrt{t}\ \mu$m when t is measured in seconds, and $8\sqrt{t}\ \mu$m for the biomolecules.

Collecting biomolecules is part of the robot's task. A nanorobot at rest with respect to the fluid will encounter biomolecules due to their diffusion. The laminar fluid flow itself only moves the molecules along streamlines which go through the workspace. An estimate of the rate at which such a nanorobot will encounter diffusing biomolecules is of order $10LDC$, where L is the size of the robot (3 μm^3), D is the diffusion coefficient in liquid, about 10^{-10} m^2 s^{-1}, and C is the concentration of molecules around the robot [1]. In the simulation, $C = 10^{16}$ m^{-3} enabling the nanorobots to have an interactive response in collecting them for a further target identification, and protein drug delivery. In our simulation, the collisions between biomolecules and the robots are determined from their individual motions, including the diffusion from Brownian motion.

Our physically based simulation includes kinetics and frictional aspects for object motion with hydrodynamics at low Reynolds number [121, 123]. Specifically, the dynamics of the objects in our environment is determined by the object positions and, for the nanorobots, their choice of locomotion force as determined from their control program. Unlike the case of inertial forces, there is no need to consider accelerations. The dynamics in the environment is processed as the boundary conditions for determining the fluid motion from equation (3). Given the fluid motion, we determine the net force and torque on each nanorobot, after which equation (8) gives its new velocity. Each biomolecule's velocity matches that of the fluid at its position. For both the nanorobots and biomolecules, this velocity is also subject to constraints from any collisions. From the perspective of each object, this process amounts to a function that evaluates its velocity v_{object}

Table 1. Parameters.

Chemical signal	
Production rate	$Q = 10^4$ molecule s^{-1}
Diffusion coefficient	$D = 100\ \mu$m^2 s^{-1}
Background concentration	6×10^{-3} molecule μm^{-3}
Parameter	**Nominal value**
Average fluid velocity	$v = 1000\ \mu$m s^{-1}
Vessel diameter	$d = 10, 20, 40\ \mu$m
Workspace length	$L = 60\ \mu$m
Density of nanorobots	$3\ \mu$m^3

in terms of the state of the system. Using a time step of Δt, we then update the object positions according to:

$$\text{object} \leftarrow F + v_{\text{object}} \Delta t + \varepsilon, \tag{10}$$

where ε is a random vector chosen from a Gaussian distribution with mean of 0 and average length $\sqrt{\Delta t}\ \mu$m (with Δt measured in seconds) for the nanorobots and 8 times as large for the biomolecules. For the nanorobots, a similar evaluation is based on the torques applied by the fluid, the nanorobots themselves as part of their locomotion, and any collisions given their angular velocities. The angular velocity then gives the change in orientation after the time Δt, and r is the applied force for manipulating an object.

7. Target identification

Nanorobots' capability for moving, sensing and manipulating is quite important for interacting with target identification for treatments of different diseases. Depending on the medical application, specific choices can be set in terms of sensors and actuators control.

7.1. Sensing

Based on the described hardware architecture, the nanorobot uses sensors allowing it to detect and identify nearby large objects in its environment, as well as the target regions for its task.

The nanorobot includes external sensors to inform it of collisions and to identify when it has encountered a chemical signal or abrupt changes of temperature for targeted areas. As a practical technique for nanorobots orientation we used chemical signals as a useful approach for medicine. A significant rise in temperature may occur every time there is some abnormality in the human body [58]. In some cases, the temperature difference at the site of some lesion from the core temperature can reach up to $\sim$2 °C [20]. Hence, in order to simulate the nanorobot intervention and interaction with the workspace, we used different organ-inlets as delivery targets, where depending on their protein demand, they will be emitting chemical and thermal signals. We simulated distinct cases to validate our study given the equation (1) and parameters on table 1 for diffusing signals.

These changes on chemical concentration will be used to guide the nanorobots. The nanorobots are able to detect obstacles over a range of about 4 μm, and within an angular resolution equivalent to a diameter of 3 μm at that range. The biomolecules are too small to be detected reliably: instead the robot relies on chemical contact sensors to detect them. The sensor capabilities allow the evaluation of the different sensing actions that the nanorobot can take. How effectively the nanorobot actuation can be improved is analyzed with chemical and thermal sensing.

7.2. Actuation

The nanorobot's task involves collecting various chemical compounds as predefined proteins, delivering them to specific target regions in the 3D environment. The nanorobots must, after identifying the biomolecules as proteins, use control strategies involving movement around the environment to identify and reach the organ-inlets requiring protein drug delivery. For the propulsion mechanism to move through the fluid, the nanorobot uses double propellers, with different velocities regarding the flow directions being adjusted. Since applied forces rapidly result in a terminal velocity through the fluid, in the simulation of the locomotion mechanism they produce a given velocity v_{force} with respect to the fluid according to equation (8). As described above, these speeds correspond to forces of the order 10^3 fN. Thus equation (8) becomes:

$$v_{\text{robot}} = v_{\text{fluid}} + v_{\text{force}}, \tag{11}$$

with v_{force} directed along the axis of the nanorobot and with one of these three magnitudes.

8. Nanorobot simulation

The simulator maintains a list of positions and orientations of all objects in the task environment, including the nanorobots. This list maintains all information relevant to the nanorobot tasks. It also introduces new biomolecules with the fluid as it enters the environment. The simulator consists of several modules, that simulate physical behaviors, determine sensory information for each nanorobot, run the control programs to determine the nanorobot actions, provide a visual display of the environment, and records the history of nanorobot behaviors for detailed analysis. The computational approach involves a multithreaded system that provides dynamic updates for the nanorobot real time sensing and activation (figure 6). This same concept and implementation is applied in relation to other nanorobots as well as to the surrounding workspace. Memory behavior is based on pre-programmed actions and defined rules, which are activated according to input signals to trigger the desired actuation.

8.1. Visualization

The development of nanosystems must be able to respond efficiently in real time for the changing aspects of microenvironments not previously examined from a control perspective. Including aspects of the physical environment in conjunction with graphical visualization provide a feasible approach for architecture prototyping, control system, and sensor design analyzes.

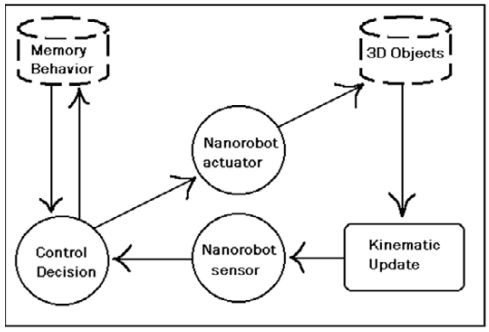

Figure 6. Nanorobot's dynamic real time interactive sensing and actuation.

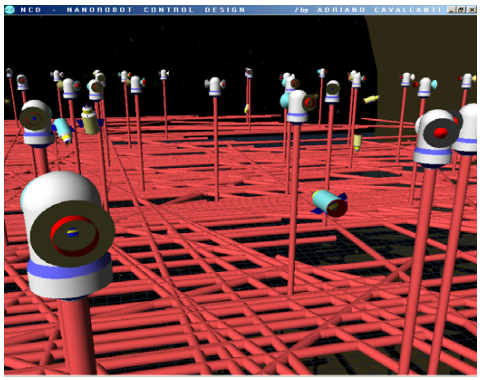

Figure 7. Nanorobots search for organ-inlets demanding protein injection.

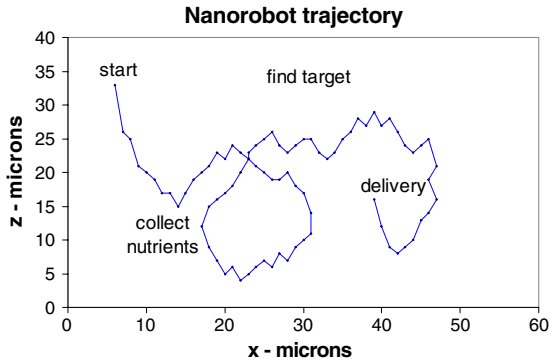

Figure 8. A detailed trajectory performed by a sensor-driven nanorobot to catch biomolecules, then to detect the target.

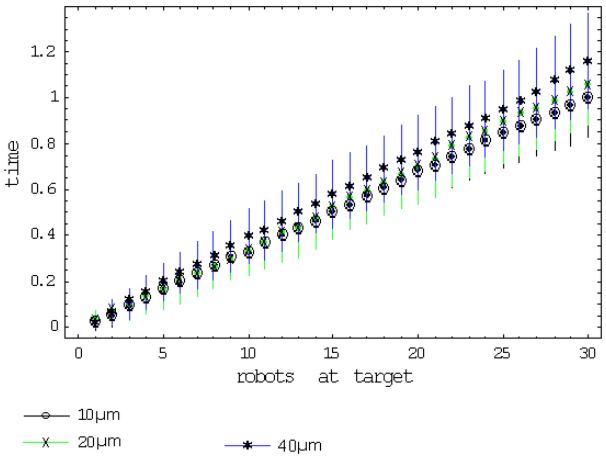

Figure 9. The time required for nanorobots to achieve the targets in the vessel with different diameters—10, 20 and 40 μm.

In our work the simulator checks for collisions to determine the actual velocities. A practical approach for implementing a physically based simulation to achieve a fast response is the use of collision detection for bounding volumes [127]. With this approach to determine the robot velocity, we update the position for the nanorobots and biomolecules according to equation (10). This is also used to provide sensor input for the nanorobot.

The 3D simulation is based on a real time clock and independent of the fps (frames per second) rate in the rendering pipeline. Thus, there is no relation between fps and the simulator timer to update the physical environment. This allows showing the behavior in fast or slow motion, as the user requests, without changing the physical simulation. We used parallel processing techniques [128], where the nanorobots react adaptively to any stimulus produced by the environment [129], with the model visualization in real time.

8.2. Numerical results

In our study 30 nanorobots perform similar tasks on detecting and acting upon medical targets demanding protein injections (figure 7). Each nanorobot is programmed to move through the workspace catching biomolecules (figure 8); after that, once identified the medical target may be requiring an injection of proteins, the nanorobot makes the drug delivery for the respective area. In case 1, the nanorobots used random motion to detect and achieve medical targets. The average and standard deviation of time were measured in seconds to get 30 nanorobots with their respective targets for the results describing vessels with different diameter sizes (figure 9). We observed the probability for a nanorobot to find the target as 0.31, 0.15 and 0.07, respectively for workspaces with 10, 20 and 40 μm diameters. So probability is inversely proportional to the vessel diameter. This is exactly what we would expect for nanorobots navigating in the vessel crowded by stochastic obstacles to find the target only based on the same parameters, such as random motion, chemical or even thermochemical based signals. In such cases, the chemical diffusion and thermal reaction is more sprayed or concentrated depending on the workspace characteristics in terms of diameters.

Comparisons were done for distinct cases for monitoring how effective the nanorobot performances could be in sensing and detecting medical targets inside the environment using different parameters (figure 10). For the 20 μm vessel, this shows the average time to have 30 nanorobots at medical targets with behavior guided for random motion (case 1), sensing chemical signal (case 2), or tracking target location

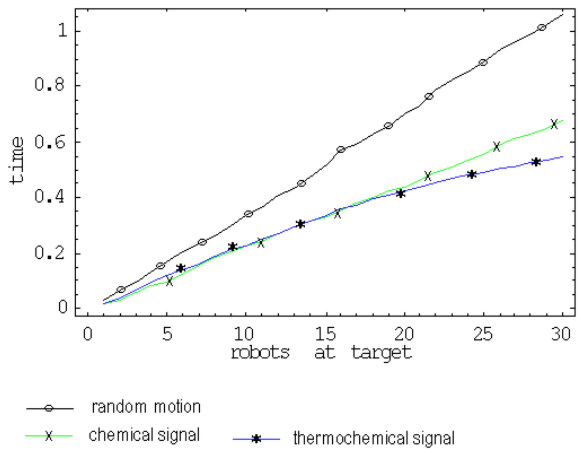

Figure 10. Comparison for random motion, chemical signals, plus the nanorobot using a thermal-chemical signal to reach the targets for a 20 μm diameter vessel.

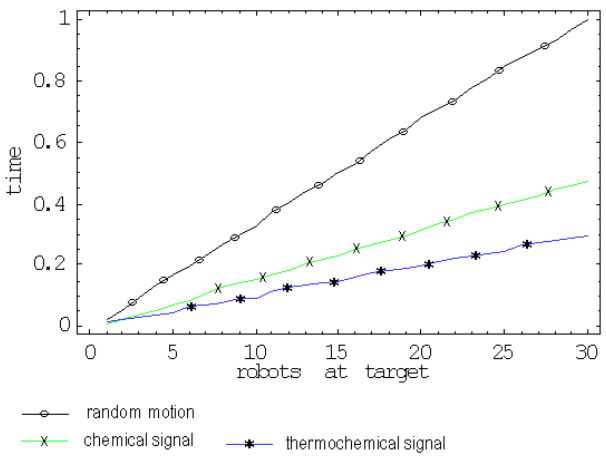

Figure 12. Nanorobot behavior with random motion, chemical, and thermochemical for a 10 μm vessel.

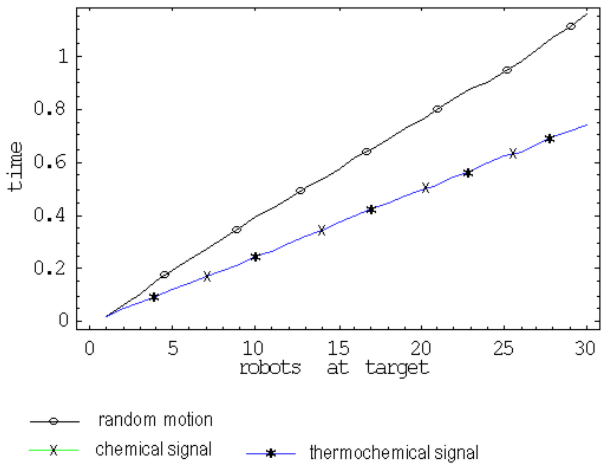

Figure 11. Nanorobot behavior for random motion, chemical detection, and thermochemical sensing, for a 40 μm diameter vessel; chemical and thermochemical lines overlap together.

through thermochemical sensory substance identification (case 3). Note how the chemical allied with thermal signals allow nanorobots to find their targets faster. Thermal signals can provide a long term improvement for nanorobots, affecting the speed to detect and reach the right target to inject protein drugs. For thermochemical the plot bends downward, while for the other two approaches the nanorobots take longer to detect and reach the medical targets.

The study for the case with a 40 μm vessel can be analyzed through the numerical results plotted in figure 11. The chemical signal shows a similar profile in comparison with the thermochemical signals. In the plot, the chemical and thermochemical signals do not differ for a larger vessel. Thus, both lines overlap together in the graph showing the same behavior for the nanorobots. Apparently, the larger vessel is too large for the extra thermal signal to make a difference in terms of nanorobot sensors to substantially improve performance. It also takes a longer time for nanorobots to find the targets detecting the signal. Thus, thermochemical signals require more time to diffuse far enough to make a difference for a larger vessel. However, the performance is still clearly better than using simple random motion for nanorobot control with no use of biosensors.

On the other side, the plot for the 10 μm vessel indicates relevant differences in performance for nanorobot behaviors when using random motion, chemical or thermochemical sensors (figure 12). The extra thermochemical sensor signal helps the performance of the nanorobot to detect and achieve medical targets demanding proteins. In fact, for smaller vessels the chemical and thermochemical signals have a faster impact with about 80% of improvement on the nanorobot efficiency. Therefore, a suitable sensing methodology can enable a successful accomplishment on target identification for drug delivery and accurate diagnostic processes of complex diseases.

9. Further development

The perspective that the same manufacturing technologies required to assemble nanorobots could also be applied to a broad range of fields, should be the main motivation for the investigation of new methodologies to achieve this accomplishment as fast as possible. The appropriate interdisciplinary effort will impact on assembly nanodevices and nanoelectronics to build nanorobots. The research and development of nanorobots can also provide new technologies and devices for enhanced industrial automation. As a result of such development, more effective and safe operations are expected for manufacturing processes, as well as better electronics, featuring higher performance and lower energy requirements.

The application of nanorobots with embedded sensor devices for drug delivery and diagnosis is an interesting subject, which can enable significant improvements as a high precision device for medical treatments. A

nanorobot architecture using embedded CMOS for sensing, communication and actuation, as the result of many breakthroughs in nanotechnology, with a complete integrated set of nanobioelectronics, should help in setting directions for the fast development and manufacturing designs of future molecular machines. The use of some techniques, such as SoC and Lithography, VHDL and 3D simulation, allied with recent nanotechnology advances, like mesoscopic nanowires, nanophotonics, quantum dots and CNTs, are contributing together with the implementation of high complex VLSI featuring functionality and exceptional performance under nanoscale sizes.

10. Conclusions

This paper has described a pathway towards an effective methodology to control nanorobots and advance nanotechnology as a valuable tool for medicine. Nanorobots should help, through medical target identification, to improve diagnosis and provide new therapeutic procedures. Numerical analysis and computational simulation was adopted to illustrate the proposed nanorobot performance in a dynamic environment used as testbed for medical instrumentation and drug delivery.

Manufacturing strategies are developing progressively along with nanoelectronics, RFID and recent achievements in biotechnology. Thus, the model for the nanorobot hardware architecture described how well-established techniques and upcoming technologies should be used to interface nanorobots with data transmission and telemetric control, also providing an overview on manufacturing possibilities. Therefore, the application of computational nanotechnology, 3D prototyping, and real time simulation helps in the process of defining integrated nanodevices and relevant interactions for transducers and actuators applicable to medical nanorobotics.

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