Nanorobot for Treatment of Patients with Artery Occlusion

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Abstract: This paper presents the study of nanorobots control activation for stenosed coronary occlusion, with the practical use of chemical and thermal gradients for biomedical problems. The recent developments on nanotechnology new materials allied with electronics device miniaturization may enable nanorobots for the next few years. New possibilities for medicine are expected with the development of nanorobots. It may help to advance the treatment of a wide number of diseases: cardiovascular problems, neurosurgery, cancer, diabetes and new cell therapies. The implementation of new methodologies to help on manufacturing analyses and system design for the development of nanoscale molecular machine is one of the most important fields for research. The use of 3D physically based simulation in conjunction with clinical data may provide ways to design practical approaches for control and transducers development.

Key words: Cardiology, CMOS, medical nanorobotics, mobile nanorobot, molecular machine, multi-sensorial simulators, nanoelectronics, nanomanufacturing design, NEMS, photonics.

1- Introduction

The advent of nanotechnology is expected to enable automated molecular machines with embedded nanoscopic devices providing new tools for medical procedures [1], [2]. Initial uses of nanorobots to health care are likely to emerge in the next 10 years [3], [4], [5], with potentially broad biomedical applications [6], [7], [8], [9]. The present work is an innovative approach to advance the study of biomedical treatments using nanorobots for coronary atherosclerosis problems. To evaluate efficient ways of activation and control of nanorobots, Real clinical data based on patients monitoring and computer analyses is used to conduct our study.

This work demonstrates how chemical and thermal parameters could be successfully applied to achieve a suitable control strategy for nanorobots, and trigger their actuation upon target areas. Such approach ensures accurate control activation as discussed through the paper. We used computer aided design tools such as Computational Fluid Dynamics (CFD) including the main parameters required for the investigation at nanoscopic levels. The simulation included its visualization with 3D real time analyses using the software Nanorobot Control Design (NCD) to perform a pre-defined set of tasks, based on environment sensing and trigger behaviors. Simulation studies based on numerical results defining design strategies, capabilities and limitations, provide a better understanding on nanorobots' behavior and manufacturing feasibilities [2], [5].

2- Medical Applications

Nanorobots are expected to enable new treatments for patients suffering from different diseases, and will result in a remarkable advance in the history of medicine. Recent developments in the field of biomolecular computing [10], [11], [12], have demonstrated the feasibility of processing logic tasks by bio-computers [13]. This is a promising first step to enable future nanoprocessors with increased complexity. Studies targeted at building biosensors [14], [15] and nano-kinetic devices [16], required to enable medical nanorobotics operation and locomotion, have also been progressing.

In recent years, the potential of nanotechnology has indeed motivated many governments to devote significant resources to this new field [17], [18]. The U.S. National Science Foundation has launched a program in "Scientific Visualization" [19], in part to harness supercomputers in picturing the nanoworld. A 1 trillion US$ market consisting of devices and systems with some embedded nanotechnology is projected by 2015 [20]. The research firm DisplaySearch predicts rapid market growth of organic light emitting diodes, from 84 million US$ in 2002 to 1.6 billion US$ in 2007 [21]. A first series of commercial nanoproducts is

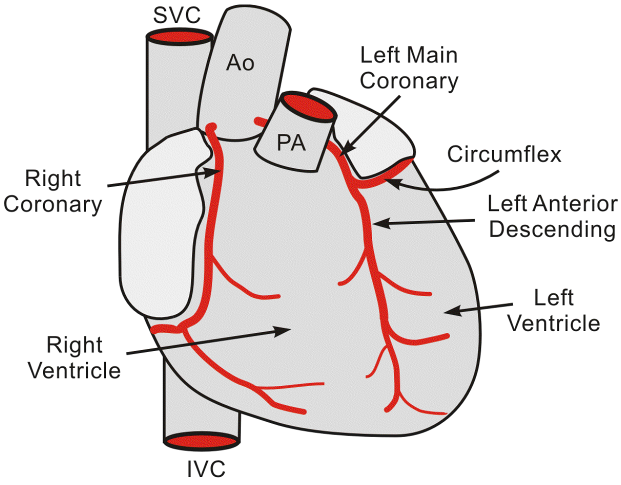

Figure 1: The coronary arteries are one of the most common sites for the localization of atherosclerotic plaques.

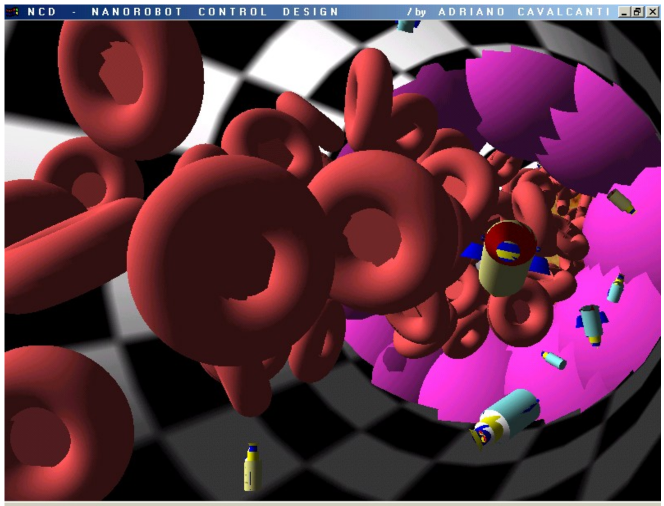

Figure 2: View of the NCD simulator workspace showing the inside view of the occluded LAD coronary artery, red blood cells and nanorobots.

foreseeable by 2007 [22]. In order to build electronics at nanoscales, firms are collaborating to produce new nanoproducts. Such companies include IBM, PARC, Hewlett Packard, Bell Laboratories, and Intel Corp., to name a few [21].

The use of nanorobots may advance biomedical intervention with minimally invasive surgeries [23], and help patients who need constant body functions monitoring, or ever improve treatments efficiency through early diagnosis of possible serious diseases [24], [25]. For example, the nanorobots may be utilized to attach on transmigrating inflammatory cells or white blood cells, thus reaching inflamed tissues faster to assist in their healing process [6]. Nanorobots will be applied in chemotherapy to combat cancer [26], [27], [28], through precise chemical dosage administration, and a similar approach could be taken to enable nanorobots to deliver anti-HIV drugs [28]. Nanorobots could be used to process specific chemical reactions in the human body as ancillary devices for injured organs. Monitoring diabetes and controlling glucose levels for patients will be a possible application of nanorobots [5]. Nanorobots might be used to seek and break kidney stones. Another important possible feature of medical nanorobots will be the capability to locate atherosclerotic lesions in stenosed blood vessels, particularly in the coronary circulation, and treat them either mechanically, chemically or pharmacologically [1]. Cardiovascular problems are generally correlated with the obesity, human sedentary lifestyle, or hereditary characteristics. Heart problem is the world biggest killer [29].

2.1 – Biomedical Flows

The bloodstream keeps the human body alive. In the blood, suspended in the plasma, is found the white blood cells, red blood cells, and platelets. The plasma represents 55% of the blood volume which is 8% of the body weight, with the size of red blood cells is about 7.5 µm in diameter and 2 µm thick. Platelets are 2 to 4 µm in diameter [30]. The heart keeps the closed circulatory system working continuously. The bloodstream flows with the pumping system comprised of a closed system of blood vessels. For mammals and human, this system is basically comprised of 2 pumps dynamically synchronized. The heart performs a key role for the human wellbeing, delivering O_2 to large range of tissues, which returns CO_2 to the lungs. The blood is pumped from the left ventricle through the arteries and arterioles to the capillaries (fig. 1). After that, the blood flows from venules into the veins back to the right atrium completing the systemic circulation. In the right atrium the blood is pumped through the lungs. The lungs equilibrate the O_2 and CO_2 in the alveolar air [30].

Although the bloodstream presents in most cases laminar flow, in the heart we have turbulent flow. The sounds produced by the heart are the result of diastolic and systolic pressures, which comes from the partially constricted vibrating arteries motions. Blood waveforms can also be analysed using Fourier models to quantify the dynamics of blood pressure and flow [31]. The fluid in the Left Anterior Descending (LAD) moves with velocity ~38cm/sec (fig. 2), as is typical of flow in aorta and arteries vessels [32]. However, the velocity under certain circumstances can even achieve up to 120cm/sec during a systolic phase [30]. The distances are large compared to the water molecules, and then physical processes in the turbulent flow are based on the Navier-Stokes and other continuum equations [33], [34]. The fluid is incompressible. Thus, the fluid velocity *v* satisfies the continuity equation $\nabla \cdot v = 0$ and the Navier-Stokes equation:

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

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.

For slow motions this equation simplifies considerably. Specifically, the nanorobot's world is dominated by viscosity while inertial and gravitational forces are negligible [1], [35]. The Reynolds number, defined as

$$\mathrm{Re} = L\rho v/\eta \quad (2)$$

for objects of size *L* with velocity *v*, characterizes this behavior by giving the ratio of inertial to viscous forces. For nanoscale robots operating in fluids of ordinary viscosities, Re is low of around 500 [31]. As an example, water has density of 1 g/cm^3 and viscosity of 1 centipoise, or 10^{-2} g/cm-sec. Thus a nanorobot of size 1μm moving at 1 mm/sec in water has Re=10^{-3}, much less than 1 and hence viscous forces dominate. As boundary conditions, the fluid 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. In practice, such a condition would be maintained by a pressure gradient imposed on the fluid.

3- Nanorobot for Medicine

Organic nanorobots are the work on ATP and DNA based molecular machines, also known as bionanorobots [36]. In this case the idea is the development of ribonucleic acid and adenosine triphosphate devices, and even the use of modified microorganisms to achieve some kind of biomolecular computation, sensing and actuation for nanorobots. Another approach for the development of molecular machines is the inorganic nanorobot. Inorganic nanorobots development is based on tailored nanoelectronics. In comparison with bionanorobots, inorganic nanorobots could achieve a considerably higher complexity of integrated nanoscale components.

There are some works on how to enable manufacturing of inorganic nanorobots [37], [38]. The use of new diamondoid rigid materials is a possible approach that may help towards achieving new materials for inorganic nanorobots [38]. Indeed it should be very helpful, and some important works were done to advance diamondoid materials development [39]. The approach taken in our work is the Nano-Build Hardware Integrated System (Nanobhis) [37]. It represents a joint set of well established techniques and new methodologies from nanotechnology with the aim of manufacturing nanorobots. It is used 3D simulation and manufacturing design with integrated nanoelectronics analyses. The challenge of manufacturing nanorobots may result from new methodologies in fabrication, computation, sensing and manipulation [40]. Real time 3D prototyping tools are import to help on nanotechnology development. It may have a direct impact on the implementation of the new approaches for manufacturing techniques. Simulation can anticipate performance of new nanodevices. Further, it can also help on nanomechatronics design and in testing control and automation strategies.

The main parameters used for the nanorobot control activation, as well as the required technology background that may lead to manufacturing nanorobots in the coming years, are described next.

3.1 – Manufacturing Technology

A nanorobot must be equipped with the necessary devices for monitoring the most important aspects of its operational workspace. Depending on the case, different gradients on temperature, concentration of chemicals in the bloodstream, and electromagnetic signature, are some of relevant parameters when monitoring patients. Teams of nanorobots may cooperate to perform predefined complex tasks on medical procedures. For such aims, computing processing, energy supply, and data transmission capabilities can be addressed through embedded integrated circuits, using advances on technologies derived from VLSI design [41]. CMOS VLSI design using deep ultraviolet lithography provides high precision and a commercial way for manufacturing nanodevices and nanoelectronics. The CMOS industry may thrive successfully the pathway in the assembly process of manufacturing nanorobots, where the jointly use of nanophotonic and nanotubes may even accelerate further the actual levels of resolution ranging from 248nm to 157nm devices [42]. To validate designs and to achieve a successful implementation, the use of VHDL has become the most common methodology utilized in the industry of integrated circuits.

3.2 – Temperature Sensor

Integrated nanothermoelectric sensors could be implemented as CMOS devices with promising uses for pattern identification [28], [43]. Such approach may permit a large production of infrared thermal sensors applied into different ranges of wavelength [44]. 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 advantage of linear self-generated response with system integration without requiring bias or temperature stabilization [45]. Thus the infrared array could be integrated on a single chip within amplifiers and signal processing capabilities. Such approach allows a fast pace towards miniaturization with no loss of efficiency due electromagnetic noise [44], [46]. CMOS could 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 based on integrated nanodevices [47]. Carbon nanotubes are able to improve performance with low power consumption for nanosensors. Its particular high precision make it quite useful for applications in infrared supersensitive sensors, with applications such as target oriented temperature detection, and measurement in changes of the body temperature. Nanosensors present important electrical properties, high thermal conductance and fast frequency response [48], [49]. The power consumption with NEMS is three times lower if compared with traditional MEMS thermal sensors, where for MEMS the operating values range in terms of mW [45].

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 [47]. 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.

3.3 – Chemical Sensor

Manufacturing silicon and chemical based sensor arrays using two-level system architecture hierarchy have been successfully conducted in the last 15 years [50], [51]. Application ranges from biomedical uses, automotive or chemical industry with detection of air to liquid element patterns recognition through embedded software programming. Through the use of nanowire significant costs of energy demand for data transferring and circuit operation can decrease around 60% [52]. CMOS sensors using nanowires as material for circuit assembly can achieve maximal efficiency for applications regarding chemical changes, enabling medical applications [53], [54]. Due resistivity characteristics, nanocrystallites and mesoscopic nanowires performance is impressive if compared with larger sensors enabled technologies [55], [56], [57], [58].

Sensors with suspended arrays of nanowires assembled into silicon circuits can drastically decrease self-heating and thermal coupling for CMOS functionality [59]. Nanometer chemical sensors using integrated circuits may generate huge profits with low cost for massively production of commercially devices with a wide range of applications in medical, industrial, environmental issues, and much more. Factors like low energy consumption and high-sensitivity are among some of advantages of nanosensors. Nanosensor manufacturing array process can uses electrofluidic alignment to achieve integrated CMOS circuit assembly as multi-element [52]. Passive and buried electrodes should 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.

Control feedback to switch the electronic sensor between active or turned off sensing are quite indicated for nanorobot medical monitoring operations. The use of nanowire for integrated sensors is to achieve new breakthroughs in high speed sensing and control technologies. For chemical sensor device the range for the CMOS operation is ~190MHz. Control of data transmission is the most suitable path for save the nanorobot's energy when the sensor is in operation, thus sample techniques can be used with time interval of 80 ns for active circumstances [52].

Some of limitations to improve actual CMOS and MOSFET methodologies are quantum-mechanical tunnelling for operation of thin oxide gates, and subthreshold slope [60]. Surpassing any expectations the semiconductor branch has moved forward to keep circuit advancing. Smaller channel length and lower voltage circuitry for higher performance are being achieved with new materials aimed to attend the growing demand of high complex VLSIs. New materials such as strained channel with relaxed SiGe layer are quoted to beat self-heating and improve performance [61]. Recent developments on 3D circuits and FinFETs double-gates have achieved astonishing results and according to the semiconductor roadmap should improve even more. To advance further manufacturing techniques, Silicon-On-Insulator (SOI) technology has been used for assembly high-performance logic sub 90nm circuits [62], [63]. Circuit design approaches to solve problems with bipolar effect and hysteretic variations based on SOI structures has been demonstrated successfully [61]. Altogether, it is turning feasible 90nm and 45nm CMOS devices as an actual breakthrough in terms of technology devices into products that can be utilized strategically.

3.4 – Energy Supply

The most effective way to keep the nanorobot operating continuously is to establish the use of power generated from the available sources in the environment where it must be working. Some possibilities to power it can be provided from ambient energy. Kinetic energy can be generated from bloodstream due motion interaction with designed devices embedded outside the nanorobot [64]. Electromagnetic radiation from light could be another option for energy generation in open workspaces [65], but not for medical nanorobotics. Temperature displacements could likewise generate radiation developing pre-established voltages. Cold and hot fields from in series connected conductors may also be useful to produce energy through the well-established Seebeck effect [48]. Temperature changes or light variations for different kinds of workspace could sharply variates depending on the application. Here, specifically on the aspect light, it does not exist inside the human body. Thus, considering a broader design choice, the energy generated by kinetic vibration is more appropriated. It is more suitable for a larger variety of applications for biomedical problems or even environmental monitoring.

A device for power generation using integrated circuits allied with Li-ion batteries is a good choice to provide electrical sources for the nanorobot operation. A system with resonance frequency as µPG (micro power generator) is suitable for power supply [66]. Bloodstream flow vibrations once captured is translated with piezoelectricity, into energy source for the nanorobot operation. Due operational aspects such as integration and power density [64], it is a more efficient approach than electrostatic or electromagnetic induction [46]. The energy generated is saved in ranges of ~1µW while the nanorobot can stay in inactive modus, just becoming active when signal patterns requires so. Allied with the power source devices, in order to save energy using such resource wisely, the nanorobots need to perform strategically defined actions in the workspace. Therefore the team of nanorobots can be prepared to acquire and transmit more or less information depending on changes in determined medical target. Some of the typical tasks may require the nanorobot to spend low power amounts, once strategically activated. For communication sending RF signals ~1mW is required. The collected data can be expressed in bits pattern signals, what permits to keep the power consumption with data transmission low.

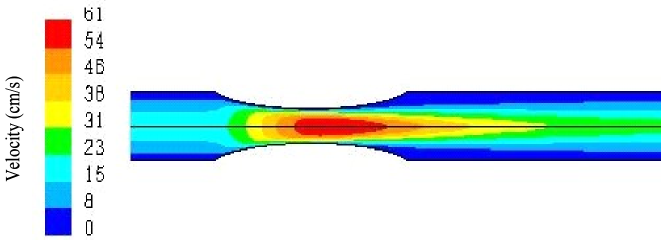

Figure 3: Blood velocity profile in the systolic phase of a 50% diameter stenotic segment of the left anterior descending coronary artery model (blood flows from left to right).

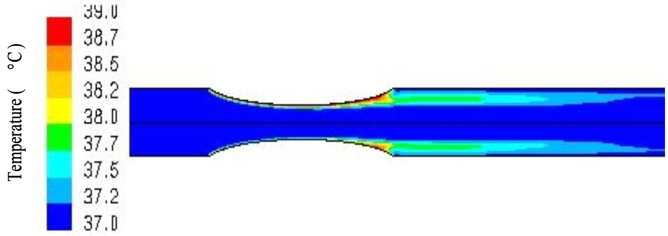

Figure 4: Blood temperature distribution in the systolic phase of a 50% diameter stenotic segment of the LAD coronary artery model (blood flows from left to right). Wall temperature at the stenosis region is set to 39ºC.

3.5 – Data Transmission

The application of devices and sensor implanted inside the human body to transmit data about the health of patients can enable great advantages on continuous medical monitoring [67], [68]. For communication in liquid workspaces, depending on the application, it is worth to quote acoustic, light, RF, and chemical signals as possible choices for communication and data transmission [69], [70]. Chemical signal is quite useful for nearby communication among nanorobots for some teamwork coordination [71]. Acoustic communication by other hand is more appropriated for long distance communication and detection with low energy consumption if compared to light communication approaches [70], [72]. Although optical communication permits faster rates of data transmission, its energy demand makes it not ideal for nanorobots.

Works with RFID (Radio Frequency Identification Device) has been developed as integrated circuit for medicine [73], [74]. Prevision of low cost polymer electronics for tiny magnetic sensors and transducers chips are expected to achieve low costs as 1 cent for circuit, what makes its use even more attractive [75]. Using integrated sensors for data transfer is the better answer to read and write data in implanted devices. The teams of nanorobots should be equipped with single-chip RFID CMOS based sensors [76]. CMOS with submicron SoC design could be used for extremely low power consumption with nanorobots communicating actively for some bit longer distances through sonar sensors [77]. For the nanorobot active sonar communication, frequencies may reach up to 20µW@8Hz as resonance rates and 3V supply [72]. Thus, strategically positioned static sensors for acquiring wireless data transmission from mobile nanorobots injected inside the patient bodies comprise a good choice to monitoring predefined patterns for biomedical applications. To accomplish that, acoustic nanosensors may be exchanging communication, and strategic data information should be transmitted when some new event was registered from nanorobots as mobile device inside the patient's body.

In our design, an electromagnetic reader is applied to launch waves and detect the current status of nanorobots inside the patient. This transponder device emits magnetic signature to the passive CMOS sensors embedded in the nanorobot, which enable sending and receiving data through electromagnetic fields. The nanorobots monitoring data convert the wave propagation generated by the emitting devices through a well defined protocol. According with a last set of event recorded in pattern arrays, information can be reflected back by wave resonance [75]. For nanorobot passive data transferring, possible ranges for data communication are ~4.5 kHz frequency with approximate 22 µs delays. While for receiving data from the nanorobots should be achieved with such passive process, sonar communication is to be used for active communication among nanorobots to perform coordinated behaviors due some more complex collective task to be fulfilled.

4- System Implementation

The simulation consists of adopting a multi-scale view of the environment. It has the physical morphology with physiological flow patterns, this allied with the nanorobot orientation, drive mechanisms, sensing and control. Thus, these simulations are used to achieve high-fidelity control modeling of nanorobots in a real physical context. The simulation includes: the NCD (Nanorobot Control Design) simulator for the nanorobot sensing and actuation; and CFD (Computational Fluid Dynamics) software for the patient parameters.

4.1 – Nanorobot Design

The nanorobot design is comprised of integrated nanoelectronics [52], [62], and components such as *molecular sorting rotors* and a robot arm (*telescoping manipulator*) [33], derived from biological models. The nanorobot exterior shape consists of a diamondoid material [39], to which may be attached an artificial glycocalyx surface that minimizes fibrinogen (and other blood proteins) adsorption and bioactivity, ensuring sufficient biocompatibility to avoid immune system attack. Different molecule types are distinguished by a series of chemotactic sensors whose binding sites have a different affinity for each kind of molecule [1]. These sensors also detect obstacles which might require a new trajectory planning.

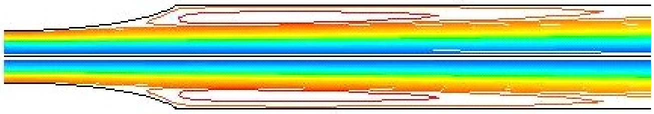

Figure 5: Flow streamlines, showing the recirculation zone after the stenosis.

We simulate the nanorobot with sensory capabilities allowing it to detect and identify the nearby possible obstacles in its environment, as well as the biomedical target for its task. A variety of sensors are possible [45], [50], [56], [59]. For instance, chemical detection can be very selective, e.g., for identifying various types of cells by markers on their surfaces. Acoustic sensing is another possibility, using different frequencies to have wavelengths comparable to the object sizes of interest [72], [76], [78]. Sensor design and capabilities depend on the details of the environment and task. Thus, the nanorobot requires transducers capabilities and smart sensors directly related to that specific biomedical application. In present study, the nanorobot is able to detect obstacles over a range of about 1μm, and within an angular resolution equivalent to a diameter of 100nm at that range. The biomolecules are too small to be detected reliably: instead the robot relies on chemical contact sensors to detect them. This description of interaction capabilities allows evaluating different nanorobot sensor based action. It also helps to choose the kind of low-level control to maximize the information acquired for an effective real time performance.

The nanorobot kinematics can be predicted using state equations, positional constraints, inverse kinematics and dynamics, while some individual directional component performance can be simulated using control system models of transient and steady-state response [5], [79], [80]. The nanorobots can use a RFID CMOS macrotransponder system for their positioning [73], which allow information about the nanorobot position, independent of nanorobot orientation [1]. Such a system could involve externally generated signals from beacons placed at fixed positions outside the skin.

4.2 – Modular Integration

Graphic interfaces enabling detailed design are progressing rapidly to produce 3D nano-structure prototypes. The Nanorobot Control Design (NCD) is multithread software. It is comprised of collision detection and physically based simulation [81], [82]. We used parallel processing techniques [83], where the nanorobots react adaptively to any stimulus produced by their partners' decisions, with the model visualization in real time. Ongoing developments in hardware and distributed processing [84] allow the increasing number of nanorobots and the level of detail for the simulator.

Virtual reality techniques provide an intuitive way to interact with nanoscale components [85]. The NCD simulator was used for the 3D investigation of a stenosed Left Anterior Descending (LAD) coronary artery (Fig. 1). The NCD simulator consists of several modules that simulate the physical conditions, run the nanorobot control programs determining their actions, provide a visual display of the environment in 3D, and record the history of nanorobot behaviors for later analysis.

The approach used aims to trigger the process of medical molecular machine activation. This trigger will turn the nanorobot "on", switching it from "seek mode" to "repair mode". It may also cause other close nanorobots switch to a "higher awareness mode". Clinical data and diagnose gives previous knowledge about the general localization of the stenosis (in large, small or microvessels), thus it requires to inject the appropriate nanorobot type, which is pre-programmed to be activated only at the pre-specified target region. The virtual environment developed is inhabited by plasma, red blood cells, nanorobots, different molecules whose concentrations are being monitored, and the blood vessel (Fig. 2). The biomedical physical parameters were implemented with Computational Fluid Dynamics (CFD); thus, the blood flow pulse is simulated in a stenosed LAD coronary artery model, differing in the degree of stenosis severity. By solving the flow governing equations it is computed the blood velocity profiles (Fig. 3). It was also defined and calculated various signaling functions, known to be indicative of stenosis, caused by an atherosclerotic plaque. Such parameters include time-averaged wall shear stress, wall shear stress gradients and oscillatory shear index [32].

5- Simulation Discussion

The use of microdevices in surgery and medical treatments is a reality which brought many improvements for clinical procedures in the last years. For example, the catheterization has been used as an important methodology for many cardiology procedures [86]. In the same way as the development of microtechnology has lead on the 80's to new tools for surgery, now nanotechnology will equally permit further advances providing better diagnosis, and new devices for medicine through the manufacturing of nanoelectronics. Nanorobots may be considered as the most suitable tool for specialists to solve several problems in medicine in the coming few year [27], [23], [54], here including cardiology interventions and medical analyses.

In our study, 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 approach for medicine, thermal and chemical parameters from the patient's body are used for the nanorobot activation. It is well known that there is significant temperature heterogeneity over inflamed plaque surfaces [87]. They are typically hotter. The temperature difference at the site of the lesion from the core temperature can reach up to ~2ºC [88]. Hence, in order to simulate various levels of inflammation, it was used different wall temperatures in the atherosclerotic plaque region, and calculated the temperature distribution in the stenosed coronary artery (Fig. 4). Significant temperature gradients were found in the recirculation zone, following the stenosis (Fig. 5).

Figure 6: Vein inside view without the red blood cells. The target plaque is represented by the pink spheres surrounding the vessel wall. The nanorobots swim in a near-wall region searching for the atherosclerotic lesion.

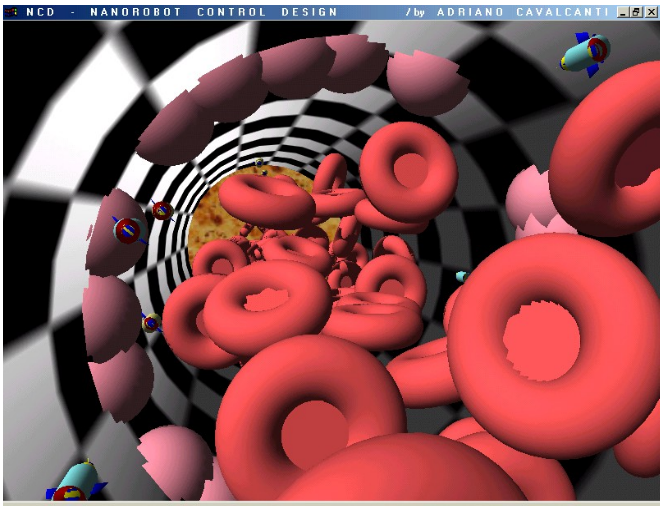

Figure 7: The atherosclerotic lesion was reduced due nanorobots activation. The temperatures in the region turn in expected levels.

The transcardiac concentration gradient of some soluble adhesion molecules has been recently found to be correlative with the progression of coronary atherosclerosis [32]. Therefore, their concentration in the blood vessel is also monitored, using a uniform distribution release from the plaque. In a similar manner, the concentrations of some specific pro-inflammatory cytokines is monitored, whose elevated concentrations are known as an evidence of formation of atherosclerotic lesions [89].

The parameters generated from the CFD simulation, namely velocities, temperature, signaling values, pro-inflammatory cytokines and soluble adhesion molecules concentrations, are transferred to the NCD simulator to be included into the nanorobots operating environment. As the nanorobot should perform a pre-defined task in a specific target area, the trigger must be activated when the nanorobot is as close as possible to the target. The nanorobot motion control in the artery keeps it near-wall region. It takes the advantage of the blood flow velocity profile in such areas, which shows significantly lower velocities [90]. Thus, the rapid activation could result in lower demand of energy (Fig. 6). Optimization of control algorithms and activating triggers is the key for rapid behavior response in minimal energy cost. The optimal trigger values are defined running the nanorobots control programs. Therefore, the investigated stenosed artery models provide important information useful to nanorobot manufacturing design in terms of sensors and actuators. The nanorobots activation goal is to decrease the artery occlusion (Fig. 7).

6- Conclusions

A study with the ways to establish a trigger and control behavior for nanorobots in cardiology was adopted as medical case in our work. The use of thermal and chemical parameters applied in the treatment of stenosed blood vessels is the most natural process for nanorobot transducer effective development. The approach presented in this paper, has successfully combined a precise physical simulation to establish the environment for operation of nanorobots. A system to study nanorobots behavior is described, and the ways to achieve their control inside the human body is also presented. The NCD and CFD have demonstrated extreme potential for scientific investigation of nanomanufacturing strategies, medical nanorobotics application, and nanorobot mobility considerations. The jointly use of nanophotonic and nanotubes may even accelerate further the actual levels of CMOS resolution ranging from 45nm devices. The Nanobhis project with the information acquired in our studies may also help on transducers design to build nanorobots with embedded nanodevices for the coming few years.

The aim in this study was to show an innovative framework for enabling designs and models of medical nanorobots. Meanwhile nanoelectronics manufacturing methodologies may advance progressively, the use of computational nanomechatronics and virtual reality may also help in the process of transducers and actuators investigation. Thus, our study points towards possible ways to advance nanotechnology as diagnostic and treatment tool using nanorobots for cardiology patients.

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8- References

[1] Freitas Jr. R.A., "*Nanomedicine, Vol. I: Basic Capabilities*", Landes Bioscience, 1999.

[2] Cavalcanti A., "Assembly Automation with Evolutionary Nanorobots and Sensor-Based Control Applied to Nanomedicine", *IEEE Transactions on Nanotechnology*, 2(2):82-87, Jun. 2003.

[3] Requicha A.A.G., "Nanorobots, NEMS and Nanoassembly", *Proceedings of the IEEE*, 91(11):1922-1933, Nov. 2003.
[4] MacNeil J.S., "Nanorobot Pioneer Reveal Status of Simulator, Stem Cell Work," *NanoBiotech News*, Vol. 2, n. 36, pp. 4-5, September 2004, www.nanorobotdesign.com/article/nanobiotech.pdf .
[5] Cavalcanti A., Freitas Jr. R.A., "Nanorobotics Control Design: A Collective Behavior Approach for Medicine", *IEEE Transactions on Nanobioscience*, Vol. 4, no. 2, pp. 133-140, June 2005.
[6] Casal A., Hogg T., Cavalcanti A., "Nanorobots as Cellular Assistants in Inflammatory Responses", *in Proc. IEEE BCATS Biomedical Computation at Stanford 2003 Symposium*, IEEE Computer Society, Stanford CA, USA, Oct. 2003.
[7] Katz E., Riklin A., Heleg-Shabtai V., Willner I., Bückmann A.F., "Glucose Oxidase Electrodes via Reconstitution of the Apo-Enzyme: Tailoring of Novel Glucose Biosensors", *Anal. Chim. Acta.*, 385, 45-58, 1999.
[8] McDevitt M.R., Ma D., Lai L.T., Simon J., Borchardt P., Frank R.K., Wu K., Pellegrini V., Curcio M.J., Miederer M., Bander N.H., Scheinberg D.A., "Tumor Therapy with Targeted Atomic Nanogenerators," *Science* 294, 16 November 2001, pp. 1537-1540, Nov. 2001.
[9] Kumar M.N.V.R., "Nano and Microparticles as Controlled Drug Delivery Devices", *J. Pharmacy Parmaceutical Science*, 3(2):234-258, 2000.
[10] Adleman L.M., "On Constructing A Molecular Computer", DNA Based Computers II: Dimacs Workshop, Jun. 10-12, 1996 (Dimacs Series in Discrete Mathematics and Theoretical Computer Science, V. 44), American Mathematical Society, 1996, pp. 1-21.
[11] Zhang M., Sabharwal C.L., Tao W., Tarn T.J., Xi N., Li G., "Interactive DNA Sequence and Structure Design for DNA Nanoapplications", IEEE Transactions on Nanobioscience, Vol. 3, No. 4, Dec. 2004.
[12] Chatterjee B., Sachdev M., "Design of a 1.7-GHz Low-Power Delay-Fault-Testable 32-b ALU in 180-nm CMOS Technology", IEEE Transactions on Very Large Scale Integration (VLSI) Systems, Vol. 13, no. 11, Nov. 2005.
[13] Hagiya M., "From Molecular Computing to Molecular Programming", in *Proc. 6th DIMACS Workshop on DNA Based Computers*, Leiden, The Netherlands, Jun. 2000, pp. 198-204.
[14] Sun J., Gao M., Feldmann J., "Electric Field Directed Layer-by-Layer Assembly of Highly Fluorescent CdTe Nanoparticles", *J. of Nanoscience and Nanotechnology*, 1(2):133-136, Jun. 2001.
[15] Cavalcanti A., Hogg T., Kretly L.C., "Transducers Development for Nanorobotic Applications in Biomedical Engineering", IEEE *NDSI Conf. on Nanoscale Devices and System Integration*, Houston TX, USA, April 2005.
[16] Stracke R., Böhm K.J., Burgold J., Schacht H., Unger E., "Physical and Technical Parameters Determining the Functioning of a Kinesin-Based Cell-Free Motor System", *Nanotechnology*, 11(2):52-56, Jun. 2000.
[17] Reppesgaard L., "Nanobiotechnologie: Die Feinmechaniker der Zukunft nutzen Biomaterial als Werkstoff", *Computer Zeitung*, no. 36, pp. 22, Sep. 2002.
[18] Wieland III C.F., "Is the US Nanotechnology Investment Paying Off?", *Small Times Magazine*, 4(1):IP1-IP3, Jan./Feb. 2004.
[19] National science foundation website, http://www.eng.nsf.gov/sbir.
[20] Fishbine G., "The investor's guide to nanotechnology & micromachines", Wiley & Sons, 2001.
[21] Moore S.K., "Just One Word - Plastics", *IEEE Spectrum Magazine*, 39(9):55, Sep. 2002.
[22] Geppert L., "The Amazing Vanishing Transistor Act", *IEEE Spectrum Magazine*, 39(10):28-33, Oct. 2002.
[23] S.P. Leary, C.Y. Liu, M.L.I. Apuzzo, "Toward the emergence of nanoneurosurgery: Part III - Nanomedicine: Targeted nanotherapy, nanosurgery, and progress toward the realization of nanoneurosurgery", Neurosurgery, vol. 58, no. 6, pp. 1009-1025 Jun. 2006.
[24] Martel S., Mathieu J.B., Felfoul O., Macicior H., Beaudoin G., Soulez G., Yahia L.H., "Adapting MRI Systems to Propel and Guide Microdevices in the Human Blood Circulatory System", *26th Annual Int'l Conf. of the IEEE Engineering in Medicine and Biology Society*, p. 1044-1047, Sept. 2004.
[25] Onion A., "RoboSnail Tackles Any Terrain - Slime Not Included", Technology and Science, *ABC News*, Jan. 2006, abcnews.go.com/Technology/story?id=1525599 .
[26] A. Cavalcanti, T. Hogg, B. Shirinzadeh, H.C. Liaw, "Nanorobot Communication Techniques: A Comprehensive Tutorial", IEEE ICARCV Int'l Conf. on Control, Automation, Robotics and Vision, Grand Hyatt, Singapore, December 2006.
[27] P. Couvreur, C. Vauthier, "Nanotechnology: Intelligent design to treat complex disease", Pharmaceutical Research, vol. 23, no. 7, pp. 1417-1450 Jul. 2006.
[28] G.M. Patel, G.C. Patel, R.B. Patel, J.K. Patel, M. Patel, "Nanorobot: A versatile tool in nanomedicine", J. of Drug Targeting, 14 (2): 63-67 Feb 2006.
[29] Kiberstis P., Marx J., "Frontiers in Biomedicine: Cardiovascular Medicine", *Science Magazine*, Vol. 272. no. 5262, pp. 663, Science 3, May 1996.
[30] Ganong W.F., "Review of Medical Physiology". 8th ed. Los Alto, CA: Lange Medical Publications, 1977.
[31] Chandran K.B., Cardiovascular Biomechanics, New York University, 1992.
[32] Yamamoto H., Uemura S., Tomoda Y., Fujimoto S., Hashimoto T., Okuchi K., "Transcardiac Gradient of Soluble Adhesion Molecules Predicts Progression of Coronary Artery Disease", *Int'l J. of Cardiology*, 84(2-3):249-257, Aug. 2002.
[33] Drexler K.E., "Nanosystems: molecular machinery, manufacturing, and computation", Wiley & Sons, 1992.
[34] Munson B.R., Young D.F., Okiishi T.H., *"Fundamentals of Fluid Mechanics"*, John Wiley & Sons, NY, 1997.
[35] Purcell E.M., "Life at Low Reynolds Number", *American J. of Physics*, 45:3-11 (1977).
[36] G. D. Bachand and C. D. Montemagno, "Constructing organic/inorganic NEMS devices powered by

biomolecular motors", *Biomedical Microdevices*, 2:179-184, 2000.

[37] A.Cavalcanti, W.W. Wood, L.C. Kretly, B. Shirinzadeh, "Computational Nanomechatronics: A Pathway for Control and Manufacturing Nanorobots", IEEE CIMCA Int'l Conf. on Computational Intelligence for Modelling, Control and Automation, IEEE Computer Society, Sydney, Australia, Nov. 2006.

[38] R.J. Narayan, "Pulsed laser deposition of functionally gradient diamond-like carbon-metal nanocomposites", Diamond and Related Materials, vol. 14, no. 8, pp. 1319-1330 Aug. 2005.

[39] Jingping Peng, Robert A. Freitas Jr., Ralph C. Merkle, James R. Von Ehr, John N. Randall, George D. Skidmore, "Theoretical Analysis of Diamond Mechanosynthesis. Part III. Positional C2 Deposition on Diamond C(110) Surface using Si/Ge/Sn-based Dimer Placement Tools," J. Comput. Theor. Nanosci., 3:28-41, Feb. 2006.

[40] W. J. Li, N. Xi, W.K. Fung, T.S. Wong, "Nanorobotics and Nanomanipulation", Encyclopedia of Nanoscience and Nanotechnology, American Scientific Publishers, vol. 7, no. 15, pp. 351-365, 2004.

[41] N. Srivastava, K. Banerjee, "Performance analysis of carbon nanotube interconnects for VLSI applications", IEEE/ACM ICCAD Int'l Conf. on Computer-Aided Design, pp. 383-390, Nov. 2005.

[42] W. Bogaerts, R. Baets, P. Dumon, V. Wiaux, S. Beckx, D. Taillaert, B. Luyssaert, J.V. Campenhout, P. Bienstman, D.V. Thourhout, "Nanophotonic Waveguides in Silicon-on-Insulator Fabricated with CMOS Technology", J. of Lightwave Technology, vol. 23, no. 1, pp. 401-412, Jan. 2005.

[43] W.W. Wood, "Nanorobots: A New Paradigm for Hydrogeologic Characterization?", Ground Water, Vol. 43, Issue 4, pp. 463, July 2005.

[44] U. Munch, D. Jaeggi, K. Schneeberger, A. Schaufelbuhl, O. Paul, H. Baltes, J. Jasper, "Industrial fabrication technology for CMOS infrared sensor arrays," in Transducers'97 Tech. Dig., vol. 1, Chicago, IL, pp. 205–208, 1997.

[45] E. Socher, O. Degani, Y. Nemirovsky, "Optimal design and design considerations of CMOS compatible thermoelectric sensors," Sens. Actuators, vol. 71, pp. 107–115, 1998.

[46] H. Trzaska, Electromagnetic field measurements in the near field, Photonic EMF Measurements, Noble, 2001.

[47] Y. Cui, C.M. Lieber, "Functional nanoscale electronic devices assembled using silicon nanowire building blocks," Science, vol. 291, pp. 851–853, Feb. 2001.

[48] A.W.V. Herwaarden, G.C.M. Meijer, "Thermal sensors," in Semiconductor Sensors, S. M. Sze, Ed. New York: Wiley, 1994.

[49] I.D. Villar, I.R. Matias, F.J. Arregui, R.O. Claus, "ESA-based in-fiber nanocavity for hydrogen-peroxide detection", IEEE Transactions on Nanotechnology, vol. 4, no. 2, pp. 187-193 Mar. 2005.

[50] K.J. Albert, N.S. Lewis, C.L. Schauer, G.A. Sotzing, S.E. Stitzel, T.P. Vaid, D.R. Walt, "Cross-reactive chemical sensor arrays", *Chem Rev.* 12;100(7):2595-626, Jul. 2000.

[51] A.J. Matzger, C.E. Lawrence, R.H. Grubbs, and N.S. Lewis. "Combinatorial approaches to the synthesis of vapour detector arrays for use in an electronic nose", *J. Comb. Chem*., 2000, 2, 301-304.

[52] W. Xu, N. Vijaykrishnan, Y. Xie, M.J. Irwin, "Design of a Nanosensor Array Architecture", ACM Proceedings of the 14th ACM Great Lakes symposium on VLSI**,** Boston, Massachusetts, USA, April 2004.

[53] R.J. Narayan, P.N. Kumta, C. Sfeir, D.H. Lee, D. Olton, D. Choi, "Nanostructured ceramics in medical devices: Applications and prospects", JOM, vol. 56, no. 10, pp. 38-43 Oct 2004.

[54] A.S.G. Curtis, M. Dalby, N. Gadegaard, "Cell signaling arising from nanotopography: implications for nanomedical devices", Nanomedicine J., Future Medicine, vol. 1, no. 1, pp. 67-72, June 2006.

[55] F. Favier, E.C. Walter, M.P. Zach, T. Benter, R.M. Penner, "Hydrogen sensors and electrodeposited palladium mesowire arrarys," Science 293, pp.2227-2231, 2001.

[56] E.C. Walter, R.M. Penner, H. Liu, K.H. Ng, M.P. Zach, and F. Favier, "Sensors from electrodeposited metal nanowires," Surf. Interface Anal. 34, pp. 409-412, 2002.

[57] H. Liu, F. Favier, K. Ng, M.P. Zach, and R.M. Penner, "Size-selective electrodeposition of meso-scale metal particles: a general method," ElectroChemica Acta , 47, pp.671-677, 2001.

[58] P. Zach, K. Ng, M. and R. M. Penner, "Molybdenum nanowires by electrodeposition," Science , 290, pp.2120-2123, 2000.

[59] C.K.M. Fung, W.J. Li, "Ultra-low-power Polymer Thin Film Encapsulated Carbon Nanotube Thermal Sensors", IEEE Conf. on Nanotechnology, pp.158-160, Aug. 2004.

[60] J.R.M. Weiss, C. Menolfi, T. Morf, M.L. Schmatz, H. Jaeckel, "Effect of body contacts on high-speed circuits in 90 nm CMOS SOI technology", IEEE ISSCS Int'l Symposium on Signals, Circuits and Systems, pp.537-540, Vol. 2, July 2005.

[61] K. Bernstein, C.T. Chuang, R. Joshi, R. Puri, "Design and CAD Challenges in sub-90nm CMOS Technologies", ACM Proc. of the Int'l Conf. on Computer Aided Design (ICCAD'03), pp. 129-136, 2003.

[62] S. Mitra, C. Putnam, R. Gauthier, R. Halbach, C. Seguin, A. Salman, "Evaluation of ESD characteristics for 65 nm SOI technology", IEEE Int'l SOI Conf., pp.21-23, 2005.

[63] F. Udrea, J.W. Gardner, **"**SOI CMOS gas sensors", in Proc. of IEEE Sensors, vol. 2, pp. 1379-1384 Jun. 2002.

[64] S. Roundy, P.K. Wright, J.M. Rabaey, "Energy scavenging for wireless sensor networks with special focus on vibrations", Springer, May 2006.

[65] W. Liu, J.D.V. Wyk, W.G. Odendaal, "Design and evaluation of integrated electromagnetic power passives with vertical surface interconnections", 9th IEEE Applied Power Electronics Conf. and Exposition, Vol. 2, pp. 958 - 963 vol.2, 2004.

[66] M. Marzencki, S. Basrour, B. Charlot, M. Colin, L. Valbin, "Design and fabrication of piezoelectric micro power generators for autonomous microsystems", in Symposium on Design, Test, Integration and Packaging of MEMS/MOEMS, Montreux, Switzerland, Jun. 2005.

[67] S.G. Thomas, S. Csutak, R.E. Jones, S. Bharatan, C. Jasper, R. Thomas, T. Zirkle and J.C. Campbell, CMOS-compatible photodetector fabricated on thick SO1 having deep implanted electrodes, *Electronics Letters 26th, Vol. 38 No. 20, pp. 1202-1204, September 2002.*

[68] T. Sumino, T. Tamura, K. Koseki,M. Nawata, M. Ogawa, T. Togawa, K. Tsuchwa, Preliminary study of calibration-free continuous glucose monitoring with microdialysis technique, *Proc. Int'l Conf. of the IEEE Engineering in Medicine and Biology Society, Vol. 20, No 4, pp. 1775-1778, 1998.*

[69] I. Vasilescu, K. Kotay, D. Rus, M. Dunbabin, P. Corke, "Data Collection, Storage, and Retrieval with an Underwater Sensor Network", SenSys'05, San Diego CA, USA, Nov. 2005.

[70] A. Cavalcanti, "Assembly Automation with Evolutionary Nanorobots and Sensor-Based Control applied to Nanomedicine", IEEE Transactions on Nanotechnology, Vol. 2, no. 2, pp. 82-87, Jun. 2003.

[71] A. Galstyan, T. Hogg, K. Lerman, "Modeling and Mathematical Analysis of Swarms of Microscopic Robots", IEEE Swarm Intelligence Symposium, pp. 201-208, Pasadena CA, USA, Jun. 2005.

[72] T.K. Horiuchi, R.E. Cummings, "A Time-Series Novelty Detection Chip for Sonar", Int'l J. of Robotics and Automation, ACTA Press, 2004.

[73] L. Ricciardi, I. Pitz, S.F.A. Sarawi, V. Varadan, D. Abbott, Investigation into the future of RFID in biomedical applications, Proc. of SPIE - The Int'l Society for Optical Engineering, v 5119, pp. 199-209, 2003.

[74] C. Sauer, M. Stanacevic, G. Cauwenberghs, N. Thakor, Power harvesting and telemetry in CMOS for implanted devices, IEEE Transactions on Circuits and Systems, Vol. 52, no. 12, pp. 2605-2613, Dec. 2005.

[75] W. Weber, "Ambient Intelligence Industrial Research on a Visionary Concept", IEEE Int'l Symp. on Low Power electrnics and Dsign, pp. 247-251, Aug. 2003.

[76] C. Panis, U. Hirnschrott, S. Farfeleder, A. Krall, G. Laure, W. Lazian, J. Nurmi, "A Scalable Embedded DSP Core for SoC Applications", IEEE Int'l Symposium on System-on-Chip, pp. 85-88, Nov. 2004.

[77] T. Kuroi, K. Horita, "Scaling of shallow trench isolation with stress control for 65nm node and beyond", IEEE Int'l Conf. on Solid-State and Integrated Circuits Technology, vol. 1, pp. 548-553, Oct. 2004.

[78] Hansen R.K., Andersen P.A., "A 3-D underwater acoustic camera - properties and applications," In P. Tortoli and L. Masotti, editors, *Acoustical Imaging*, Plenum Press, pp. 607-611, 1996.

[79] Whitcomb L.L., "Underwater Robotics: Out of the Research Laboratory and Into the Field", in *Proc. IEEE Int'l Conf. on Robotics and Automation*, San Francisco, CA, USA, Apr. 2000, pp. 709-716.

[80] A. Cavalcanti, T. Hogg, B. Shirinzadeh, "Nanorobotics System Simulation in 3D Workspaces with Low Reynolds Number", IEEE-RAS MHS Int'l Symposium on Micro-Nanomechatronics and Human Science, Nagoya, Japan, Nov. 2006.

[81] Baraff D., "Fast contact force computation for nonpenetrating rigid bodies", in Computer Graphics Proceedings, Annual Conf. Series. ACM SIGGRAPH, pp. 23-34, 1994.

[82] Mirtich B., Canny J., "Impulse-based simulation of rigid bodies", Proc. of Symposium on Interactive 3D Graphics, pp. 392-398, 1995.

[83] C. Wurll, D. Henrich, and H. Wörn, "Parallel on-line Motion Planning for Industrial Robots," *3rd ASCE Specialty Conf. on Robotics for Challenging Environments, Robotics 98*, pp. 308-314, New Mexico, USA, 1998.

[84] K. H. Kim, "The Distributed Time-Triggered Simulation Scheme Facilitated by TMO Programming", *IEEE Fourth Int'l Symposium on Object-Oriented Real-Time Distributed Computing*, Magdeburg, Germany, May, 2001.

[85] T. Fukuda, T. Arai, "Prototyping Design and Automation of Micro/Nano Manipulation System," *Proc. of IEEE Int'l Conf. on robotics and Automation (ICRA'00)*, Vol. 1, pp. 192-197, 2000.

[86] J.I. Fann, F.G.S. Goar, J. Komtebedde, M.C. Oz, P.C. Block, E. Foster, J. Butany, T. Feldman, T.A.Burdon, "Beating Heart Catheter-Based Edge-to-Edge Mitral Valve Procedure in a Porcine Model: Efficacy and Healing Response", Circulation, 110: 988-993, Aug 2004, circ.ahajournals.org/cgi/content/full/110/8/988 .

[87] Stefanadis C., Toutouzas K., Tsiamis E., Stratos C., Vavuranakis M., Kallikazaros I., Panagiotakos D., Toutouzas P., "Increased Local Temperature in Human Coronary Atherosclerotic Plaques: An Independent Predictor of Clinical Outcome in Patients Undergoing a Percutaneous Coronary Intervention", *J Am Coll Cardiol*, 37(5):1277-1283, Apr. 2001.

[88] Stefanadis C., Diamantopoulos L., Dernellis J., Economou E., Tsiamis E., Toutouzas K., Vlachopoulos C., Toutouzas P., "Heat Production of Atherosclerotic Plaques and Inflammation Assessed by the Acute Phase Proteins in Acute Coronary Syndromes", *J Mol Cell Cardiol*, 32(1):43-52, Jan. 2000.

[89] Ito T., Ikeda U., "Inflammatory cytokines and cardiovascular disease", *Current Drug Targets - Inflammation and Allergy*, 2(3):257-265, Sep. 2003.

[90] Xu C., Wootton D.M., "Platelet Near-Wall Excess in Porcine Whole Blood in Artery-Sized Tubes Under Steady and Pulsatile Flow Conditions", *Biorheology* 41(2):113-125, Apr. 2004.