Nanorobot for Brain Aneurysm

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Abstract

In this paper we present how nanoelectronics should advance medicine, providing details on the teleoperated techniques and equipment design methodology necessary for the effective development of nanorobots. The platform architecture describes how to use a nanorobot for intracranial prognosis, and shows how it should be integrated for medical instrumentation. Furthermore, the current study establishes proteomics, nanobioelectronics, and electromagnetics as the basis to advance medical nanorobotics. To illustrate the proposed approach, the nanorobots must search for protein overexpression signals in order to recognize initial stages of aneurysm. An advanced nanomechatromics simulator, using a three-dimensional task-based environment, is implemented to provide an effective tool for device prototyping and medical instrumentation analysis. Thus, based on clinical data and nanobioelectronics, the proposed model offers details about how a nanorobot should help with the early detection of cerebral aneurysm.

KEY WORDS—architecture, biochip, medical nanorobotics, nanobioelectronics, nanobiosensor.

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1. Introduction

The research and development of nanorobots with embedded nanobiosensors and actuators is considered to provide a new possibility to provide health specialists with new high-precision tools (Frist 2005). In the same way that the development of microtechnology in the 1980s has led to new medical instrumentation, emerging nanotechnologies, such as the manufacturing of nanoelectronics (Chau et al. 2007), will similarly permit further advances in medicine, providing efficient methods and new devices for patient treatment (LaVan et al. 2003; Leary et al. 2006).

The use of microdevices in surgery and medical treatments is a reality which has brought many improvements in clinical procedures in recent years (Elder et al. 2008). For example, among other medical instrumentation, catheterization has been used successfully as an important methodology for intracranial surgery (Ikeda et al. 2006). Now the advent of biomolecular science and new manufacturing techniques is helping to advance the miniaturization of devices from microelectronics to nanoelectronics (Andrews 2007).

The three main approaches proposed in the current scientific literature for the future development of nanorobots are positional nanoassembly, DNA nucleic acid robots, and bacteria-based nanorobots. Although such methods reported previously are quite interesting and important as initial stages for the study of nanomachines, they suffer from some serious lim-

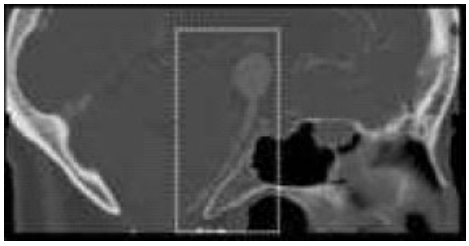


Fig. 1. Computer tomography slice image used for three-dimensional reconstruction.

itations. Positional nanoassembly is inadequate in terms of efficiency in building nanodevices, and such an approach is also not used in nanoelectronics manufacturing, which integrates the current methodology in use towards the commercialization of high-performance nano-integrated circuits (ICs). The DNA approach to build nucleic acid robots does not allow complex nanodevices, as required to enable precise instrumentation for medical applications etc., to be realized. The third approach using bacteria-based nanorobots presents serious concerns and limitation: bacteria are living organisms and can self-replicate, making their use in medicine inappropriate due to safety reasons.

In our work, we propose a new fourth approach to developing nanorobots for common use in medicine: the nanorobot should be achieved as an IC. The methodology requires hybrid materials, photonics, and wireless communication for nanorobot manufacturing and control. The present nanorobot architecture provides a medical nanorobotics model in accordance with engineering, physics concepts, and current trends in nanoelectronics and extracellular proteomic signaling for device prototyping and biomedical instrumentation. This nanorobot platform offers a practical architecture for *in vivo* instrumentation, and is proposed for brain aneurysm.

A key factor to increase the chances for patients in having a satisfactory treatment from intracranial aneurysm relies on the detection of vessel deformation in the early stages of bulb development. The current procedure is to monitor patients with some sort of history of aneurysm using ultrasound computer tomography (CT) every 6 to 12 months (Figure 1), requiring a regular basis of medical accompaniment. To visualize how stages of the actual and upcoming technologies can be applied to medicine, the nanorobots are used to detect NOS (nitric oxide synthase) protein overexpression inside an intracranial blood vessel. Therefore, the implemented work provides a practical approach for a nanorobot control interface and equipment design analyses. As described in this paper, the model can be equally useful for other biomedical problems.

1.2. Paper Overview

In this paper we present a nanorobot architecture for cerebral aneurysm prognosis, using computational nanotechnology for medical device prototyping. The paper is organized to cover three main aspects: (i) equipment prototyping; (ii) the manufacturing approach; and (iii) inside-body transduction.

(i) Equipment prototyping: computational nanotechnology provides a key tool for the fast and effective development of nanorobots, helping in the investigation to address major aspects on medical instrumentation and device prototyping. A similar approach was previously taken by industry to build racing cars, airplanes, submarines, ICs, and medical devices. Now, the same can be used to benefit the development and research of medical nanorobots.

(ii) Manufacturing technology: for manufacturing purposes, the nanorobot should be integrated as a biochip device. Thus, new materials, photonics, and nanobioelectronics are presented with a description of the nanorobot architecture.

(iii) Inside-body transduction: cell morphology, microbiology, and proteomics are used as parameters for nanorobot morphology and inside-body interaction. Changes on chemical gradients and telemetric instrumentation are used for medical prognosis, with the nanorobots activation based on proteomic overexpression.

As presented in the paper, these three points comprise the key pieces required to advance the development and implementation of medical nanorobotics.

The manuscript is therefore organized as follows. In Section 2 we present the medical device platform, describing the nanorobot architecture. Section 3 provides an overview of current nanoelectronics manufacturing techniques, and upcoming new methodologies that should advance three-dimensional nanodevice integration. Then, in Section 4, special attention is devoted to cell biology, providing details on biochemical sensing and physical aspects incorporated into the model, as well as the main intracranial bloodstream kinematics and extracellular signaling. Section 5 provides the numerical results, and the conclusion and outlook are presented in Section 6.

2. Equipment Prototyping

The medical nanorobot should comprise a set of IC blocks as an application-specific IC (ASIC). The architecture has to address functionality, providing asynchronous interface for the antenna, sensor, and a logic nanoprocessor, which should be able to trigger actuator and activate ultrasound communication when appropriate (Figure 2). The main parameters used for the nanorobot architecture and control activation, as well as the required technology background that can advance manufacturing hardware for molecular machines, are described next. As a practical rule, the number of nanodevices to integrate into a nanorobot should be kept small to ensure that the hardware size is suitable for inside-body application.

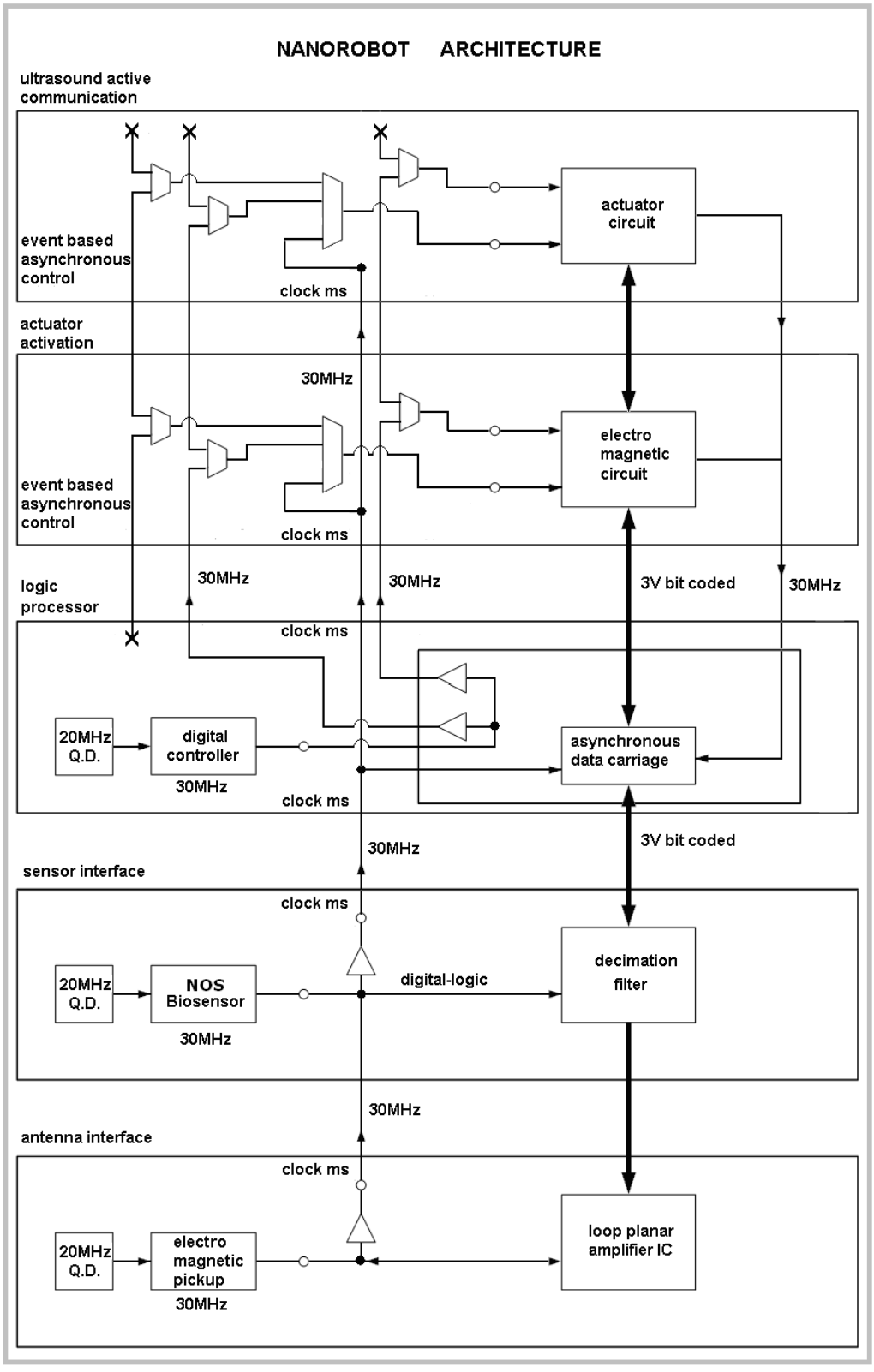


Fig. 2. Integrated circuit block diagram.

2.1. Chemical Sensor

Manufacturing silicon-based chemical- and motion-sensor arrays using a two-level system architecture hierarchy has been successfully conducted in the last 15 years. Applications include the automotive and chemical industries, including biomedical uses, with the detection of air to water elements and different pattern recognition through embedded software programming. Through enhanced nanowires, existing significant costs of energy demand for data transfer and circuit operation can be decreased by up to 60% (Cavalcanti et al. 2008b). Complementary metal oxide semiconductor (CMOS)-based sensors using nanowires as the material for circuit assembly can achieve maximal efficiency for applications with regards to chemical changes, enabling new medical applications.

Sensors with suspended arrays of nanowires assembled into silicon circuits decrease self-heating and thermal coupling for CMOS functionality drastically. Factors such as low-energy consumption and high sensitivity are some of the advantages of nanosensors. Nanosensor manufacturing array processes can use electrofluidic alignment to achieve integrated CMOS circuit assembly as multi-element systems. 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 loss of processed signals. With regards to nanosensor signal noise, proper impedance can be regulated and improved with ion radiation and proper photonics calibration to achieve a faster protein detection and response for nanobiosensors. Biomaterial such as serum antigen and CNT hybridization should be used for the ion process to neutralize accumulative increasing orbital electron energy. The type of antigen should be customized according to the proposed medical target application.

For the nanorobot architecture, the antibody CAB002167 is included for modeling the IC sensor; the antibody serves to identify higher concentrations of proteins that couple NOS isoforms to intracellular bloodstream signaling (Kishimoto et al. 1992). The nanobiosensor provides an efficient integrated way for nanorobots to identify the locations where NOS occurs, which is denoted by changes in the gradients of the brain enzymes. Carbon nanotubes (CNTs) serve as an ideal material for the basis of a CMOS IC nanobiosensor.

2.2. Actuator

There are different kinds of actuators, such as electromagnetic, piezoelectric, electrostatic, and electrothermal, which may be utilized depending on the aim and the workspace where the actuator is to be applied (Fukuda et al. 1995). A set of fullerene structures was presented as a nanoactuators (Crowley 2006). The use of CNTs as conductive structures permits electrostatically driven motions providing the forces necessary for nanomanipulation. CNTs can be used as a material for commercial applications on building devices and nanoelectronics such as nanotweezers and memory systems. Silicon-on-insulator (SOI) technology has been used for transistors with high performance, low heating and energy consumption for very-large-scale integration (VLSI) devices. CNT self-assembly and SOI properties can be combined in a CMOS design to enable high-performance nanoelectronics and nanoactuators to be manufactured. Owing to the maturity of silicon CMOS technology, as well as the unique properties of CNTs, the integration of CNT and the CMOS technology can make use of the benefits of both (Bogaerts et al. 2005; Chau et al. 2007).

For a medical nanorobot, applying CMOS as an actuator based on biological patterns and CNTs is proposed for the nanorobot architecture as a natural choice. In the same way that DNA can be used for coupling energy transfer, and proteins may serve as the basis for ionic flux with electrical discharge in the range 50–70 mV dc voltage gradient in cell membranes (Jenkner et al. 2004), an array format based on CNTs and CMOS techniques could be used to achieve nanomanipulators as an embedded system for integrating nanodevices of molecular machines (Cavalcanti et al. 2008a). Ion channels can interface electrochemical signals using sodium for the energy generation which is necessary for mechanical actuators operation (Jenkner et al. 2004). Embedded actuators are programmed to perform different manipulations, hence enabling direct active interaction with the bloodstream patterns and the molecular parameters for nanorobots inside the body.

Precise trajectory motion and nanorobot collective communication can be useful for some biomedical problems, such as nanosurgery and intracellular drug delivery, but it is not required in aneurysm detection. The most crucial problem in cerebral aneurysm is identifying endothelial vessel deformation before a stroke happens. Current clinical practice to contain aneurysm growth involved medication reaching vessel bifurcations, pharmacokinetically enhancing lipid peroxidation and blood pressure, and does not require any propulsion system. Similarly, the nanorobots as a bloodborne device can be released directly inside the patient's bloodstream. No thrust force or propulsion system is required from the nanorobot to the major task of aneurysm prognosis.

2.3. Power Supply

The use of CMOS for active telemetry and power supply is the most effective and secure way to ensure energy as long as necessary to keep nanorobots in operation. The same technique is also appropriate for other purposes such as digital bit encoded data transfer from inside a human body (Cavalcanti et al. 2008a). Thus, nanocircuits with resonant electric properties can operate as a chip to provide electromagnetic energy, which supplies 1.7 mA at 3.3 V for power, allowing the operation of many tasks with few or no significant losses during transmission (Sauer et al. 2005). Radiofrequency (RF)-based telemetry

procedures have demonstrated good results in patient monitoring and power transmission with the use of inductive coupling (Schnakenberg et al. 2004), using well-established techniques already widely used in commercial applications of radiofrequency identification device (RFIDs). Around 1 μW of energy received can be also saved while the nanorobot stays in inactive mode, 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, around 1 mW is required to send RF signals. 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 obtain both energy and data transfer capabilities for nanorobots by employing cell phones in such a process (Cavalcanti et al. 2008b). The mobile phone should be uploaded with the control software that includes the communication and energy transfer protocols.

2.4. Data Transmission

The application of devices and sensors implanted inside the human body to transmit data about the health of patients can provide great advantages in continuous medical monitoring (Schnakenberg et al. 2004). Most recently, the use of RFID for *in vivo* data collecting and transmission was successfully tested for electroencephalograms (Sauer et al. 2005). CMOS with sub-micrometer system-on-chip (SoC) design can provide extremely low power consumption with nanorobots communicating collectively for longer distances through acoustic sensors. For communication, as well as for navigational purposes, the use of nanoacoustics for nanorobot interactions can effectively achieve resolutions of 700 nm (Norris 2006). For data recognition, the acoustic phonons scattered from the origin should be propagated at sufficient distances, and the acoustic wavefield should be measured by diffraction propagation. In fact, electric and acoustic fields provide practical ways for nanorobot active communication inside the body. An embedded nano-IC can be used as an electric discharge device, allowing acoustic communication with frequencies reaching up to 20 μW at 10–20 Hz at resonance rates with a 1–3 V supply (Cavalcanti et al. 2008b; Solberg et al. 2008). The typical time duration for interactive communication among nanorobots is set as 200 ms, with a repeating signal duration of 10 ms long and separated by 30 ms. Thus, it provides some choice for establishing a set of predefined collective actions for nanorobots, using distinct acoustic field signals.

For data transfer, using integrated sensors is the best answer to read and write data in implanted devices. Thus, the nanorobot model comprises a customized single-chip IC CMOS-based sensor. Typical antenna on RFIDs use wired coils, which takes up more space in the IC. In our design, to set an embedded antenna with 200 nm size for the nanorobot RF communication, a small loop planar device is proposed as a RFIC electromagnetic pick-up having a good matching on low noise amplifier (LNA); it is based on a gold nanocrystal with 1.4 nm^3, CMOS and nanobioelectronic circuit technologies (Schifferli et al. 2002; Cavalcanti et al. 2008b). Frequencies at 20 MHz can be successfully used for biomedical applications without any damage (Sauer et al. 2005).

More widely accepted and available than a RF CMOS transponder, mobile phones can be extremely practical and useful as sensors for acquiring wireless data transmission from medical nanorobots implanted inside the patient's body. Such phones can be a good choice for monitoring predefined patterns in various biomedical treatments, such as helping with the instrumentation and detection of brain aneurysm. To accomplish that, chemical nanobiosensors should be embedded into the nanorobot to monitor NOS levels. The nanorobot emits signals to send an alarm in case it detects any NOS protein overexpression, which normally denotes the start of aneurysm.

Electromagnetic radio waves are used to command and detect the current status of nanorobots inside the patient (Cavalcanti et al. 2008a). This occurs with the cell phone used as a transmitter device. It emits a magnetic signature to the passive CMOS sensor embedded in the nanorobot, which enables data to be sent and received through electromagnetic fields (Schnakenberg et al. 2004). From the last set of events recorded in pattern arrays, information can be reflected back by wave resonance. For nanorobots, passive data transferring at a frequency of around 4.5 kHz with approximately 22 μs delays are possible ranges for data communication.

3. Manufacturing Technology

In the present approach, the proposed nanorobot architecture is assembled using a nanoelectronic biochip integration process (LaVan et al. 2003; Cavalcanti et al. 2008b). The ability to manufacture nanorobots should result from current trends and new methodologies in fabrication, computation, transducers and manipulation (Montemagno and Bachand 1999; Mavroidis and Dubey 2003; Narayan 2005). CMOS VLSI design using deep ultraviolet lithography provides high precision and a commercial way for manufacturing early nanodevices and nanoelectronics systems. The innovative CMOS field effect transistor (FET) and some hybrid techniques should successfully lay the foundations for the assembly processes needed to manufacture nanorobots, where the joint use of nanophotonic and nanotubes can even further accelerate the actual levels of resolution ranging from 248 to 157nm devices (Bogaerts et al. 2005). To integrate designs and achieve a successful implementation, the use of VHDL (very high speed IC hardware description language) has become a common technique utilized in the IC manufacturing industry.

Some limitations to improving bipolar CMOS (BiCMOS), CMOS and metal oxide semiconductor field effect transistor (MOSFET) methodologies include the quantum-mechanical tunneling needed to operate thin oxide gates, and the subthreshold slope. 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 at meeting the growing demand for high complex VLSIs. Recent developments in three-dimensional circuits and FinFETs (fin field effect transistor) double-gates have achieved astonishing results and according to the semiconductor roadmap should improve even more. To further advance manufacturing techniques, SOI technology has been used to assemble high-performance logic sub-90-nm circuits. New materials such as strained channels with relaxed SiGe (silicon–germanium) layers can reduce self-heating and improve performance. Circuit design approaches to solve problems with bipolar effect and hysteretic variations based on SOI structures have been demonstrated successfully (Park et al. 2005). Thus, already-feasible 90-nm and 45-nm nano-CMOS ICs represent breakthrough technology devices that are already being utilized in products. Hence, further development on nanobioelectronics and proteomics should enable fully operational nanorobots, integrated as molecular machines, for use in common medical applications (Cavalcanti et al. 2008a).

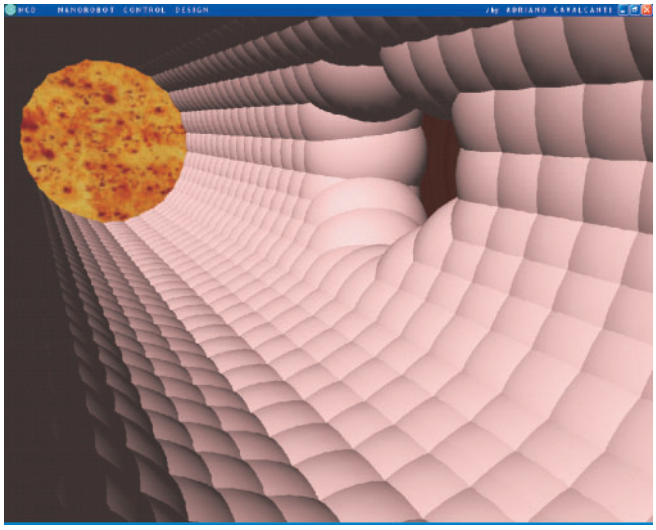
Progress in technology has historically shown that technical challenges can be converted into opportunities (Frist 2005). Thus, although important breakthroughs are demanded for the fully implementation of hardware to enable nanorobots, the main barriers could be successfully overcome by research and continuous development. For example, lithography has successfully enabled manufacturing of compact components comprising several nanowire layers to integrate nanoelectronics (Chau et al. 2007; Lee et al. 2008). CMOS has enhanced miniaturization and industrial manufacturing techniques, which have provided ways to achieve commercialized products as nanoelectronics integrated devices. Nanosensors using DNA and CNT as innovative materials were successfully demonstrated for protein detection (Cui et al. 2001; Mavroidis and Dubey 2003). The recent implementation of high-K metal gates in the 45-nm silicon technology node should result in a positive impact on the progress of high-K research for InSb (indium antimonide) and InGaAs (indium gallium arsenide), enabling new ways to achieve smaller nano-IC packaging. At the same time, block copolymers can be viewed as a promising methodology to improve manufacturing miniaturization of current nanoelectronics, even enabling complex three-dimensional nanodevices, not previously allowed by traditional CMOS techniques. Those methods and new materials should therefore be investigated together to enable more complex nanoelectronic packaging, such as is necessary for the integration of nanorobots. To extend the CMOS performance improvements found with dimensional scaling, new materials for planar MOSFETs and non-classical MOSFET structures are currently in development, which should also advance nanoelectronics and new biosensors that will mostly be useful for nanomedicine (Cavalcanti 2003; Leary et al. 2006).

4. Inside-body Transduction

The nanorobot model and analysis consist of a task-based design and simulation for intracranial aneurysm detection, adopting a multi-scale view of the scenario. It incorporates the physical morphology of the biological environment along with physiological fluid flow patterns (Figures 3 and 4), and this is allied with the nanorobot systems for data transmission and medical instrumentation. The real-time three-dimensional simulation is used to achieve high-fidelity on control modeling and equipment design. Hence, the nanorobot control design (NCD) software was implemented, and is used for nanorobot sensing and actuation. Real-time 3D prototyping and simulation are important tools in nanotechnology development and biomedical prototyping (Cavalcanti 2003; Ikeda et al. 2006; Hamdi et al. 2008). Such methodologies have significantly helped the semiconductor industry to achieve faster VLSI development. It has similarly had a direct impact on the implementation of nanomanufacturing techniques and also on nanoelectronics progress (Chau et al. 2007). Simulation can anticipate performance and help in new device design and equipment manufacturing, as well as in nanomechatronics control and hardware investigation (Park et al. 2005; Cavalcanti et al. 2008a).

Endovascular treatment of brain aneurysms (Figure 5), arteriovenous malformations, and arteriovenous fistulas are biomedical problems expected to benefit from current research and developments in the field of medical nanorobotics (Elder et al. 2008). Nanorobots using chemical sensors as embedded nanoelectronics can be programmed to detect different levels of NOS pattern signals as medical targets in the early stages of aneurysm development. For such a task, and to assist physicians in taking any action required, the nanorobot antenna interface activates the RF wireless communication every time changes in proteomic signal intensity are found. Therefore, nanorobots should provide a precise detection of aneurysm in the initial stages of development. The nanorobot is programmed for sensing and detects concentrations of NOS in the bloodstream (Fukuda et al. 2000; Genov et al. 2006). The nanorobot uses a RFIC CMOS transponder system for *in vivo* positioning, using well-established communication protocols that provide tracking information about the nanorobot position. Hence, the nanorobot model includes embedded IC nanoelectronics, and the platform architecture involves the use of cell phones for data transmission and coupling energy (Cavalcanti et al. 2008b).

The exterior shape of the nanorobot consists of a carbon–metal nanocomposite (Narayan 2005), to which an artificial



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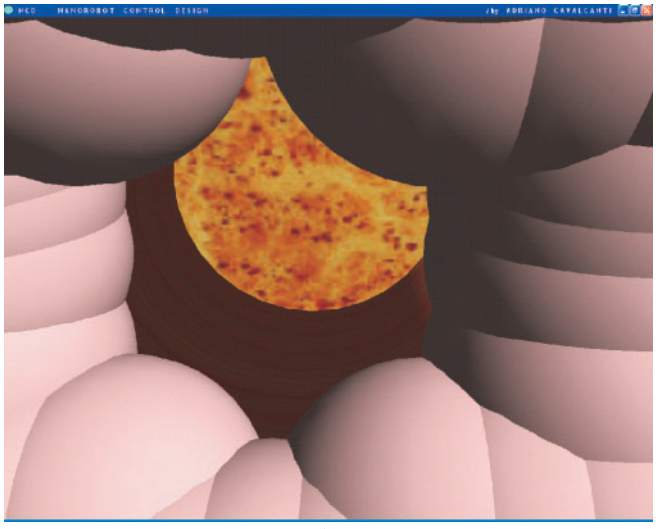


(b)

Fig. 3. Intracranial vessel model: (a) endothelial cells forming the vessel walls; (b) vessel wall deformation, resulting in the development of aneurysm.

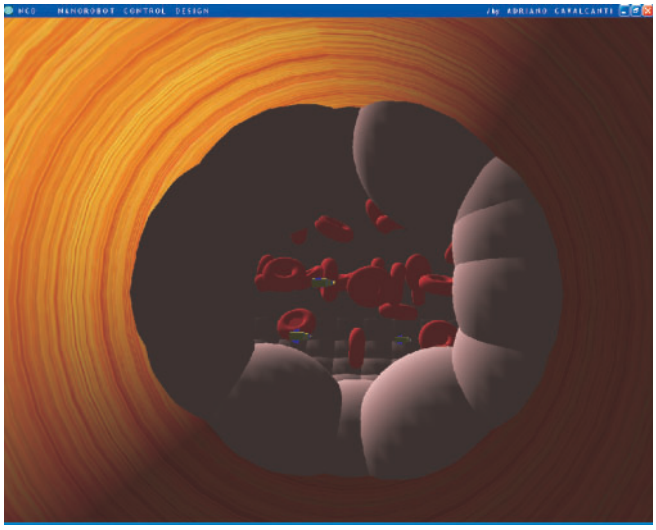


Fig. 4. A view from inside the aneurysm cavity.

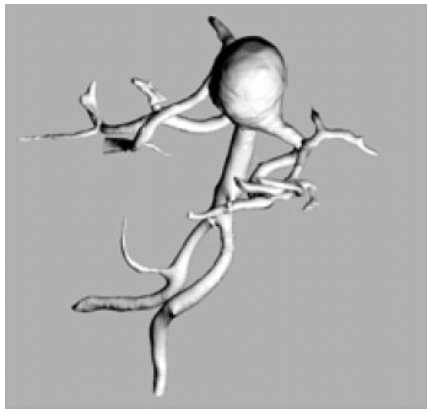


Fig. 5. Basilar artery with vessel aneurysm, based on CT angiography.

glycocalyx surface may be attached that minimizes the adsorption or bioactivity of fibrinogen and other blood proteins, ensuring sufficient biocompatibility to avoid immune system attack (Freitas 2005; Marchant et al. 1999). The nanorobot sensory capabilities are simulated (Lo 2006), allowing it to detect and identify the nearby possible obstacles in its environment, as well as NOS protein overexpression for prognosis purposes.

4.1. Physical Parameters

The microenvironments of the circulatory system vary considerably in size, flow rates, and other physical properties. Chemicals in the blood can present distinct diffusion coefficients, and like any other surgical, prognosis, or automatic drug delivery integrated system, there is a range of plausible designs for the nanorobots depending on customized requirements. In defining the nanorobot application, the physical parameters are the key point in determining the hardware prototype, sensor-based actuation, and strategies to increase the medical instrumentation efficiency.

Changes in chemical gradients serve to identify aneurysm in the early stages of development, helping physicians to take action before an intracranial stroke happens. Typically, small vessels have diameters of up to several tens of micrometers, and lengths of about a millimeter. The workspace used in the simulator comprised an environment consisting of a segment of the vessel of length L with a small aneurysm as the med-

ical target on the wall, emitting a chemical into the fluid (Figure 6). In our study, the focus of interaction and sensing with nanorobots is addressed giving details of the vessel proteomic signals dispersing through a three-dimensional intracranial vessel as testbed for prototyping and analysis. The medical three-dimensional environment comprises clinical data based on main morphological parameters from patients with cerebral aneurysm (Figure 7) (Ikeda et al. 2006). We choose the workspace length sufficient to include the region where the chemical from the target is significantly above the background level. The cells occupy about a fifth of the workspace volume, a typical *hematocrit* value for small blood vessels.

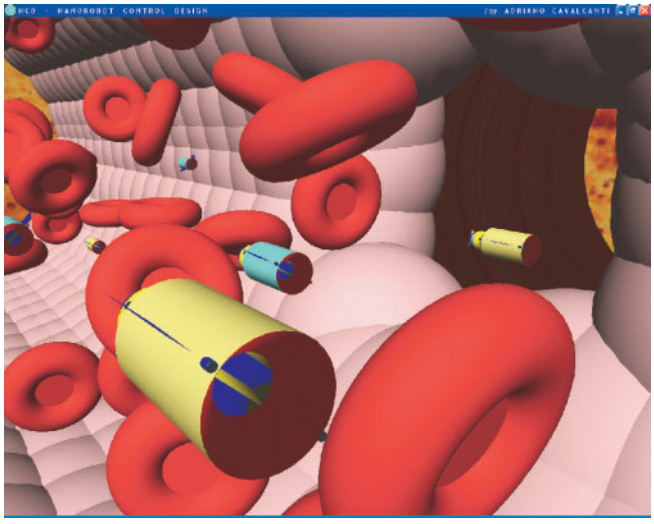
The nanorobot morphology is based on microbiology, presenting a cylindrical shape 2 μm in length and 0.5 μm in diameter, which allows free operation inside the body (Rau et al. 2002). Therefore, the nanorobot's customized design is useful for aneurysm detection, but it also enables the nanorobot to cross the blood brain barrier for other biomedical applications, such as required for the treatment of Alzheimer's disease and other neurological disorders (Cavalcanti et al. 2008b). This prototyping allows the nanorobot to have complete kinematic motion control with regards to Brownian motion events inside microenvironments with a low Reynolds number.

The simulator comprises a mathematical, chemical-based, and computational dynamic model, which is a real-time three-dimensional environment, including the bloodstream, nanorobots, and proteomic signaling. Most of the cells are red blood cells, with 6 μm diameter. The number densities of platelets and white blood cells are about one 20th and one 1,000th that of the red cells, respectively.

The nanorobot density is equal to 10^{12} nanorobots in the entire 5-liter blood volume of a typical adult. Thus, a similar number of nanorobots may be used in medical applications (Freitas 2005). The total mass of all of the nanorobots is about 0.2 g. Owing to fluid drag and the characteristics of locomotion in viscous fluids, nanorobots moving through the fluid at approximately 1 mm s^{-1} dissipate a picowatt (Berg 1993). Thus, if all of the nanorobots moved simultaneously they would use about 1 W.

The human genome mapping showed from chromosome 12 that the protein NOS has a direct influence on the lifespan of cell and tissues (Kishimoto et al. 1992). In particular, the NOS protein can have positive or negative effects on cells and tissues, also affecting vessel living processes (Fukuda et al. 2000). In the NOS subgroups, while eNOS (endothelial NOS) acts as a positive protein, the nNOS (neuronal NOS) is generally related with neurodegenerative diseases, such as Alzheimer's and Parkinson's, and can play a special role in endothelial cell degenerative changes (Kishimoto et al. 1992). In particular, nNOS may result in negative effects with nitrosative stress accelerating intracranial aneurysm rupture.

As a specific example, we consider the NOS protein signal produced in response to the aneurysm. It has a molecular weight of 58 kDa, with chemical signaling near the aneurysm



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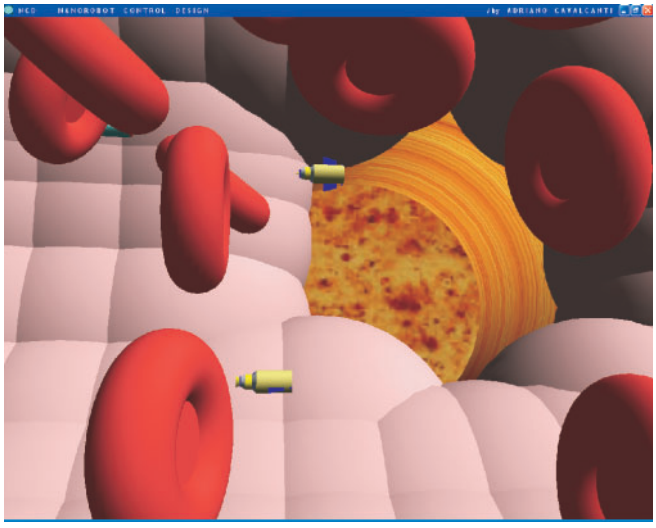

(b)

Fig. 6. Cerebrovascular disease: (a) the environment comprises the vessel wall with endothelial cells, bloodstream, nanorobots, and the saccular aneurysm; (b) near the aneurysm cavity, the nanorobot's sensor is activated due to protein overexpression.

at around 30 ng ml^{-1} and a background concentration in the bloodstream about 300 times smaller. This choice provides an interesting nanorobot task, although we could equally well study tasks involving proteomic overexpression with different concentrations relevant for other biomedical engineering problems.

Typical concentrations of NOS in bloodstream are less than 1 μm. A critical issue on cerebral aneurysm is detecting and locating the vessel dilation, preferably before a subarachnoid hemorrhage occurs. Sensing and detection of NOS signals has

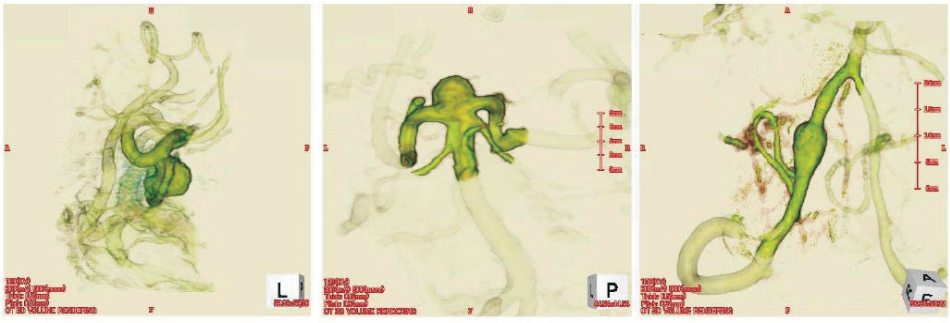

Fig. 7. Aneurysm morphologies: middle cerebral artery (MCA), basilar trunk (BT), and basilar artery (BA).

a lifetime of 250 ms (Genov et al. 2006), which requires high precision and fast response biosensors. Carbon-based sensors have already been used successfully for *in vivo* NOS detection (Fukuda et al. 2000; Genov et al. 2006). In our study, the chemical signal was taken to be produced uniformly over the target region at a rate Q. The background concentration is a significant sensory parameter, because the signal rapidly dilutes as it diffuses from the source.

4.2. Target Identification

Based on clinical analysis, the NOS proteins could also be well established as medical targets for early stages of aneurysm development. Nanorobots using chemical sensors as embedded nanoelectronics can be programmed to detect different levels of NOS pattern signals. Integrated nanobiosensors and RF wireless communication are incorporated into the nanorobot model. Thus, the nanorobot is applied to inform changes of gradients for intracranial NOS signals, providing a new tool for precise aneurysm prognosis. The nanorobot model includes IC nanobioelectronics, and the platform architecture can alternatively use cell phones for data transmission and coupling energy. The nanorobot computation is performed through asynchronous IC architecture, and the embedded nanobiosensor is used for the detection of NOS concentrations in the bloodstream. Owing to background compounds, some detection occurs even without the NOS concentrations specified as the aneurysm target. Therefore, for the chemical diffusion a capture rate α is adopted for the aneurysm identification, given the radius R for a region with concentration as

$$\alpha = 4\pi DRC. \tag{1}$$

Here D represents the diffusion coefficient, and C is the chemical concentration (Hogg 2007). With independent random motions for the molecules, detection over a time interval Δt is based on a Poisson process with mean value $\alpha \Delta t$. When objects occupy only a small fraction of the volume, the velocity at distance r from the center of the vessel is represented by

$$w = 2v(1 - (r/(d/2))^2). \tag{2}$$

The velocity has a parabolic flow in relation to the cells. For a fluid moving at velocity v in the positive x-direction, it is passing a plane containing a point of a chemical source produced at a rate $\dot{Q}$ (molecules per second), and a diffusion coefficient D. Thus, the diffusion equation is defined as

$$D\nabla^2 C = v\partial C/\partial x. \tag{3}$$

The boundary conditions attain a steady point source at the origin, having no net flux across the boundary plane at $y = 0$; thereby the steady-state concentration C (molecules per cubic micrometer) is determined at point (x, y, z) by

$$C(x, y, z) = \frac{\dot{Q}}{2\pi Dr} e^{-v(r-x)/(2D)} \tag{4}$$

and r is the distance to the source:

$$r = \sqrt{x^2 + y^2 + z^2}. \tag{5}$$

5. Nanorobot Simulation and Results

The chemical detection in a complex dynamic environment is an important factor to consider for nanorobots when interacting with the human body. For brain aneurysm prognosis, nanorobots need to track the vessel endothelial injury before a subarachnoid hemorrhage occurs. In our study, given the parameters in Table 1 and Equation (3), extracellular diffusion signals are simulated. These changes on chemical concentration are used to guide the nanorobots to identify brain aneurysm in the early stages of development. The biomolecules are too small to be detected reliably: instead the robot relies on chemical nanobiosensor contact to detect them.

The stochastic environment, consisting of bloodstream flow and chemical dynamic patterns, was implemented as a testbed for nanorobot task-based analysis (Figure 8), which provides an effective approach for medical device prototyping. In a typical molecular dynamics simulation, a set of molecules is introduced initially with a random velocity for each molecule

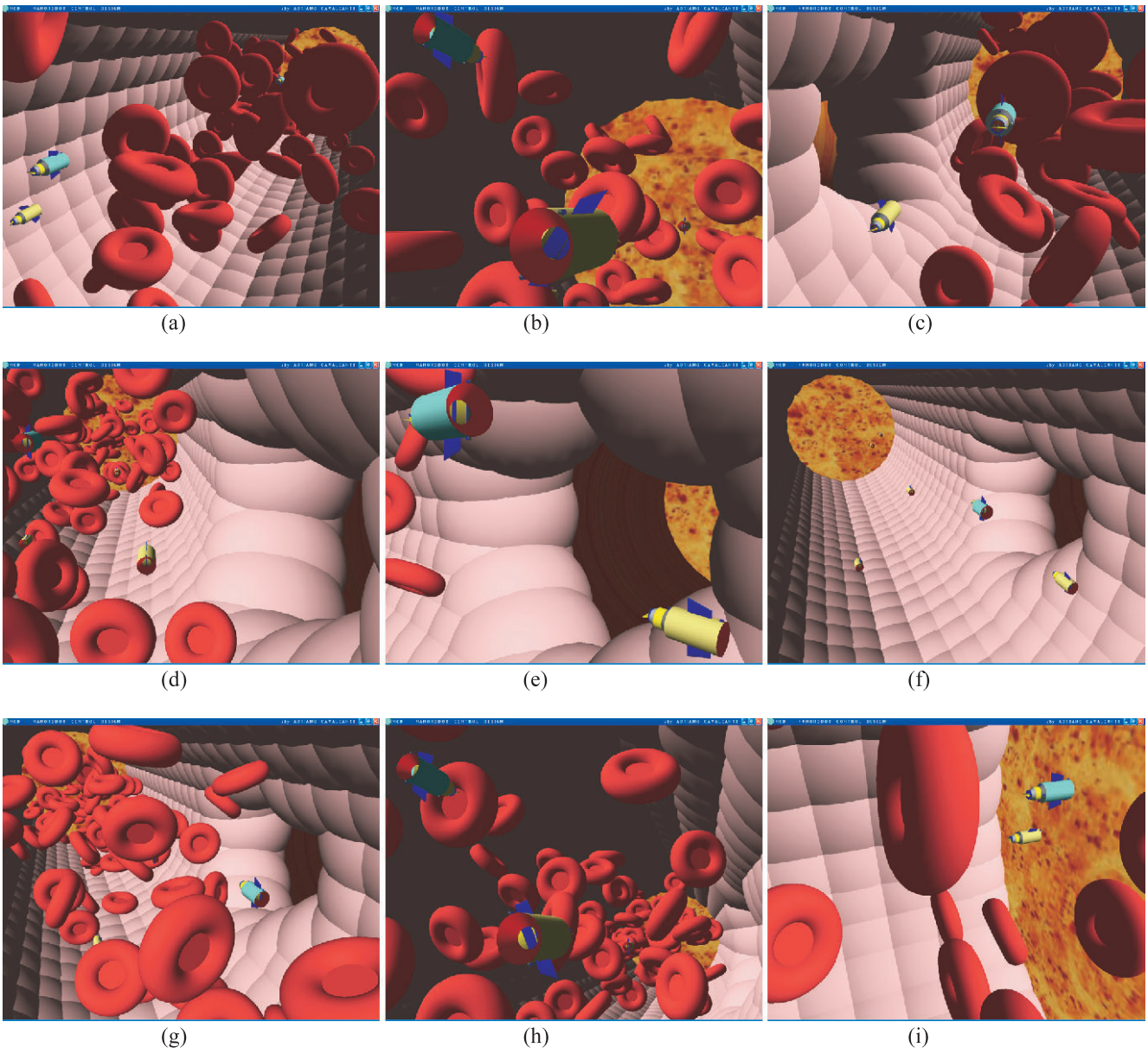

Fig. 8. Nanorobots used to detect brain aneurysm: (a) the nanorobots enter the vessel and flow with the bloodstream; (b) the nanorobots are moving through the vessel with the fluid; (c) the aneurysm saccular bulb begins to become visible at the vessel wall; (d) nanorobots move closer to the vessel deformation; (e) mixed with the plasma, NOS signals can be detected as the chemical gradient changes, denoting proteomic overexpression; (f) the same workspace viewed without red cells; (g) the nanobiosensor is activated as the nanorobots move closer to the aneurysm, emitting RF signals sent to the cell phone; (h) as the nanorobots keep flowing, the chemical signals become weaker, deactivating the nanorobot transmission; (i) red cells and nanorobots flow with the bloodstream until they leave the vessel.

and the intermolecular interactions can be expressed, using the Lennard–Jones potential:

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

The fluid is described by the classical continuum equations. The continuity condition $\nabla \cdot v = 0$ and the Navier–Stokes equation are applied for the velocity v of the fluid:

$$\frac{\partial v}{\partial t} + (v \cdot \nabla)v = f - \frac{1}{\rho}\nabla P + \frac{\eta}{\rho}\nabla^2 v, \tag{7}$$

Table 1. Parameters

Chemical signal	
Molecular weight	NOS = 58 kDa
Production rate	$\dot{Q} = 10^4$ molecules s^{-1}
Diffusion coefficient	$D = 100\ \mu m^2\ s^{-1}$
Background concentration	6×10^{-3} molecules μm^{-3}
Parameter	**Nominal value**
Average fluid velocity	$v = 1,000\ \mu m\ s^{-1}$
Vessel diameter	$d = 30\ \mu m$
Workspace length	$L = 60\ \mu m$
Density of nanorobots	$L \times d : 2\ \mu m \times 0.5\ \mu m$

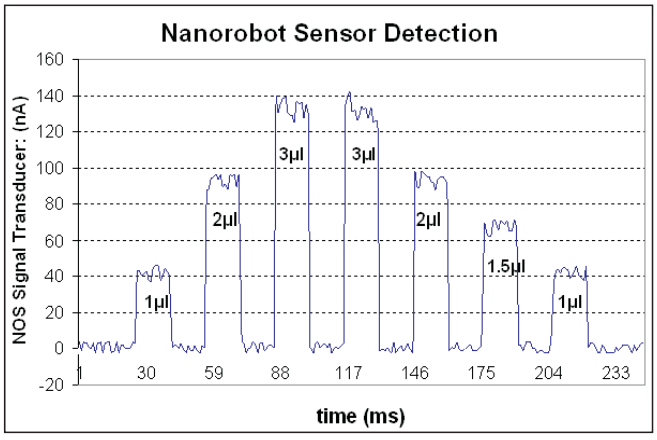

Fig. 9. Nanobiosensor activation.

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 main morphologic aspects related to brain aneurysm are taken for modeling the study of nanorobots sensing and interaction within the deformed blood vessel. Intracranial concentrations of NOS are small and some false positives can even occur due to some positive functions of N-oxide with semicarbazone (pNOS). Cells and nanorobots continually enter one end of the workspace along with the fluid flow. The nanorobots must detect protein overexpression, and the setup for sensing and control activation can be modified for different values, such as adjusting the detection thresholds. We treat any nanorobots not responding while within the workspace as if they did not detect any signal, so they flow with the fluid as it leaves the workspace.

If the nanorobot's electrochemical sensor detects NOS in low quantities or inside normal gradient it generates a weak signal lower than 50 nA. In such a case the nanorobot ignores the NOS concentration assuming that it is within the expected levels of intracranial NOS. However, if the NOS reaches a concentration higher than 1 μm, it activates the embedded sensor generating a signal higher than 90 nA (Figure 9). Every time this happens, the nanorobot is activated, emitting an electromagnetic signal detected by a receiver, such as a handheld, which records the nanorobot position where the signal happened.

As a practical threshold for medical prognosis, to avoid noise distortions and achieve a higher resolution, each time the cell phone has received at least a total of 100 nanorobots higher proteomic signal transduction, the model considers this as strong evidence of intracranial aneurysm (Figure 10). When activated, the nanorobots' sensors also indicate their respective position at the moment that they detected a high NOS protein concentration (Figure 11), providing useful information about the vessel bulb location and dimensions.

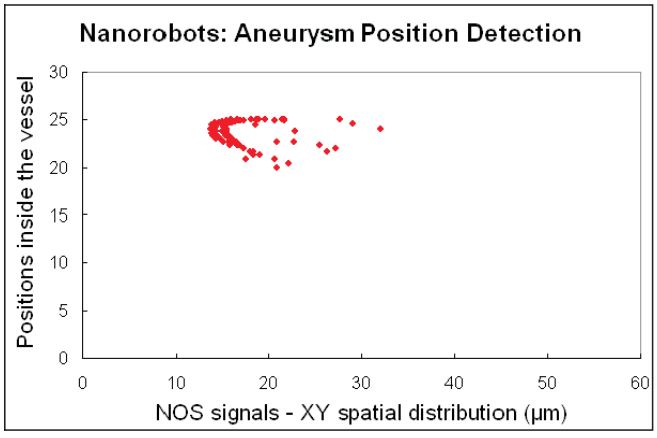

Fig. 10. Nanorobots detect NOS high concentration inside a small vessel within the intracranial bloodstream.

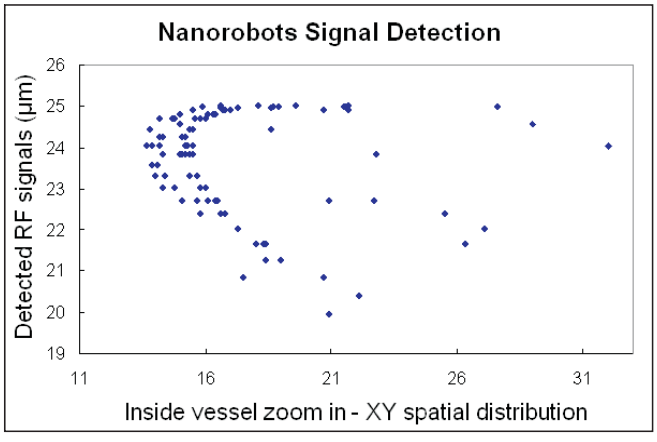

Fig. 11. Electromagnetic waves allow tracking nanorobot positions.

6. Conclusion and Outlook

The use of nanomechatronics and computational nanotechnology helps in the process of transducer investigation and in defining strategies to integrate nanorobot capabilities. Through embedded nanobiosensors, nanorobots should be programmed to detect extracellular changes in different levels of some proteomic signals, offering physicians a cutting-edge medical nanoelectronic device to improve *in vivo* treatment of intracranial diseases.

Details on current stages of nanobioelectronics technology have been described, highlighting pathways to achieve nanorobots as an advanced molecular machine system for nanomedicine. Moreover, based on achievements and trends in nanotechnology, new materials, nanoelectronics, photonics, and biotechnology, an integrated approach on hardware architecture design and analysis, which is suitable for the teleoperation of nanorobots, has provided a practical device platform that would be useful for medical prognosis.

A nanorobot prototype with telemetric control and data transmission for cerebral aneurysm applications has been presented, with embedded nanobiosensors for the detection of NOS overexpression. The architecture offers possible choices for manufacturing approaches, major control interface requirements, and inside-body information retrieval for the development of prognosis instrumentation using medical nanorobots. The nanomachine platform design was based on clinical data, proteomic signals, cell morphology, and numerical analysis. For the proposed model, the nanorobots were able to recognize chemical gradient changes in the bloodstream, retrieving information about the position inside the vessel as intracranial aneurysm detection.

An important and interesting aspect in the current development is the fact that this platform, presented in terms of device prototyping and system architecture integration, can also be useful for a broad range of applications in medicine.

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References

Andrews, R. J. (2007). Neuroprotection at the nanolevel—Part I introduction to nanoneurosurgery. *Annals of the New York Academy of Sciences*, **1122**: 169–184.

Berg, H. C. (1993). *Random Walks in Biology*, 2nd edn. Princeton, NJ, Princeton University Press.

Bogaerts, W., Baets, R., Dumon, P., Wiaux, V., Beckx, S., Taillaert, D., Luyssaert, B., Campenhout, J. V., Bienstman, P. and Thourhout, D. V. (2005). Nanophotonic waveguides in Silicon-on-Insulator fabricated with CMOS technology. *Journal of Lightwave Technology*, **23**(1): 401–412.

Cavalcanti, A. (2003). Assembly automation with evolutionary nanorobots and sensor-based control applied to nanomedicine. *IEEE Transactions on Nanotechnology*, **2**(2): 82–87.

Cavalcanti, A., Shirinzadeh, B., Freitas, R. A. Jr. and Hogg, T. (2008). Nanorobot architecture for medical target identification. *Nanotechnology*, **19**(1): 015103.

Cavalcanti, A., Shirinzadeh, B., Zhang, M. and Kretly, L. C. (2008). Nanorobot hardware architecture for medical defense. *Sensors*, **8**(5): 2932–2958.

Chau, R., Doyle, B., Datta, S., Kavalieros, J. and Zhang, K. (2007). Integrated nanoelectronics for the future. *Nature Materials*, **6**(11): 810–812.

Crowley, R. J. (2006). Carbon nanotube actuator. US Patent Specification 7099071.

Cui, Y., Wei, Q., Park, H. and Lieber, C. M. (2001). Nanowire nanosensors for highly sensitive and selective detection of biological and chemical species. *Science*, **293**(5533): 1289–1292.

Elder, J. B., Liu, C. Y. and Apuzzo, M. L. J. (2008). Neurosurgery in the realm of 10^{-9}, Part 2: Applications of nanotechnology to neurosurgery-present and future. *Neurosurgery*, **62**(2): 269–285.

Freitas, R. A. Jr. (2005). What is nanomedicine?. *Nanomedicine: Nanotechnology, Biology and Medicine*, **1**(1): 2–9.

Frist, W. H. (2005). Health care in the 21st century. *New England Journal of Medicine*, **352**(3): 267–272.

Fukuda, S., Hashimoto, N., Naritomi, H., Nagata, I., Nozaki, K., Kondo, S., Kurino, M. and Kikuchi, H. (2000). Prevention of rat cerebral aneurysm formation by inhibition of nitric oxide synthase. *Circulation*, **101**(21): 2532–2538.

Fukuda, T., Kawamoto, A., Arai, F. and Matsuura, H. (1995). Steering mechanism and swimming experiment of micro mobile robot in water. *Proceedings of the IEEE MEMS Micro Electro Mechanical Systems*, pp. 300–305.

Genov, R., Stanacevic, M., Naware, M., Cauwenberghs, G. and Thakor, N. V. (2006). 16-Channel integrated potentiostat for distributed neurochemical sensing. *IEEE Transactions on Circuits and Systems I—Regular Papers*, **53**(11): 2371–2376.

Hamdi, M., Ferreira, A., Sharma, G. and Mavroidis, C. (2008). Prototyping bio-nanorobots using molecular dynamics simulation and virtual reality. *Microelectronics Journal*, **39**(2):190–201.

Hogg, T. (2007). Coordinating microscopic robots in viscous fluids. *Autonomous Agents and Multi-Agent Systems*, **14**(3): 271–305.

Ikeda, S., Arai, F., Fukuda, T., Negoro, M., Irie, K. and Takahashi, I. (2006). Patient-specific neurovascular simulator for evaluating the performance of medical robots and in-

struments. *Proceedings of the IEEE International Conference on Robotics and Automation*, pp. 625–630.

Jenkner, M., Tartagni, M., Hierlemann, A. and Thewes, R. (2004). Cell-based CMOS sensor and actuator arrays. *IEEE Journal of Solid-State Circuits*, 39(12): 2431–2437.

Kishimoto, J., Spurr, N., Liao, M., Lizhi, L., Emson, P. and Xu, W. (1992). Localization of brain nitric oxide synthase (NOS) to human chromosome 12. *Genomics*, **14**(3): 802–804.

LaVan, D. A., McGuire, T. and Langer, R. (2003). Small-scale systems for in vivo drug delivery. *Nature Biotechnology*, **21**(10): 1184–1191.

Leary, S. P., Liu, C. Y. and Apuzzo, M. L. I. (2006). Toward the emergence of nanoneurosurgery: Part III—Nanomedicine: Targeted nanotherapy, nanosurgery, and progress toward the realization of nanoneurosurgery. *Neurosurgery*, **58**(6): 1009–1025.

Lee, K. N., Kim, K. S., Kim, N.-H. and Roh, Y. (2008). Fabrication of SiO2 nano-dots by block copolymer lithography and liquid phase deposition. *Materials Science and Engineering B—Solid State Materials for Advanced Technology*, **147**(2): 209–212.

Lo, W. (2006). High resolution semiconductor bio-chip with configuration sensing flexibility. US Patent Specification 20060252143.

Marchant, R. E., Zhang, T., Qiu, Y. and Ruegsegger, M. A. (1999). Surfactants that mimic the glycocalyx. US Patent Specification 6759388.

Mavroidis, C. and Dubey, A. (2003). Biomimetics: from pulses to motors. *Nature Materials*, **2**(9): 573–574.

Montemagno, C. D. and Bachand, G. D. (1999). Constructing nanomechanical devices powered by biomolecular motors. *Nanotechnology*, **10**(3): 225–231.

Narayan, R. J. (2005). Pulsed laser deposition of functionally gradient diamond-like carbon–metal nanocomposites. *Diamond and Related Materials*, **14**(8): 1319–1330.

Norris, T. B. (2006). Nanoacoustics: towards imaging nanostructures using picosecond ultrasonics. *The Journal of the Acoustical Society of America*, **119**(5): 3284–3285.

Park, J. G., Lee, G. S. and Lee, S. H. (2005). Method of fabricating nano SOI wafer and nano SOI wafer fabricated by the same. US Patent Specification 6884694.

Rau, C.-S., Chang, W.-N., Lin, Y.-C., Lu, C.-H., Liliang, P.-C., Su, T.-M., Tsai, Y.-D., Chang, C.-J., Lee, P.-Y., Lin, M.-W. and Cheng, B.-C. (2002). Brain abscess caused by aerobic Gram-negative bacilli: Clinical features and therapeutic outcomes. *Clinical Neurology and Neurosurgery*, **105**(1): 60–65.

Sauer, C., Stanacevic, M., Cauwenberghs, G. and Thakor, N. (2005). Power harvesting and telemetry in CMOS for implanted devices. *IEEE Transactions on Circuits and Systems I—Regular Papers*, **52**(12): 2605–2613.

Schifferli, K. H., Schwartz, J. J., Santos, A. T., Zhang, S. and Jacobson, J. M. (2002). Remote electronic control of DNA hybridization through inductive coupling to an attached metal nanocrystal antenna. *Nature*, **415**(6868): 152–156.

Schnakenberg, U., Krüger, C., Pfeffer, J.-G., Mokwa, W., Bögel, G. V., Günther, R. and Rode, T. S. (2004). Intravascular pressure monitoring system. *Sensors and Actuators A: Physical*, **110**(1–3): 61–67.

Solberg, J. R., Lynch, K. M. and Maciver, M. A. (2008). Active electrolocation for underwater target localization. *The International Journal of Robotics Research*, **27**(5): 529–548.