Hardware Architecture for Nanorobot Application in Cancer Therapy

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***Abstract*—This paper presents an innovative hardware architecture for medical nanorobots, using nanobioelectronics, clinical data, and wireless technologies, as embedded integrated system devices for molecular machine data transmission and control upload, and show how to use it in cancer therapy. The therapeutic application of nanorobots for cancer may be the natural result from some ongoing developments and trends in nanoelectronics, wireless communication, remote power transmission, nanotubes, lithography, biomedical instrumentation, genetics, and photonics. To illustrate the proposed approach, we applied advanced 3D simulation techniques as a practical choice on methodology for medical nanorobotics integrated system analyses and instrumentation prototyping.**

***Keywords*—Cancer, DNA molecular machine, E-cadherin signal, electromagnetic coupling, medical nanorobotics, nanobioelectronics, nanomechatronics, nanomedicine, nanotubes, transducers.**

I. Introduction

Nanorobots are expected to provide advances in medicine through the miniaturization from microelectronics to nanoelectronics. This work presents a nanorobot architecture based on nanobioelectronics [5] for the gradual development and future use of nanorobots to combat cancer [8], [32], [27]. Cancer can be successfully treated with current stages of medical technologies and therapy tools. However, a decisive factor to determine the chances for a patient with cancer to survive is: how earlier it was diagnosed; what means, if possible, a cancer should be detected at least before the metastasis has began. Another important aspect to achieve a successful treatment for patients, is the development of efficient targeted drug delivery to decrease the side effects from chemotherapy. Considering the properties of nanorobots to navigate as bloodborne devices [5], they can help on such extremely important aspects of cancer therapy.

Nanorobots with embedded chemical biosensors can be used to perform detection of tumor cells in early stages of development inside the patient's body [17], [9]. Integrated nanosensors can be utilized for such a task in order to find intensity of E-cadherin signals [19], [33]. Therefore a hardware architecture based on nanobioelectronics [5] is described for the application of nanorobots for cancer therapy [19]. Analyses and conclusions for the proposed model is obtained through real time 3D simulation.

II. Medical Nanorobot Architecture

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

A. Manufacturing Technology

The ability to manufacture nanorobots may result from current trends and new methodologies in fabrication, computation, transducers and manipulation. Depending on the case, different gradients on temperature, concentration of chemicals in the bloodstream, and electromagnetic signature are some of relevant parameters for diagnostic purposes [13]. CMOS VLSI (Very Large Scale Integration) Systems design using deep ultraviolet lithography provides high precision and a commercial way for manufacturing early nanodevices and nanoelectronics systems. The CMOS (Complementary Metal

Oxide Semiconductor) industry may successfully drive the pathway for the assembly processes needed to manufacture nanorobots, where the joint use of nanophotonic and nanotubes may even accelerate further the actual levels of resolution ranging from 248nm to 157nm devices [4]. To validate designs and to achieve a successful implementation, the use of VHDL (Verification Hardware Description Language) has become the most common methodology utilized in the integrated circuit manufacturing industry [20].

B. Chemical Sensor

Manufacturing silicon-based chemical- and motion-sensor arrays using a two-level system architecture hierarchy has been successfully conducted in the last 15 years. Applications range from autmotive 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% [35]. CMOS-based biosensors using nanowires as material for circuit assembly can achieve maximal efficiency for applications regarding chemical changes, enabling new medical treatments [9]. Chemical nanosensors can be embedded in the nanorobot to monitor E-cadherin gradients. Thus, nanorobots programmed for such task can make a detailed screening of the patient whole body. In our medical nanorobotic architecture, the mobile phone is applied [1], [16], [30], to retrieve information about the patient conditions. For that, it uses electromagnetic waves to command and detect the current status of nanorobots inside the patient.

New materials such as strained channel with relaxed SiGe layer can reduce self-heating and improve performance [3]. Recent developments in 3D circuits and FinFETs double-gates have achieved astonishing results and according to the semiconductor roadmap should improve even more. To further advance manufacturing techniques, Silicon-On-Insulator (SOI) technology has been used to assemble high-performance logic sub 90nm circuits [26]. Circuit design approaches to solve problems with bipolar effect and hysteretic variations based on SOI structures has been demonstrated successfully [3]. Thus, already-feasible 90nm and 45nm CMOS devices represent breakthrough technology devices that are already being utilized in products.

C. Power Supply

The use of CMOS for active telemetry and power supply is the most effective and secure way to ensure energy as long as necessary to keep the nanorobot in operation (Fig. 1). The same technique is also appropriate for other purposes like digital bit encoded data transfer from inside a human body [23]. Thus, nanocircuits with resonant electric properties can operate as a chip providing electromagnetic energy supplying 1.7 mAat 3.3V for power, allowing the operation of many tasks with few or no significant losses during transmission [30]. RF-based telemetry procedures have demonstrated good

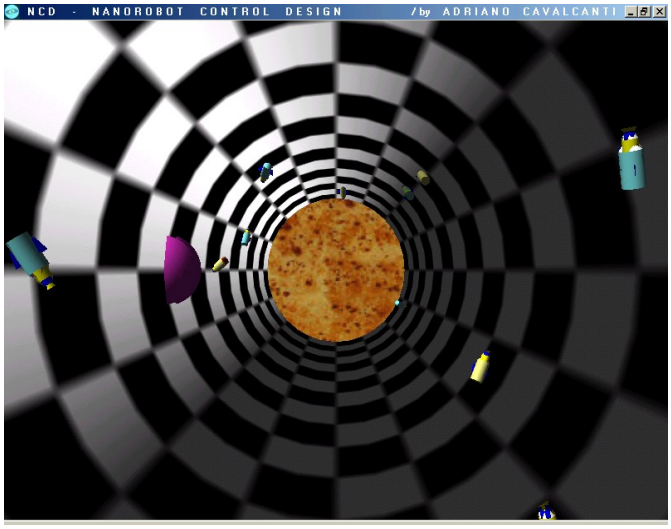

Fig. 1. All the nanorobots swim near the wall to detect cancer signals. Vein internal view without the red cells. The tumour cell is the target represented by the pink sphere located left at the wall.

results in patient monitoring and power transmission with the use of inductive coupling [10], using well established techniques already widely used in commercial applications of RFID [28]. The energy received can be also saved in ranges of ~1μW while the nanorobot stays in inactive modes, just becoming active when signal patterns require it to do so. Some typical nanorobotic tasks may require the device only to spend low power amounts, once it has been strategically activated. For communication, sending RF signals ~1mW is required.

A practical way to achieve easy implementation of this architecture will obtain both energy and data transfer capabilities for nanorobots by employing mobile phone in such process [1]. The mobile phone should be uploaded with the control software that includes the communication and energy transfer protocols.

D. 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 [5]. Most recently, the use of RFID for in vivo data collecting and transmission was successfully tested for electroencephalograms [30]. For communication in liquid workspaces, depending on the application, acoustic, light, RF, and chemical signals may be considered as possible choices for communication and data transmission [6]. Chemical signaling is quite useful for nearby communication among nanorobots for some teamwork coordination [5], [14].

Work with RFID (Radio Frequency Identification Device) has been developed as an integrated circuit device for medicine [28], [30]. Using integrated sensors for data transfer is the better answer to read and write data in implanted devices. Teams of nanorobots may be equipped with single-chip RFID CMOS based sensors [25]. CMOS with submicron SoC design could be used for extremely low power

TABLE I
PARAMETERS

Chemical signal	
production rate	$Q = 10^4 molecule/s$
diffusion coefficient	$D = 100\mu m^2/s$
background concentration	$6 \times 10^{-3} molecule/(\mu m)^3$
Parameter	**Nominal value**
average fluid velocity	$v = 1000\mu m/s$
vessel diameter	$d = 20\mu m$
workspace length	$L = 50\mu m$
density of cells	$2.5 \times 10^{-3} cell/(\mu m)^3$
nanorobot	$2\mu m^3$

consumption with nanorobots communicating collectively for longer distances through acoustic sensors. For the nanorobot active sonar communication frequencies may reach up to 20μW@8Hz at resonance rates with 3V supply [18].

In our molecular machine architecture, to successfully set an embedded antenna with 200nm size for the nanorobot RF communication, a small loop planar device is adopted as an electromagnetic pick-up having a good matching on Low Noise Amplifier; it is based on gold nanocrystal with $1.4nm^3$, CMOS and nanoelectronic circuit technologies [31], [30]. Frequencies ranging from 1 to 20MHz can be successfully used for biomedical applications without any damage [30].

III. System Implementation

Real time 3D prototyping tools and simulation are important aids in nanotechnology development. Such tools have significantly helped the semiconductor industry to achieve faster VLSI development [34]. It may have similarly direct impact on the implementation of nanomanufacturing techniques and also on nanoelectronics progress [29]. Simulation can anticipate performance and help in new device design and manufacturing, nanomechatronics control design [7] and hardware implementation [5], [26]. In the present work, the simulation includes the NCD (Nanorobot Control Design) software for nanorobot sensing and actuation. The software implemented from our group is used as a practical tool for control and manufacturing design analyses.

The nanorobot architecture includes integrated nanoelectronics [5], [35]. The nanorobot architecture involves the use of mobile phones for, e.g., the early diagnosis of E-cadherin levels for smart chemotherapy drug delirey, and new cancer tumor detection for cancer treatments [19], [1], [28]. The nanorobot uses a RFID CMOS transponder system for in vivo positioning [11], [28], using well established communication protocols which allow track information about the nanorobot position [1]. This information may helps doctors on detecting tiny malignant tissues even in initial stages of development.

The nanorobot exterior shape consists of a diamondoid material [24], to which may be attached an artificial glycocalyx surface [22], that minimizes fibrinogen (and other blood proteins) adsorption and bioactivity, ensuring sufficient biocompatibility to avoid immune system attack [11], [15]. Different molecule types are distinguished by a series of chemotactic biosensors whose binding sites have a different affinity for each kind of molecule [11], [21]. These sensors can also detect obstacles which might require new trajectory planning [7]. We simulate the nanorobot with sensory capabilities allowing it to detect and identify changes of E-cadherin proteins gradients beyond the expected levels, which in case may guide the nanorobots to detect a tumor for a cancer still in early stages. A variety of sensors are possible [35], [12]. For instance, chemical detection can be very selective [36], e.g., for identifying various types of cells by markers [11]. Acoustic sensing is another possibility, using different frequencies to have wavelengths comparable to the object sizes of interest [18], [25].

IV. Chemical Signals Inside the Body

Chemical signals and the interaction with the bloodstream is a key aspect to address the application of nanorobots for cancer therapy. The nanorobot sensing for the simulated architecture in detecting gradient changes on E-cadherin signals is examined. To improve the response and biosensing capabilities, the nanorobots maintain positions near the vessel wall instead of floating throughout the volume flow in the vessel (Fig. 1). In the render modeling was used a vein wall with grid texture to enable better depth and distance perception in the 3D workspace. An important choice in chemical signaling is the measurement time and detection threshold at which the signal is considered to be received. Due to background concentration, some detection occurs even without the target signal. As a guide for the choice of threshold, we use the diffusive capture rate α for a sphere of radius R in a region with concentration as:

$$\alpha = 4\pi DRC \quad (1)$$

where the concentration for other shapes such as cylinders are about the same [2]. With independent random motions for the molecules, detection over a time interval Δt is a Poisson process with mean value $\alpha \Delta t$. Using Table I, $\alpha \approx 0.5 molecule/s$ at the background concentration and ≈ 150 near the source. With the plaque on the vessel wall, fluid velocity near the target is lower than the average velocity v in Table I. When objects occupy only a small fraction of the volume the velocity at distance r from the center of the vessel is:

$$w = 2v(1 - (r/(d/2))^2), \quad (2)$$

and with the cells, the velocity shows somewhat a parabolic flow [11], but similar enough for this parabolic profile to give

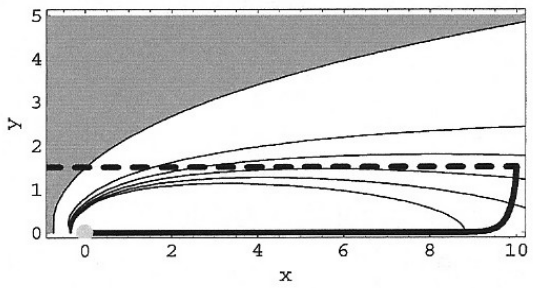

Fig. 2. Nominal behavior of a nanorobot passing above the target (small gray circle) with the fluid moving to the right. Thick dashed line shows initial passive motion, lasting about 10ms, as the nanorobot determines signal concentration is significantly above background. Distances are in microns.

a useful design guideline.

After the first nanorobot has detected a tumor for medical treatment, it can be programmed to attach on it. Then, beyond attracting a predefined number of other nanorobots to help for incisive chemotherapeutic action with precise drug delivery above the tumor, the architecture permits it to use wireless communication to send accurate position for the doctors informing that a tumor was found.

Similarly to quorum sensing in bacteria, from monitoring the concentration of signals, chemical substances for near communication can attract or repeal nanorobots, and permit to estimate how many are at the target. Thus, the nanorobots stop attracting others once enough nanorobots have responded. This amount can change depending on the stage of cancer, the tumor size, and can be defined by the oncologist in charge according with the information retrieved from the nanorobots through RF electromagnetic waves. For investigation purposes, a value of *N={20}* were set up in the simulator as a reasonable amount of nanorobots to the plaque lesion. The nanorobots at the plaque emit a different signal that others, not already at the target, interpret as an indication they no longer need to respond, thereby leaving them free to continue monitoring for other malignant tissues inside the body. The nanorobots may enable drug delivery and are loaded with therapeutic chemicals avoiding the cancer to advance further.

The following control methods were considered:

- *Random*: nanorobots moving passively with the fluid reaching the target only if they bump into it due to Brownian motion.
- *Follow gradient*: nanorobots monitor concentration intensity for E-cadherin signals, when detected, measure and follow the gradient until reaching the target. If the gradient estimate subsequent to signal detection finds no additional signal in 50ms, the nanorobot considers the signal to be a false positive and continues flowing with the fluid.
- *Follow gradient with attractant*: as above, but nanorobots arriving at the target, they release in addition a different chemical signal used by others to improve their ability to find the target.

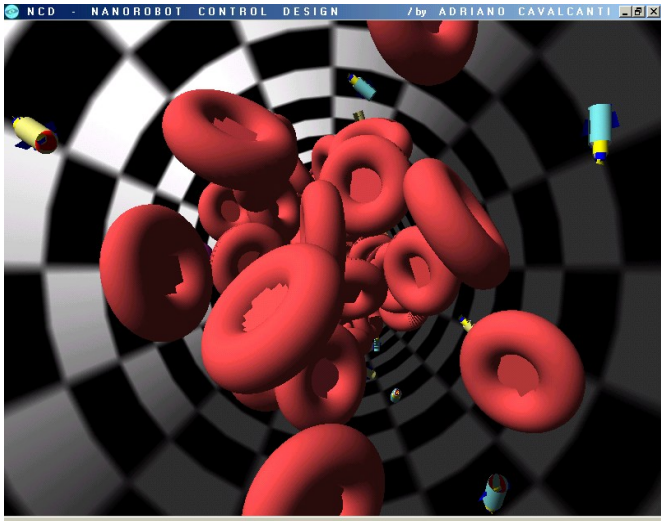

Fig. 3. View of simulator workspace showing the vessel wall, cells and nanorobots. The nanorobot is considerably smaller than the $6\mu m$ cell diameter.

The third technique involving communication among the nanorobots is quite suitable to improve the nanorobots' behavior performance. By comparing these techniques, we can evaluate the benefit of chemical communication among nanorobots to work on typical biomedical applications.

V. Simulator Results

To illustrate some design choices, we first examine an analytically solvable version of the fluid environment and then describe the results from the simulator. Consider a fluid moving uniformly with velocity *v* in the positive x-direction past a plane. It contains a point source of chemical produced at a rate Q, which is the chemical signal as molecules per second. The diffusion coefficient is represented by *D*, and the diffusion equation is:

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

with the boundary conditions of a steady point source at the origin and no net flux across the boundary plane at $y = 0$, determines the steady-state concentration C, which is molecules per μm^3 or chemical concentration at point (*x, y, z*):

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

where

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

is the distance to the chemical signal source [2].

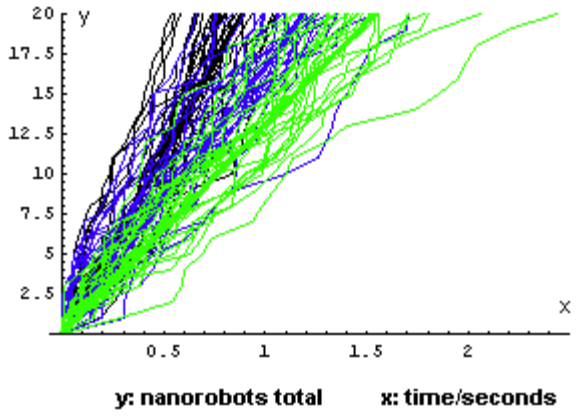

Fig. 4. Detailed results depicting 90 simulations with the amount of 1/3 for each control method. The cases for nanorobot behavior described as (a) dark for gradient with attractant, (b) blue for follow gradient, or (c) green for random motion.

Fig. 2 is an illustration of nanorobot behavior. The fluid flow pushes the concentration of the diffusing signal downstream. Consequently a nanorobot passing more than a few microns from the source won't detect the signal while it is still relatively near the source. As an example, considering the parameters from Table I, when nanorobots passing close enough, they detect on average the higher signal concentration within about 10ms. Thus, keeping their motion near the vessel wall, the signal detection happens after these have moved at most $10\mu m$ past the source. Therefore, it provides about 5nanorobot/s arriving at the tumor cell in the small venule. The venule is one among many types of vessels from the human body.

Eq. (4) also illustrates a design trade-off for chemical signals the nanorobots could release. Instead of the diffusion coefficient associated with the chemical from the target, such additional signals would use other molecules which could, by design, have a different diffusion coefficient. From Eq. (4), the effect of the fluid motion becomes significant at distances beyond $O(D/v)$. Thus, notwithstanding the fluid flow, larger diffusion constants allow further spread upstream. On the other hand, the $O(1/D)$ overall factor in Eq. (4) means lower concentrations. Furthermore, the concentration of the new signal is time dependent since the source strength increases as more nanorobots reach the target and the signal from each nanorobot requires time $O(r^2/D)$ to reach a distance *r*. Therefore, faster diffusion results in lower concentrations, requiring more time for other nanorobots to determine gradients. Hence, chemical diffusion could be more efficient for nanorobot communication, if the signals are increasing in a steady, constant and progressively manner.

Nanorobots passing within $\approx 0.1\mu m$ of the target usually bump into it. Those passing within a few microns often detect the signal, which spreads a bit further upstream and away from the single tumor due to the slow fluid motion near the venule's wall and the cells motion. Nanorobots close to the wall also benefit from the slower fluid motion by having more time to detect the signal, as discussed previously. Thus, the present 3D simulation provides guidelines for nanorobot communication and activation control, as well as for sensor manufacturing design. We use an "attractant" signal with the same value of *D* as the original signal. Each nanorobot can release at one-tenth the rate of the target over the times considered here.

TABLE II
NANOROBOTS: TIME IN SECONDS TO REACH THE TARGET

Control method	10 robots	20 robots
Random motion	0.73 (0.18)	1.47 (0.28)
Follow gradient	0.54 (0.17)	1.14 (0.24)
Gradient with "attractant"	0.46 (0.13)	0.79 (0.14)

Distinct performances were observed throughout a set of analyses obtained from the NCD software, where the nanorobots use also chemical sensors as the communication technique to interact dynamically with the 3D environment, and to achieve a more successful collective coordination. Fig. 3 shows the virtual environment in our study, comprised a small venule vessel which contains nanorobots, the red blood cells (RBCs) and a single tumor cell, which is the target area on the vessel wall. Here, the target area is overleaped by the RBCs. In the simulation, the nanorobots search for possible small cancer tumor into the workspace crowded by RBCs.

In Fig. 4 it could be observed in a detailed fashion the information about the nanorobots behaviors. Table II provides a summary and comparison of the control techniques evaluated using the NCD simulator. It shows the time required for 20 robots to identify and reach the target. Each value is the mean of 30 repetitions of the simulation, with standard deviation in parentheses. The error estimate for these mean values is $\sqrt{30}$ times smaller than the standard deviations listed here. For comparison, if every nanorobot passing through the vessel found the target, 20 nanorobots would arrive at the target in about 0.2s. As one would expect, enabling nanorobots to detect and follow gradient concentration increases the probability for nanorobots to find the target, where in comparison with random motion the nanorobots show a better performance of 23%. Further, for gradient with "attractant", we see that using the signals allows the nanorobots to find and reach the target in the 3D workspace 46% faster than that with random motions. This is a remarkable improvement in performance for response time, improving the chance to detect a small tumor what may help combat cancer.

VI. Conclusion and Remarks

In our study nanorobots using chemical nanobiosensors were programmed to detect different levels of E-cadherin and beta-catenin in primary and metastatic phases. Our investigation has established a comprehensive methodology on tracking single tumor cell in a small venule, where nanorobots used

communication techniques to increase their collective efficiency.

The results obtained in the simulation established that chemical signaling devices is a key issue on design, and has to be incorporated into the future manufacturing nanorobot architecture model. The simulation has also demonstrated how better time responses can be achieved for tumor detection, if communication capabilities are incorporated as part of nanorobot control strategy. As observed in the study, the follow gradient with attractant signal is a practical method for orientation and coordination of nanorobots. It has enabled a better performance for nanorobots to detect and reach cancerous targets.

The research and development of nanorobots can result in significant improvement of medical instrumentation and unprecedented advances in cancer therapy.

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