

Nanorobotics Control Design: A Collective Behavior Approach for Medicine

Adriano Cavalcanti, *Member, IEEE*, and Robert A. Freitas Jr.

Abstract—The authors present a new approach using genetic algorithms, neural networks and nanorobotics concepts applied to the problem of control design for nanoassembly automation and its application in medicine. As a practical approach to validate the proposed design, we have elaborated and simulated a virtual environment focused on control automation for nanorobotics teams that exhibit collective behavior. This collective behavior is a suitable way to perform a large range of tasks and positional assembly manipulation in a complex 3D workspace. We emphasize the application of such techniques as a feasible approach for the investigation of nanorobotics system design in nanomedicine. Theoretical and practical analyses of control modelling is one important aspect that will enable rapid development in the emerging field of nanotechnology.

Index Terms—Biomedical engineering, control systems, mechatronics, nanotechnology, virtual reality.

I. INTRODUCTION

FOLLOWING the first steps toward molecular manufacturing in the 80's and 90's in the sense of nanoscale building blocks, we now face more complex challenges in achieving the next generation of nanotechnology advances, in the sense of building bionanoelectronics and molecular machines. This paper presents the simulation of mobile multi-robot teams operating at atomic scales to perform biomolecular assembly manipulation for nanomedicine [20]. In such a virtual nanoworld, the teams must cooperate with each other in order to achieve a productive result in assembling biomolecules into larger biomolecules. The assembled biomolecules must be sequentially delivered into a set of predefined organ inlets, and the nanorobot teams must also keep the nutritional levels of the larger organism under control [8], [9]. The motivation for such study is the likelihood that in the emerging era of molecular engineering, the development of methodologies that help focus experimental investigations enabling the automation and the evaluation of new approaches for a better comprehension and visualization of virtual nanoworlds can have a great impact on effective design and on the future development of nanotechnology.

One important challenge that has become evident as a vital problem in nanotechnology industrial applications is the automation of atomic-scale manipulation. The starting point of

nanotechnology to achieve the main goal of building systems at the nanoscale is the development of control automation for molecular machine systems, which could enable the massively parallel manufacture of nanodevice building blocks. Governments all around the world are directing significant resources toward the fast development of nanotechnology. In Germany, the Federal Ministry of Education and Research has announced 50 million Euros to be invested in the years 2002-2006 in research and development on nanotechnology [51]. The U.S. National Science Foundation has launched a program in "Scientific Visualization" [48] in part to harness supercomputers in picturing the nanoworld. A US\$ 1 trillion market consisting of devices and systems with some kind of embedded nanotechnology is projected by 2015 [46], [14]. More specifically, the firm DisplaySearch predicts rapid market growth from US\$ 84 million today to \$ 1.6 billion in 2007 [47]. A first series of commercial nanoproducts has been announced as foreseeable by 2007. To reach the goal of building organic electronics, firms are forming collaborations and alliances that bring together new nanoproducts through the joint efforts of companies such as IBM, Motorola, Philips Electronics, Xerox/PARC, Hewlett-Packard, Dow Chemical, Bell Laboratories, and Intel Corp., among others [22], [47]. For such goals, new methodologies and theories to explore the nanoworld are the key technology [13].

II. ASSEMBLY NANOMANIPULATION

Building patterns and manipulating atoms with the use of SPMs as in Atomic Force Microscopy (AFM) and Scanning Tunneling Microscopy (STM) has been demonstrated with satisfactory success as a promising approach for the construction of nanoelectromechanical systems (NEMS) with 3D precision at 0.01 nm resolution [52]. However, such manual manipulations require much time, and even for a repetitive task these manipulations tend to produce imprecise work when performed manually for a large number of molecules. Practical approaches for nano planning systems have been presented as a first step towards automating assembly tasks in nanorobotics, as for example in 2D positional assembly automation [38]. The use of artificial intelligence as the appropriate means to enable some aspects of intelligent behavior in the control of nanorobots during molecular manufacturing automation has been discussed in the nano community [58]. The use of concepts derived from collective robotics and behavior control was investigated for nanomedicine dealing with a common goal to destroy malignant tissues in the human body [36]. More recent work is progressing towards the development of a nanorobotics autonomous system capable of performing 200,000 accurate measurements per second at atomic scale [39]. An Intel

Manuscript received January 18, 2004; revised in October 12, 2004.

A. Cavalcanti is with the Computational Nanomechatronics Lab, Center for Automation in Nanobiotech, Herminio Lemos 449, Cambuci, Sao Paulo, SP 01540-000 Brazil (e-mail: adriancavalcanti@canbiotechnems.com).

R. A. Freitas Jr. is with the Institute for Molecular Manufacturing, P.O. Box 605, Pilot Hill, CA 95664 USA (e-mail: rfreitas@rfreitas.com).

prototype 90-nm process facility has already produced a fully functional 52 Mb SRAM with transistor gate lengths of 50 nm and SRAM cell sizes of just $1\mu\text{m}^2$, or roughly half the cell size of today's most advanced SRAMs [22]. This downscaling will continue, according to the Semiconductor Industry Association's roadmap. By 2016, high-performance ICs will contain more than 8.8 billion transistors in a 280 mm^2 area - more than 25 times as many as on today's chips built with 130-nm feature sizes [22].

Through the use of nanotechnology techniques [22], genetics advances [55], and biomolecular computing [1], we may also have biological nanorobots being applied in specific biomedical and environmental applications. For example, in microbiology engineering the construction of digital circuits in living cells has been demonstrated [62]. The Synthetic Biology Lab at MIT is creating a standardized set of biological building block components designed for logic operations inside a cell and are being accumulated in the MIT Registry of Standard Biological Parts [44]. Bacteria have been used as physical system components [32], and radio remote control of biological processes has been demonstrated experimentally [27]. Following similar proposals on nanorobots being injected inside living cells and controlled for biomedical purposes [20], we can expect the first artificial biological nanorobots, a possibility extensively reviewed elsewhere [17], [15], [16], to become available in five years or less [41]. More complex nanorobots will be manufactured using diamondoid or other similarly rigid materials awaiting primarily our ability to perform positional mechanosynthesis, and work leading in this direction has progressed recently [49]. Initial uses of nanorobots in health care are likely to emerge within the next ten years [20], [58] with potentially broad biomedical applications [20], [15], [40], [42].

A useful starting point for achieving the main goal of building nanoscale devices is the development of generalized automation control for molecular machine systems which could enable a manufacturing schedule for positional nanoassembly manipulation. In this paper we consider a more specialized scheduling problem with a focus on nanomedicine: describing in a detailed fashion the nanorobot control design and the surrounding virtual workspace modelling that is required for the main kinematics aspects of a physically-based nanoworld simulation. Here the biomolecular assembly manipulation is automatically performed by smart agents, which are given the task of improving the nutritional state of an organism via the injection of appropriate assembled substances into pre-established delivery points in a complex 3D environment.

III. NANOMEDICINE

In future decades the principal focus in medicine will shift from medical science to medical engineering, where the design of medically-active microscopic machines will be the consequent result of techniques provided from human molecular structural knowledge gained in the 20th and early 21st centuries [20]. For the feasibility of such achievements in nanomedicine, two primary capabilities for fabrication must be fulfilled: fabrication and assembly of nanoscale parts. Through the use of different approaches such as biotechnology, supramolecular chemistry, and

scanning probes, both capabilities had been demonstrated to a limited degree as early as 1998 [20]. Despite quantum effects which impart a relative uncertainty to electron positions, the quantum probability function of electrons in atoms tends to drop off exponentially with distance outside the atom. Even in most liquids at their boiling points, each molecule is free to move only $\sim 0.07\text{ nm}$ from its average position [20]. Developments in the field of biomolecular computing [1] have demonstrated positively the feasibility of processing logic tasks by bio-computers [26], a promising first step toward building future nanoprocessors with increasing complexity. There has been progress in building biosensors [57] and nanokinetic devices [56], [2], which also may be required to enable nanorobotic operations and locomotion. Classical objections related to the feasibility of nanotechnology, such as quantum mechanics, thermal motions and friction, have been considered and resolved and discussions of techniques for manufacturing nanodevices are appearing in the literature with increasing frequency [29].

IV. PROPOSED DESIGN

Assemblers are molecular machine systems that could be described as systems capable of performing molecular manufacturing at the atomic scale [8]. The collective nanorobotics approach presented here is one possible method to perform a massively-parallel positional nanoassembly manipulation. In our described workspace representing a simplification of the human body, the multi-nanorobot teams perform a pre-established set of tasks building nutrient molecules, crudely analogous to the work done by a ribosome which is a natural assembler. Three well-known design approaches for nano-manipulation in liquid and air environments [13] include the telescoping robotic arm, the Stewart platform, and the five-strut crank model. For our experiment we chose a robotic arm with nano-manipulation in a liquid environment, the most suitable for an in vivo nanomedical application. It is also well-known that computation is relatively cheap for macroscale robotic actuators whereas arm motion is relatively cheap for nanoscale robotic actuators [13], [20]. Thus the moment-by-moment computer control of arm trajectories is the appropriate paradigm for macroscale robots, but not for nanoscale robots. For nanoscale robots, the appropriate manipulator control paradigm is often trajectory trial and error, also known as sensor based motion control [31].

A. Virtual Environment and Nanorobot Design

Techniques to enable rapid design while incorporating complex aspects of physical principles used for production of final 3D prototypes have been progressing rapidly. Virtual reality techniques are currently being explored successfully in nanoscience and nanotechnology research to provide researchers with an intuitive way to interact with materials and devices at the nanoscale [37]. Guthold [24] tried to provide a virtual-environment interface to Scanning Probe Microscopes (SPMs), giving a virtual telepresence on the surface but downscaled by a factor of about a million to one. The introduction of direct human-SPM interaction creates not only enhanced measurement capability (for instance, special transducers can provide a sense of touch to the nanomanipulator), but also presages a more fully

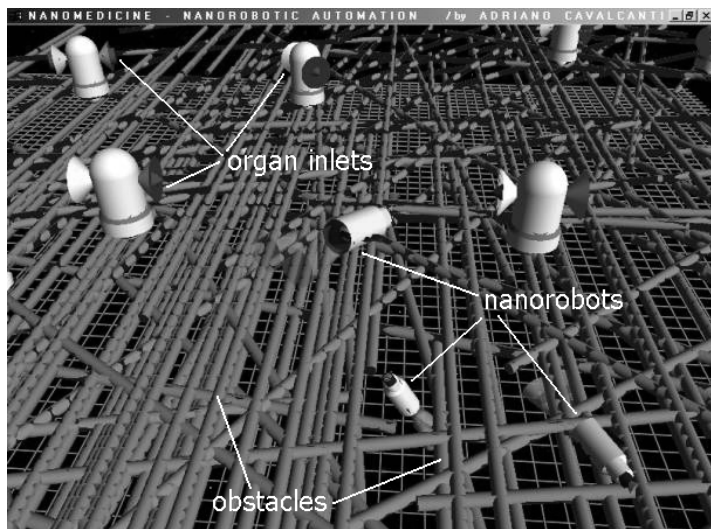


Fig. 1. Virtual environment, top camera view.

automated technology that will enable nanofabrication and/or repair of nanostructures. A 3D bio-nanomanipulation system integrated with a real-time virtual reality simulator has been proposed [21]. Nanoscale object manipulation systems have been applied with the use of computer graphics for teleoperation, where the requirements for such systems have been clearly established [54].

Virtual Reality was considered a suitable approach for nanorobot design and for the use of macro- and micro-robotics concepts given certain theoretical and practical aspects that focus on its domain of application. The nanodevice design must be robust enough to operate in an aqueous environment with movement having six-degrees of freedom (see Fig. 1). The virtual environment in our study is inhabited by nanorobots, biomolecules, obstacles, and organ inlets. Each nanorobot measures 650 nm in length and 160 nm in diameter. The biomolecule has a diameter of ~10 nm and each obstacle has a diameter of 120 nm. The organ inlets are 400 nm in height and width with inlet orifices 720 nm in diameter.

The trajectories and positions of each molecule which must be captured and assembled were generated randomly, and each one also has a probabilistic velocity and acceleration. In the simulation, while some molecules have been captured (Fig. 2) other molecules are manipulated and assembled internally by the robot arm inside the proposed nanorobot.

The nanorobot design (Fig. 2) is derived from biological models and is comprised of components such as *molecular sorting rotors* and a robot arm (*telescoping manipulator*) [13], [20]. The nanorobot exteriors considered in our design assumes a diamondoid material to which may be attached an artificial glycocalyx surface that minimizes fibrinogen (and other blood protein) adsorption and bioactivity, thus ensuring sufficient biocompatibility for the nanorobot to avoid immune system attack [18]. Different molecule types are distinguished by a series of chemotactic sensors whose binding sites have a different affinity for each kind of molecule [20].

Some concepts provided from underwater robotics [60] were assumed for nanorobot locomotion. The nanorobot kinematic

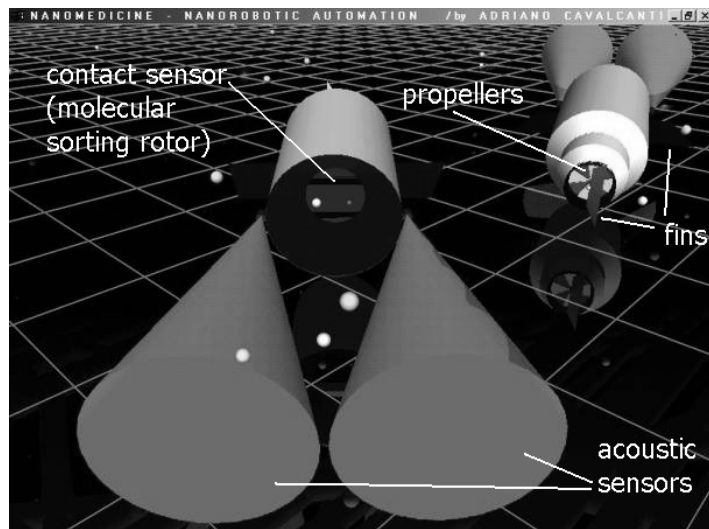


Fig. 2. Molecular identification.

response 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 [6]. Plane surfaces (three fins total) and bi-directional propellers provide navigation, while two simultaneously counter-rotating screw drives provide the propulsion [20]. The nanorobot lives in a world of viscosity, where friction, adhesion, and viscous forces are paramount and the gravitational force here is relatively negligible [13], [20]. In this world a very low Reynolds number (Re) is assumed for the kinetic calculations [50], where the fluid mechanics in small structures can usually be described by the classical continuum equations [13]. The ratio of inertial to viscous forces is determined by Re as expressed in (1):

$$Re = \rho V L / \eta \quad (1)$$

where η is the absolute viscosity of the fluid, V is the velocity, ρ is the fluid density, and L is a characteristic dimension. Re indicates whether the flow will be laminar or turbulent around an object of a given shape at a given flow velocity. For nanoscale dimensions in fluids of ordinary viscosities and velocities, Re is low and the flow is laminar [20]. The inertial force on the object is of order $F_{inertial} \cong \rho V^2 L^2$ and the viscous drag force is of order $F_{viscous} \cong \eta V L$. In order to keep moving forward, a nanorobot of size $L \cong 1$ micrometer and velocity $V \cong 10$ micrometer/sec must apply $F_{inertial} \cong 10^{-4} fN$ (femtonewtons, $1fN = 10^{-15} N$) and a much larger $F_{viscous} \cong 10 fN$ of motive force [20]. For instance, if motive power to a swimming nanorobot with radius $R_{nano} = 1$ micrometer, and velocity $V_{nano} = 1$ cm/sec, is suddenly stopped, then the nanorobot will "coast" to a halt in a time t_{coast} given by (2):

$$t_{coast} = \rho R_{nano}^2 / 15\eta = 0.1 \quad (2)$$

where 0.1 is expressed in microsecond, and in a distance $X_{coast} \cong V_{nano} t_{coast} = 1nm$ [4]. Similarly with ν as the rotational frequency, if the nanorobot is rotating at a frequency

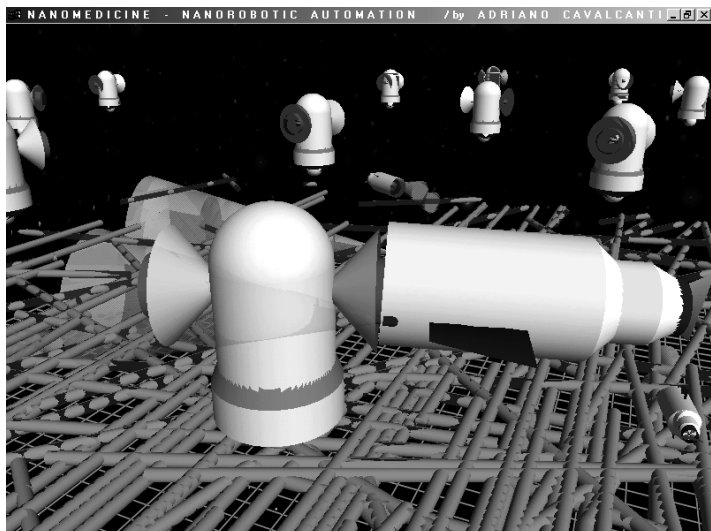


Fig. 3. Nanorobot molecule delivery.

$v_{nano} = 100$ Hz when its rotational power source is suddenly turned off, v_{nano} decays exponentially to zero in a time $t_{coast} \cong 0.1$ microsecond and stops after turning through an angle θ_{coast} , as expressed by (3):

$$\theta_{coast} = 2\pi v_{nano} \rho R_{nano}^2 / 15\eta \quad (3)$$

or 40 microradians in this instance [20].

The nanorobots use a macrotransponder navigational system for the main aspects of the nanorobot positioning, which may allow high positional accuracy in each nanorobot's orientation [20]. Such a system might involve externally generated signals from beacons placed at fixed positions outside the skin [20], [43]. Thus the delivery positions that represent organ inlets requiring proteins to be injected are located in well-known locations for the nanorobot. If these organ inlets are or are not scheduled for injection at time t , they change the team A (blue nanorobots) and team B (yellow nanorobots) delivery orifice colors in the simulation, opening or closing the orifice (Fig. 3). This better enables visualization of the organ inlets in which the agents are performing their delivery in the current time step of the simulation. The assembled molecules are thus delivered to specific locations by nanorobots docking at $2\text{-}\mu\text{m}^2$ ($\sim 1.4\text{-}\mu\text{m}^2$) sites embedded at appropriate spatial intervals across the organ inlets' orifice [19], which is open for the delivery. The assembled molecule can be pumped by the molecular sorting rotors in ~ 10 seconds [19].

The use of local perception should in most cases be quite sufficient for the overall set of tasks that our nanorobots are designed to perform. An explicit communication between each nanorobot partner sending the signal is required when a delivery is completed for the determined organ inlet, whereupon nanorobot B awaits a message from nanorobot A confirming that A has finished the delivery to the given organ inlet. Acoustic communication sensors [20] mounted within the nanorobot hull permit the nanorobot to communicate with its partner whether or not the organ inlet has received the required substance. By using the nanorobot's local perception as much as possible and by

sending the fewest possible messages to other nanorobots, unnecessary communication between the agents is reduced, thus minimizing energy consumption by the nanorobots. Nanorobots satisfy their energy requirements via the chemical combination of oxygen and glucose [20], both of which are plentiful in the human body.

The nanorobot includes external sensors to inform it of collisions and to identify when it has encountered an obstacle which will require a new trajectory planning. Aspects of the non-structured opaque surrounding workspace, like the interior of the human body where the nanorobot is acting, must be considered in the navigational sensing design. In robotics fields there are often many kind of sensors such as infrared, computer vision, chemical sensors, and so forth which are normally used for robotics navigational purposes. Optical sensors have been widely applied in terrestrial mobile robotics but these have an extremely limited range in a liquid environment. Types of sensors such as laser rangefinders [6] could be also used for underwater robotics but not for nanorobotics sensing because, for instance, the laser energy might excite or chemically alter the surrounding biomolecules that the nanorobot is trying to capture. Although the infrared sensor seems preferable for macroscale terrestrial robots, for underwater robots the most common sensor approach involves the use of sonar systems. Similarly the most addressable approach for nanorobots in nanomedicine is to use acoustic waves [20]. The blue cones shown in Fig. 2 represent regions that the robot's sonar can "hear". Scientific visualization techniques permit rapid and precise geometric analysis to simulate a sonar classification system [6].

The authors used physically-based simulation [3] to consider kinematics and frictional aspects specifically required for rigid body motion with hydrodynamics at low Reynolds number for molecular assembly manipulation.

B. Evolutionary Decision

We intend to construct and demonstrate the applicability of multi-robot teams in timely sequenced work for capture, assembly, transport and delivery of biomolecular pieces to a predefined set of organ inlets. The use of multi-robot teams working cooperatively to achieve a single global task applied to nanotechnology is a field of research that is relatively new [9]. Research on collective robotics suggests that we should consider emulating the methods of the social insects [53] to build decentralized and distributed systems that are capable of accomplishing tasks through the interaction of agents with the same structures and pre-programmed actions and goals. Thus a careful decomposition of the main problem task into subtasks with action based on local sensor-based perception could generate multi-robot coherent behaviors [33].

The approach for the nanomedicine problem here could be described as two multi-robot teams which must cooperate interactively to feed a set of organ inlets in the virtual environment under study. The importance of cooperative teamwork has led us to choose a high level decision control model with adaptive evolutionary characteristics. Note that the proposed nanorobot model here includes no kind of nanorobot self-replicating behavior [12]. Instead, our model uses an evolutionary

approach strictly for the combinatorial analyses, allowing the nanorobots to react cooperatively in an uncertain environment with a well defined pre-programmed set of actions. The model used here, often cited in the literature as Genetic Algorithms (GA), relies on concepts derived from evolution and genetics [8]. Each solution here is described as a chromosome regarding the nanorobot decision on how, when, and what organ inlets to attend in the dynamic scenery. Each decision required to be taken by the nanorobot always follows the programmed set of actions rigidly pre-established in our design by the fitness/objective function. Equation (4) represents our fitness function, where the nanorobots maximize the protein levels for the selected organ inlets. The variable y induces the nanorobot to catch a number of molecules as closely as possible to the desired delivery mean, while z brings the nutritional levels as close as possible to w_i^* .

$$\text{Max } f(r_\Omega) = \sum_{t=1}^n \sum_{i=1}^m w_i^t - |y^t| - |z_i^t| \quad (4)$$

$$\text{s.t. } z_i^t = w_i^{t+1} - w_i^* \quad (5)$$

$$y^t = Q^t - d \quad (6)$$

$$Q^t = \sum x_i^t \leq L \quad (7)$$

$$x_i^t = \mu_i^t x_i^{\max} \quad (8)$$

$$\mu_i^t \leq \Delta_i^{\max} \quad (9)$$

$$w_i^{t+1} = w_i^t - \gamma s_i^t + x_i^t \quad (10)$$

$$w_i^{\min} \leq w_i^t \leq w_i^{\max} \quad (11)$$

$$\mu_i^t \in \{\{0,100\} \vee \{0,1\}\} \quad (12)$$

$$\Omega \in \{A, B\} \quad (13)$$

where

r, t, i : subscript denoting: robot, time, organ inlet.

w_i^* : organ inlets' desirable nutritional target level.

y^t : surplus/deficit to the desired assembled mean.

z : keep the nutritional levels close to the target.

max, min: upper and lower bound parameter.

A, B: respective robotics teams.

n : size of time in the simulated scenery.

m : total of organ inlets to be fed.

L : robot load capacity.

x_i^t : substance amount injected in the organ inlet i .

Q^t : total assembled molecule by r in t .

w_i^t : chemical state of the organ inlet i at time t .

s_i^t : nutrients consumption by the organ inlet i .

d : desired assembled substances rate.

γ : parameter to look ahead at nutritional levels.

μ_i^t : Boolean variable.

Ω : determines if r belongs to team A or B .

Δ : maximum to be injected at organ i in t .

We have decomposed the total set of organ inlets, assigning for each pair of nanorobots a specified number of organ inlets to be attended by the nanorobots at each time-step of the simulation.

TABLE 1
COLLECTIVE NANOROBOTIC TEAMS INTERACTION RULE

Step 1:	r_Ω walk randomly to capture β and δ ;
Step 2:	if $\sum \beta = \sum \delta \rightarrow$ assemble $f(r_\Omega) = \beta + \delta$;
Step 3:	if $\sum f(r_\Omega) < \min$ repeat step 1;
Step 4:	r_Ω achieve next delivery goal regarding the delivery queue;
Step 5:	if $\text{delivery_Orifice_is_Open} = \text{true} \rightarrow$ next step; otherwise: go to step 9;
Step 6:	if $\text{delivery_Permission} = \text{true} \rightarrow$ next step; otherwise: go to step 9;
Step 7:	if $\text{NOT_overdose} = \text{true} \rightarrow$ next step; otherwise: go to step 9;
Step 8:	delivery: $f(r_\Omega) = f(r_\Omega) - 1$;
Step 9:	if $f(r_\Omega) > 0 \rightarrow$ repeat step 4;
Step 10:	$r_\Omega \rightarrow$ complete the verification route;
Step 11:	repeat step 1;

Each pair is comprised of nanorobots from team A , and B . The organ inlets selected to be fed at time t have to be fed first by the agent A , then by B , and so forth. Both agents must take care to avoid applying an overdose or deficiency of the injected substances. The multi-robot team behavior interaction rule is described in Table 1, with $\Omega \in \{A, B\}$, Ω denoting if the robot r belongs to team A or B ; \min is the minimum defined to be captured by each robot at time step t , where e, g , and h represent the kind of molecule to be assembled by r , therefore:

$$\beta \begin{cases} \Omega = A & \Rightarrow \beta = e, \\ \Omega = B & \Rightarrow \beta = h, \end{cases} \quad (14)$$

$$\delta = g. \quad (15)$$

We used real time [35], [45] and parallel processing techniques [61], where both teams react adaptively to any stimulus produced by their partners' decisions, with the model visualization in real time. The study of smart multi-robot behavior in a single global environment enables concepts related to the use of local perception for reactive agents [5], [33]. Multidisciplinary control design addresses the nanorobot's multi-modular system architecture [10]. A feedforward neural networks model discussed below was used for the nanorobot motion control, wherein each nanorobot visits in a shorter time the organ inlets that were pre-attributed to that nanorobot in order to gather information for the next time-step decision from the 3D workspace.

C. Neural Motion

A connectionist model using Artificial Neural Networks was chosen for the motion control and shortest-path problem solution, beginning with a dynamic combinatorial problem for each time-step simulation. The classical problem of finding an optimal three-dimensional shortest path avoiding 3D polygonal obstacles is typically NP-hard [3]. The use of a non-deterministic approach to solve the motion control seems to be the appropriate technique

in such cases [23]. We have implemented a feedforward or acyclic network due to its suitability for probabilistic calculations. The particular model implemented here is a stochastic feedforward neural network [28], which requires a lower computational effort in comparison with a backpropagation algorithm [25] and a better performance in comparison with a *greedy* heuristic approach [59]. The features of the algorithm for the implemented neural network and could be represented by (16):

$$pa(X_j) \subseteq \{X_1, X_2, \dots, X_{j-1}\} \quad (16)$$

where X represents a vector, consisting of the two-valued random variables X_1, X_2, \dots, X_n , defining a topology composed of N stochastic neurons. With n representing the range of hidden layers, which leads the network to be optimized at the time-step t , it represents each destiny to be achieved for r_Ω throughout the simulation. The units in the network are organized into a two-dimensional matrix A_{mn} , with n rows by m columns, where n and m are the costs matrix of destinations for each evolutionary agent, which tries to complete its set of tasks successfully as fast as possible. Let the output of the unit in row i and column j be $v_{ij} = 1$, where $i \neq j$. This means that the referred destination is visited at the i^{th} stop, with $v_{ij} = 0$ otherwise. Therefore, a solution cost for

each agent routing could be expressed by (17).

$$\text{Min} \quad P_r^t = \sum_{i=1}^m \sum_{j=1}^n v_i w_{ij} \quad (17)$$

Once having obtained both routes (route on and route off), which are comprised respectively of the organ inlets to be supplied and the organ inlet whose nutritional level is to be verified, then the nanorobot performs the trajectory visiting the subset of organ inlets assigned to it, first executing the whole delivery route, and afterwards beginning the verification route.

One positive aspect of a feedforward neural network is that it requires low computational effort to achieve motion control in a workspace with six-degrees of freedom [25]. We use binary cues to trigger the behavioral response as a common mechanism for action and for governing different phases of activity in tasks – as is done by social insects [11]. In this manner, activation of a motor behavior is not dependent on a specific perceptual cue, but rather on the decision that results from sensor processing. The advantage is that the design of the motor behavior does not change when different sensor types or alternate feature extraction techniques are used, since the information needed by the motor behavior is the same binary vector in both cases [33]. The obstacles are located in probabilistic positions (Figs. 4 and 5).

V. SIMULATION AND CONCLUSIONS

Biomolecular machine system designs that are capable of accomplishing successfully a set of pre-programmed tasks in a 3D workspace is a new challenge for control investigation. We described the study of an automation model and the respective visualization tools to follow up the analyses for the control theory development based on experimental results.

Nanorobots monitoring nutrient concentrations in a three dimensional workspace is a possible application of nanorobots in medicine, among other biomedical problems [20]. One interesting nanorobot application is to assist inflammatory cells (or white cells) leaving blood vessels to repair injured tissues [7]. Also the nanorobot could be used to process specific chemical reactions in the human body as ancillary devices for injured organs [41]. Nanorobots equipped with nanosensors could be developed to detect glucose demand in diabetes patients [30]. Nanorobots could also be applied in chemotherapy to combat cancer through superior chemical dosage administration [34], and a similar approach could be taken to enable nanorobots to deliver anti-HIV drugs [42]. Such drug-delivery nanorobots have been termed "pharmacytes" by Freitas [20].

The nanorobot has required a decision control that demonstrates the most effective methodology for stochastic surroundings when only a low-level action description does not attend a large number of complex circumstances in a dynamic environment. A coherent team behavior was suitably achieved demonstrating satisfactory performance in controlling the organ inlets' nutritional levels. We have adopted as an exemplar target the nutritional level value of 50% of the relative organ inlet nutritional capacity. Levels lower than 20% or higher than 80%

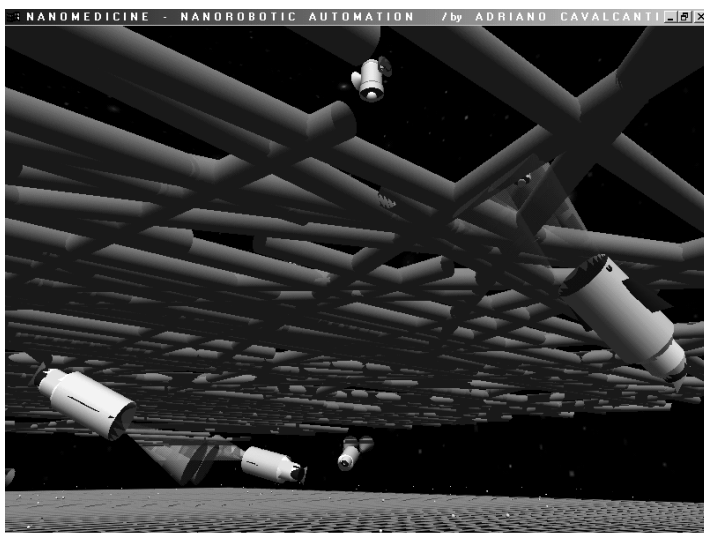


Fig. 4. Sensing obstacles.

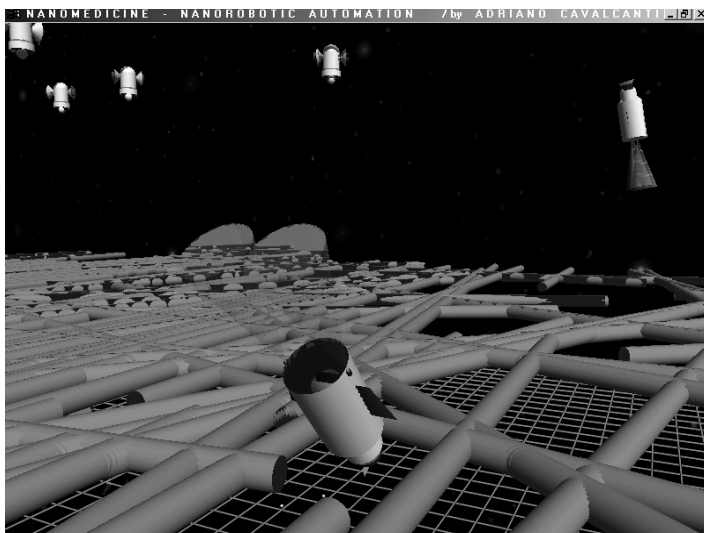


Fig. 5. Nanorobot obstacle avoidance.

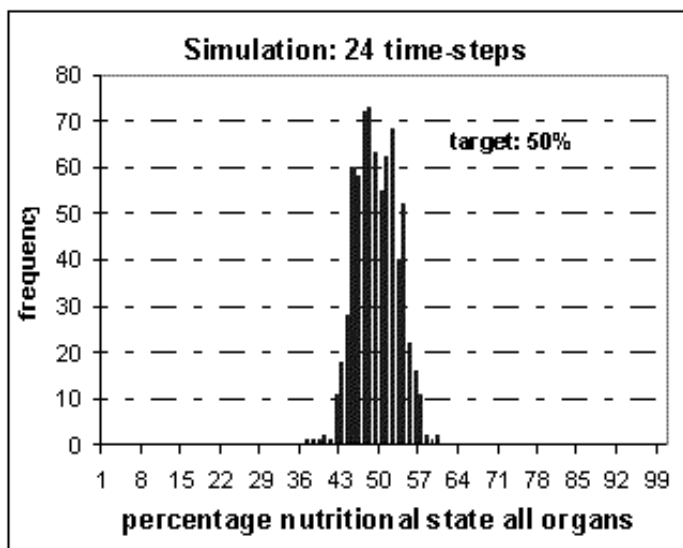


Fig. 6. Histogram with nutritional levels behaviors.

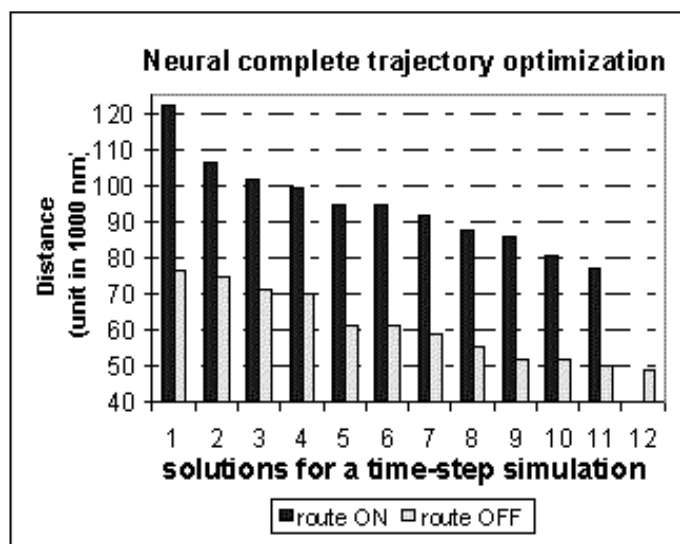


Fig. 7. Motion control cost minimization.

are then characterized as a possible deficiency or overdose case. In our simulations (Fig. 6), we observed no occurrences of nutritional levels beyond desired ranges, illustrating successful collective nanorobot coherent behavior.

Furthermore, the nanorobot has required a motion control model having one or two main aspects: dynamic optimization of the trajectory distances, and real time analyses for a required trajectory to enable the delivery of assembled biomolecules with avoidance of obstacles. The neural motion control was successfully used with real time response for the circumstance where the nanorobots must capture molecules and visit a pre-defined set of delivery points, avoiding random obstacles and collision with other mobile nanorobots, and trying at the same time to minimize the time required. These tasks were satisfactorily accomplished using the neural networks approach, wherein the nanorobots calculated their complete trajectories with a cost minimization of ~37% in the required distance (Fig. 7), which shows good improvement in comparison with a *greedy* solution for the motion control optimization.

Realizing revolutionary applications of nanorobots to health or

environmental problems raises new control challenges. The design and the development of complex nanosystems with high performance should be addressed via simulation to help pave the way for future medical nanorobotic systems.

ACKNOWLEDGMENT

The authors thank Tad Hogg for helpful comments on an earlier version of this paper.

REFERENCES

- [1] L. M. Adleman, "On Constructing A Molecular Computer," *DNA Based Computers*, 1995, <http://olymp.wu-wien.ac.at/usr/ai/frisch/local.html>.
- [2] G. D. Bachand and C. D. Montemagno, "Constructing organic/inorganic NEMS devices powered by biomolecular motors," *Biomedical Microdevices*, 2:179-184, 2000.
- [3] D. Baraff, "Dynamic Simulation of Non-Penetrating Rigid Bodies", PhD Thesis, Department of Computer Science, Cornell University, Ithaca, NY, 1992.
- [4] H. C. Berg, "Dynamic properties of bacterial flagellar motors," *Nature* 249, May 1974.
- [5] H. Bojinov, A. Casal, and T. Hogg, "Multiagent Control of Self-reconfigurable Robots," *Proc. of IEEE ICMAS Int'l Conf. on Multiagent Systems*, pp. 441-455, IEEE Computer Society, Boston, MA, USA, July 2000.
- [6] D. P. Brutzman, Y. Kanayama and M. J. Zyda, "Integrated Simulation for Rapid Development of Autonomous Underwater Vehicles," *IEEE Autonomous Underwater Vehicle Conference*, IEEE Oceanic Engineering Society, Washington DC, pp. 3-10, June 1992.
- [7] A. Casal, T. Hogg and A. Cavalcanti, "Nanorobots as Cellular Assistants in Inflammatory Responses," *IEEE BCATS Biomedical Computation at Stanford 2003 Symposium*, IEEE Computer Society, Stanford CA, October 2003.
- [8] 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, June 2003.
- [9] A. Cavalcanti and R. A. Freitas Jr., "Autonomous multi-robot sensor-based cooperation for nanomedicine," *Int'l J. Nonlinear Science Numerical Simulation*, Vol. 3, No.4, pp.743-746, August 2002, <http://www.nanorobotdesign.com>.
- [10] W. Chen and K. Lewis, "A Robust Design Approach for Achieving Flexibility in Multidisciplinary Design," *AIAA Journal*, 37(8), pp. 982-990, 1999.
- [11] H. A. Downing and R. L. Jeanne, "Nest construction by the paperwasp, *Plistes*: a test of stigmergy theory," *Animal Behavior*, 36, pp. 1729-1739, 1988.
- [12] K. E. Drexler, R. A. Freitas Jr., J. S. Hall, N. Jacobstein, T. McKendree, R. Merkle, C. Peterson, "A Debate about Assemblers," Institute for Molecular Manufacturing, 2001, <http://www.imm.org/SciAmDebate2/whitesides.html>.
- [13] K. E. Drexler, "Nanosystems: molecular machinery, manufacturing, and computation", John Wiley & Sons, 1992.
- [14] G. Fishbine, "The Investor's Guide to Nanotechnology & Micromachines", John Wiley & Sons, 2001.
- [15] R. A. Freitas Jr., "Progress in Nanomedicine and Medical Nanorobotics," in Michael Rieth, Wolfram Schommers, eds., *Handbook of Theoretical and Computational Nanotechnology*, American Scientific Publishers, Stevenson Ranch, CA, 2005. In press.
- [16] R. A. Freitas Jr., "Current Status of Nanomedicine and Medical Nanorobotics," (Invited Survey) - *J. Comput. Theor. Nanosci.* 2(2005). In press.
- [17] R. A. Freitas Jr., R. C. Merkle, "Kinematic Self-Replicating Machines", Landes Bioscience, Georgetown, TX, 2004. <http://www.MolecularAssembler.com/KSRM.htm>.
- [18] R. A. Freitas Jr., "Nanomedicine", Vol. IIA: Biocompatibility, Landes Bioscience, 2003, <http://www.nanomedicine.com>.
- [19] R. A. Freitas Jr. and C. J. Phoenix, "Vasculoid: A personal Nanomedical Appliance to Replace Human Blood," *J. Evol. Technol.*, Vol. 11, 2002, <http://www.jetpress.org/volume11/vasculoid.html>.
- [20] R. A. Freitas Jr., "Nanomedicine", Vol. I: Basic Capabilities, Landes Bioscience, 1999, <http://www.nanomedicine.com>.
- [21] 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.
- [22] L. Geppert, "The Amazing Vanishing Transistor Act," Cover story, *IEEE Spectrum Magazine*, pp. 28-33, October 2002.
- [23] R. Grzeszczuk, D. Terzopoulos, G. Hinton, "NeuroAnimator: Fast neural network emulation and control of physics-based models," In M. Cohen, ed., *Proc. of ACM SIGGRAPH 98 Conf.*, pp. 142-148, 1998.

- [24] M. Guthold, "Controlled Manipulation of Molecular Samples with the Nano-Manipulator," *IEEE/ASME Transactions on Mechatronics*, Vol. 5, No.2, pp. 189-198, 2000.
- [25] M. T. Hagan, H. B. Demuth, and O. D. Jesús, "An introduction to the use of neural networks in control systems," *International Journal of Robust and Nonlinear Control*, John Wiley & Sons, Vol. 12, no. 11, pp. 959-985, September 2002.
- [26] M. Hagiya, "From Molecular Computing to Molecular Programming," *Proc. 6th DIMACS Workshop on DNA Based Computers*, pp. 198-204, Leiden, Netherlands, 2000.
- [27] K. Hamad-Schifferli, J. J. Schwartz, A. T. Santos, S. Zhang, J. M. Jacobson, "Remote electronic control of DNA hybridization through inductive coupling to an attached metal nanocrystal antenna," *Nature* 415 (10 January 2002), pp. 152-156; <http://www.media.mit.edu/molecular/HamadNature.pdf>.
- [28] S. Haykin, "Neural Networks A Comprehensive Foundation", 2nd edition, Prentice Hall, New Jersey, USA, 1999.
- [29] A. Hellems, "German Team Creates New Type of Transistor-Like Device," News Analysis, *IEEE Spectrum Magazine*, pp. 20-21, January 2003.
- [30] E. Katz, A. Riklin, V. Heleg-Shabtai, I. Willner and A. F. Bückmann, "Glucose Oxidase Electrodes via Reconstitution of the Apo-Enzyme: Tailoring of Novel Glucose Biosensors", *Anal. Chim. Acta.*, 385, pp. 45-58, 1999.
- [31] M. Khatib, B. Bouilly, T. Simeon, and R. Chatila, "Indoor Navigation with Uncertainty using Sensor Based Motions," *Proc. 1997 IEEE Int'l Conf. on Robotics and Automation*, pp. 3379-3384, Albuquerque, New Mexico, USA, 1997.
- [32] J.-W. Kim, A. Malshe, S. Tung, "Bio-inspired MEMS: A novel microfluidics system actuated by biological cell motors", 2003 Institute of Biological Engineering (IBE) Annual Meeting, Athens, GA, 2003.
- [33] C. R. Kube and H. Zhang, "Task Modelling in Collective Robotics," *Autonomous Robots*, 4(1), pp. 53-72, 1997.
- [34] M. N. V. R. Kumar, "Nano and Microparticles as Controlled Drug Delivery Devices," *J. Pharmacy Pharmaceutical Science*, 3(2), pp. 234-258, 2000.
- [35] J. Lehoczky, L. Sha, and Y. Ding, "The Rate Monotonic Scheduling Algorithm," IEEE Computer Society Press, pp. 166-171, Santa Monica, California, USA, December 1989.
- [36] M. A. Lewis and G. A. Bekey, "The Behavioral Self-Organization of Nanorobots Using Local Rules", In Proc. of IEEE Int'l Conf. on Intelligent Robots and Systems, Raleigh, NC, 1992.
- [37] K. Lyons, Y. Wang, "An Open Architecture for Virtual Reality in Nano-scale Manipulation, Measurement and Manufacturing (M3)," *8th Foresight Conference on Molecular Nanotechnology*, Bethesda MD, USA, November 2000.
- [38] J. H. Makaliwe and A. A. G. Requicha, "Automatic planning of nanoparticle assembly tasks," *Proc. IEEE Int'l Symp. on Assembly and Task Planning*, pp. 288-293, Fukuoka, Japan, 2001.
- [39] S. Martel, P. Madden, L. Sosnowski, I. Hunter, and S. Lafontaine, "NanoWalker: a fully autonomous highly integrated miniature robot for nano-scale measurements," *Proc. of the European Optical Society and SPIE Int'l Symposium on EnviroSense, Microsystems Metrology and Inspection*, Vol. 3825, pp. 64-76, Munich, Germany, 1999.
- [40] M.R. McDevitt, D. Ma, L.T. Lai, J. Simon, P. Borchardt, R.K. Frank, K.Wu, V. Pellegrini, M.J. Curcio, M. Miederer, N.H. Bander, D.A. Scheinberg, "Tumor Therapy with Targeted Atomic Nanogenerators," *Science* 294, 16 November 2001, pp. 1537-1540, Nov. 2001. <http://www.sciencemag.org/cgi/content/full/294/5546/1537>.
- [41] J. S. MacNeil, "Nanorobot Pioneer Reveal Status of Simulator, Stem Cell Work," *NanoBiotech News*, Vol. 2, n. 36, pp. 4-5, September 2004, <http://www.nanorobotdesign.com/papers/nanorobotNanoBiotechNews.pdf>.
- [42] A. J. Menezes, V. J. Kapoor, V. K. Goel, B. D. Cameron and J.-Y. Lu, "Within a Nanometer of your Life," *Mechanical Engineering Magazine*, Vol. 123, n. 8, pp. 54-58, August 2001.
- [43] R. C. Merkle, "Nanotechnology and Medicine," *Advances in AntiAging Medicine*, Vol. 1, pp. 277-286, Mary Ann Liebert Press, 1996.
- [44] MIT Registry of Standard Biological Parts, formerly *BioBricks Alpha Data Book*, <http://parts.syntheticbiology.org>.
- [45] A. Mok and D. Chen, "A Multiframed Model for Real-Time Tasks," *IEEE Transactions on Software Engineering*, vol. 23, no. 10, pp. 635-645, 1997.
- [46] N. Mokhoff, "Education Overhaul Urged for Nanotech Revolution", *EE Times*, Feb. 2003, <http://www.theworkcircuit.com/news/OEG20030206S0026>.
- [47] S. K. Moore, "Just One Word - Plastics," Special R&D Report, *Organic Electronics, IEEE Spectrum Magazine*, pp.55-59, September 2002.
- [48] National Science Foundation, <http://www.eng.nsf.gov/sbir>.
- [49] J. Peng, R. A. Freitas Jr., R. C. Merkle, "Theoretical Analysis of Diamond Mechano-synthesis. Part I. Stability of C2 Mediated Growth of Nanocrystalline Diamond C(110) Surface," *J. Comput. Theor. Nanosci.* 1(March 2004), pp. 62-70.
- [50] M. Ramia, D. L. Tullock, N. P. Thien, "The role of hydrodynamic interaction in the locomotion of microorganisms," *Biophys. J.* 65:755-778, 1993.
- [51] L. Reppesgaard, "Nanobiotechnology: Die Feinmechaniker der Zukunft nutzen Biomaterial als Werkstoff," *Computer Zeitung*, no. 36, pp. 22, 2 September 2002.
- [52] A. A. G. Requicha, R. Resch, N. Montoya, B. E. Koel, A. Madhukar, and P. Will, "Towards hierarchical nanoassembly," *IEEE/RJSJ Int'l Conf. on Intelligent Robots & Systems*, Kyongju, Korea, 1999.
- [53] T. D. Seely, S. Camazine, J. Sneyd, "Collective Decision-making in honey bees: how colonies choose among nectar sources," *Behavioral Ecology and Sociobiology*, 28:277-290, 1991.
- [54] M. Sitti, K. Hashimoto, "Teleoperated Nano Scale Object Manipulation," in *Recent Advances on Mechatronics*, pp. 172-178, Springer Verlag Pub., Ed. O. Kaynak, 1999.
- [55] E. Smalley, "Tools design DNA-nanotube logic," *Technology Research News*, Vol. 139, n.2, pp. 26-28, September 2004.
- [56] R. Stracke, K. J. Böhm, J. Burgold, H. Schacht, and E. Unger, "Physical and technical parameters determining the functioning of a kinesin-based cell-free motor system," *Nanotechnology* 11, pp. 52-56, UK, 2000.
- [57] J. Sun, M. Gao, and J. Feldmann, "Electric Field Directed Layer-by-Layer Assembly of Highly Fluorescent CdTe Nanoparticles," *Journal of Nanoscience and Nanotechnology*, Vol.1, No.2, pp. 21-27, American Scientific Publishers, 2001.
- [58] T. Toth-Fejel, "Agents, assemblers, and ANTS: scheduling assembly with market and biological software mechanisms," *Nanotechnology* 11, pp. 133-137, 2000.
- [59] S. Voss, "Meta-Heuristics: Advances and Trends in Local Search Paradigms for Optimization," *Meta-Heuristics International Conference*, Kluwer Academic Pub, 1998.
- [60] L. L. Whitcomb, "Underwater Robotics: out of the research laboratory and into the Field," *IEEE Int'l Conf. on Robotics and Automation*, pp. 85-90, San Francisco, CA, USA, 2000.
- [61] C. Wurl, 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.
- [62] Y. Yokobayashi, R. Weiss, F.H. Arnold, "Directed evolution of a genetic circuit," *Proc. Natl. Acad. Sci.* 99, 24 December 2002, pp. 16587-16591, USA, Dec. 2002.



Adriano Cavalcanti (M'02) received the B.S.C.S. degree from Sao Paulo State University, Brazil, in 1996 and the M.S.E.E. degree focusing on control automation from Unicamp, Brazil, in 1999. He is currently working toward the Ph.D. degree in electrical and computer engineering in the Department of Optics and Microwave, University of Campinas, Campinas, Brazil. He was with the DAAD PhD Sandwiche program and a Visiting Fellow of the Technical Staff at Fraunhofer Institute and TU Darmstadt Computer Science Department in Germany from 2001-2003, through the Unicamp-TUD exchange program. He is Chairman and CEO of the Center for Automation in Nanobiotech (CAN), Sao Paulo.



Robert A. Freitas Jr. received a BS in Physics and a BS in Psychology from Harvey Mudd College, Claremont, California, in 1974, and a JD from the University of Santa Clara in 1979. He is Senior Research Fellow at the Institute for Molecular Manufacturing in Palo Alto, CA USA, and the author of *Nanomedicine* (Landes Bioscience, 1999 (Vol. I) and 2003 (Vol. IIA)), the first technical book on the medical applications of molecular nanotechnology and medical nanorobotics, and of *Kinematic Self-Replicating Machines* (Landes Bioscience, 2004), the first systematic

survey of the field ever written.