New York Nano-Bio-Molecular Information Technology (NYNBIT) Incubator

Digendra K Das
Principal Investigator & Professor
Department of Mechanical & Industrial Engineering Technology
SUNY Institute of Technology
P.O. Box 3050
Utica, NY 13504-3050

Final Scientific/Technical Report
US Department of Energy (DOE)
Grant No. DE-FG02-06ER64281

Recipient: The Research Foundation of SUNY
35 State St.
Albany, NY 12207

December, 2008

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Executive Summary

This Scientific / Technical report presents the outcome of an effort made by a consortium of six universities in the State of New York to develop a Center for Advanced Technology (CAT) in the emerging field of Nano Bio- Molecular Information Technology.

The collaborating Institutions are:

1. SUNY-Binghamton
2. SUNY- Geneseo
3. SUNY-Oneonta
4. SUNYIT
5. New York University (NYU)
6. Rochester Institute of Technology (RIT)

The activities of the NYNBIT incubator project are as follows:

1. Organization of the NYNBIT Incubator
2. Collaborative Research Projects
3. Development of course work
4. High School Educational Program
5. Commercial start-up program.

The project has been successfully completed in two years (September2006 – September 2008) and some of the outcomes of the project are shown below:

1 Publications: 10
Journal: 4
Conference: 6
Papers in preparation for publication shortly: 7
2. No of faculty participated: 15
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4. No of High school students participated: 20 (Representing 8 Central NY school districts).
5. No of Math, Science & Technology High school teachers participated : 10
6. No of Labs developed: 2
7. No of B.S. degree level courses developed: 7
8. No of Central NY industries identified for future collaborative projects in the field of Nano Technology: 9

New York Nano-Bio-Molecular Information Technology (NYNBIT) Incubator

1.0 Introduction

Six New York Universities met in the Fall of 2004 at a workshop held at the SUNY Institute of Technology (SUNYIT), Utica, NY, and explored the possibility of establishing a Center for Advanced Technology (CAT) in the emerging field of Nano and Bio Information Technology. All the participants agreed that in order to achieve this goal an initial organization would have to be formed for a period of two years, which would be located at SUNYIT, Utica, NY, and named "New York Nano-Bio-Molecular Information Technology (NYNBIT) Incubator".

The mission and purpose of this organization is to set up a plan to establish a Center for Advanced Technology (CAT) focused on fostering an environment of research, development and education and creating a new industrial base in New York State in this unique technology area.

The collaborating Institutions are:

1. SUNY-Binghamton
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1. Organization of the NYNBIT Incubator
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5. Commercial start-up program.

These are briefly described in the following sections:

2.0 Organization of the NYNBIT Incubator

The participating institutions selected a Director for the NYNBIT Incubator, who was given the charge of setting up the organization and exploring possible sources of funding. This involved the following tasks leading to the current structure of the organization:

a) Select a proper location for the office of the NYNBIT incubator at SUNYIT.
b) Procure office furniture and computers, printers and other peripherals.
c) Set up the furniture and the computers and its peripherals in the office and establish the net work connections.
d) Identify and select the members for an Executive Advisory Board. Initially the board was constituted with four members selected from the federal government, local industries and the small business development center (SBDC). One of the members acted as the chairman of the board. The board advised the director of the NYNBIT incubator in all aspects of the project.
e) A Research and Development Advisory Committee was formed with representative from all the participating Institutions. The committee advised the director in various aspects of the research and development projects.
f) An Industrial Liaison officer was hired to identify possible commercial partners for the incubator and also to help the Director in the various aspects of the daily operations of the NYNBIT office.
g) An organizational consultant was hired to advise the Director in various aspects of the organization.
h) A work study student assistant was hired to assist in the daily operations of the NYNBIT office.

3.0 Collaborative Research Projects

One of the major objectives of the NYNBIT Incubator has been to develop collaborative research projects amongst the participating institutions and explore the possibility of commercial start- ups. All six institutions have participated in this collaboration; each project has been led by a principal investigator from the respective campus and there has been active participation by other faculty members and graduate students. However, senior undergraduate students have also been strongly encouraged to participate in these research projects. The participating institutions and the projects are shown below:

a) SUNY-Binghamton, "New technologies to measure human cancer proteins"

b) SUNY- Geneseo, "Bio-molecular Computing Technologies: DNA Library Analysis"

c) SUNY- Oneonta, "Molecular Quantum-Dot Cellular Automata and Nano-wires: Nano-scale charge transfer characterization for information processing".

d) SUNYIT, Utica, "DasWPS: a Web-based P System Simulator with Query Facilities"

e) New York University, New York, "GRIN: Technology combining Genomics, Robotics, Informatics and Nanotechnology for Single Molecule Analysis."

f) New York University, New York, "Self-Assembled DNA Arrays and Devices for Diverse Structural Patterning."

g) Rochester Institute of Technology, Rochester, *Three-Dimensional Biomolecular Computing Architectures*

The research Projects are briefly described below:

a) SUNY-Binghamton.

Project Title: *New technologies to measure human cancer proteins*

Principle Investigator: Susannah Gal, PhD
Associate Professor
Department of Biological Sciences
Binghamton University

Human cancer arises from changes in the genes in a human cell. This results in changes to the protein components manifested as disease symptoms. Some of the more important changes are in DNA binding proteins that regulate the function of specific genes in the human genome. By developing assays to measure these DNA binding proteins we will be in a position to follow the course of cancer and to make diagnostic predictions based on these tests. Two new assays for DNA binding proteins will be used and developed in this project. One uses a protocol we developed for a human cancer protein produced in insect cells. We will expand its use to analysis of this important protein in human cells. The other assay uses gold nanoparticles and should be convenient and easy to use. This system has the potential to be used inside cells within a tissue. Both of these assays are much faster and easier to quantify than conventional DNA binding, so provide a necessary addition to the arsenal of diagnostic tests that could be used to analyze the status of a tumor.

The detailed out come of this Research Project is presented in Appendix A.

b) SUNY- Geneseo

Project Title: "Bio-molecular Computing Technologies: DNA Library Analysis"

Principal Investigator: Anthony J. Macula, Associate Professor,
Department of Mathematics, SUNY-Geneseo.

Co-Principal Investigator: Susannah Gal, SUNY-Binghamton.

DNA code sequences generated by the program SynDCode were used to construct a 5-site, 2-variable computational DNA library by parallel overlap self-assembly. From a Birthday Problem like analysis, this suggests that we likely have all 32 different molecules in our library mixture. We then developed new protocols using DNA hybridization to successfully identify single members of this library. We have also used this to analyze mixtures of clones from the library. This approach shows the experimental validation of the ability to distinguish different sequences generated from the SynDCode program. We are in the process of working out protocols to separate out specific library members.

The detailed out come of this Research Project is presented in Appendix B.

c) SUNY- Oneonta

Project title:

Molecular Quantum-Dot Cellular Automata and Nano-wires: Nano-scale charge transfer characterization for information processing

Principal Investigator: Dr. Monisha Kamala Mahanta
Associate Professor, Department of Physics & Astronomy,
SUNY College at Oneonta
Oneonta, NY 13820.

National Academy of the Sciences/NRC Senior Fellow (2004-2006).

The SUNY College at Oneonta collaborated in the New York Nano-Bio-molecular Information Technology (NYNBIT) Incubator project initiated by a group of New York universities, funded by the U.S. Department of Energy and administered by the SUNY Institute of Technology at Utica, NY., in the years 2006-2008, with a two-prong proposal for a feasibility study in the areas of Quantum Cellular Automata (QCA) and Nano-wire technology.

QCA and Nano-wires are two significant developments in the field of nano-science and technology with great potential for miniature technology based on a bottom-up process rather than the top-down process that governs our practical applications till now. The availability of a thin film lab equipped with a couple of thermal evaporation units and a spin-coater at SUNY-Oneonta led to the anticipation that a feasibility study into one or both of these areas of nano-science and technology would be worthwhile and might lead to some useful experimentation. Initially QCA was thought to have better prospects than the nano-wire research. However, the Situation seemed to develop more favorably toward the latter. Therefore the research progressed accordingly.

As written in the proposal, the QCA effort aimed at reaching the molecular level ultimately because of its temperature and size related benefits; however, due to the complexity of the process and lack of equipment, the first attempt had to be made at the relatively simple level of very thin coatings of pure metal with the idea of depositing islands which could be observed under an Atomic Force Microscope (AFM), the search itself for which was a part of the proposed feasibility research since Oneonta does not have the AFM. Several attempts to establish contact with the nano-technology center at Albay, NY were unsuccessful and that almost brought the QCA effort to a halt and SUNY-Oneonta's efforts were directed toward nano-wires. In that process, however, a window opened with the kind offer from the New York university collaborators of NYNBIT to allow the PI of this project to use their AFM to observe the thin films made at the SUNY-Oneonta lab. Some of those data are submitted in this report. The data on ordinary thin films of copper and gold on silicon substrates were found to be encouraging for both QCA and Nano-wires since a quantitative measurement of the hills and valleys of the coatings at the nano level was made possible for the project by the AFM. The next phase would be to design strategies for developing a variety of coatings of better quality and more suitable for QCA studies and in a variety of environments for nano-wire experimentation which would then lead to some characterization experiments. It is to be noted that with metal coatings, QCA work would need cryogenic temperatures (about 100K) which might be difficult; however molecular QCA might be more approachable due to its ambient temperature possibilities. The spin coater is anticipated to be useful for this purpose. It has not been possible, however, to test it in this feasibility study owing to the lack of a fume hood, much needed for health safety, in the thin film laboratory. Once the appropriate coatings are made for QCA work, experiments can be designed on Coulomb force effects, electrical conductivity, quantum tunneling effect to shed light on how to analyze the charge transfer phenomena for information processing at the nano-level.

The feasibility study on nano-wires has benefited from the availability of the AFM at NYU, a furnace in the Department of Chemistry and Bio-chemistry of SUNY-Oneonta and the prior experience of the PI in the field of Laguerre-Gaussian (LG) beams with orbital angular momentum built into it, acquired during her senior fellowship from the national Academy of the Sciences. An exhaustive survey of the literature has shed light on the experimental approach for nano-wire fabrication using materials such as ZnO, gold-coated silicon substrates etc. A successful fabrication of nano-wires at the Oneonta labs will be well served in observation and measurement by the AFM available at NYU, although an effort is currently under way to acquire an AFM at SUNY-Oneonta. The feasibility study has made it possible to envision the use of the LG beams for studying the mechanical and optical properties of nano-wires. The grant has enabled the enhancement of the lab at Oneonta for this purpose, thereby pushing the nano-

science and technology effort at SUNY-Oneonta beyond the limits proposed for the feasibility study.

Additional accomplishments on the NYNBIT grant:
1. A student was recruited to help with the literature review and the initial planning of the research. This in turn helped to use a part of the grant for educational and training purposes. The student presented his work titled "Synthesis of Nano-Structures: A Feasibility Study" at the Twenty-six Rochester Symposium for Physics Students, SPS Zone 2 Regional Meeting held at Rochester University on April 21, 2007.

2. The thin film lab at SUNY-Oneonta was used in the summer of 2007 to introduce the practical thin-film aspect of nano-technology to two summer camps of promising high school students hosted by SUNYIT, Utica, NY. The fabrication of thin films and the furnace to be used for nano-wire fabrication were demonstrated following a Power Point presentation of some of the fundamentals and applications of nano-wire technology.

3. CONMED Inc. has expressed interest in collaborating with SUNY-Oneonta in the nano-wire research. The focus of this research is likely to be on medical application of the nano-wire technology. The focus will however have to be narrowed further to areas with the greatest relevance. One possibility is the Optical Nerve system and the literature is being reviewed.

In conclusion, this feasibility study has been a successful venture on the part of SUNY College at Oneonta leading to future possibilities worth pursuing.

The detailed out come of this Research Project is presented in Appendix C.

d) SUNYIT, Utica

Project title:

DasWPS: A Web-based P System Simulator with Query Facilities

Principal Investigator:

Digendra K Das
Professor
Department of Mechanical & Industrial Engineering Technology
SUNY Institute of Technology
P.O. Box 3050

Being introduced to P systems by its creator, Prof. Georghe Paun, we have started to

become quite interested in this field, and in order to learn in an active manner since we

felt we detected a relative lack of easy, user friendly and complete P system software simulators we started developing our own P system simulator using CLIPS. As we found out this idea isn't at all new in the Membrane Computing community and there are several noteworthy implementations based on this approach and some based on other approaches as well. However, we persisted in our project and now we believe we can responsibly say that it has some novel and interesting features, some related to efficiency, some related to ease of use and generality, which hopefully warrant the simulator as a useful tool for the Membrane Computing community at large.

The functionality of the DasWPS simulator is available at three distinct levels:

CLIPS level

–this is where all our knowledge about the theoretical simulation of P systems is contained, the result being a library of CLIPS functions, (meta)rules and templates.

C level

–since CLIPS is easily embeddable in C as its name "C Language Integrated Production System" suggests, it is very easy to control the DasWPS simulator from a C program and we include such example programs to illustrate how this is to be done.

–this level will soon be strengthened by introducing a C library for modeling and simulating P systems based on the CLIPS library.

Web application level

–by this we are trying to offer a most user-friendly interface to the DasWPS simulator, and which we hope will become, after the addition of more solid debugging

and visualization features a true rapid P system development tool.

To describe the CLIPS level the core level of the simulator, we must first address the crucial issue how we implemented in a sequential context the famed "maximally parallel and nondeterministic execution" of P systems. To meet the maximally parallel execution requirement we relied on constraining our simulation cycle to these distinct steps:

•Maximally parallel execution

1) the React step here is where all the reaction rules that are activated are sequentially executed.

2) the Spawn step where all the new created objects created by rules inside their membranes are asserted as object facts they become visible for future React steps.

3) the Inject step where all the objects injected/ejected by rules in different membranes are asserted as objects facts.

4) the Divide step that handles possible membranes' divisions.

5) the Dissolve step that handles membranes' dissolving processes.

By constantly recording the state of the P system after the first three steps which can be viewed as a single item for abstraction and the executed reaction rules, we can get an execution trace.

• To address the nondeterministic execution requirement we used since the beginning CLIPS' random strategy. However, prof. Ciobanu's questioning of the validity of this choice made us look more closely at the random strategy and found it lacking in a great way it would always make the same choices for the same rules and facts configurations upon program entry. We suspected this is related to CLIPS' random

function and found that the random strategy indeed uses it by calling the random function we changed the choices for the random strategy commuting the random number generator into a distinct state.

The other important choices we had to make were related to data representation.

We chose to represent P system objects and membrane structure as CLIPS facts (with CLIPS' set fact duplication option set to on) and the reaction rules as CLIPS rules. This contrasts other implementations that have represented reaction rules as CLIPS facts, and while their choice might leave place for more general rules for execution (meta rules), we think we've managed to realize a sufficiently flexible framework and that we needed the efficiency boost given by representing reaction rules as CLIPS rules, thereby making direct use of the inference engine's pattern matching and rule activation capabilities. This choice was validated later by the ease of the definition of the "dissolve with rules" and "divide" operations, that implied a lot of moving around and copying of rules, which actually meant (re)building them dynamically.

The detailed out come of this Research Project is presented in Appendix D.

e) New York University, New York

Project title

"GRIN: Technology combining Genomics, Robotics, Informatics and Nanotechnology for Single Molecule Analysis."

Principal Investigator:

Bhubaneswar Mishra
Professor
Computer Science, Mathematics & Cell Biology
Courant Institute & School of Medicine
New York University (NYU), New York.

Emergence of nanoscale devices, biological applications requiring single cell/molecule monitoring, and information technology capable of handling massive amount of data in real-time are expected to revolutionize science and technology of the most immediate future. To contribute this Nano/Bio/Info consilience, we aimed in this NYNBIT project to integrate expertise from many different fields to create device geometry, mathematical models, model-based design rules and design rule checker, and fast and accurate real-time data analysis algorithms. In our project, we have created designs based on nano-cantilever, physically a rather simple device, but that can be engineered to accurately measure presence and concentration of mixture of large classes of biomolecules (nucleotides and proteins) either *in vitro* or *in vivo*. We have created a faithful mathematical model to understand how the geometry determines the bending of the cantilever as a function of the ambient concentration of the target molecules and the affinity of the probes to the target molecule. Surprisingly, the model has predicted that average bending and resonance frequencies of bending are sufficiently informative to deconvolve the measurements of target concentrations. In parallel, we have also concentrated in creating nano-cantilever based design for transcriptomic profiling

Key Accomplishments

- Briefly, we have made significant progress in many important directions in the area of biosensor design and modeling: This work was in collaboration with Drs. T.S. Anantharaman, J. Reed, A. Sundstrom, and also Mr. M. Kramer. We have created statistical Bayesian tools to interpret the data derived from the simulated system and identify the key parameters that determine the system performance. A computer science graduate student Mr. P. Franquin worked on improving the efficiency and accuracy of the resulting technology through simulation implemented in Simapthica.
- We have designed a nano-cantilever based measurement scheme for DNA profiling. This systems has been shown to be capable of detecting mRNA, expressed in very small copy number and do so accurately. We have recently also shown the capability of this system in directly charactering the secondary structure of RNA.
- We have published and submitted following papers in this area:
    - 1. “Single Molecule Transcription Profiling with AFM,” (J. Reed, B. Pittenger, B. Mishra, S. Magonov, J. Troke, M.A. Teitell, and J.K. Gimzewski), Nanotechnology, 18, 1-15, 2007.
    - 2. “Image Analysis of Single Molecule Transcription Profiles with AFM,” (S. Cirrone et al.), 2008.(To be published).
    - 3. “AFM observation of Branching in Single Transcript Molecules Derived from Human Cardiac Muscle ,” (J. Reed, C. Hsueh B. Mishra, and J. Gimzewski), Nanotechnology, 2008.

- There have been several oral presentations in colloquia, seminars and conference on these topics by Prof. Mishra. Mishra presented many of the ideas developed in this project in his invited talks at Broad Institute (Harvard and MIT), UCLA, ASU, Dupont, NIST, CMU-Pittsburgh Univ, Columbia, and TAMU.

Future tasks to be accomplished

Below are listed additional tasks to be accomplished if funding is available.

- Long Term Goals
  - Streamline "inverse" algorithm;
  - Increase complexity of peptide concentration models and determine if current model and algorithm are still workable and efficient;
  - Research Artificial Neural Network approaches and explore the connection;
  - Continue work on Bayesian algorithms; explore other more rigorous statistical non-heuristic methods;
  - Determine how much "ambient noise" affects the accuracy of the probes;
  - Experimentally validate a simple model.

The detailed out come of this Research Project is available in the Journal Publications 1 & 3 as shown above.

f) New York University, New York

Project Title

Self-Assembled DNA Arrays and Devices

for Diverse Structural Patterning

Principal Investigator

Nadrian C. Seeman, Professor
Department of Chemistry
New York University
New York, NY 10003
ned.seeman@nyu.edu
212-998-8395

The key goal of the project was to develop a system that was capable of capturing a variety of tiles, depending on the programming of DNA cassettes inserted into DNA origami. This goal has been achieved. We have found that we can capture tiles with different structural features in a DNA origami tile, depending on the programming of two cassettes that face each other. The most important aspect of that

work is that we have developed a correction procedure to ensure the fidelity of the captured tiles. This will be of great importance in the development of algorithmic assembly(Gu *et al).*

We were able to build a robust 3-state DNA nanomechanical device. This system adds a state to a previously developed robust 2-state DNA nanomechanical device. This will be of use in a variety of systems, including the development of molecular-based trinary logic. (Chakraborty *et al.*)

A third piece of work is the development of a nanoparticle-based system that assays the robustness of DNA motifs. We attach gold nanoparticles to the vertices of a variety of DNA motifs and demonstrate which ones are the most robust. In an era when the need for robust DNA motifs is increasing, this is a valuable procedure. (Zheng et al.).

Thus, we have achieve our goals for the NYNBIT project and we have accomplished considerably more, as well. Other manuscripts ultimately will result from this support, but they are at stages that are a little too early to include.

Publications

1. H. Gu, J. Chao, S. Xiao & N. C. Seeman, "Programmed Patterns produced by DNA Tile Capture" (To be published: being reviewed)
2. B. Chakraborty, R. Sha & N. C. Seeman, "A DNA- Based Nanomechanical Device with Three Robust States",Proc. Nat. Acad. Sci. (USA) 105, 17245 – 17249 (2008).
3. J. Zheng, P.S. Lukeman, W.B. Sherman, C. Michee, A.P. Alivisatos, P.E. Constantinou & N.C. Seeman "Metallic Nanoparticles used to estimate the Structural Integrity of DNA Motifs", Biophysical Journal 95, 3340-3348 (2008).

The detailed out come of this Research Project is available in the Journal Publications 2 & 3 as shown above.

g) Rochester Institute of Technology, Rochester, "Nanobiocomputing Architectures and Molecular Electronics."

Project title

Three-Dimensional Biomolecular Computing Architectures

Principal Investgator: Dr. Sergey Edward Lyshevski
Department of Electrical Engineering, Rochester Institute of Technology, Rochester, New York 14623-5603, USA
E-mail: Sergey.Lyshevski@mail.rit.edu Web: http://people.rit.edu/seleee

We initiated developments of an enabling CAD-supported design of high-performance molecular processing platforms (^{M}PPs) in three-dimensional (3D) space by applying a premise of molecular computing. These ^{M}PPs utilize novel 3D architectures and organizations. The proposed hardware is envisioned to be implemented by bio, organic or inorganic molecular aggregates. The device physics of multi-terminal molecular devices is based on *microscopic* electrochemomechanical transitions. Molecular hardware (lattices, assemblies, networks, circuits, etc.) for combinational logics and memories can be synthesized by aggregating neuronal hypercells ($^{\aleph}$hypercells). These $^{\aleph}$hypercells can be engineered using molecular devices (~1 nm) which exhibit specific phenomena and characteristics. We examine the feasibility of design and synthesis of complex molecular processing (computing) systems advancing theory of computing. At the system level, we developed and demonstrated efficient design methods which ensure massive parallel distributed computing and large-scale data manipulations. Proof-of-concept processing modules were designed and analyzed. We departed from von Neumann architectures by proposing a novel technology which utilizes a two-fold innovative solution: (1) Enabling CAD-supported design methods; (2) Advanced hardware formed by aggregated $^{\aleph}$hypercells. We initiated developments of a revolutionary paradigm which promises super-high-performance computing

The detailed out come of this Research Project is presented in Appendix E.

4.0 Development of course work

One of the important objectives of the NYNBIT has been the development of educational packages for the work force in the field of Nano-Bio-Information Technology. In the two years of the operation of the NYNBIT incubator, seven courses were developed at the baccalaureate (B.S.) level on various aspects of Nano-Bio-Information Technology. These courses will be used toward a concentration in Nano-Technology within the B.S. degree program in Mechanical Engineering Technology at SUNYIT. The courses will also be available, on-line, as electives for students in the collaborating institutions. The names of the courses are shown below:

i) Introduction to Nano-Science and Nano- Technology:	3 Cr.
ii) Introduction to Nano-Technology	3 Cr.
iii) Introduction to Carbon Nanotubes	3 Cr.
iv) Cell Biology	3 Cr.
v) Biomolecular Mathematics	3 Cr.
vi) Membrane Computing:	3 Cr.
vii) DNA Laboratory:	3 Cr.

Several faculty members from the participating institutions with five to twenty years of teaching and research experience in these fields were actively involved in the development of these under-graduate level courses.

Two labs were developed to support the courses mentioned above. These labs are located at the SUNY Oneonta Campus.

The names of the labs are:

1) Thin Film Lab
2) DNA Lab.

Another federal grant in the amount of a quarter of a million dollars was awarded to equip the DNA lab with the state of the art lab equipments.

5.0 High School Educational Program

A high school level educational package was developed based on the courses mentioned in the previous section. The intended audience for this package is high school students in the sophomore, junior and senior grades. All the faculty members involved in the development of college level courses, shown in the previous section, were actively involved in the development of this package.

The educational package was presented to a selected audience in two summer camps in the summer of 2007 at the SUNYIT campus. Field trips were organized for the participants to visit the Thin film lab and DNA lab at SUNY-Oneonta campus. A total of twenty high school students and ten high school Math, Science and Technology teachers attended the summer camps. The student's participation in the summer camps was free and the participating teachers were awarded appropriate stipends to attend the summer camps.

6.0 Commercial start-up program.

One of the major objective of the NYNBIT incubator project was to transfer the know how of this emerging technology to the interested local industries of the New York state. The activities to achieve this goal are indicated below:

a) An Industrial Liaison Officer (ILO) was hired and his responsibility was to take all the actions necessary to establish a link between the local industries and the NYNBIT incubator under the supervision of the director. The ILO was also responsible for helping the director in the daily operation of the incubator office.
b) A data base of the local industries (initially Mohawk Valley region) was created with the help of the Small Business Development Center (SBDC, currently located at the SUNYIT campus).
c) In the first two years of the operation of the incubator about nine local industries were identified for possible commercial collaboration with the incubator.
d) Currently plans and discussions are in progress to identify possible application projects and exploratory attempts are being made to identify sources of funds such as SBIR grants.

7.0 Plans for the future and concluding remarks.

The main objective of the NYNBIT incubator project was to establish a Center for Advanced Technology (CAT) in the emerging field of Nano & Bio Information Technology. The activities described in the previous sections were all focused on achieving that goal.
The project has been successfully completed in two years (September 2006 – September 2008) and some of the outcomes of the project are shown below:

1. Publications: 10
   Journal: 4
   Conference: 6
   Papers in preparation for publication shortly: 7
2. No of faculty participated: 15
3. No of graduate / undergraduate students participated: 10
4. No of High school students participated: 20 (Representing 8 Central NY school districts).
5. No of Math, Science & Technology High school teachers participated: 10
6. No of Labs developed: 2
7. No of B.S. degree level courses developed: 7
8. No of Central NY industries identified for future collaborative projects in the field of Nano Technology: 9

The State of York has recently approved the development of an Advanced Technology Center, including the necessary funds. This center will be located at the SUNYIT campus and the construction of the building is expected to start in the summer of 2009.

9.0 Acknowledgements

The Principal Investigator of the NYNBIT Incubator project would like to thank Dr. Marvin Stodolsky, DOE Project Officer and Ms. Stephanie Davis, DOE Award Administrator for their support and patience during the course of the project. He would also like to thank all the faculty, graduate / undergraduate students & administrative staff for their enthusiastic participation in the various aspects of the project.
Finally, he would like to thank the US Department of Energy (DOE) for providing the necessary fund for the successful completion of the NYNBIT Incubator project.

Appendices

Appendix A

Project Title: *New technologies to measure human cancer proteins*

Principle Investigator: Susannah Gal, PhD
Associate Professor
Department of Biological Sciences

Introduction

Human cancer arises from changes in the genes in a human cell. This results in changes to the protein components manifested as disease symptoms. Some of the more important changes are in DNA binding proteins that regulate the function of specific genes in the human genome. By developing assays to measure these DNA binding proteins we will be in a position to follow the course of cancer and to make diagnostic predictions based on these tests. Two new assays for DNA binding proteins will be used and developed in this project. One uses a protocol we developed for a human cancer protein produced in insect cells. We will expand its use to analysis of this important protein in human cells. The other assay uses gold nanoparticles and should be convenient and easy to use. This system has the potential to be used inside cells within a tissue. Both of these assays are much faster and easier to quantify than conventional DNA binding, so provide a necessary addition to the arsenal of diagnostic tests that could be used to analyze the status of a tumor.

Data summary of work

Task 1: ***Scintillation proximity assay (SPA) for DNA binding of human p53***

a. *Test DNA binding for human p53 in different cell lines*

We define the functional status of the p53 protein by its DNA binding ability as it is a transcription factor. There are many assays to analyze the DNA binding properties of a protein, but there are very few assays for DNA binding that are very rapid, can be quantitative and can measure a large number of samples at the same time. Recently our lab has developed a rapid assay that is quantitative, fast and sensitive with the help of scintillation proximity assay (SPA) beads. The p53 DNA binding protein is associated with SPA beads via specific antibodies and when radioactively labeled DNA binds to the p53, the energy from the radioactivity can be transferred to the scintillant in the beads and light is produced. We have used this SPA to measure DNA binding by human p53 expressed by insect cells and found it to be sensitive and quantitative (Gal et al. 2006; see Figure 1). In our hands, this assay is as sensitive as EMSA (Electrophoretic mobility shift assay) for the p53 expressed in insect cells, but the assay can be done much faster with the SPA approach, usually complete in 10 minutes. Also, it can be done in a microtiter plate allowing many samples to be analyzed easily at the same time, a potential benefit for a diagnostic screen. We have found that the counts from this assay increase with increasing p53 protein (Gal et al. 2006).

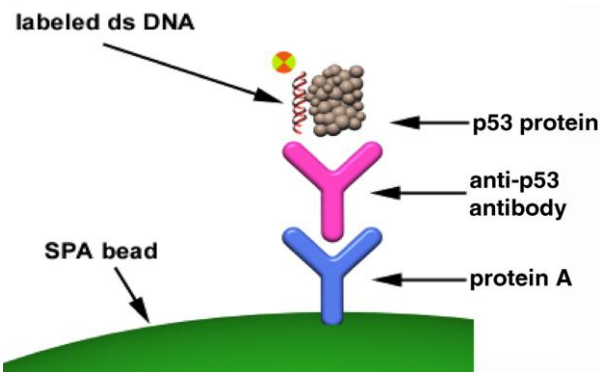

Figure 1. Scheme for measuring DNA binding using SPA beads. These beads contain embedded chemical scintillant and protein A on their surface that can bind a mouse monoclonal antibody to human p53 and then the p53 protein. If the p53 protein is able to bind ^{3}H-labeled DNA, the complex will bring that radioactivity close to the SPA beads and they will produce light. This light can be easily measured using a microtiter plate (96-wells) scintillation counter (such as the TopCount, Perkin Elmer) (Figure from Gal et al. 2006).

We have moved now to testing the DNA binding SPA assay with extracts from human cell lines. We have done some experiments with three thyroid cancer cell lines ARO, NPA and WRO, each having different mutations in the p53 gene (Fagin et al. 1993) as well as the MCF-7 breast cancer cell line having wild-type p53 (Ma et al. 2000). Nuclear extracts were prepared from these cell lines using a standard protocol. The nuclear extracts were incubated with the ^{3}H labeled DNA, anti-p53 antibodies and the SPA beads and the specific counts detected by the TopCount (Perkin Elmer). We found that there is a linear relationship between the amount of protein and the specific counts detected (Xie and Gal, data not shown). We have analyzed the initial rate of DNA binding detected as well as the amount of competition afforded by different DNA sequences and found that the p53 binds at different rates and has different apparent affinities to the DNA sequences (Figure 2 and Tables 1 and 2).

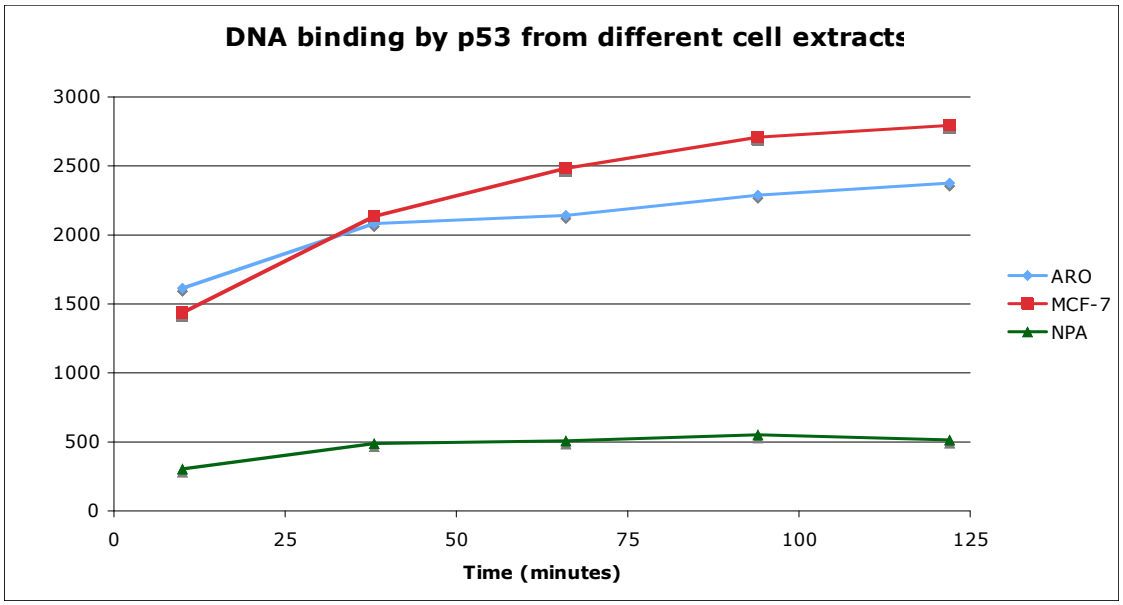

Figure 2. Differential rate of DNA binding by the p53 in different cell extracts.
SPA DNA binding was measured with 0.5pmole ^{3}H-labeled cyclin G DNA fragment (125Ci/mmole) using ARO (465pg p53, 68ug total protein), MCF-7 H_2O_2 treated (39pg p53, 74ug total protein) and NPA (30pg p53, 71ug total protein) nuclear cell extracts in binding buffer (20mM Hepes, pH7.5, 1mM EDTA, 1mM DTT, 10mM $(NH_4)_2SO_4$, 30mM KCl and 0.2% Tween-20) with 100ng anti-p53 monoclonal antibody (pAb421, Oncogene Research Products), 1mg non-specific DNA (polydAdT) in 20µl as described in [4].

Specific radioactivity bound to the SPA bead was measured using a TopCount Microplate Counter

Table 1. Competition for DNA binding by various sequences with human cell extracts

	Cell Extracts (% binding compared to no competitor)		
Competitor DNA sequence	MCF-7	ARO	NPA
Wild-type cyclin G	25.6%	23.9%	94.7%
Mutant cyclin G	31.0	124	108
p21	19.9	28.3	92.5
Mdm2	29.1	41.2	100

Counts taken after 122 minutes. Without competitor set at 100% [For MCF-7 2790 cpm, ARO 2380cpm, and NPA 514cpm] Competitor was added at 20X labeled DNA

(Packard Biosciences, Meriden, CT) reading the wells every 30 minutes.

The DNA binding SPA helps to functionally quantify one aspect of the p53 protein in extracts. As an alternative to this assay, we have developed an approach that uses biotinylated DNA and streptavidin magnetic beads to isolate p53 via sequence specific DNA binding (See Figure 3 below). We propose to use this purification scheme to isolate proteins that interact with DNA bound p53 from human cell extracts. Binding reactions with extracts from four different cell lines using three different DNA sequences were performed. The bound and the unbound fractions were separated on SDS PAGE and

Table 2. Differential binding activity of p53 in cell extracts

Cell extract source plus mutation status (amino acid wt #codon new amino acid)	Specific binding counts (CPM)	Total p53 amount (pg)	Counts/pg p53
MCF-7 wild-type p53 (H_2O_2 treated)	2790+/-680	39	71
ARO mutant Arg273His	2380+/-1550	465	5.1
NPA mutant Gly266Glu	514+/-16	30	17

Counts taken after 122 minutes.

then immunoblotted to detect the p53 protein (Figure 4)

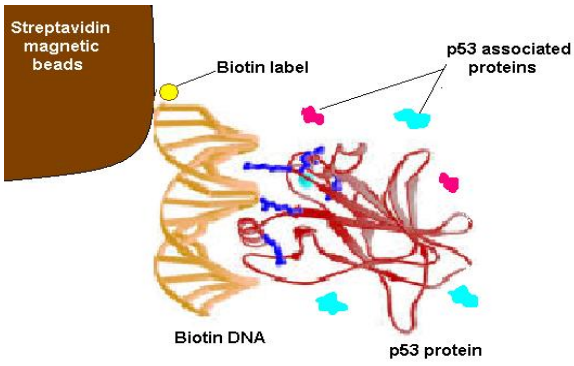

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Figure 3. Scheme for using streptavidin magnetic beads to isolate p53 bound to DNA.
The p53 protein then binds to the DNA since it has a recognition site for the protein. Proteins associated with DNA bound-p53 are expected to also be part of this complex. In a few seconds, the complex can be separated from the rest of the solution using a small magnet. This can be visually monitored because the beads are brown. After separation, the surrounding solution can be removed to separate material not bound from that bound to the beads. The DNA along with the p53 protein can be separated from the beads by boiling the solution and quickly removing the material not associated with the brown precipitate. The separated DNA can be analyzed by dot blot and the protein by western blot. The objects are not necessarily drawn to scale

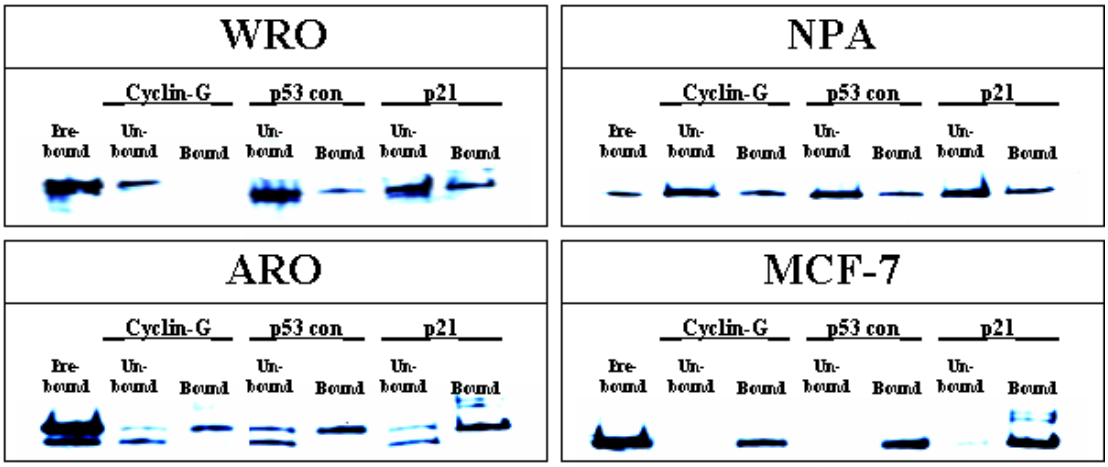


Figure 4. Western blot for p53 protein from 4 different cell lines isolated using 3 different DNA sequences

One hundred twenty (120) pmoles of biotinylated DNA (Integrated DNA) with a p53 recognition site (cyclin G, p53 consensus (con) and p21sequences) was incubated at room temperature with either p53 from ARO, WRO, NPA (3 different thyroid cancer cell lines) or an extract from MCF-7 cells treated with H_2O_2 (Active Motif, Carlsbad, CA) (each approximately 100pg of p53 protein) in a total volume of 20ul. This was added to 400ug washed streptavidin beads for 1 hour at room temperature. The magnetic beads were separated using the Magnetic Particle Separator and the supernate was removed (unbound). The beads were then washed and then boiled in 20ul H_2O for 5 minutes. The released material was then removed (bound). The samples representing prebound, unbound and bound (14ul of each) boiled in Laemmli buffer and then loaded on a 10% polyacrylamide Tris-HCL gel (Biorad, Hercules, CA). The proteins were separated in the gel then transferred onto PVDF membrane (Millipore, Billerica, MA). The membrane was incubated overnight using the blocking solution and then in primary antibody to p53 (Ab-12, DO-7 (Calbiochem, San Diego, CA), 1:1000 dilution) for 2 hr at room temperature. The membrane was washed three times and then incubated in blocking solution containing anti mouse IgG, HRP linked (1:1000 dilution; Cell Signaling, Danvers, MA). The membrane was then washed three times and developed using a chemiluminescent substrate [SuperSignal West Pico Chemiluminiscent Substrate, Pierce]. (Chandrachud and Gal, manuscript in preparation)

sequence. The p53 from the NPA cells binds equally well to all sequences (about 20% binding of p53 is seen in the bound sample). The p53 from ARO cells binds to the p21 sequence better than the other sequences. The p53 from the MCF-7 cells treated with H_2O_2 interacts with all of the sequences equally well (about 90% binding of p53 is seen in the bound sample). The information obtained from this assay will help corroborate the SPA results with the different cell lines. We also expect that this approach will allow us to detect different proteins attached to the p53 bound to DNA and have preliminary results to support this hypothesis (Chandrachud and Gal, data not shown).

b. *Measure total levels of p53 and create ratio data*

Using our system for measuring total protein levels of p53, we have developed a method to measure the level of this protein in the same human cell extracts as those used for DNA binding and create ratio data for p53 DNA binding and p53 total protein. In this case, the p53 protein is bound to the SPA beads using one anti-p53 monoclonal antibody, then the p53 bound is detected using a radioactive second antibody. Due to product availability, we have chosen to use a goat polyclonal anti-p53 antibody linked with biotin and ^{35}S-labeled streptavidin (GE Healthcare) that binds to the biotin moiety. This sandwich reaction allows the specific detection of the p53 protein in a manner similar to the DNA binding SPA (Figure 5).

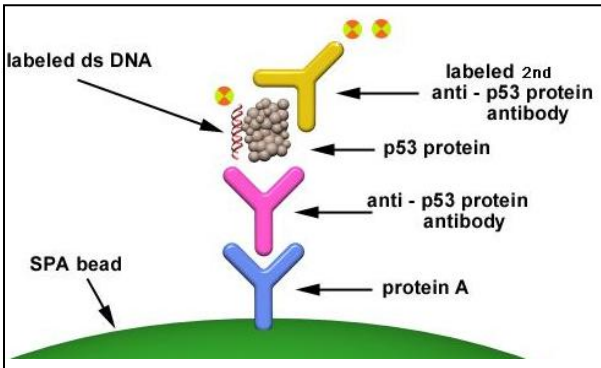


Figure 5. Scheme for measuring DNA binding and total amount of p53 protein using SPA beads. Addition of a radioactive 2nd anti-p53 antibody (or a biotinylated anti-p53 and a radiolabeled steptavidin) to the DNA bound reactions as in Figure 1 should yield additional counts due to the radiolabeled antibody binding. It has been found this signal is dependent on the amount of p53 present (Xie, Oberlander and Gal, unpublished results).

Applying this total p53 SPA to human cell extracts.

We have used this assay to measure the amount of p53 protein in human cell extracts and found the light signal dependent on the amount of the p53 protein present. Initially we measured the p53 amount in an ARO nuclear cell extract using an ELISA, then applied variable amounts of the extract to a reaction configured as in Figure 5 and measured the light counts detected (Figure 6) (Xie, Oberlander and Gal, unpublished data). The amount of specific counts was linearly dependent on the amount of p53 protein and could be used to determine how much p53 was in a particular sample. At present, our assay can reproducibly detect between 100 and 1000 pg of p53 from the ARO cell extract in up to 20ul sample. This is about 200-fold less sensitive than the ELISA we use in the laboratory (from Calbiochem). Part of this sensitivity is dependent on the different antibodies we are using as well as the amounts and timing of addition of our reagents. Other antibodies and conditions can be tested to see if more sensitivity can be obtained with this total p53 SPA. Although, the sensitivity of our total p53 SPA is lower than that detected by commercially available ELISAs, this will not likely be a problem in a dual assay set–up since the minimum amount of wild-type p53 detected in the DNA binding assay is 0.5ng (500pg) p53 (Gal et al. 2006). This amount of p53 is in the same range as the amount of p53 protein detected in our total p53 SPA (Figure 6). This assay takes 2-4 hours to reach equilibrium, significantly longer than that observed with the DNA binding assay (Gal et al. 2006). This time may in part be due to antibody-antigen interactions using the present antibodies. Despite this, the amount of researcher time needed to perform an ELISA is significantly more than for our total p53 SPA where at present all of the reagents are being added together within a few minutes. Also, we feel this method for measuring p53 protein quantitatively has the potential to be done at the same time as our DNA binding assay.

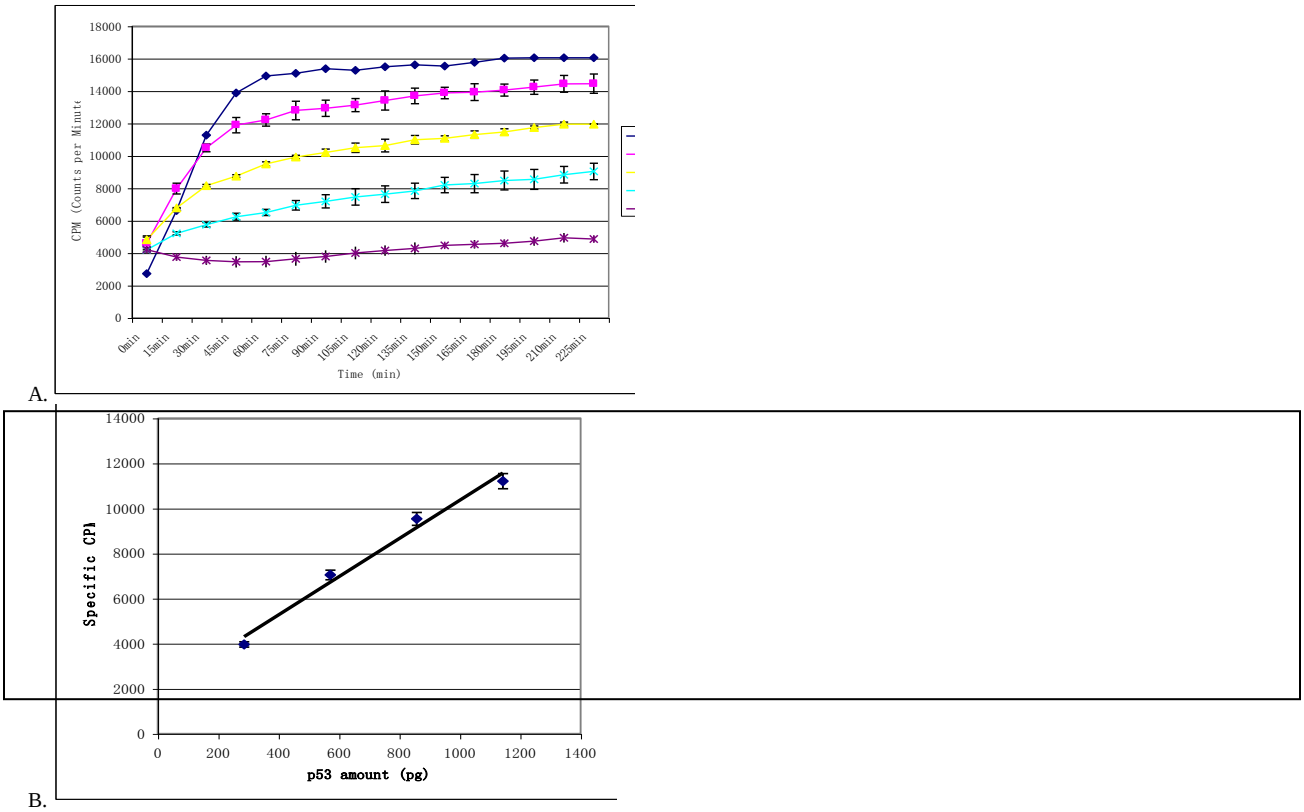


Figure 6: The total p53 SPA using different amounts of ARO cell extract
A. Samples contained 0pg-1143pg p53 from ARO cell extracts (based on the ELISA), 200ng mouse monoclonal anti-p53 antibody, 25ng biotinylated polyclonal anti-p53 antibody, 0.5pmole (0.1uCi) ^{35}S-streptavidin and 1mg SPA beads. Each of the conditions was duplicated and the error bars show the variation between the duplicates. This is a representative experiment of three performed. B. Scatter plot of p53 amount vs. specific counts. The equation for this line is $y=8.4763x + 1879.5$ ($R^2=0.9833$). The counts used in this plot are the average of the counts detected from 195 to 225 minutes after addition of the SPA beads. This is when the assay seems to reach equilibrium.

Application of the total SPA to other cells

We have used the total p53 SPA to develop a standard curve to determine the amount of p53 in other cell extracts. For this, we used one ARO nuclear cell extract to create a standard curve (like in Figure 6 above), then, the counts obtained with another ARO nuclear cell extract as well as an extract from three different cancer cell lines. NPA thyroid cancer cells are heterozygous for a Gly to Glu mutation at amino acid position 266, WRO thyroid cancer cells are homozygous for a proline to leucine substitution at amino acid position 223 (Fagin et al. 1993), while peroxide-treated MCF-7 breast cancer cells have wild-type p53 (Ma et al. 2000). We have found the detection of the p53 proteins by this total p53 SPA to be highly consistent with the level seen in western blots (Oberlander, Xie, Chandrachud, and Gal, manuscript in preparation).

Task 2: ***Nanoparticle assay for p53 DNA binding (done in collaboration with Dr. CJ Zhong)***

a. *Prepare nanoparticle sensors of DNA binding*

Attachment of gold nanoparticles to DNA sequences:

The techniques for studying DNA-protein interactions are generally based on detection techniques that involve radioactive, fluorescent, or chemiluminescent probes. Here we are trying to develop a new technique to monitor the DNA-protein interactions using gold nanoparticles. The detection of DNA binding with this assay is based on the distance dependent optical properties of aggregated gold nanoparticles when they are linked to a thiol modified DNA (Rosi and Mirkin 2005; Storhoff *et al.* 1998). When gold nanoparticles are assembled into a lattice using double-stranded DNA as linker, there is a detectable color change due to changes in the inter-particle resonance. This property of nanoparticles has a high sensitivity and hence is capable of detecting complementary DNA strands in very small amounts (10 fmole) (Rosi and Mirkin 2005). Disassembly of this lattice using restriction enzymes that cut the DNA linker between the gold nanoparticles changes the color of the solution from purple to red (Figure 7) (Kanaras et al. 2007 and references therein). Our hypothesis is that if the lattice connecting the nanoparticles contains a sequence recognized by a DNA binding protein, the binding of that protein to the DNA in the lattice will disrupt the resonance between the nanoparticles and also result in a color change (Figure 7). This hypothesis is something we are in the process of testing.

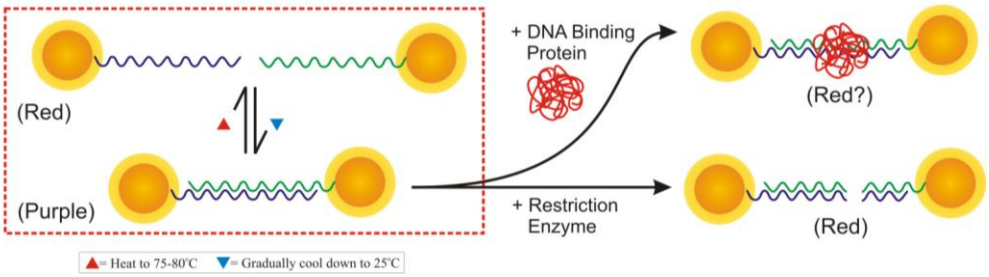


Figure 7. Scheme for detecting DNA binding and restriction enzyme cutting using DNA linked gold nanoparticles.

Nanoparticles were linked to the *cyclin G* DNA sequence recognized by the p53 protein that contains sites for recognition by the restriction enzymes SmaI and MspI. We followed the procedure for attachment of the nanoparticles to the DNA given by Storhoff and colleagues (1998). The top and the bottom strands of the *cyclin G* DNA sequence are attached to the nanoparticles separately. These strands were then assembled to make a double-stranded DNA, by heating a solution containing nanoparticles with the same concentration of the two single stranded DNA sequences and then gradually cooling the solution (Zanchet et al. 2001). So far we have tried to attach a 36bp *cyclin G* DNA sequence to gold nanoparticles. We observed a change in the color of the solution of the nanoparticles when the top strand was attached (data not shown). However we did not see a color change when the bottom strand was attached and we suspect that there was some problem while processing the DNA to attach to the nanoparticles. We then combined those two types of nanoparticles, one having the top strand attached, the other with the bottom strand. We then heated the mixture and allowed it to cool slowly

monitoring the changes in the absorbance pattern (Figure 8). We found a shift in the surface plasmon resonance bands indicative of the formation of a lattice due to the hybridization of the top and bottom strands as in the scheme in Figure 7.

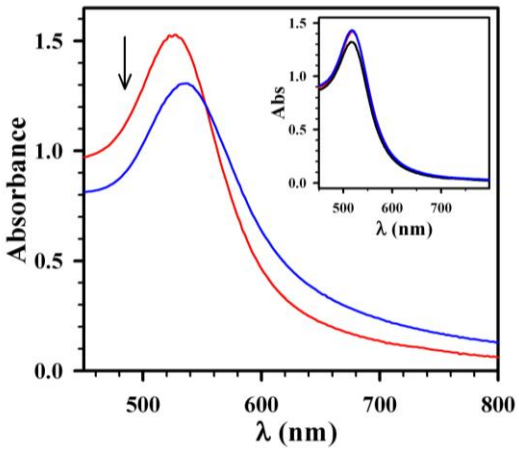


Figure 8. Spectral evolution of the surface plasmon band showing the assembly of the DNA capped nanoparticles upon heating (90°C, red) and cooling (25°C, blue). The color change indicates the formation of a lattice as in the scheme in Figure 7. Insert: Control experiment of unmodified gold nanoparticles upon heating (90°C) and cooling down to room temperature. (Lim, Wang, Chandrachud, Gal and Zhong, manuscript in preparation)

We next wanted to confirm the formation of double-stranded DNA using restriction enzyme digestion and Southern blot detection of DNA strands. As indicated above, we have engineered the DNA linking the gold nanoparticles to have sites for two different restriction enzymes so that if the strands are indeed double stranded, they should be cleaved by the addition of the enzyme. We initially incubated the enzyme SmaI (about 40 units) with our assembled nanoparticles, then removed the DNA from the lattice using dithiothreitol so that it could be separated on a polyacrylamide gel and visualized using ethidium bromide. In this case, we did not see evidence of digestion by the enzyme although the enzyme could cut the DNA fragment when it was not attached to the nanoparticles (data not shown; Lim, Wang, Chandrachud, Gal and Zhong, manuscript in preparation). One possibility to explain the lack of digestion was that the DNA in the lattice was not double-stranded so we performed a Southern blot to detect the individual top and bottom strands using labeled probes specific to each. We did detect both strands in the DNA released from the nanoparticles indicating the likelihood that the DNA was in fact double-stranded in the assembled nanoparticle lattice (data not shown; Lim, Wang, Chandrachud, Gal and Zhong, manuscript in preparation).

We next tested the digestion of the linked DNA using a different restriction enzyme, MspI using more enzyme (230 units). Following different incubation times of the assembly with the enzyme, the DNA was removed from the lattice and separated on a polyacrylamide gel (Figure 9). In this case, we did detect a time-dependent digestion of the DNA strands released from the particles. The SmaI and MspI enzymes are believed to have a similar molecular size (Heidmann et al. 1989; Lin et al. 1989), so that would not be a likely reason why the former enzyme would be unable to cut the DNA in the nanoparticle lattice. The latter enzyme cuts most efficiently at 37°C while the other enzyme works only at 25°C. Warmer temperatures may in fact make a difference in the availability of the DNA between the nanoparticles making it easier for the MspI enzyme to reach it's target. But another likely explanation is that we used nearly 6 times more enzyme activity for the successful reaction with MspI than the unsuccessful digestion with SmaI. This may be enough of a difference to allow digestion of the interparticle DNA strands.

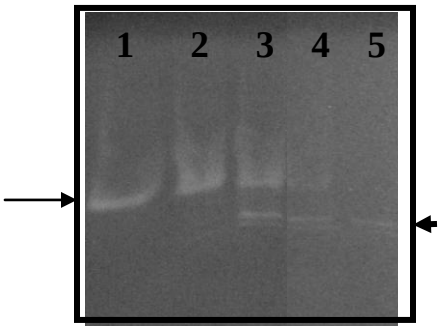


Figure 9. Gel electrophoresis of cut DNAs from assembled nanoparticles. Assembled DNA/Au (51ul) treated without (lane 1) and with 230 units of the MspI restriction enzyme for 0 minutes (lane 2), 1 hour (lane 3), 5 hours (lane 4) and 7 hours (lane 5) followed by addition of DTT and EDTA, and concentration via evaporation, was separated on a 15% TBE polyacrylamide gel then stained with ethidium bromide. The arrow and arrowhead mark the positions of uncut and cut DNAs, respectively. (Lim, Wang, Chandrachud, Gal and Zhong, manuscript in preparation)

References

Fagin J, Matsuo K, Karmakar A, Chen D, Tang S, and Koeffler H. 1993. High prevalence of mutations of the p53 gene in poorly differentiated human thyroid carcinomas. *J Clin Invest*. 91:179-184.

Gal S, Cook.J, and Howells L. 2006. Scintillation proximity assay for DNA binding by human p53. *BioTechniques*. 41:303-308.

Heidmann, S., Seifert, W., Kessler, C., Domdey, H. 1989. Cloning, characterization and heterologous expression of the SmaI restriction-modification system. *Nucleic Acids Res.* 17: 9783-9796.

Kanaras, AG, Wang, Z, Brust, M, Cosstick, R, and Bates, AD 2007. Enzymatic Disassembly of DNA-Gold nanostructures. *Small*. 3: 590-594.

Lin, P.M. Lee, C.H., Roberts, R.J. 1989. Cloning and characterization of the genes encoding the MspI restriction modification system. *Nucleic Acids Res.* 17: 3001-3010.

Ma Y, Yuan R, Meng Q, Goldberg ID, Rosen EM, and Fan S. 2000. p53-independent down-regulation of Mdm2 in human cancer cells treated with adriamycin. *Mol Cell Biology Res Comm.* 3:122-128.

Rosi N and Mirkin C. 2005. Nanostructures in biodiagnostics. *Chem Rev*. 105:1547-1562.

Storhoff J, Elghanian R, Mucic R, Mirkin C, and Letsinger R. 1998. One-Pot Colorimetric Differentiation of Polynucleotides with Single Base Imperfections Using Gold Nanoparticle Probes. *J. Am. Chem. Soc.* 120:1959-1964.

Zanchet D, Micheel C, Parak W, Gerion D, and Alivisatos A. 2001. Electrophoretic isolation of discrete Au Nanocrystal/DNA conjugates. *Nano Letters*. 1:32-35.

Future activities:

Task 1: Scintillation proximity assay (SPA) for DNA binding of human p53

We are finalizing the preparation of 2 manuscripts on this work. One describes the SPA measurement of DNA binding in human cell extracts and the use of the streptavidin-biotinylated DNA approach to isolate the DNA bound p53 (Chandrachud and Gal, manuscript in preparation). The other manuscript describes the total p53 scintillation proximity assay and its use in conjunction with measuring DNA binding (Oberlander, Xie, Chandrachud and Gal, manuscript in preparation). These manuscripts are expected to be submitted by May 1st this year.

Task 2: Nanoparticle assay for DNA binding

We have published one paper from this work describing the formation of the gold nanoparticle DNA lattice (Lim et al. 2008) and are preparing another to describe the digestion of this lattice by the MspI restriction enzyme (Lim, Wang, Chandrachud, Gal and Zhong, manuscript in preparation). This second manuscript is expected to be submitted by May 1st this year. We are in the process of further analyzing the DNA digestion of the assembled gold nanoparticle lattice using optical measurements, gel electrophoresis and transmission electron microscopy. We will then add the pure 53 protein to the lattice and observe any changes in the properties of the gold nanoparticles. We will confirm the association of the p53 protein to the lattice using specific antibodies and the lack of digestion by the MspI restriction enzyme. We expect to prepare another publication on these experiments within the next year.

Publication from this grant:

Lim, I-I S., Wang, L., Chandrachud, U., Gal, S., & Zhong, C.J.: Assembly-Disassembly of DNA-Au Nanoparticles: A Strategy of Intervention. (2008) Research Letters in Nanotechnology, in press. Work also supported by the National Science Foundation (Grant No. CHE0349040 to CJ Zhong), and a National Science Foundation Graduate Research Fellowship to I-I S. Lim.

Publications in preparation from this grant:

Lim, I-I S., Wang, L., Chandrachud, U., Gal, S., & Zhong, C.J.: Assembly-Disassembly of DNA-Au Nanoparticles: A strategy of intervention based on and restriction enzymes, manuscript in preparation. Work also supported by the National Science Foundation (Grant No. CHE0349040 to CJ Zhong), and a National Science Foundation Graduate Research Fellowship to I-I S. Lim.

Chandrachud, U. & Gal, S.: Differential DNA binding of p53 from human cell lines to unique
gene sequences, manuscript in preparation. Work also supported by National Institutes of Health grant (R15 CA101783-01A1) to SGal.

Oberlander, S., Xie, T., Chandrachud, C. and Gal, S.: Scintillation proximity assay (SPA) for total p53 protein can be performed with DNA binding analysis, manuscript in preparation. Work also supported by National Institutes of Health grant (R15 CA101783-01A1) to SGal.

Appendix B

"Bio-molecular Computing Technologies: DNA Library Analysis"

Principal Investigator: Anthony J. Macula, Associate Professor,
Department of Mathematics, SUNY-Geneseo.

Co-Principal Investigator: Susannah Gal, SUNY-Binghamton.

Introduction

The successful use of molecular biology methods as computational tools by Adelman (1994) has led to the development of a variety of DNA nanotechnology techniques. Many of these techniques require collections of oligonucleotides that do not produce erroneous cross-hybridizations. When these collections consist of complementary pairs of oligonucleotides, *i.e.*, are closed under complementation, they are called *DNA tag-antitag systems* (Kaderali et al. 2003) and *DNA codes* (D'yachkov et al. 2003, 2005, 2006). When the collections need not be closed under complementation, they are called *DNA words* (Andronescu et al. 2003; Shortreed et al. 2005; Tulpan et al. 2005) and *DNA barcodes* (Eason et al. 2004). These collections of non-cross-hybridizing collections have applications in single nucleotide polymorphism (SNP) multiplexing (Cai et al. 2000; Kaderali et al. 2003; Fish et al. 2007), gene function identification (Eason et al. 2004), nanostructure self-assembly (Valignat et al. 2005), universal microarrays (Hardenbol et al. 2003) and biomolecular computing (Braich et al. 2002; Rose et al. 2004). Combinatorial, heuristic and biological methods have been suggested as a means by which DNA codes can be found and programs exist that generate DNA codes (see Andronescu et al. 2003; Bishop et al. 2006; Chen et al. 2006; D'yachkov et al. 2006; Penchovsky and Ackermann 2003; Tulpan et al. 2005). One of these programs, SynDCode (Bishop et al. 2006), allows for the specification of thermodynamic properties of concatenated combinations of strands taken from the generated DNA code. These concatenated strands are known as a computational DNA library and are used as the search space in DNA computing experiments.

In this paper, we move these SynDCode theoretical DNA code sequences into the experimental laboratory to verify their usefulness in DNA library construction. Rather than the synthesis method used by Braich and colleagues (2002), we have used a self-assembly method to construct a DNA library using sequences generated from the SynDCode program for finding non-cross-hybridizing DNA strands. The library had 5 variables, each with two possible states (we call True

and False). We have successfully created this 32-member DNA library using these methods, partially analyzed this library and developed a method to screen specific members of the library. The creation of this physical DNA library provides us with the ability to correlate the actual experimental parameters with the SynDCode programmable features.

Materials and Methods

Construction and analysis of DNA library

From DNA sequences designed by SynDCode (Bishop et al. 2006), we ordered several DNA oligonucleotides (from Integrated DNA Technologies, Coralville, IA) to create a library using parallel overlap assembly (Kaplan et al. 1997; Ouyang et al. 1997). The DNA sequences are given in Table 1. These sequences were initially mixed as follows. In one tube, 0.5nmoles of 5'PCRT1T2L, 5'PCRF1T2L, 5'PCRT1F2L, 5'PCRF1F2L, T2RF3L , T2RT3L, F2RF3L, F2RT3L with 1nmole of C(F2), C(T2), C(T1), and C(F1) were combined. In another tube, 0.5nmoles of F4RF5L, T4RT5L, F3RF4L, T4RF4L, F3RT4L, F4RT5L, T3RF4L, T3RT4L with 1nmole of C(F3), C(T3), C(F4), and C(T4) were combined. These tubes were heated in a boiling water bath for 10 minutes, then allowed to cool slowly to room temperature. These annealed oligonucleotides were treated with polynucleotide kinase (New England Biolabs, Ipswich, MA) and then ligated for 15 minutes at room temperature with a DNA ligase (New England Biolabs). Next, a portion of the second tube was combined with a tube containing 1nmole of T5R3'PCR, F5R3'PCR, C(T5)3'PCR-BIOTIN, C(F5)3'PCR-BIOTIN oligonucleotides that had been annealed and treated with polynucleotide kinase. These combined oligonucleotides were ligated and then added to the first tube and ligated. Portions of these samples were then amplified with PCR for 30 cycles using the 5'PCR and 3'PCR primers with Taq polymerase (New England Biolabs) and analyzed on 10% polyacrylamide gels in Tris-borate-EDTA (BioRad Corporation, Richmond, CA). For cloning, we cut the PCR products with BamHI and HindIII (sites incorporated into the 5'PCR and 3'PCR primers, respectively; enzymes from New England Biolabs), ligated the fragments into a similarly cut pBluescript SKII vector (Stratagene, Incorporated, La Jolla, CA) [for map see http://www.fermentas.com/techinfo/nucleicacids/mappbluescriptiiskks.htm] and transformed into E. coli cells (DH5α from Invitrogen Corp., Carlsbad, CA). Using restriction digestion, isolated plasmids were confirmed to have inserts, then sequenced using the M13 reverse primer and the Big Dye Terminator V1.1 sequencing reactions (Applied Biosystems, Foster City, CA), and separated on an ABI Model 310 DNA sequencer.

Table 1. Oligonucleotide sequences for construction of DNA library

Oligonucleotide name	Sequence
5'PCRT1T2L	TTGTAAAACGACGGCCAGTGGATCC CCAAACCTCCACTTT CCAAC ACACAACTCC
5'PCRT1F2L	TTGTAAAACGACGGCCAGTGGATCC CCAAACCTCCACTTT CCAACCCTACACCAC
5'PCRF1T2L	TTGTAAAACGACGGCCAGTGGATCC CAACCAACCACTCTA CCAACACACAACTCC
5'PCRF1F2L	TTGTAAAACGACGGCCAGTGGATCC CAACCAACCACTCTA CCAACCCTACACCAC
C(T1)	GTTGGAAAGTGGAGGTTTGG
C(F1)	GTTGGTAGAGTGGTTGGTTG
T2RT3L	TCCACAATCA CCTTTCCTCC
T2RF3L	TCCACAATCA TCACACACAC
F2RT3L	CTACACCTTT CCTTTCCTCC
F2RF3L	CTACACCTTT TCACACACAC
C(T2)	TGATTGTGGA GGAGTTGTGT
C(F2)	AAAGGTGTAG GTGGTGTAGG
T3RT4L	ATCACCTCAT CCTCACTCTC
T3RF4L	ATCACCTCAT CACCTCTCTC
F3RT4L	ACACACAATT CCTCACTCTC
F3RF4L	ACACACAATT CACCTCTCTC
C(F3)	AATTGTGTGTGTGTGTGTGA
C(T3)	ATGAGGTGATGGAGGAAAGG
T4RT5L	ACTTCCTTCA TCTCCTCTCC
T4RF4L	ACTTCCTTCA TTTCCACCAC
F4RT5L	ACTTCTTCCA TCTCCTCTCC
F4RF5L	ACTTCTTCCA TTTCCACCAC
C(T4)	TGAAGGAAGT GAGAGTGAGG
C(F4)	TGGAAGAAGTGAGAGAGGTG
T5R3'PCR	ACTCAAAACC A AGC TTC ATG GTC ATA GCT GTT TCC
F5R3'PCR	CTCAACACAT A AGC TTC ATG GTC ATA GCT GTT TCC
C(T5)3'PCR-BIOTIN	/5Bio/GGAAACAGCTATGACCATGAAGCTTGGTTTTGAGT GGAGAGGAGA
C(F5)3'PCR-BIOTIN	/5Bio/GGAAACAGCTATGACCATGAAGCTT ATGTGTTGAG GTGGTGGAAA
5'PCR (M13-UP BamHI)	TTGTAAAACGACGGCCAGTGGATCC
3'PCR (M13-RP HindIII)	GGAAACAGCTATGACCATGAAGCTT

Tagging library cloned DNAs using Alexa-fluor and hybridization to confirm sequence:

DNA labeling of specific clones was accomplished primarily using an Alexa-fluor labeled 5'PCR primer or biotin labeled 3'PCR primer in the PCR under standard conditions. We performed hybridization of labeled DNA to dot blots with specific complement oligonucleotides on membranes and then detected any hybridized DNA to the membrane using antibodies to Alexa-fluor or strepavidin for biotin. For this, 1-100 pmole of oligonucleotides plus positive and negative controls were dotted on a nylon membrane (Roche Diagnostics, Indianapolis, IN), and treated with UV light to permanently attach the DNA. The labeled PCR product from a clone or clones (120-200 pmoles) was heated at 95^{o}C for 10 minutes and then added to 1.8 ml hybridization solution containing 0.25M sodium phosphate, pH 7.2 1mM EDTA and 7% SDS.

The membrane was pre-hybridized in the hybridization solution without the probe for 2 hours at 30°C, then the solution with probe was added and hybridization occurred overnight at 35°C. After incubation, the membrane was washed once in 2X SSC 1% SDS (10X SSC contains 0.15M sodium citrate, pH 7.0, 1.5M NaCl) for 5 minutes, once in 1X SSC, 1% SDS for 15 minutes each and finally rinsed once with 0.2X SSC, all at 35°C. For detection of the Alexa-fluor attached to any hybridized DNA, the membrane was then incubated for 1 hour at room temperature in blocking buffer (1X TBS 5% bovine serum albumin 0.1% Tween-20; 1X TBS contains 57mM NaCl 27mM Tris-HCl, pH 7.4) before the addition of a 1:5000 dilution of the anti-Alexa-fluor antibody (Invitrogen Corporation) in the blocking buffer. The membrane was incubated in the antibody for 1 hour at room temperature, then washed three times in 1XTBS with 0.1% Tween-20 for 10 minutes each time. The membrane was incubated with an anti-rabbit antibody linked to horse radish peroxidase (1:1000 diluted in blocking buffer) (Cell Signaling Technology, Inc., Beverly, MA) for 1 hour at room temperature, then washed as above. For detection of the biotin attached to any hybridized DNA, the membrane was pre-incubated in blocking buffer as above before the addition of a 1:10,000 dilution of streptavidin linked horse radish peroxidase (Pierce Biotech, Inc., Rockford, IL) in the blocking buffer. After 1 hour incubation at room temperature, the membrane was washed as above. In both cases, the horse radish peroxidase was detected using a chemiluminescent substrate (Pierce Biotech, Inc.), with light from the reaction detected by X-ray film.

Results

Theoretical basis for construction of complemented DNA codes

Single strands of DNA are, abstractly, (A, C, G, T) -quaternary sequences, with the four letters denoting the respective nucleic acids. DNA sequences are oriented, either $5' \to 3'$ or $3' \to 5'$, a notation that reflects the asymmetric covalent linking between consecutive bases in the DNA strand backbone. In this paper, when we write DNA molecules without indicating the direction, it is assumed that the direction is $5' \to 3'$. To obtain the reverse complement of a strand of DNA, first reverse the order of the letters and then substitute each letter with its complement, A for T, C for G and vice-versa. For example, the reverse complement of AACGTG is CACGTT. For strand x, we let $\overline{x}$ denote its reverse complement. A (perfect) *Watson-Crick (WC) duplex* results from joining reverse complement sequences in opposite orientations so that every base of one strand is paired with its complementary base on the other strand. However, when two, not necessarily complementary, oppositely directed DNA strands "mirror" one another sufficiently,

they too are capable of coalescing into a double stranded DNA duplex. The process of forming DNA duplexes from single strands is referred to as *DNA hybridization*. Given two DNA strands x and y, we let x:y denote the DNA duplex formed between x and y. It is assumed that x and y are oppositely oriented in x:y. Henceforth a WC duplex will simply be denoted $x:\bar{x}$. Note that two oppositely directed copies of a single strand x can form a duplex, in other words a sequence x can be self-complementary, e.g., $x = ACGT = \bar{x}$. The greatest Gibbs free energy, ΔG, of duplex formation is obtained when the two sequences are reverse complements of one another and the DNA duplex formed is a WC duplex. However, there are many instances when the formation of non-WC duplexes are energetically favorable and have a $\Delta G < 0$. In this paper, a non-WC duplex is referred to as a *cross-hybridized (CH) duplex*. We note that complementary sequences can also form a DNA duplex that is not in perfect alignment. Regardless of whether the alignment is perfect or not, any time a strand and its complement form a duplex we call that a WC duplex.

A *complemented DNA Code* of length n, $C = \{\{x_i, \bar{x}_i\}\}$ is a set of Watson-Crick pairs of complementary DNA sequences, each of which, has n bases (n is also called the *length* of the sequences in the code). We say that a strand x is in C if $\{x, \bar{x}\}$ is an element of C. The size of C is equal to its cardinality, so a complemented DNA Code of size N has 2N strands. In DNA hybridization assays, the formation of WC duplexes is required, while the formation of CH duplexes leads to errors. Thus the formation of each WC duplex must be much more energetically favorable then any possible CH duplex. A DNA code with this property is said to have *high binding specificity*. Below we give a probabilistic model for binding specificity.

Partition function approach to binding specificity of a (n, ω, χ) -DNA code

Definition 1. Let $\omega < \chi \leq 0$. An (n, ω, χ)-DNA code C is a *complemented* DNA code of length n with the following properties:

a. For each pair $\{x, \bar{x}\}$ in C, the ΔG of the WC duplex $x:\bar{x}$ is less than ω.

b. For any strand x in C, the ΔG of the CH duplex x:x is greater than χ.

c. For non-complementary strands x and y in C the ΔG of the CH duplex x:y is greater than χ.

Partition function approach to binding specificity of a (n,ω,χ) -DNA code

In Bishop et al. (2007), a partition function model was used to bound the probability that a (n,ω,χ)-DNA code self-assembles entirely into WC duplexes in a multiplexing situation so that there are no cross-hybridizations. From Bishop et al. (2007), *the probability* that the (n,ω,χ)-DNA code of size *N self assembles in this way is at least*

$$\left(\frac{1}{1+(2N-1)exp((\omega-\chi)/RT)}\right)^{2N}. \quad (1)$$

The important factor in the above expression is $\omega-\chi$, which we call the *free energy gap*. It should be noted that a somewhat similar "free energy gap" approach to code specificity was taken by (Tulpan et al. 2005).

Table 2. SynDCode generated sequences for construction of the DNA library

C C A A A C C T C C A C T T T C C A A C= T_1	*G T T G G A A A G T G G A G G T T T G G*= C(T_1)
C A A C C A A C C A C T C T A C C A A C= F_1	*G T T G G T A G A G T G G T T G G T T G*= C(F_1)
A C A C A A C T C C T C C A C A A T C A= T_2	*T G A T T G T G G A G G A G T T G T G T*= C(T_2)
C C T A C A C C C A C C T A C A C C T T T= F_2	*A A A G G T G T A G G T G G T G T A G G*= C(F_2)
C C T T T C C T T C C A T C A C C T C A T= T_3	*A T G A G G T G A T G G A G G A A A A G G*= C(T_3)
T C A C A C A C A C A C A C A C A A T T= F_3	*A A T T G T G T G T G T G T G T G T G A A*= C(F_3)
C C T C A C T C T T C A C T T T C C T T C A= T_4	*T G A A G G A A G T G A G A G T G A G G*= C(T_4)
C A C C T C T C T T C A C T T T C T T C C A= F_4	*T G G A A G A A G T G A G A G A G G T G*= C(F_4)
T C T C C T C T T C C A C T C A A A A C C= T_5	*G G T T T T G A G T G G A G A G G A G A A*= C(T_5)
T T T C C A C C A C C T C A A C A C A T= F_5	*A T G T G T T G A G G T G G T G G A A A*= C(F_5)

The sequences used to generate the library are given as the strand or its complement (C). Each sequence is shown as the full 20-base sequence with the 2 halves of the cut codes shown in either *italics* or **bold**.

Partition function model applied to DNA codes used in the library construction

The DNA strands used in the formation of the DNA library are given in Table 2. There are two distinct complemented codes presented in Table 1. The twenty strands of length 20 labeled by T_i, F_i, C(T_i) or C(F_i) that we will call the *ambient code* and the forty strands of length 10 that consist of right (bold) and left (italics) halves of the strands in the ambient code that we call the *cut code* of the ambient code. The ambient code was generated by SynDCode (Bishop et al. 2006) to be a (20,-29,-17)-DNA code at 23^{o}C *with the additional property that its cut code was a* (10,-14.2,-8.2)-DNA Code at 23^{o}C. Thus, the free energy gap of the ambient code was -12, and that of the cut code was -6.2. The partition function model (1) gives a *lower bound* of 0.99999 for the

probability that the ambient code (N=20) correctly assembles. It also gives a *lower bound* of 0.79098 for probability that the cut code (N=40) correctly assembles. The result for the cut code is that which gives a most certain *lower bound* for the specificity in our methods as the strands in the cut code are the sticky ends for the blocks that we intend to assemble (See Figure 1).

Construction of the DNA library

We prepared a library of a 5-site, 2-variable library of sequences using codes designed by SynDCode (Bishop et al. 2006). The library was constructed by combining the oligonucleotides using a parallel overlap assembly approach (Kaplan et al. 1997; Ouyang et al. 1997) (see Methods section and Figure 1). We combined the oligonucleotides in 3 stages and monitored the appearance of appropriate bands during the assembly using polyacrylamide gel electrophoresis (Figure 2). A ~175bp band appeared in the final ligation step as expected (Figure 2, lanes 2 and 4). PCR amplification of this mixture using primers at the ends of the library sequences, produced primarily the appropriate sized products (Figure 2, lane 6).

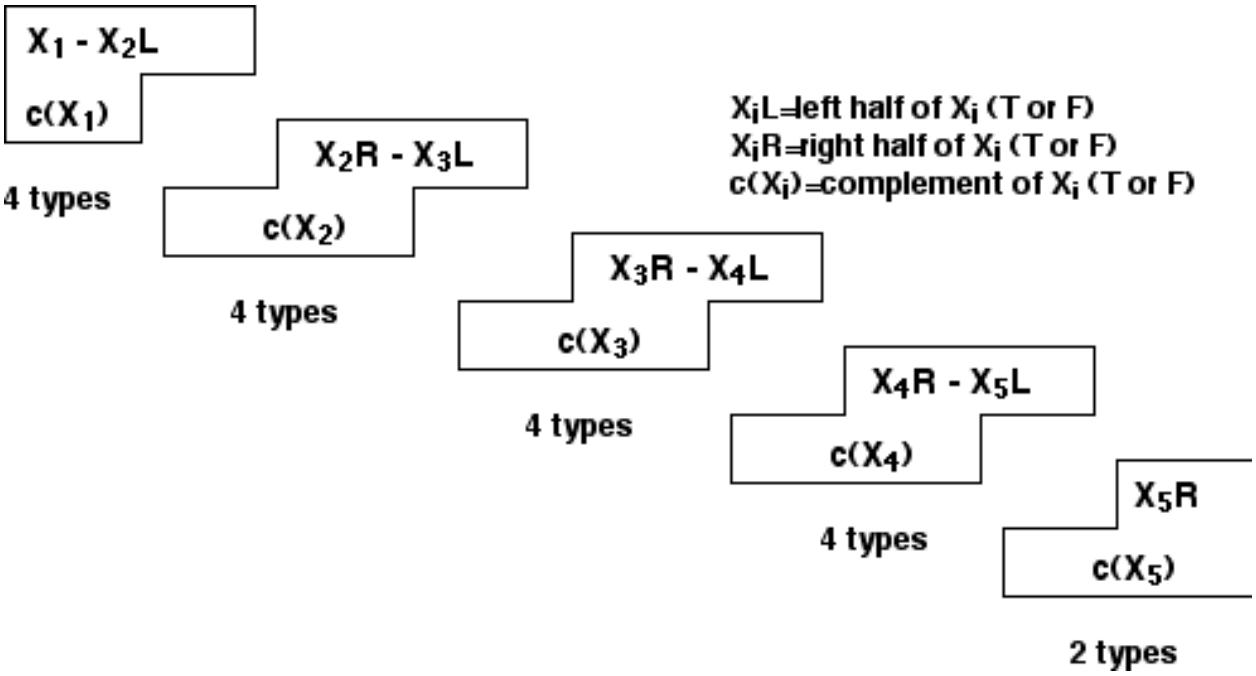


Figure 1- Parallel overlap assembly of a 5-site 2-variable library

The DNA oligonucleotides used to synthesize the library represent the left and right of 2 of the 5 sites, each as either True or False. The complementary sequences of each of the 5 sites were included and thus reconstituted overlapping, complementary sequences put together as represented in this visual image. There are 4 types of each of the internal fragments since the left half of T or F is merged with the right half of the next site again as T or F. For example, there exists one oligonucleotide that is F2RF3L, as well as one that represents combining the F2R with the T3L. The listing of all of the oligonucleotides synthesized is given in Table 1.

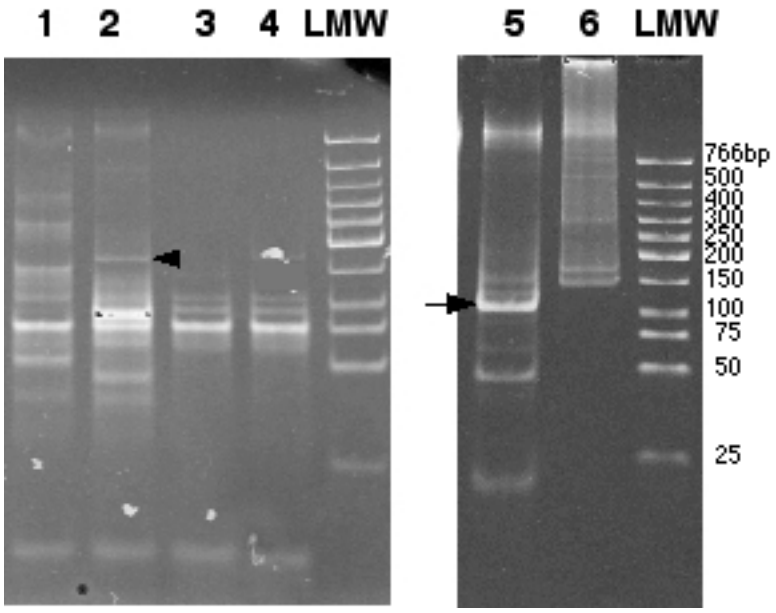


Figure 2. Final steps of library preparation, amplification and digestion of library fragments

DNAs were separated on a 10% polyacrylamide gel in TBE along with a low molecular weight marker (LMW). Fragments representing sites 1-2 were combined and ligated and produced primarily fragments at 75bp as expected (lanes 3 and 4) while fragments representing sites 3-4 (lane 1) and sites 3-5 (not shown) showed major fragments within the mixture at 75bp and ~85bp, respectively. Ligation of fragments representing sites 1-5 produces a ~175bp fragment (marked with an arrowhead in lane 2; also present in lane 4). PCR of the ligation mixture from lane 2 with primers representing sequences outside site 1 and site 5 (3'PCR and 5'PCR) produces two bands at 150 and ~175bp (lane 6). When this DNA is cut with BamHI and HindIII (situated just inside the primer sites), a strong ~110bp band is produced (marked with an arrow in lane 5). This is the

expected size for a library of 5 sites, each 20 bp with the extra sequences for the restriction sites on the ends. This digested band was cloned into the vector pBluescript for sequencing.

Analysis of the DNA library:

We next wanted to characterize the library to check whether representative sequences were present. One way we have successfully done this is by cloning out fragments of the library and sequencing them. For cloning and sequencing of these library DNAs, we cut the amplified product with BamHI and HindIII and purified the expected ~110bp fragment from the gel (Figure 2, lane 5), ligated that DNA into a similarly cut pBluescript vector and transformed *E. coli*. A number of colonies were obtained and 12 were sequenced. Table 3 contains the sequences of the clones and the site identifications for each. The 12 sequences obtained represented fragments of the predicted library with one clone having a mutation in the T3 site (clone 10) and one clone having a mutation in the T1 site (clone 11). Of these 12, only 1 was a repeat sequence (clone 11 is a repeat of clone 10; see Table 4). Our method is designed to have 32 distinct strands in the library, but explicit verification of this is difficult, if not impossible. Below we give a variety of approaches to *indicate* success. These indications are derived from data obtained by sequencing clones from the library. We assume that selecting a clone is equivalent to selecting (with replacement) one of the members of the library.

As can be seen from Tables 3 and 4, of the 12 sequenced clones, each was a member of the desired library (except for the point mutations). So, if we assume that the cut code correctly assembled with probability *less* than the 85% lower bound prediction by the partition function argument above, then the probability of selecting 12 correctly assembled sequences in 12 tries is at most 14%. Thus we hold that this is a good indication that no cross-hybridizations occurred in the assembly process, i.e., no strand with T_i or F_i in the jth position with $i \neq j$ exists. From this we assume the library size is at most 32. To get an indication that *all* of the desired 32 library strands were assembled, we focus on repetitions found in the data. It is important to note that the set of variable values contained in at least one of the 12 sequenced library strands cover all ten of the possible values and do so in reasonably expected proportions. Specifically, among the 12 sequences clones the sites T1, T2, T3, T4 and T5 appeared 9, 9, 7, 5, and 4 times and all in the correct positions (see table 4).

In Table 4, we concisely summarize the clone sequencing results and use the notion of repetitions to get statistical estimates on the size of the library. There are many ways to interpret the data and information on the clones. We focus on the following three events:

F ≡ the first repeated (sub)pattern.

D ≡ the number of distinct (sub)patterns.

U ≡ the number of unique (sub)patterns.

For example, from column 2 in Table 4, the first repeated complete pattern occurred at clone 11 and the number of unique and distinct complete patterns are 10 and 11 respectively. The events F, D, and U are also considered for sample space of subpatterns that arise by ignoring the value at a single position. This information is recorded in columns 3-7 in Table 4.

One way to analyze the data is to use a Bayesian approach. However, to do this a prior assumption about the success of the method must be made. Let L_N be the event that the library has *N* strands. Since our indications are that $N \leq 32$, we assume a uniform prior distribution over all possible library sizes from 0 to 32.

Given a library of size N and selecting with replacement, the probability that the first repeat occurs in the eleventh try is

$$Pr(F \mid L_N) = \frac{10N \cdot P(N-1,9)}{N^{11}}. \qquad (2)$$

Then by Bayes' theorem we have that:

$$Pr(L_{N_0} \mid F) = \frac{Pr(F \mid L_{N_0}) Pr(L_{N_0})}{\sum_{N=0}^{32} Pr(F \mid L_N) Pr(L_N)} = \frac{Pr(F \mid L_{N_0})}{\sum_{N=0}^{32} Pr(F \mid L_N)}. \qquad (3)$$

Then, the *expected* size of *N* given *F* is

$$Exp(N \mid F) = \sum_{N=0}^{32} N \cdot Pr(L_N \mid F) = \frac{\sum_{N=1}^{32} N \cdot Pr(F \mid L_N)}{\sum_{N=1}^{32} Pr(F \mid L_N)} = 25.17 \qquad (4)$$

While the result in (4) is considerably less than the desired 32, it should be noted that it does follow from an *unbiased uniform prior* on the size of the library. Note, however, given the proposed 79% success of correct assembly, it is reasonable to allow N to be any natural number and assume a prior Poisson distribution on *N* with mean 32. Then in this case we have

$$Pr(L_N) = \frac{32^N e^{-32}}{N!}. \qquad (5)$$

If such a prior is used in (3), then expected size of *N* given *F* computed as in (4) is.

$$Exp(N \mid F) = 32.83. \qquad (6)$$

The Bayesian approach can also be applied to subpatterns and this is presented in Table 4 (even though the subpattern data is not independent of the data for the complete patterns). Again, we assume a uniform prior distribution, but here it is over all possible library sizes from 0 to 16. The conditional probability in these cases is

$$Pr(F \mid L_N) = \frac{(f-1)N \cdot P(N-1, f-2)}{N^f} \qquad (7)$$

where *f* is the position of the first repeated subpattern. In each case, the desired expected number of subpatterns is 16.

A more combinatorial way to approach library size determination is discussed in Ritter (1994) where the size of a population is approximated by reversing calculations of expected value. Although the exact methods of Ritter (1994) can be applied here, we take a more straightforward combinatorial interpretation than is presented there. If one samples with order and replacement s times from a population of size N, then the expected number of distinct objects that appear *exactly* (8) or *at least* (9) once are, respectively:

$$E_U \equiv s \cdot \left(\frac{N-1}{N}\right)^{s-1}. \qquad (8)$$

$$E_D \equiv N \cdot \left(1 - \left(\frac{N-1}{N}\right)^{s}\right) \qquad (9)$$

(8) and (9) follow from the additivity of expectation (over N) and probability that a given object of the population appears exactly once or at least once in the ordered s-tuple are respectively:

$$\frac{s \cdot (N-1)^{s-1}}{N^s}. \qquad (10)$$

$$\left(1 - \left(\frac{N-1}{N}\right)^{s}\right) \qquad (11)$$

Note that *exactly once* is synonymous with *unique* and *at least once* is synonymous with *distinct*. What is suggested in Ritter (1994) is to substitute observed values for *U* and *D* (*u* and *d*,

respectively) for E_U and E_D, solve for N and use the solution as an estimate of N. For example, the number of complete patterns in column 2 in Table 4 that appear exactly once is u=10 while the number that appear at least once is d=11. Then, numerically solving for N in each case (with s=12) we have that the E_U and E_D estimates of N are respectively:

If $10 = \frac{12 \cdot (N-1)^{12-1}}{N^s}$, then the E_U estimate is $N_{E_U} = 60.83$

If $11 = N \cdot \left(1 - \left(\frac{N-1}{N}\right)^{12}\right)$, then, the E_D estimate is $N_{E_D} = 62.61$

These values of 60.83 and 62.91 are nearly double the desired expected value of 32. However, given the assumption that N is at most 32, then these results are more reassuring. Similar E_U and E_D estimates on the number of subpatterns are recorded in Table 4. Note that the E_D estimate on the number of subpatterns in column 4 of Table 4 is 18.47 which is very close to the desired expected value of 16.

Table 3. Sequences of individual clones from the DNA library

Clone name	Clone sequence (site 1->site 5 direction)	Site designations
1	CCAAACCTCCACTTTCCAAC-ACACAACTCCTCCACAATCA-TCACACACACACACACAATT-CACCTCTCTCACTTCTTCCA-TTTCCACCACCTCAACACAT	T1 T2 F3 F4 F5
2	CCAAACCTCCACTTTCCAAC-CCTACACCACCTACACCTTT-TCACACACACACACACAATT-CACCTCTCTCACTTCTTCCA-TCTCCTCTCCACTCAAAACC	T1 F2 F3 F4 T5
3	CCAAACCTCCACTTTCCAAC-ACACAACTCCTCCACAATCA-CCTTTCCTCCATCACCTCAT-CCTCACTCTCACTTCCTTCA-TCTCCTCTCCACTCAAAACC	T1 T2 T3 T4 T5
4	CCAAACCTCCACTTTCCAAC-CCTACACCACCTACACCTTT-TCACACACACACACACAATT-CACCTCTCTCACTTCTTCCA-TTTCCACCACCTCAACACAT	T1 F2 F3 F4 F5
5	CAACCAACCACTCTACCAAC-CCTACACCACCTACACCTTT-CCTTTCCTCCATCACCTCAT-CCTCACTCTCACTTCCTTCA-TTTCCACCACCTCAACACAT	F1 F2 T3 T4 F5
6	CCAAACCTCCACTTTCCAAC-ACACAACTCCTCCACAATCA-CCTTTCCTCCATCACCTCAT-CACCTCTCTCACTTCTTCCA-TTTCCACCACCTCAACACAT	T1 T2 T3 F4 F5
7	CCAAACCTCCACTTTCCAAC-ACACAACTCCTCCACAATCA-CCTTTCCTCCATCACCTCAT-CACCTCTCTCACTTCTTCCA-TCTCCTCTCCACTCAAAACC	T1 T2 T3 F4 T5
8	CCAAACCTCCACTTTCCAAC-ACACAACTCCTCCACAATCA-TCACACACACACACACAATT-CCTCACTCTCACTTCCTTCA-TTTCCACCACCTCAACACAT	T1 T2 F3 T4 F5
9	CAACCAACCACTCTACCAAC-ACACAACTCCTCCACAATCA-CCTTTCCTCCATCACCTCAT-CACCTCTCTCACTTCTTCCA-TTTCCACCACCTCAACACAT	F1 T2 T3 F4 F5
10	CCAAACCTCCACTTTCCAAC-ACACAACTCCTCCACAATCA-CCTTTCCTCCATCACCTCAT-CCTCACTCTCACTTCCTTTA-TTTCCACCACCTCAACACAT	T1 T2 T3 T4* F5 (has a C→T mutation in T4 sequence)
11	CAACCAACCACTCTACCAAC-ACACAACTCCTCCACAATCA-TCACACACACACACACAATT-CACCTCTCTCACTTCTTCCA-TCTCCTCTCCACTCAAAACC	T1* T2 T3 T4 F5 (has C→T mutation in T1 sequence)
12	TCAANCCTCCACTTTCCAAC-ACACAACTCCTCCACAATCA-CCTTTCCTCCATCACCTCAT-CCTCACTCTCACTTCCTTCA-TTTCCACCACCTCAACACAT	F1 T2 F3 F4 T5

Isolated clones from the library in the vector pBluescript were sequenced with the sequence given in the site 1 to the site 5 orientation. Dashes (-) are inserted in the sequence between the sites to make it easier to visualize. The individual site identities are then given with a * indicating a site with a mutation. The clones were isolated in 2 groups, 1-7 first, then 8-12.

Table 4. Clone data pattern analysis

clone	all sites	site 1 ignored	site 2 ignored	site 3 ignored	site 4 ignored	site 5 ignored
1	***T1T2F3F4F5***	****T2F3F4F5***	***T1*F3F4F5***	**T1T2*F4F5**	**T1T2F3*F5**	***T1T2F3F4****
2	***T1F2F3F4T5***	****F2F3F4T5***	**T1*F3F4T5**	***T1F2*F4T5***	**T1F2F3*T5**	**T1F2F3F4***
3	***T1T2T3T4T5***	****T2T3T4T5***	***T1*T3T4T5***	***T1T2*T4T5***	**T1T2T3*T5**	**T1T2T3T4***
4	***T1F2F3F4F5***	****F2F3F4F5***	T1*F3F4F5 #	***T1F2*F4F5***	T1F2F3*F5 #	T1F2F3F4* #
5	***F1F2T3T4F5***	****F2T3T4F5***	**F1*T3T4F5**	***F1F2*T4F5***	***F1F2T3*F5***	***F1F2T3T4****
6	***T1T2T3F4F5***	***T2T3F4F5**	***T1*T3F4F5***	T1T2*F4F5 #	**T1T2T3*F5**	**T1T2T3F4***
7	***T1T2T3F4T5***	****T2T3F4T5***	***T1*T3F4T5***	***T1T2*F4T5***	T1T2T3*T5 #	T1T2T3F4* #
8	***T1T2F3T4F5***	****T2F3T4F5***	***T1*F3T4F5***	**T1T2*T4F5**	T1T2F3*F5 #	***T1T2F3T4****
9	***F1T2T3F4F5***	*T2T3F4F5 #	***F1*T3F4F5***	***F1T2*F4F5***	***F1T2T3*F5***	**F1T2T3F4***
10	**T1T2T3T4F5**	***T2T3T4F5**	***T1*T3T4F5***	T1T2*T4F5 #	T1T2T3*F5 #	T1T2T3T4* #
11	T1T2T3T4F5 #	*T2T3T4F5 #	T1*T3T4F5 #	T1T2*T4F5 #	T1T2T3*F5 #	T1T2T3T4* #
12	***F1T2F3F4T5***	****T2F3F4T5***	***F1*F3F4T5***	***F1T2*F4T5***	***F1T2F3*T5***	F1T2F3F4* #
F:=first repeat position=f	11	9	4	6	4	4
U:=number of unique patterns=u	10	8	8	7	3	3
D:=number of distinct patterns=d	11	10	10	9	7	7
Bayesian prediction of N	25.17	13.62	8.77	11.31	8.77	8.77
E_U prediction of N	60.83	27.63	27.63	20.91	8.45	8.45
E_D prediction of N	62.61	29.55	29.55	18.47	9.5	9.5

All distinct patterns in a given column (i.e., appear at least once) are in bold. Unique patterns in a given column (i.e., appear exactly once) are in italics. The first repeated pattern in a given column is marked with #. The desired prediction of N is 32 in the "all sites" column and 16 in all others. The Bayesian prediction assumes a uniform prior.

Analysis of different probe sequences using hybridization

We used hybridization to specific complement sequences of the 5 sites to correctly identify the clones. In this case, DNA oligonucleotides were dotted onto membranes and an Alexa-fluor or biotin labeled upper strand of one of the clones was incubated with the membrane (see Figure 3 for scheme). Sites with complementary sequences should allow hybridization of the labeled DNA that can then be detected using antibodies to the Alexa-fluor or biotin modification. We have used this method successfully to confirm the identity of 6 of the clones, three of which are shown (Figure 4). We have also used this approach to detect hybridization in mixtures. In this case, approximately equal amounts of each of 2 or 3 individual probes were combined, then hybridized to the filter and detected. We expected to see multiple dots for some of the sites and that is what was observed (Figure 4).

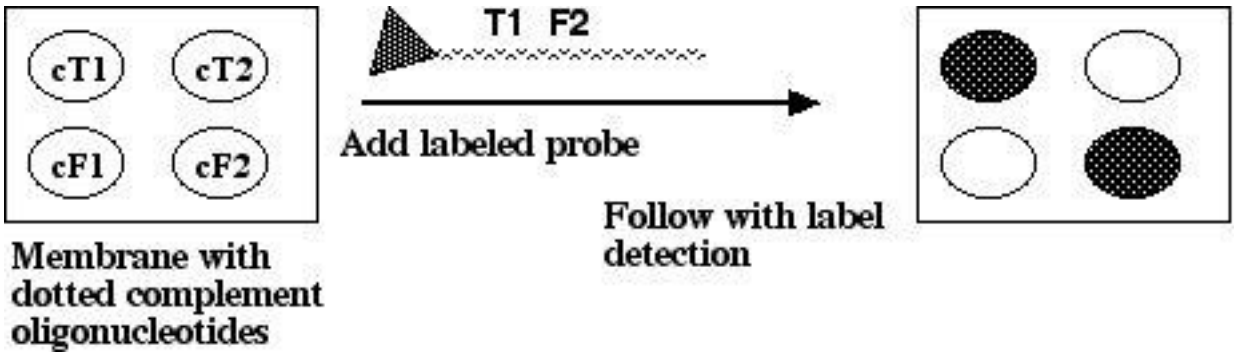


Figure 3- Scheme for identification of single members of the library using DNA hybridization

Specific complementary oligonucleotides are dotted onto a nylon membrane at specific sites, then a labeled probe (triangle represents label) containing one member of the library is added to the membrane in a hybridization solution. Where the complement to the probe is present on the membrane, the probe should hybridize. The hybridized probe is then detected by the presence of the label and dark spots appear on the membrane. The position of the dark spots relative to the position of the complement oligonucleotides sequence of the probe.

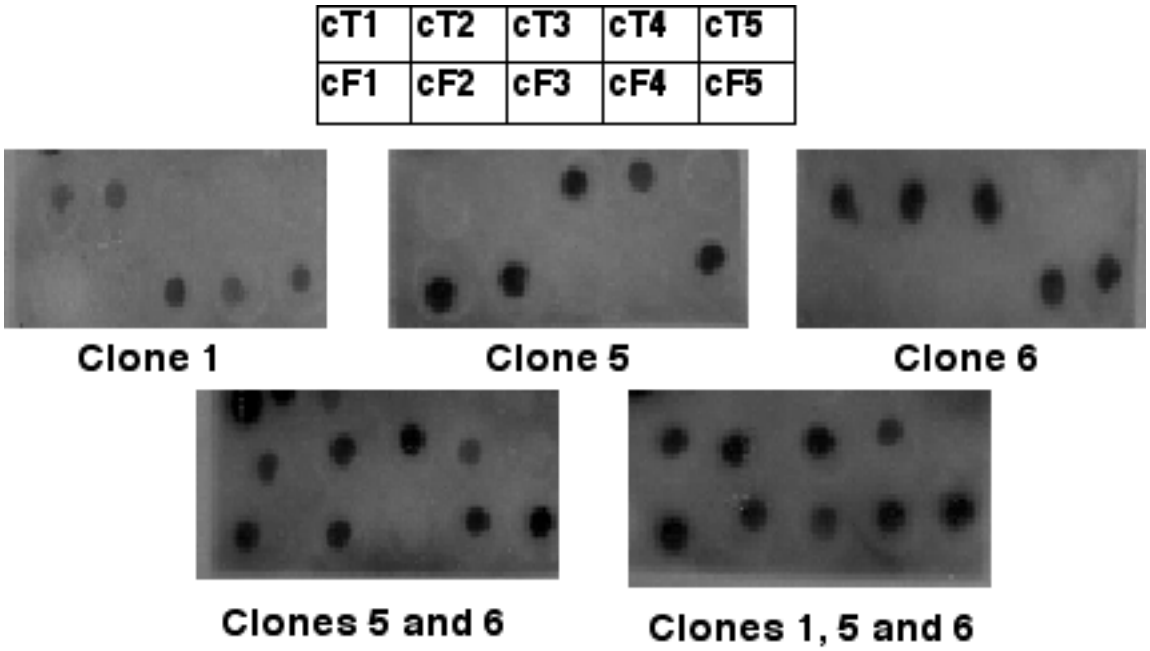


Figure 4- Identification of single members and mixtures of the library using DNA hybridization

Specific clones were hybridized to filters containing 1 pmole of all 10 of the complement oligonucleotides in the arrangment shown at the top of the figure. In this experiment, hybridization occurred with 120 pmole of biotinylated clone DNA library strands at 35^{o}C overnight. After hybridization, the membrane was processed for detection of the biotin using streptavidin conjugated to horse radish peroxidase. The images show the detection of the location of the hybridized probe for clones 1, 5 and 6 individually, then one with a mixture containing equal amounts of clones 5 and 6 or clones 1, 5 and 6. A dark spot indicates a position where the biotin labeled clone hybridized. The spots correspond with the expected sequences for the individual clones and in the 2 mixtures tested. This experiment was repeated for many of the other clones and several mixtures, always with the expected results.

Conclusions and Future Work

We have used a self-assembly method to successfully construct a 5-site 2-variable DNA library using sequences provided by SynDCode. Probabilistic and combinatorial analysis of the data obtained from 12 sequenced clones from this library suggest that it is a complete 32-member library. The process of cloning the prepared library fragments and then randomly isolating single clones from this collection is akin to random selection of a single member of a population with replacement. We feel this laboratory technique, coupled with the mathematical methods of library size estimation can be useful in the analysis of even larger libraries and for other systems trying to analyze the composition of a DNA collection.

We detected a single base error in different sites in two members of the library that were sequenced. These errors could have been caused by incorporation of an oligonucleotide with a mutation in the site. These mutations could have been included during oligonucleotide synthesis. Another option is that the mutation appeared during preparation and amplification of the library sequences. *Taq* polymerase has a published error rate between 0.05 and 2.1 errors per 10^4 duplications with most reports showing errors between 0.1 and 0.3 errors per 10^4 duplications (Bracho et al. 1998 and references therein). So it is possible that this enzyme inadvertently incorporated these single nucleotide differences during one of the amplification steps. With this error rate and our library of only 100 bp, we would expect only 1 error to be incorporated after about 500 cycles of PCR. We only amplified the fully constructed library for 30 cycles before

cloning the fragments so it is unlikely these 2 mutations occurred at that stage. Thus, it is more likely an alteration of the sequence of these two oligonucleotides was incorporated during the synthesis phase. However, the oligonucleotides containing the mutations were also present as the correct sequences in other clones (*i.e.*, the correct T1 is in 8 other sequenced clones, T3 is in 6 others) suggesting that if alterations were present in the original oligonucleotides used, they were a small proportion of those used to create the library.

We have successfully used DNA hybridization for detection of specific members of the library. In this case, complementary oligonucleotides representing all of the possible 10 sites were immobilized and single members of the library were hybridized to these oligonucleotides. We found no cross-hybridization of the individual complementary sites representing the variables. This supports the quality of the SynDCode program for identifying unique non-cross-hybridizing strands. This is consistent with other work using different sequences designed by SynDCode (Pogozelski et al. 2006). The hybridized library member was detected using a specific modification on the primer used to amplify the DNA fragment. In this work, we have used Alexa-fluor and biotin modified primers for this detection. Other modified nucleotides could also be used in this detection as we have shown (Pagano and Gal, in press). We used a single labeled DNA species for this hybridization as well as 2 or 3 clones in a mixture. In this case, we could determine that DNA fragments carrying a specified site were contained in the mixture, but not which particular fragments were present (For instance, one could tell that there was T1, F1, T2, and F2 present, but not whether one fragment had T1-T2 or T1-F2; see Figure 4). But, library members with distinct labels could be used simultaneously and the distinct modifications detected on the blots. We have used the incorporation of 4 different modified nucleotides in DNA and successfully detected them specifically using binding proteins or antibodies (Pagano and Gal, in press). This would allow DNA sequences to be identified in a mixture.

We are now in the process of developing methods to select for specific members of this library using bound complement probes. We will be working towards covalent probe linkages to magnetic beads to reduce the problem of complement probe carryover and to make the selection efficient. Once the protocols for this process are worked out, we should be able to test computations by selecting for specific sites (T1 or F3, etc.). The information we have learned from this library preparation and experimental analysis should be useful for creating a larger library either from scratch or by linking additional 2-variable sites onto our existing library.

References:

1. Adleman L (1994) Molecular computation of solutions of combinatorial problems. Science 266: 1021-1024

2. Andronescu M, Aguirre-Hernandez R, Condon, A, et al. (2003) RNAsoft: a suite of RNA secondary structure prediction and design software tools. Nucleic Acids Res 31: 3416-3422

3. Bishop M, Macula A, Renz T (2006) SynDCode suite, http://syndcode.geneseo.edu/, Cited 19 Mar 2007

4. Bishop M, D'yachkov A, Macula A, et al. (2007) Free Energy Gap and Statistical Thermodynamic. J Comp Biol (in press)

5. Bracho MA, Moy A, Barrio E (1998) Contribution of *Taq* polymerase-induced errors to the estimation of RNA virus diversity. J Gen Virol 79: 2921-2928

6. Braich S, Chelyapov N, Johnson C, et al. (2002) Solution of a 20-Variable 3-SAT Problem on a DNA Computer. Science 296: 499 - 502

7. Cai H, White P, Torney D, et al. (2000) Flow cytometry-based minisequencing: a new platform for high throughput single nucleotide polymorphism scoring. Genomics 66:135-143

8. Chen J, Deaton R, Garzon M (2006) Characterization of non-crosshybridizing DNA oligonucleotides manufactured in vitro. Nat Comp 5: 65-181

9. D'yachkov A, Erdös P, Macula AJ et al. (2003) Exordium for DNA Codes. J Combinatorial Optimization 7(4): 369-380

10. D'yachkov AG, Vilenkin PA, Ismagilov IK et al. (2005) On DNA codes. Problems of Information Transmission 41(4): 349-367

11. Eason R, Pourmand N, Tongprasit W et al. (2004) Characterization of synthetic DNA bar codes in Saccharomyces cerevisiae gene-deletion strains. Proc Natl Acad Science USA 101:11046-11051

12. Fish D, Horne M, Searles R, et al. (2007) Multiplex SNP Discrimination. Biophysical J 92: L89-L92

13. Hardenbol P, Baner J, Jain M, et al. (2003) Multiplexed genotyping with sequence-tagged molecular inversion probes. Nat Biotechnol 6: 673-678

14. Kaderali L, Deshpande A, Nolan J, et al. (2003) Primer-design for multiplexed genotyping. Nucleic Acids Res 31: 1796 - 1802

15 Kaplan PD, Ouyang Q, Thaler DS et al. (1997) Parallel overlap assembly for the construction of computational DNA libraries. J Theor Biol 188:333-4116.

16. Macula AJ (2005) SynDCode web site: http://syndcode.geneseo.edu/ which has a link to run the SynDCode program as well as a manuscript describing the program and the parameters used; Cited 7 Sept 2007.
17. Mathews D, Zuker, M, Turner D (2006) RNAstructure 4.2, available at http://rna.chem.rochester.edu.
18. Ouyang Q, Kaplan PD, Liu S, et al. (1997) DNA solution of the maximal clique problem. Science 278:446-9
19. Pagano A, Gal S (2007) An approach to using modified nucleotides in aqueous DNA computing. Lecture Notes in Computer Science (in press)
20. Penchovsky R, Ackermann J (2003) DNA library design for molecular computation. J Comput Biol 10: 215-229
21. Pogozelski WK, Bernard MP, Priore SF et al. (2006) Experimental validation of DNA sequences for DNA computing: Use of a SYBR green assay. Lecture Notes in Computer Science 3892: 322-331
22. Ritter T (1994) Estimating Population from Repetitions in Accumulated Random Samples. Cryptologia 18(2):155-190
23. Rose J, Deaton R, Francescetti D, et al. (1999) A statistical mechanical treatment of error in the annealing biostep of DNA computation. In: Proceedings of the Genetic and Evolutionary Computation Conference, Volume 2, 829-1834, AAAI, Morgan Kaufmann, San Francisco
24.Rose J, Deaton R, Suyama A (2004) Statistical thermodynamic analysis and design of DNA-based computers. Nat Comp 3: 443-359
25.SantaLucia J (1998) A unified view of polymer, dumbbell, and oligonucleotide DNA nearest-neighbor thermodynamics Proc Natl Acad Science USA 95: 1460-1465
26 Shortreed M, Chang S, Hong D (2005) A thermodynamic approach to designing structure-free combinatorial DNA word sets. Nucleic Acids Res 33: 4965--4977
27. Tulpan D, Andronescu M, Chang S et al. (2005) Thermodynamically based DNA strand design. Nuc Acids Res 33: 4951–4964
28. Valignat M, Theodoly O, Crocker J, et al. (2005) Reversible self-assembly and directed assemblyof DNA-linked micrometer-sized colloids. Proc Natl Acad Science USA 102: 4225--4229
29.Zhang Y, Hammer D, Graves D (2005) Competitive hybridization kinetics reveals unexpected behavior patterns. Biophysical J 89(5):2950-2959
30. Zuker M, Mathews D, Turner D (1999) Algorithms and Thermodynamics for RNA Secondary Structure Prediction: A Practical Guide, In: Barciszewski J and Clark BFC (eds) RNA

Biochemistry and Biotechnology, NATO ASI Series, Kluwer Academic Publishers, also available at http://www.bioinfo.rpi.edu/~zuker

Appendix C

Molecular Quantum-Dot Cellular Automata and Nano-wires: Nano-scale charge transfer characterization for information processing

Dr. Monisha Kamala Mahanta
Associate Professor, Department of Physics & Astronomy,
SUNY College at Oneonta
Oneonta, NY 13820.

National Academy of the Sciences/NRC Senior Fellow (2004-2006).

Abstract:

The SUNY College at Oneonta collaborated in the DOE/ NYNBIT (New York Nano-Bio-molecular Information Technology) Incubator project, initiated by a group of New York universities, funded by the U.S. Department of Energy and administered by the SUNY Institute of Technology at Utica, NY. in the years 2006-2008, with a two-prong proposal for a feasibility study in the areas of Quantum-Dot Cellular Automata (QCA) and Nano-wire technology. The availability of equipment such as thermal evaporation units, a spin-coater and a furnace at SUNY-Oneonta, access to an Atomic Force Microscope (AFM) at the New York University and, the purchase of some optical equipment on the grant for LG beams has made this feasibility study a successful venture that leads to future possibilities worth pursuing.

Introduction:

Limits of shrinking devices:

The serious limitations experienced in the miniaturization of devices with the current-switch paradigm of turning the current "on" and "off" giving binary digits 0 and 1 include the inability to turn the current on and off cleanly, needing longer time to charge the interconnect lines between devices, presence of large statistical current fluctuations caused by charge quantization, occurrence of considerable energy dissipation.

At the macroscopic level of large dimension devices, charges are considered to flow in a continuous manner making the flow of current analogous to fluid flow so that the laws of fluid mechanics can be applied to the motion of charges. In miniaturized structures, however, charges can no longer be treated as a continuous fluid and need to be quantized into finite and small numbers that follow the laws of quantum mechanics. For such structures a noticeable fluctuation in voltage is observed due to the tunneling or similar effect of a quantum of charge moving from

one conductor to another causing a change of energy and potential. The reduction in the capacitance with the shrinking size in the relationship between charge, voltage and capacitance $\Delta Q = C\Delta V$ is at the root of this sensitivity since at a capacitance of 10^{-17}F or less, ΔV is likely to be larger than the thermal voltage for a single electron moving from one side to the other (1). Such effects cause degradation in the performance of CMOS technology ultimately limiting the device densities attainable with transistors. These limits have led to the growing importance of developing alternative bottom up approaches such as nano-technology which allows scaling at the limits of molecular dimensions. QCA and Nano-wires are two such approaches and our interest in these two areas has been guided by the PI's prior experience in the field of Quantum Information Technology using Laguerre Gaussian beams of laser light acquired during her senior fellowship from the US National Academy of the Sciences.

Thus, **QCA and Nano-wires** are two significant developments in the field of nano-science and technology with great potential for miniature technology based on a bottom-up process rather than the top-down process that governs our practical applications till now. The process of miniaturization to the nano-level is, however, fraught with as much difficulties as it offers promises due to the fact that as we shrink to small dimensions, fundamental limits are faced in device behavior. Classical dynamics reaches its limits and quantum mechanics starts to play a role and physical effects resembling optical behavior such as quantization of motion, diffraction and interference effects, tunneling modify the performance of devices.

Quantum-Dot Cellular Automata (QCA)

The QCA approach to nano-scale electronics for encoding information involves Coulomb interactions and tunneling between metal dots that operate at cryogenic temperatures or molecular cells that operate at room temperatures. QCA cells have no current flowing between the cells. Metal dot QCA devices such as logic gates, clocked shift registers have been demonstrated to have power gain; however, the disadvantage is the need of cryogenic temperatures. QCA molecules with redox centers, on the other hand, offer the advantage of working at room temperature.

The literature review shows a fair amount of research done in both metal-dot and molecular cell QCA. An idealized QCA cell is like a box with dots or charge containers at its four corners (2), and two extra mobile electrons in that confinement can orient themselves in those dots creating charge configurations in a polarized cell which can be interpreted as a binary "0" and a binary "1". Thus the binary information of "0" and "1" is stored in the bistable charge configuration of the cell in stead of the on off states of a current switch since there is no current flowing from cell to cell. The dots or charge containers in the cell can be created by a) electrostatically forming quantum dots in a semiconductor, or, b) small metallic islands connected by tunnel junctions, or, c) redox centers in a molecule. The electrons can have quantum tunneling between the dots; however, they are not allowed to tunnel between cells. The cells are connected by Coulomb electrostatic forces only, thereby making it possible to configure binary circuits.

As reported in ; ref 2, the Notre Dame group (Orlov et al) demonstrated in 1997 the first metal dot QCA cell using aluminum islands as the dots coupled by aluminum oxide tunnel junctions. The procedure used for the formation of these dots and junctions involved e-beam lithography

and two angled metal evaporations with an intervening oxidation step. The tunnel junctions were realized by overlapping two metal layers.

Lent et al have reported the use of metal dot cells as prototypes for molecular QCA cells. The shadow evaporation technique they used kept the capacitance at a relatively high value and enabled experimentation at 70mK temperature, yet to reach the room temperature performance of molecular devices.

QCA research using metal dots has reported results such as the demonstration of the first functioning QCA cell, signal transmission down a QCA line, construction of a QCA logic gate, clocked QCA switching, power gain. The QCA feasibility research proposed by SUNY-Oneonta was encouraged by the success of this line of research and the availability of some of the equipment necessary for the work.

In contrast to metal dots cells, single molecule QCA cells generate much larger Coulomb energies due to their small size making room temperature operation possible and have low power requirements and heat dissipation making high density molecular logic circuits and memory feasible. A single molecule implementation of a QCA cell requires a molecule in which charge is localized on specific sites and can tunnel between these sites. These molecules have their redox center playing the role of dots or charge containers and the tunneling paths are provided by bridging ligands. The Aviram molecule composed of two allyl groups separated by an alkane/butyl bridge illustrates the basic features of molecular QCA as reported by Lent et al. The literature review brought us to the conclusion that although our first QCA effort has been at the metal island level, that approach would ultimately have to be abandoned in favor of a single molecule approach due to the room temperature advantage. However, it is to be noted that the next phase of our research is likely to concentrate more on nanowire research due to the availability of facilities.

Nano-wire

Nanowires are quasi-one-dimensional structures of nano-scale diameter and micron length rationally assembled on atoms or other nanosize building blocks, with unique quantum properties and the potential to be integrated into electronic and opto-electronic devices at the nanoscale. One dimensional structures are the smallest dimension structures that can be used for efficient transport of electrons and optical excitations which makes these critical to the function and integration of nanoscale devices. The emphasis on nanowires as foundation of the bottom-up paradigm is driven by the realization that nanowires can function both as active devices and interconnects simultaneously which is critical in any integrated nanosystem.

Semiconductor nanowires represent one the best defined and best controlled class of nanoscale building blocks and can be rationally and predictably synthesized in single crystal form with all of their key parameters such as chemical composition, geometric dimensions, doping etc. controlled during their growth. A wide range of device concepts and integration strategies have been enabled by these novel structures due to the fact that it is possible to combine them in ways beyond the scope of conventional electronics.

Nanowire applications include individual nano-wire-based biological sensors, crossed p-n junction light-emitting diodes, integrated nanowire logic devices.

Nanowires of various compound semiconductors such as ZnO, GaN, In_2O_3, Si_3N_4, Ga_2O_3, and MgO have been synthesized successfully. However we have been interested in ZnO because of the advantages it offers (3). It is a semiconductor with a wide and direct band-gap of 3.37eV at room temperature and a large exciton binding energy (60 meV), which is much greater than the thermal energy at room temperature, has a high piezoelectric constant. Also it is considered to be bio-safe and bio-compatible. These characteristics make this material highly valuable for fabricating mechanical devices such as acoustic transducers, sensors and actuators, for application in opto-electronics, , biomedical science.

We are interested in the optical, electrical and thermal characterization of nano-wires and decided to prepare for future experimentation on ZnO. Accordingly we reviewed the literature for fabrication and characterization techniques and found fabrication techniques such as sputter deposition, template assisted growth, chemical vapor deposition growth using vapor-liquid-solid (VLS) for nanowire synthesis in the literature. The thermal evaporation units and the furnace available at SUNY-Oneonta are anticipated to be useful for this kind of experimentation on nano-wires.

Optical manipulation:

An additional interest in the feasibility study was the optical manipulation of nanowires using Laguerre Gaussian profiles which carry orbital angular momentum (4). The PI has experience in the field of Laguerre Gaussian beams (5) shown below and would like to apply those for nanowire characterization.

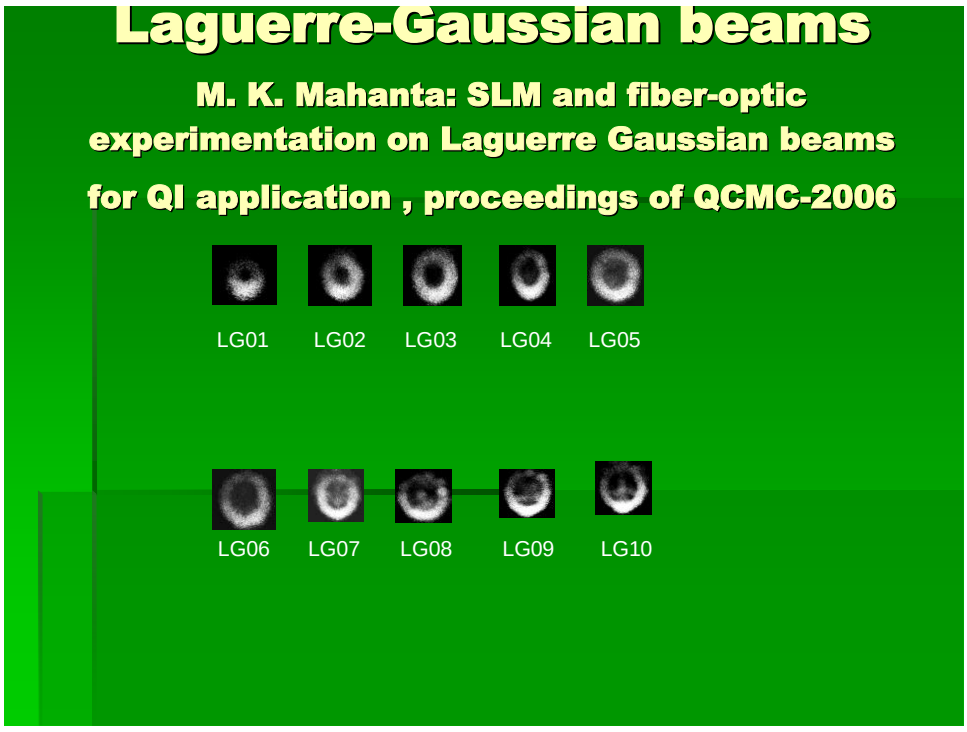


Fig. 1. LG beam profiles created by the PI in an earlier research (ref 5)

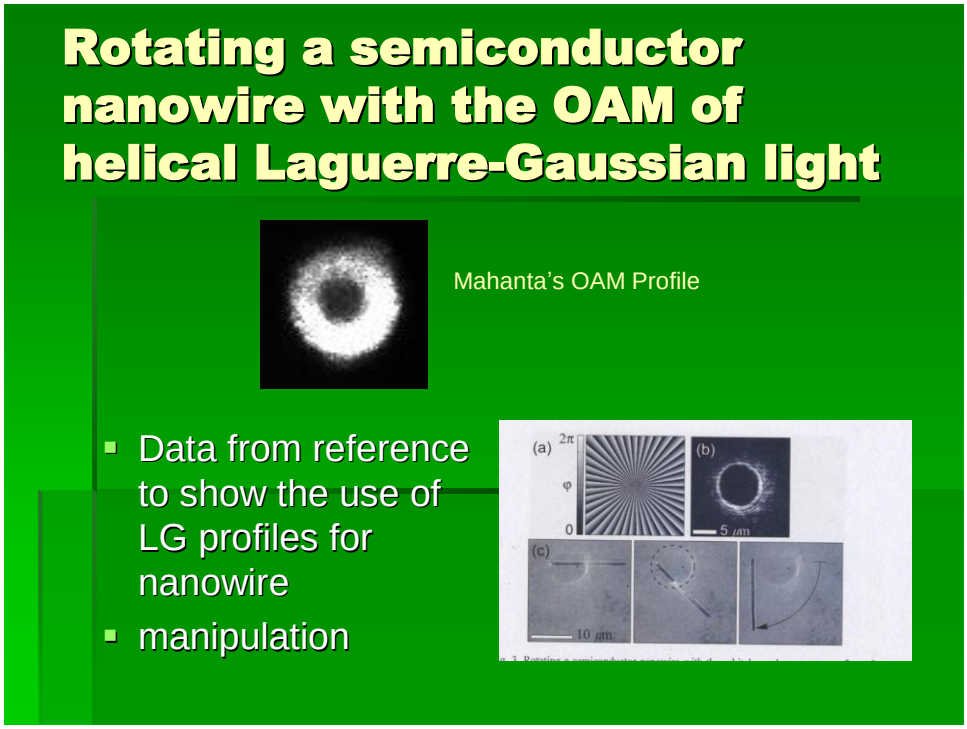


Fig 2. The reference (6) data has been used to compare and show the possibility carried by the PI's light profile

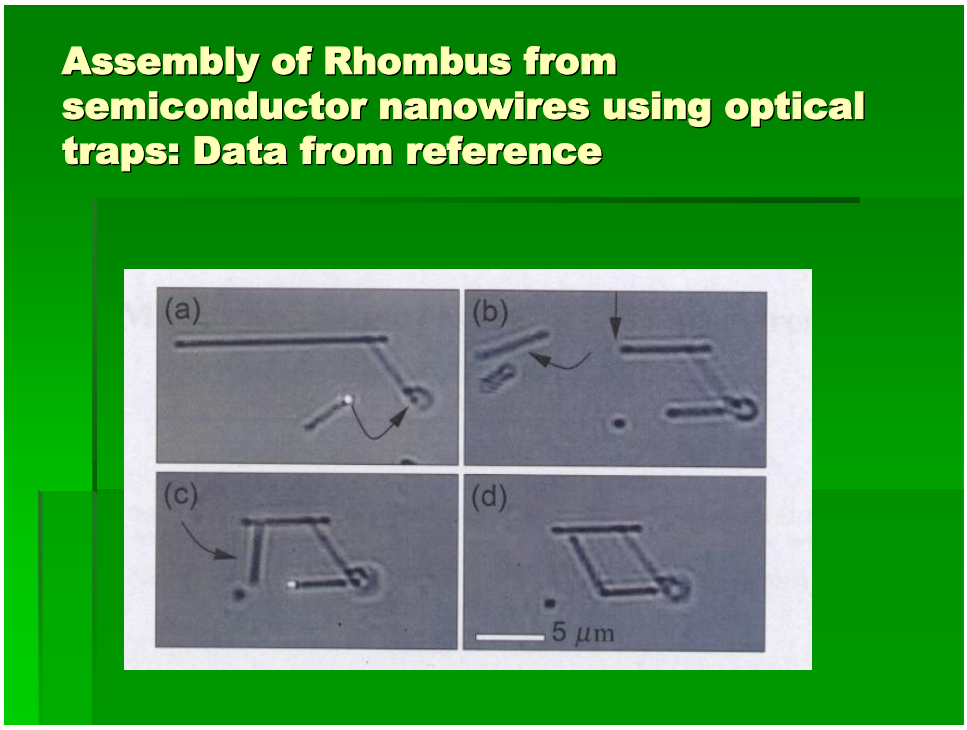


Fig 3, Reference (6) data used to show the possibilities offered by trapping; these effects need to be investigated using the PI's LG profiles.

The Oneonta effort:

The availability of a thin film lab equipped with a couple of thermal evaporation units and a spin-coater at SUNY-Oneonta led to the anticipation that a feasibility study into one or both of these areas of nano-science and technology would be worthwhile and might lead to some useful experimentation. Initially QCA was thought to have better prospects than the nano-wire research. However, the situation seemed to develop more favorably toward the latter. Therefore the research progressed accordingly.

As written in the proposal, the QCA effort aimed at reaching the molecular level ultimately because of its temperature and size related benefits; however, due to the complexity of the process and lack of equipment, the first attempt had to be made at the relatively simple level of very thin coatings of pure metal with the idea of depositing islands which could be observed under an Atomic Force Microscope (AFM), the search for which was itself a part of the proposed feasibility research since Oneonta does not have the AFM. Several attempts to establish contact with the nano-technology center at Albany, NY were unsuccessful and that almost brought the QCA effort to a halt which forced SUNY-Oneonta's efforts to be directed toward nano-wires. In that process, however, a window opened with the kind offer from the New York university collaborators of NYNBIT to allow the PI of this project to use their AFM to observe the thin films made at the SUNY-Oneonta lab. Some of those data are submitted in this report in Figures 4a, 5, and 6. The data on ordinary thin films of copper and gold on silicon substrates were found to be encouraging for both QCA and Nano-wires since a quantitative measurement of the hills and valleys of the coatings at the nano level was made possible for the project by the AFM as shown in the figures below. For comparison, a figure (Fig. 4b) from the reviewed literature (7) has been included.

The next phase would be to design strategies for developing a variety of coatings of better quality and more suitable for QCA studies and use in a variety of environments for nano-wire experimentation which would then lead to some characterization experiments. It is to be noted that with metal coatings, QCA work would need cryogenic temperatures (about 100K) which might be difficult; however molecular QCA might be more approachable due to its ambient temperature possibilities. The spin coater is anticipated to be useful for this purpose. It has not been possible, however, to test it in this feasibility study owing to the lack of a fume hood, much needed for health safety, in the thin film laboratory. Once the appropriate coatings are made for QCA work, experiments can be designed on Coulomb force effects, electrical conductivity, quantum tunneling effect to shed light on how to analyze the charge transfer phenomena for information processing at the nano-level. However, it must be noted that due to better preparation, the nanowire research is likely to be given a higher priority to the QCA research.

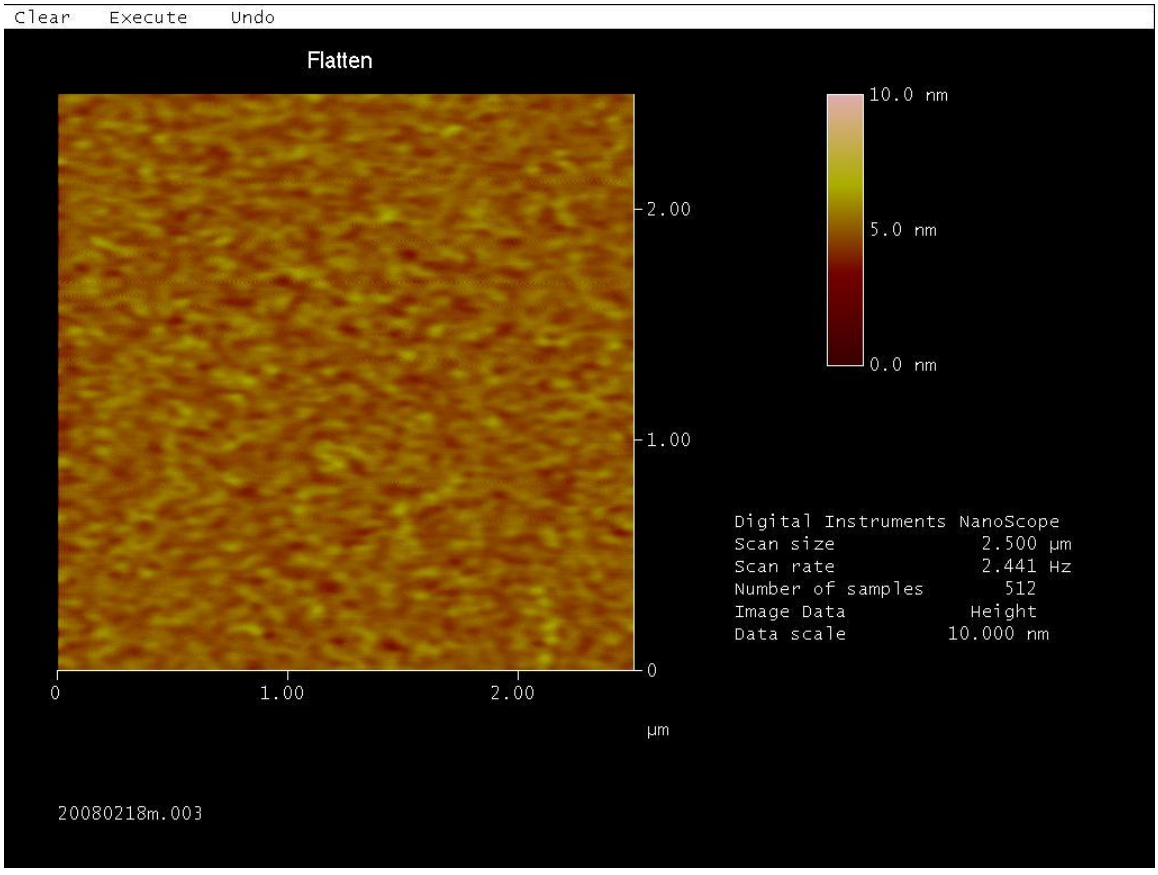


Fig 4a. AFM data: A color coded view of the hills and valleys of the coating. The darker spots correspond to 0-5nm and the brighter spots correspond to 5-10nm as shown on the scale on the side.

Fig. 4b below from ref (7) shows an array of ZnO wires at different resolutions. The 2 micron view appears to have the same graininess as the 2.5 micron view of our simple thin coating data shown in fig. 4a above. This lends feasibility to our line of thought. We are planning to generate in the next phase of our research, data similar to those in the rest of the figure below.

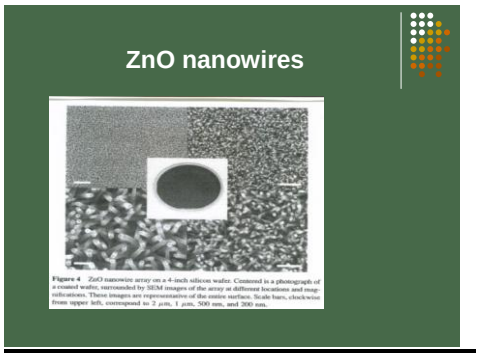


Fig. 4b. ZnO nanowires at various resolutions (Ref. 7)

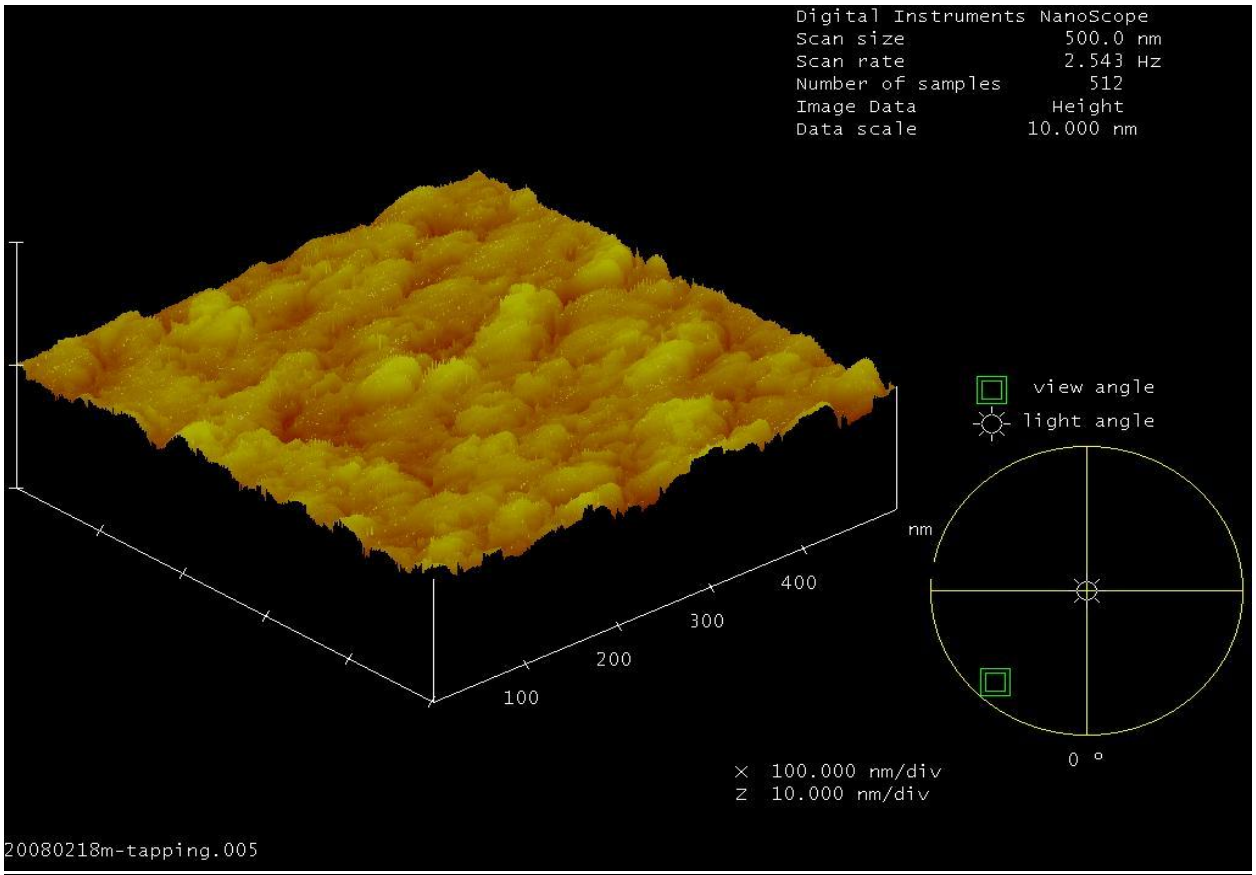


Fig 5. AFM data: An angular view of the roughness of the coating

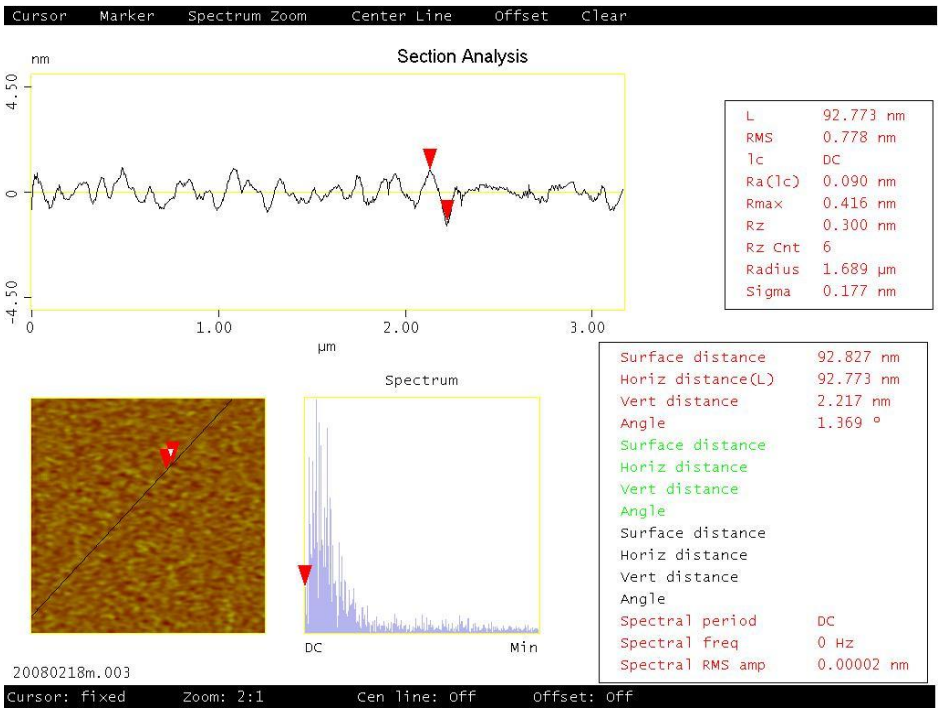


Fig 6. AFM data: Analysis of a small section on the thin coating.

The feasibility study on nano-wires has benefited from the availability of the AFM at NYU, a furnace in the Department of Chemistry and Bio-chemistry of SUNY-Oneonta and the prior experience of the PI in the field of Laguerre-Gaussian (LG) beams with orbital angular momentum built into it. An exhaustive survey of the literature has shed light on the experimental approach for nano-wire fabrication using materials such as ZnO, gold-coated silicon substrates etc. A successful fabrication of nano-wires at the Oneonta labs will be well served in observation and measurement by the AFM available at NYU, although an effort is currently under way to acquire an AFM at SUNY-Oneonta. The feasibility study has made it possible to envision the use of the LG beams for studying the mechanical and optical properties of nano-wires. The grant has enabled the enhancement of the lab at Oneonta for this purpose, thereby pushing the nano-science and technology effort at SUNY-Oneonta beyond the limits proposed for the feasibility study.

Additional accomplishments on the NYNBIT grant:

1. SUNY-Oneonta desires of its undergraduate students to get involved in faculty research which is also a goal of the NYNBIT Incubator. This research was able to accomplish that by using a part of the grant for educational and training purposes

A student was recruited to help with the literature review and the initial planning of the research. The student presented his work titled "Synthesis of Nano-Structures: A Feasibility Study" at the XXVI Annual Rochester Symposium for Physics Students, SPS Zone 2 Regional Meeting held at Rochester University on April 21, 2007 (8). Also an

abstract (9) has been submitted to the ASEE for presentation at its 2009 Austin conference.

2. The thin film lab at SUNY-Oneonta was used in the summer of 2007 to introduce the practical thin-film aspect of nano-technology to two summer camps of promising high school students hosted by SUNYIT, Utica, NY. The fabrication of thin films and the furnace to be used for nano-wire fabrication were demonstrated following a Power Point presentation of some of the fundamentals and applications of nano-wire technology.

3. CONMED Inc. has expressed interest in collaborating with SUNY-Oneonta in the nano-wire research. The focus of this research is likely to be on medical application of the nano-wire technology. The focus will however have to be narrowed further to areas with the greatest relevance. One possibility is the Optical Nerve system, the literature on which is being reviewed.

Conference presentations and Publications from this research project:

1. Corey Lemley (Supervisor M. K. Mahanta): "Synthesis of Nano-Structures: A Feasibility Study" presented at the XXVI Annual Rochester Symposium for Physics Students, SPS Zone 2 Regional Meeting held at Rochester University on April 21, 2007. Published in the proceedings of abstracts of the conference.

2. M. K. Mahanta: "A Nanotechnology Research and Education Effort at SUNY-Oneonta", Abstract submitted for review for presentation at the 2009 ASEE Annual Conference and Exposition, Austin, Texas, June, 2009.

Conclusion:

In conclusion, this feasibility study has been a successful venture on the part of SUNY College at Oneonta leading to future possibilities worth pursuing. The next phase of the research has been geared toward the fabrication and characterization of ZnO and Si_3N_4 nanowires using Laguerre Gaussian beams of light. Further equipment will be necessary for that phase; however, we are hoping to break new grounds and generate interesting data.

References:

1. Lynn E. Foster: Nanotechnology: Science, Innovation and Opportunity, Prentice Hall/Pearson Education, Inc., 2006.
2. C. S. Lent, T. P. Fehlner, G. Bernstein, G. Snider, M. Lieberman: Molecular Quantum-Dot Cellular Automata, University of Notre Dame, In.
3. Zhong Lin Wang: Nanostructures of Zinc Oxide, Materials today, June 2004
4. H. Rubinsztein-Dunlop, T. A. Nieminen, M. E. J. Friese and N. R. Heckenberg: Optical Trapping of Optical Particles, Advances in Quantum Chemistry, Volume 30, 469-492, 1998.

5. M. K. Mahanta: SLM and fiber-optic experimentation on Laguerre Gaussian beams for QI application , proceedings of QCMC-2006
6. Peter J. Paulzauski et al: Optical trapping and Integration of semiconductor assemblies in water, Nature Materials, Volume 5, February 2006
7. Matt Law, Joshua Goldberger, and Peidong Yang: Semiconductor Nanowires and Nanotubes, Annual Review of Materials Research, 2004, 34:83-122.
8. Corey Lemley (Supervisor M. K. Mahanta): "Synthesis of Nano-Structures: A Feasibility Study" presented at the XXVI Annual Rochester Symposium for Physics Students, SPS Zone 2 Regional Meeting held at Rochester University on April 21, 2007. Published in the proceedings of abstracts of the conference.
9. M. K. Mahanta: "A Nanotechnology Research and Education Effort at SUNY-Oneonta", Abstract submitted for review for presentation at the 2009 ASEE Annual Conference and Exposition, Austin, Texas, June, 2009.

Appendix D

DasWPS: A Web-based P System Simulator with Query Facilities

Digendra K. Das,

SUNY Institute of Technology

P.O. BOX 3050

Utica, NY 13504

Abstract. In this project we designed a web-enabled simulator for P systems named DasWPS. We used CLIPS embedded in C, and designed the simulator as a web based application, complemented by a query language to specify the results.

1. Introduction

Transitional P systems and deterministic P systems with active membranes [1] are simulated in various programming languages, and some of them have been used to solve NP-complete problems as Hamiltonian Path Problem (HPP), SAT, Knapsack, and partition problems. P systems with active membranes, input membrane and external output are simulated in CLIPS, and used to solve NP-complete problems [2]. New variants of these simulators provide symport-antiport rules, and catalysts. A more complex simulator written in Visual C++ for P systems with active membranes and catalytic P systems is presented in [3]. It provides a graphical simulator, interactive definition, visualization of a defined membrane system, a scalable graphical representation of the computation, and step-by-step observations of the membrane system behavior.

A parallel and cluster implementation for transition P systems in C++ and MPI is presented in [4]. The rules are implemented as threads. At the initialization phase, one thread is created for each rule. Since each rule is modeled as a separate thread, it should have the ability to decide its own applicability in a particular problem.
In order to detect if the P system halts, each membrane must inform the other membranes about its inactivity. It can do so by sending messages to others, and by using a termination detection algorithm. In this report we present a new simulator based on CLIPS. The previous CLIPS implementations represent P systems rules by CLIPS facts; we get a significantly faster execution by using CLIPS rules to implement P systems rules. In [2], the P system data are inserted directly into code, and so they cannot be easily modified, as opposed to our implementation where a P system is an input data, providing considerable amount of flexibility. P systems as input data are described by XML documents; this fact provides a standard method to access information, making it easier to use, modify, transmit and display. XML is readable and therefore is quite straight-forward, it expresses metadata easily in a portable format, just because many applications can process XML on many existent platforms. Moreover, by using XML, it becomes easy to define new features and properties of P systems. XML allows an automated document validation, restricting wrong input data, and warning the user before execution with respect to the possible errors in their P systems description. From a user point of view, all these features facilitate an efficient description and reconfiguration of the P systems.

An important advantage of the DasWPS simulator is given by its availability as a Web

application. Web applications do not require an installation. As with any Web application, it can be used from any machine anywhere in the world, without any previous preparation. A simple and easy to use interface allows the user to supply an XML input both as text and as rules. A friendly way of describing P systems is given by a helpful interactive JavaScript-based P system designer. The interface provides a high degree of reusability during the development and simulation of the P systems. The initial screen offers an example, and the user may find useful documentation about the XML schema, the rules, and the query language. The query language helps the user to select the output of the simulation.

The next section presents the DasWPS structure, and describes why it is unique compared with previous simulators. Several examples implemented in the DasWPS system are described in Section 3. Finally, further development directions are identified.

2. DasWPS Software Architecture

The software structure of the simulator has three distinct levels. The inner level is the CLIPS level. This level integrates part of the knowledge about the theoretical description of P systems, the result being a library of CLIPS functions, meta-rules and templates. Since CLIPS is easily embeddable in C (as its name "C Language Integrated Production System" suggests), we can control the CLIPS level from a C program, and we include some example to illustrate how this is done. The C level is strengthened by introducing a C library for modeling and simulating

P systems based on the CLIPS library. The DasWPS web based application level offers a user-friendly interface to the simulator, and can become, after the addition of debugging and visualization features a powerful P system development tool.

2.1 CLIPS level

This is the core level of the simulator. We address here some crucial issues, namely how the simulator implements in a sequential context the *maximally parallel* and *nondeterministic execution* of P systems.

Maximally parallel execution

The maximally parallel execution requirement relies on constraining our simulation cycle to the following distinct steps:

1. React step: where the activated reaction rules are sequentially executed.
2. Spawn step: where the new objects created by rules inside their membranes are asserted as object facts; they become visible for a future React step.
3. Communication step: where the objects injected or ejected by communication rules in different membranes are asserted as objects facts.
4. Divide step: it handles possible division processes of membranes.
5. Dissolve step: it handles dissolving processes of membranes.

By constantly recording the state of the P system after each React, Spawn and Communication steps, we can get a trace of an execution.

Nondeterministic execution

CLIPS uses RETE algorithm to process rules; RETE is a very efficient mechanism for solving many-to-many matching problem [5]. The nondeterministic execution requirement is fulfilled by the CLIPS *random* mechanism. We have looked closely at the random strategy, and we found it makes the same choice for the same configurations in different executions. By calling the random function of CLIPS, the random mechanism uses the random number generator. The failure is related to the improper seeding of the random number generator. We have corrected this error, and properly seed the random number generator by using */dev/urandom*, the entropy gathering device on GNU/Linux systems. This aspect can be also useful for other CLIPS implementations possibly affected by the same failure.

Data representation

An important choice regarding an implementation is given by data representation. We decide to represent P system objects and membrane structure as CLIPS facts (with set-fact-duplication option of CLIPS set to on), and the P systems reaction rules as CLIPS rules. This contrasts the previous implementations which have represented reaction rules as CLIPS facts; while their choice might allow general meta-rules for execution, we get a flexible and efficient framework by representing reaction rules as CLIPS rules. The efficiency is gained by making direct use of the CLIPS pattern-matching mechanism, and rule activation capabilities. This choice is also confirmed by the efficiency of the dissolve and divide operations which imply

a substantial amount of moving and copying. Initially we think to represent membranes as modules, but later we see that this representation decreases the efficiency and flexibility of the entire system. It is useful to note that the DasWPS simulator supports division, promoters/inhibitors, and symport/antiport rules for membranes.

2.2 C level

In the C level we use CLIPS API, although we plan to develop a complete library that encapsulates the C-CLIPS interface, namely a C library which wrap nicely around CLIPS (see Figure 1).

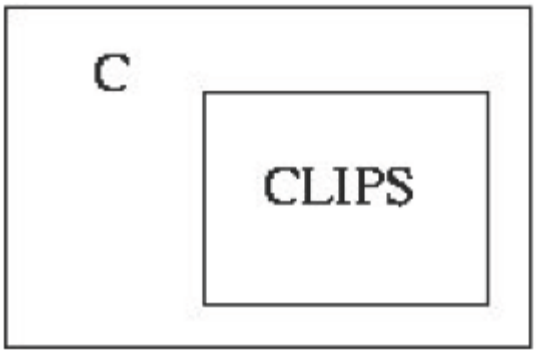


Figure 1. **Relationship between the C and CLIPS levels**.

We represent a P system using XML (Figure 2), and define an XML Schema for this kind of document. A special library is developed to handle XML parsing of the input for the CLIPS part of the simulator. Figure 2 below represents a P system in graphical format, here the simulator is commanded to multiply the number of *a* objects in membrane *1* with the number of *b* objects in membrane *0*, the result being the number of *d* objects in membrane *0*.

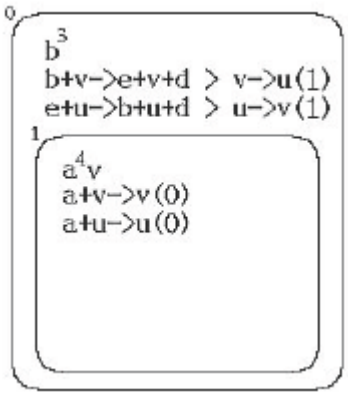


Figure 2. Example DasWPS multiplication operation graphical format

2.3 Web level

The Web level of the simulator allows the user to choose between a user-friendly P system designer written in JavaScript and a traditional HTML input form transmitting an XML description by uploading a file or by editing. Aside from the XML P system description editing, the user can specify a number of executions of the P system. The DasWPS system simulator aims to facilitate the description of the P system without requiring the user to write XML, but generating it based on the user's interaction with a dynamic interface (see Figure 3).

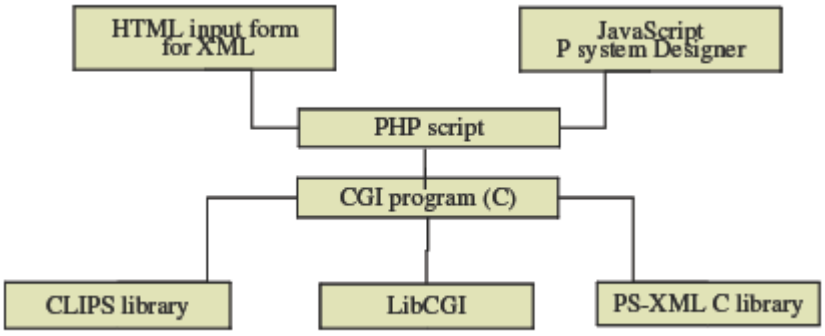


Figure 3. Structure of the Web level.

After the XML is input it is transmitted to a PHP script description, it is transmitted to a PHP script which does some further processing, and sent then to a CGI program written in C (Figure 3). The C program uses a specific P system XML library called PS-XML, as well as LibCGI and a CLIPS library in order to simulate the evolution of the P system. Finally it returns the results to the user. It is possible to select various information provided as results, and in order to help the user to select the desired information we defined a query language referred to as DasPSQL.

DasPsQL (P systems Query Language)

We designed DasPSQL as an SQL-like language for querying the state of a P system. Additionally, we developed a CLIPS library for parsing and interpreting this language. At the Web level, the queries can be included in the XML input; these queries are activated after the execution of the specified P system. If it does not exist any query, the P system is simulated, but no output is generated. At the CLIPS level it is possible to specify queries for the P system in a dynamic manner, not just before starting the simulation. At the syntactic level, DasPSQL is supported by a small CLIPS library of list-handling functions.

Multiplication

The first example is a P system that computes the multiplication of two natural numbers. Figure 4 below graphically represents the P system. As inputs we consider the

number of *a* objects in membrane *1*, and the number of *b* objects in membrane The result is given by the number of *d* objects in membrane *0*.

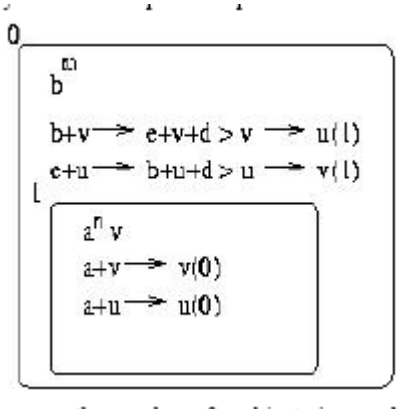


Figure 4. DasWPS Multiplication Example

This P system differs from other similar ones by that it does not have exponential space complexity, and does not require active membranes. As a particular case, it would be quite easy to compute *n*2 by just placing the same number *n* of *a* and *b* objects in its membranes. Another interesting feature is that it may continue computing the multiplication after reaching a certain result. Thus if initially there are *m b* objects and *n a* objects, the system evolves and reaches a state with *n ¢m d* objects in membrane *0*. If the user wish to continue in order to compute (*n* + *k*) ¢ *m*, it is enough to inject *k a* objects in membrane *1* at the current state, and the computation can go on. Therefore this example emphasizes a certain degree of reusability.

Recursive sum

The P system depicted in Figure 5 computes the recursive sum:  .

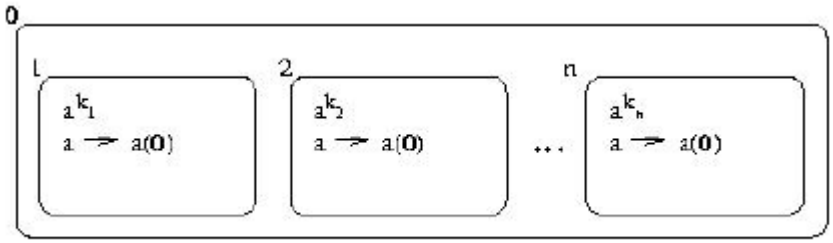


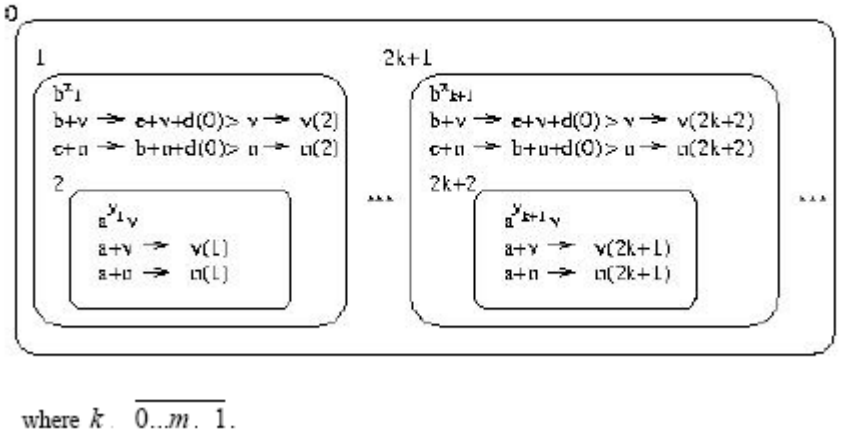
Figure 5. DasWPS system for recursive sum.

The numbers of *a* objects in the membranes 1*:::n* are the summands, and the result of the computation is the number of *a* objects in membrane 0. The PsQL query to determine this result is: (count of (objects from 0)). While this example is rather trivial, it illustrates the expressiveness of the query language (PsQL). Using PsQL queries, it is not necessary to apply the rules and execute the specified P system. Given the initial multiset, the same recursive sum is obtained by using the following query: (count of (objects from (membranes from 0)))

Dot product of two vectors

Combining the previous two examples, we can compute the dot (scalar) product *x ¢ y* of two vectors *x; y 2* N*m*, where *m 2* N. Let us denote the components of the vectors by *xi* and *yi*, respectively; these components are given by the number of *b* and *a* in the membranes labeled by 2*i* and 2*i*+1, respectively. Then *x ¢ y* is given by the number of *d* objects obtained in membrane 0 after the P system halts.

This P system is described in Figure 6: where *k* = 0*;m ¡* 1. The PsQL query for retrieving the result is: (count of (objects from 0))



where k $\overline{0...m}$. 1.

Figure 6. DasWPS for dot product example

4. Conclusion and Further Work

We presented DasWPS, a new Web based simulator of P systems. It is efficient, flexible, and does not require any previous knowledge in P systems, or expertise in computers. Since the DasWPS simulator has some novel and interesting features related to efficiency, ease of use and generality, it can become a useful tool for the community, both theoretically and practically. We intend to make the simulator available as a web service. Moreover, continuing the commitment to standards compliance, we will strive for SBML compatibility for our specification language. Further improvements are related to better debugging and visualization capabilities (including a flexible and coarse-grained tracer), developing a library of macros and methodologies using the principles of modularity, extensibility and structured design from software engineering, introducing flexible rules for the development of macros for P systems.

References

1. Gh. P¸aun: *Membrane Computing. An Introduction*. Springer-Verlag, Berlin, 2002.

2. M.J. Perez-Jimenez, F.J. Romero-Campero: A CLIPS simulator for recognizer P systems with active membranes, *Proceedings 2nd Brainstorming Week on Membrane Computing*, University of Sevilla Tech. Rep 01/2004, 387-413.

3. G. Ciobanu, D. Paraschiv: P system software simulator. *Fundamenta Informaticae*, 49, 1-3 (2002), 61-66.

4. G. Ciobanu, W. Guo: P systems running on a cluster of computers. *Proceedings 4th Workshop on Membrane Computing*, LNCS 2933, Springer-Verlag, Berlin, 2004, 123-139.

5. C.L. Forgy: RETE. A fast algorithm for the many pattern/ many object pattern match problem. *Artificial Intelligence*, 19 (1982), 17-37.

Publications:

1. **"**New York Nano-Bio-Molecular Information Technology (NYNBIT) Incubator" ASEE Annual Conference & Exposition June 22 – 25, 2008, Pittsburgh, PA

2. " Designing a Web-based P System Simulator with Query Facilities" (To be published shortly)

Appendix E

Three-Dimensional Biomolecular Computing Architectures

PI: Dr. Sergey Edward Lyshevski
Department of Electrical Engineering, Rochester Institute of Technology, Rochester, New York 14623-5603, USA
E-mail: Sergey.Lyshevski@mail.rit.edu Web: http://people.rit.edu/seleee

I. MOTIVATION, GOALS, OBJECTIVES AND ACCOMPLISHMENTS

Novel computing, processing, communication and memory paradigms have been sought. Various design, software and hardware solutions were examined attempting to utilize molecular and *natural*-centric processing at the device and system levels. Molecular device- and system-level solutions ensure fundamental soundness and unprecedented capabilities. Therefore, various concepts are under intensive research [1-8]. With a focus on enabling computing architectures and super-high-performance processing, we develop and demonstrate sound premises and advanced design methods for ^{M}PPs. The reported solutions promise to surpass any existing microelectronics platforms. The use of ^{M}PPs, implemented as molecular ^{N}hypercells or integrated circuits (^{M}ICs), promises drastically improve overall performance and functionality ensuring unprecedented processing and memory capabilities. We examine practicality of different design methods for complex PPs [4, 9-11].

Natural, biomolecular, *fluidic* and *solid* processing devices and systems exhibit distinct performance and capabilities. Furthermore, device physics and system topologies/organizations/architectures are distinct. Figure 1 reports some performance estimates at the device level [4]. The system-level performance of *natural* systems is largely unknown because basics, system architectures and other key governing principles have not been comprehended. However, *engineered* ^{M}PPs can be developed and concept of molecular processing is sound. We focus on signal and data processing for which there is an evidence of applicability and fundamental soundness of the design methods and premises reported. Our motivation is to approach the benchmarks of data processing performance and capabilities observed in living systems by means of *engineered* molecular computing. This may be accomplished only by solving a spectrum of fundamental theoretical problems and utilizing 3D molecular processing hardware.

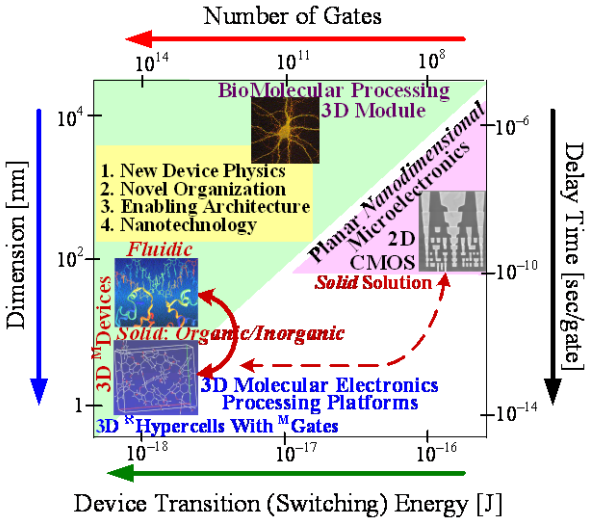


Figure 1. Towards molecular processing and memory platforms

There are a number of open problems related to the *natural processing hardware* and *software*. In particular, (1) How information processing is accomplished; (2) Which biomolecular assemblies form the *biomolecular processing hardware* within a reconfigurable networked organization; (3) Which phenomena, effects and mechanisms within *biomolecular processing hardware* constitute and execute the *software* tasks; (4) Which electrochemomechanically-induced transitions, interactions and events lead to processing, memory storage and other related tasks at the device and system levels; (5) Which device- and system-level topological, organizational and architectural solutions are utilized? Those open-ended questions are under intensive research [4]. We depart from a premise of *natural* information processing focusing on *engineered* data (signal) processing solutions which typify some features observed in living systems. Our goals are to:

- Advance design methods and principles of data processing, e.g., perform basic research and developments in theory of computing;
- Develop and demonstrate a sound design paradigm supported by highly-effective methods, algorithms and tools.

We foster research and developments on the following fundamental problems:

1. Apply *natural* spatially-distributed processing to *engineered* computing, e.g., develop and demonstrate a *neurocomputing* paradigm;
2. Develop, examine and verify methods for massive vector processing utilizing robust and reconfigurable processing;
3. Apply and utilize coherent algebraic and graph-based representations of data structures to perform a coherent design embedding these data structures into 3D neural hypercubes (^{N}hypercubes) with a subsequent technology-centric mapping by neuronal hypercells ($^{\aleph}$hypercells);
4. Research reconfigurable neural networks;
5. Develop CAD-supported tools to model and design high-performance computing platforms.

The proposed solutions ensure: (i) Rationality between *engineered* and *natural* (living) systems despite of limited knowledge even on communication (signaling) in neurons; (ii) Overall soundness of envisioned ^{M}PPs. The developed approaches associate with emerging *solid* and *fluidic* molecular processing, electronics, ^{M}ICs, etc. Enabling multi-terminal *microscopic* devices and 3D processing systems (multiple-valued logics, 3D topology, enabling organizations and advanced architectures) ensure superior performance and capabilities. Far-reaching processing benchmarks can be approached. Our fundamental results and accomplishments relax current limits, uncertainties and technology dependency. Our findings in the theory of computing and a paradigm of massive vector, parallel and distributed (pipelined due to systolic processing) computing are theoretically verified, substantiated and demonstrated.

II. NEURONAL PROCESSING AND *NEUROCOMPUTING*

Studying biomolecular PPs (^{BM}PPs), biomolecules (receptors, microtubules, neurotransmitters, enzymes, etc.) and ions were examined in [4]. The *information* carriers could accomplish processing and memory storage, while the *routing* carriers may accomplish interfacing and reconfiguration. We envisioned *engineered* ^{M}PPs which typify ^{BM}PPs. Our objective is to develop and verify fundamentally and technologically sound design paradigms. The ability to design ^{M}PPs largely depends on the system-level solutions and design methods which are under our developments.

Consider biomolecular processing between neurons using the *axo-dendritic* inputs and *dendro-axonic* outputs [4]. Each neuron may consist of m_i

neuronal processing-and-memory primitives. *Natural* processing is inherently three dimensional. Utilizing this *3D-premise*, we focus on a *neurocomputing* paradigm to accomplish high-performance processing. The *neurocomputing* paradigm centers on:

1. Realization of computing arithmetics by 3D neural hypercubes (^{N}hypercubes) which can be designed utilizing:
   - Efficient design methods applying enabling principles of embedding of computing and combinational logics into 3D structures;
   - Preeminent design and optimization algorithms which are supported by CAD tools;
2. Implementation of computing structures by $^{\aleph}$hypercells.

We study 3D reconfigurable neural networks (^{3D}NNs) to design ^{M}PPs. This leads to *engineered natural-centric* computing (processing) in 3D. We developed, applied and verified:

1. Enabling computing architectures;
2. Advanced techniques of computing arithmetics and data structure design (decision diagrams). We depart from 2D-centered computing arithmetics and design methods;
3. Design methods which utilize 3D ^{N}hypercubes.

The proposed ^{N}hypercube is a 3D-topology homogeneous aggregated assembly for massive super-high-performance parallel computing. The $^{\aleph}$hypercell is a 3D-topology multi-input/multi-output processing entity engineered from molecular aggregates (or solid-state microelectronic devices) which utilize and exhibit unique phenomena and capabilities. The proposed 3D design and hardware solutions uniquely compliment, unify and strengthen each other. The proposed algorithm is represented as:

Neuron Model (*Computing/Algebraic Function*) ↔ *Decision Diagram* ↔
3D Computing Structure (^{N}*Hypercube*) ↔ $^{\aleph}$*Hypercell*.

III. COMPUTING ARCHITECTURES

Applying a 3D-centric premise, we develop massively-parallel computing structures which are based on: (i) Embedding of decision trees and diagrams within ^{N}hypercube spatial dimensions; (ii) Computing arrays; (iii) Multiple-valued data representation. To analyze and design ^{3D}NNs, we develop and apply: (1) Advanced optimization techniques; (2) New class of decision diagrams; (3) Libraries of primitives. Using our design methods, we foster the developments of a 3D©*NeuroComputing* toolbox.

Our *neurocomputing* paradigm can be used for the representation of arbitrary computations in the form of computing expressions performed by combinational functional and sequential modules. Utilizing the proposed approach, several of the most complex problems which cannot be solved utilizing known methods, were successfully solved. In particular, the homogenous and parallelism principles of computing were implemented and demonstrated. Very promising proof-of-concept results for complex ^{3D}NNs and processing structures, embedded within various 3D topological solutions, are obtained as reported below.

We researched and integrated the following fundamental principles.

***Principle* 1 – *Natural Processing Mapping*. Computing (processing) and its realization must be performed in 3D utilizing the adequate computational models and arithmetics. The computing function is $f=f(X,Y,Z)$. Here, X, Y and Z are the functionalities (decomposition of f with respect to X, Y and Z) of a computing function f corresponding to dimensions of the computing structure in 3D. The third dimension Z maps the *computing plasticity*. From the data structure prospective, the third dimension Z leads to the ability to**

accomplish neuromorphological massive parallelism and vector concepts guarantying an efficient 3D *array* processing [4, 9-11]. The *computing plasticity Z* typifies *natural* processing. Principle 1 is applied to the *engineered* computing at the cell level (neuron) and the system level (aggregated neurons) ensuring a *natural*-centric solution.

Principle 2 – *Topological Plasticity*. Processing structures must be reconfigurable to various spatial configurations and organizations. This will ensure adaptability and soundness of enabling configurations and organizations in 3D typifying the *topological plasticity* of *natural* neurons and their aggregates.

Principle 3 – *Fault Tolerance and Robustness*. Computational models must be fault tolerant and robust. These models should perform the desired functions under stochastic behavior of processing primitives.

Principle 4 – *Compatibility and Testability*. Computing in 3D must be supported by CAD tools which must be compatible and verifiable applying existing advanced analysis/design methods and tools.

There is a need for new sound computing techniques to efficiently manipulate data. The computational principles imply that the proposed *neurocomputing* paradigm must satisfy the following properties: (i) Efficient delegation of computing (processing) and functionalities within a 3D configuration; (ii) Computational characteristics (topological redundancy, critical paths, performance, etc.) and computational capabilities must be optimized with respect to spatial configurations; (iii) Efficient control, testing and verification of 3D computing structures; (iv) Effective utilization of the state-of-the-art analysis/design techniques and tools which are applicable for design in 2D.

IV. Computing in Three-Dimensional Space and Design Method

There are several approaches for computing in 3D. The first approach is based on the idea that 2D computational structures can be layered and assembled by utilizing 2D layers as $f=f_1(X,Y)\times\ldots\times f_k(X,Y)$, where functions $f_1,f_2,\ldots,f_k$ correspond to the first-, second-, …, and k-th levels; × denotes an assembling operation. The layers of this logic network (with a physical implementation as a planar 2D microelectronics) are interconnected to achieve the desired functionality as supported by VLSI and ULSI designs. The interconnected layers form the "third dimension". In this approach, the "third dimension": (i) Does not carry or contain any functional information with respect to the variables on the implemented logic functions; (ii) Only indicates the number i of the sub-function f_i in f. This computational concept is not adequate to approach ether *natural* or emerging *engineered* problems. The second approach is based on the mapping of a logic function by "three coordinates" [12]. This approach requires complex transformations of logic functions with respect to each dimension. Each logic function requires an expansion. This approach is very complex as well as requires a complete revision of the previously developed methods, algorithms, techniques, tools, etc. The third approach is related to the 3D cellular arrays, e.g., 3D systolic arrays [13]. These structures are complex in analysis, design and optimization. Therefore, they have not been fully implemented in practice. However, the linear systolic arrays are found to be practical to perform 3D computing structure designs [10, 11].

A 3D embedding problem within two schemes is illustrated in Figure 2 [10. 11]. Figure 2.a documents the *direct* embedding, e.g., for a given guest data structure, find an appropriate topology for its representation. The *inverse* embedding is represented in Figure 2.b. E.g., for a given topological structure, find a corresponding data structure which is suitably represented by this topology. The properties of the host representation and data structures specificity, which satisfy certain criteria, are used. Within *direct* embeddings, the topology is not specified, and computing properties can be delegated to spatial dimensions without topological limitations. The

inverse formulation of the problem assumes that the topology is considered under a set of constrains.

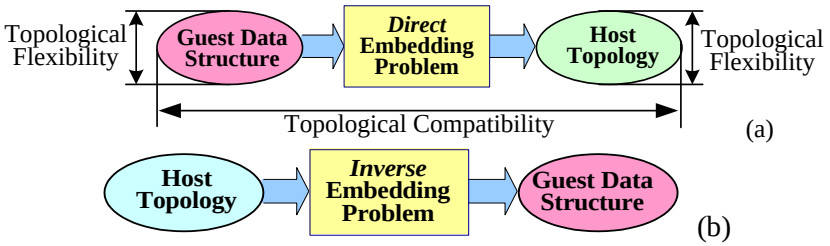


Figure 2. Embedding solutions: (a) *Direct* embedding; (b) *Inverse* embedding

To solve the embedding problem, the initial (guest) structure must be specified with respect to computational abilities. A topological structure becomes a computing network as the properties of data structures for the representation of computing functions are delegated. We utilize the fact that a decision tree is topologically isomorphic to the H-tree, which can be embedded into a 3D ^{N}hypercube. Hence, computational abilities are delegated to the H-tree. The 3D H-tree topology is constructed recursively from 2D elementary H-clusters.

The ^{N}hypercube is a topological representation of a computing function by *n*-dimensional graph. The computing function is

$$\underset{\text{Computing Function}}{f} \Rightarrow \underset{\text{Operation}}{\overset{2^n-1}{\underset{i=0}{\mathbf{L}}}} \underset{\text{Coefficient}}{\mathbf{K}_i} \left(x_1^{i_1} \ldots x_n^{i_n} \right) \Rightarrow \underset{\text{Form of Computing Function}}{f_F} .$$

The data structure is described in matrix form using the truth vector $\boldsymbol{F}$ of a given computing function *f* as well as the vector of coefficients **K**. The logic operations are represented by **L**. The design flow is

$$\underset{\text{Step 1}}{\text{Function } f} \Leftrightarrow \underset{\text{Step 2}}{\text{Graph}} \Leftrightarrow \underset{\text{Step 3}}{^{N}\text{Hypercube}}.$$

The linear word-level decision diagram (LDD) allows one to perform the compact representation of logic functions utilizing linear arithmetic polynomials (LPs) [4, 9-11]. The following mapping is established

LDD(a_0,a_1,…,a_{n-1},a_n) ↔ LP.

The algorithm is: Function (Circuit) ↔ BDD Model ↔ LDD Model ↔ Realization.

The polynomial representation of logical functions ensures the description of a many-output function in a word-level format. The expression of a Boolean function *f* of *n* variables (x_1,x_2, …,x_{n-1},x_n) is

$$LP = a_0 + a_1 x_1 + a_2 x_2 + \ldots + a_{n-1} x_{n-1} + a_n x_n = a_0 + \sum_{j=1}^{n} a_j x_j .$$

The nodes of LP correspond to a positive Davio expansion. Thus, LDDs are obtained by mapping LPs where the nodes correspond to the positive Davio expansion, and functionalizing vertices related to the coefficients of LPs. The LDD design flow is: Primitive ↔ LP Model ↔ LDD Model ↔ Realization.

It is found that ^{N}hypercubes can compute arbitrary complex *f*. Our approach is based on embedding a decision tree into a ^{N}hypercube. Consider a computing function *f* of *n* variables. Applying conventional concepts, a complete tree and the corresponding H-tree are characterized by a complexity $O(2^n)$, where *n* is the number of logic variables. It is impossible to embed large *f* of several hundreds of variables into ^{N}hypercubes. We represent each neuron or logic gate by its ^{N}hypercube equivalent. A 3D topology is obtained by assembling ^{N}hypercubes which represent neurons or logic gates. The complexity of the proposed approach depends on the number of gates,

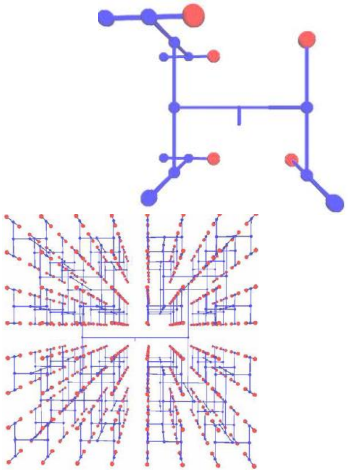
and the complexity is $kO(n)$. We significantly reduced the overall complexity thereby ensuring computational tractability and soundness of design of processing (computing) platforms.

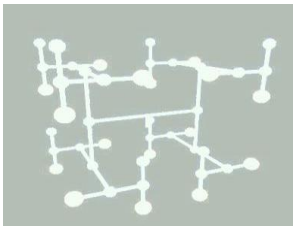
V. 3D®*NEUROCOMPUTING* TOOLBOX AND DESIGN OF PROCESSING PLATFORMS

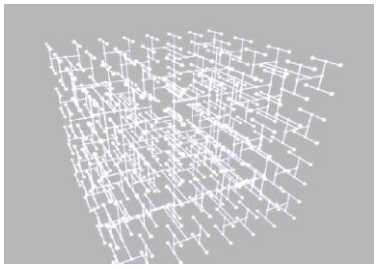
A hierarchical CAD tools must be developed to attain a coherent cost-effective design of high-performance computing and processing platforms. An interactive CAD must guarantee optimal technology-driven design, rapid prototyping, performance evaluation, etc. Ideally, CAD tools should provide a concurrent support to research transfer as well as technology developments.

A 3D©*NeuroComputing* toolbox, which utilizes the fundamental developments reported, is under developments and verification. It this toolbox, models and characteristics of neurons and connections within and between them can be specified. The proof-of-concept version of our toolbox provides a solution for modeling of feedforward ^{3D}NNs with ~1000 inputs and outputs in 3D. The known *artificial* NNs have $\sim 1\times10^3$ active inputs and $\sim 1\times10^4$ active processing primitives (gates) with from 1×10^2 to 1×10^3 inputs each. It corresponds to $\sim 1\times10^8$ connections and to the processing speed of $\sim 1\times10^{11}$ *connections-per-second*. These results are based on the state-of-the-art 2D design methodology [14]. The *natural-centric* processing implies at least $\sim 1\times10^{14}$ connections with the speed of $\sim 1\times10^{17}$ *connections-per-second* in 3D. A 3D©*NeuroComputing* toolbox is aimed to approach super-large-scale problems, e.g., computing networks of neurons with $\sim 1\times10^9$ connections. This is accomplished by utilizing the solutions reported and methods developed which significantly reduce the complexity by applying linear polynomials and advanced design approaches.

Embedding of 2D Decision Trees and Diagrams Into 3D Structures – Optimization of decision trees was achieved to accomplish embedding by solving a large-scale problem. The optimized 2D decision tree is a 2D decision diagram which can be embedded into incomplete ^{N}hypercubes. The established combinational circuit benchmarks from the ISCAS database of logic networks are used. The successful designs for these benchmarks provide evidence of soundness of the proposed design, optimization and embedding methods and algorithms. To perform computing and processing, we replace logic primitives (AND, OR, NAND, NOR and other gates) by 3D ^{N}hypercubes as illustrated in Figures 3.a and 3.b. A node in the decision tree realizes the Shannon expansion $f = \bar{x}_i f_0 \oplus x_i f_1$, where $f_0=f(x_i=0)$ and $f_0=f(x_i=1)$ for all variables in f. The terminal nodes carry information of computing flow. Figure 3.c illustrates a spatial topology neuron network, consisting of 546 ^{N}hypercubes, which models a neuron with 46 inputs and 32 outputs.







(a) (b) (c)

Figure 3. (a) Optimized spatial topology of a 4-input neuron;
(b) Aggregated 5-input neuron; (c) Neuron in 3D with 46 inputs and 32 outputs

***Binary and High-Radix Design in 3D* – Our goal is to increase the computational power of ^{3D}NNs. We represent a neuron by a multiple-valued structure which processes data on radix 3, 4, …,16. A 3D©*NeuroComputing* toolbox can manipulate multiple-valued data structures. A high radix enhances processing performance, capabilities and efficiency. Multiple-valued data was encoded by binary codes. The design and modeling for 4-valued ^{3D}NNs are given in Table 1. In particular, c2670 ALU/control, c5315 ALU, and c7552 adder/comparator are reported. Enhancing information content (quaternary versus binary) does not require the doubling of computational resources. The results are verified for 8- and 16-valued data. These results demonstrate and validate the reported design. There are virtually no limits on the size of ^{3D}NNs. We conducted the studies for ^{3D}NNs with ~1×10^{10} connection.**

Table 1. Modeling of 3D neural networks using multiple-valued data structures

BENCHMARK	I / O	#LEVEL	#CONN	#CELL	SIZE
C2670	233/140	40	16606	1374	1375×40×140
C5315	178/123	68	62834	3192	3192×68×123
C7552	207/108	64	49168	4627	4627×64×108

2D and 3D Designs for a 9-bit ALU – The studied ALU performs arithmetic and logic operations simultaneously on two 9-bit input data words, as well as computes the parity of the results. Conventional 2D logic design of a 9-bit ALU (c5315 circuit) with 178 inputs and 123 outputs results in 2406 gates. The proposed 3D binary design leads to 1413 gates which are networked and aggregated in 3D. We utilize the developed 3D©*NeuroComputing* toolbox to carry out the design. The designed network is visualized in Figure 4 using various data structures, such as: (i) 2D and 3D representations; (ii) Network and netlist descriptions; (iii) Decision trees and diagrams. All design phases can be observed, verified and controlled.

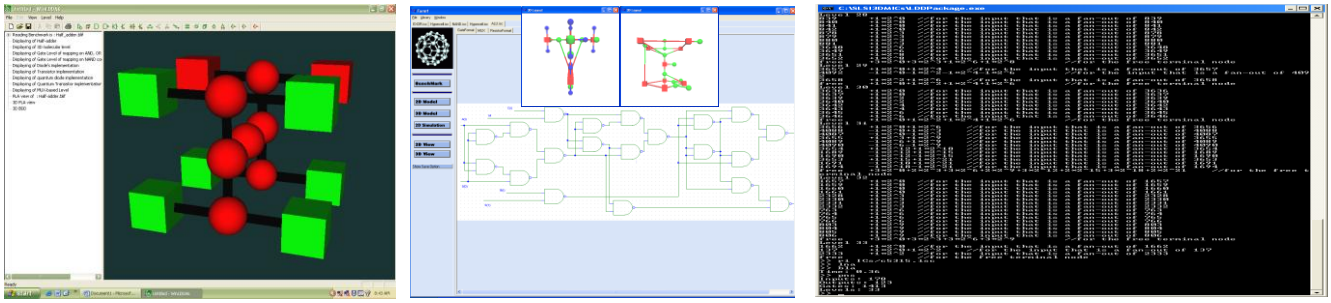


Figure 4. Design in 3D: Interactive 3D©*NeuroComputing* toolbox performs design, embedding, optimization, visualization, etc.

VI. CONCLUSIONS

The proposed 3D computing architectures utilize two major innovations at the system level, e.g. (1) Enabling 3D organization, topology, aggregation and neuronal networking to accomplish reconfigurable neurocomputing; (2) Advanced design, optimization and modeling methods supported by CAD tools. The reported concept leads to far-reaching system-level innovations and advances. The proposed computing and processing platforms will enable:

1. Enormous advantages guarantying information processing preeminence and computing superiority;
2. Strong commercial potential with immediate applications in new generations of preeminent processors and memories;
3. Far-reaching and practical technologies with technology transfer features.

Through this DoE subcontract to RIT, under the RIT statement of work, the following major tasks were successfully accomplished:

1. Basic theory of computing and 3D *natural*-centric molecular processing paradigm were further developed:
   - Enabling synthesis taxonomy and computing architectures were documented;
   - Sound and efficient design methods for high-performance computing and processing were developed and demonstrated;
   - Enabling design methods were applied and verified;
2. We initiated the developments of interactive and adaptable CAD tools to support major design tasks at the system level.

REFERENCES

1. J. R. Heath and M. A. Ratner, "Molecular electronics," *Physics Today*, no. 1, pp. 43-49, 2003.
2. J. C. Ellenbogen and J. C. Love, "Architectures for molecular electronic computers: Logic structures and an adder designed from molecular electronic diodes," *Proc. IEEE*, vol. 88, no. 3, pp. 386-426, 2000.
3. *International Technology Roadmap for Semiconductors*, Edition, Semiconductor Industry Association (SIA), SEMATECH, Austin, Texas, USA, 2005.
4. S. E. Lyshevski, *Molecular Electronics, Circuits, and Processing Platforms*, CRC Press, Boca Raton, FL, 2007.
5. S. E. Lyshevski, *Molecular Computing and Processing Platforms*, *Handbook of Nanoscience, Engineering and Technology*, Ed. W. Goddard, D. Brenner, S. E. Lyshevski and G. Iafrate, CRC Press, Boca Raton, FL, pp. 7.1 – 7.82, 2007.
6. S. E. Lyshevski, "Neuroarchitectronics and neuromorphological molecular processing

platforms," *Proc. IEEE Conference on Nanotechnology*, Arlington, TX, pp. 399-402, 2008.
7. S. E. Lyshevski, *Three-Dimensional Molecular Electronics and Integrated Circuits For Signal and Information Processing Platforms*, *Handbook on Nano and Molecular Electronics*, Ed. S. E. Lyshevski, CRC Press, Boca Raton, FL, pp. 6-1 – 6-102, 2007.
8. M. A. Lyshevski and S. E. Lyshevski, "BioMEMS and molecular processing: Engineering *biomimetics* and its applications," *Proc. IEEE Conference on Prospective Technologies and Methods in MEMS Design*, Polyana, Ukraine, pp. 29-36, 2007.
9. S. E. Lyshevski, V. P. Shmerko, M. A. Lyshevski and S. N. Yanushkevich, "Neuronal processing, reconfigurable neural networks and stochastic computing," *Proc. IEEE Conference on Nanotechnology*, Arlington, TX, 2008.
10. S. N. Yanushkevich, V. P. Shmerko and S. E. Lyshevski, *Computer Arithmetics for Nanoelectronics*, CRC Press, Boca Raton, FL, 2008.
11. S. N. Yanushkevich, V. P. Shmerko and S. E. Lyshevski, *Logic Design of NanoICs*, CRC Press, Boca Raton, FL, 2005.
12. A. Al-Rabady and M. Perkowski, "Shannon and Davio sets of new lattice structures for logic synthesis in three-dimensional space," *Proc. 5th Int. Workshop on Applications of the Reed-Muller Expansion in Circuit Design*, Mississippi State University, pp.165-184, 2001.
13. S. Y. Kung, *VLSI Array Processors*, Prentice Hall, Upper Saddle River, NJ, 1988.
14. S. Haykin, *Neural Networks: A Comprehensive Foundation*. Prentice Hall, Upper Saddle River, NJ, 1999.

PUBLICATIONS WHICH ACKNOWLEDGES THE DOE FUNDING

The following papers, published by Dr. S. E. Lyshevski (PI of the subcontract to RIT), as well as co-authored with Drs. M. Lyshevski, V. Shmerko and S. Yanushkevich, acknowledge the DoE support:

1. S. E. Lyshevski, "Neuroarchitectronics and neuromorphological molecular processing platforms," *Proc. IEEE Conference on Nanotechnology*, Arlington, TX, pp. 399-402, 2008.
2. M. A. Lyshevski and S. E. Lyshevski, "BioMEMS and molecular processing: Engineering *biomimetics* and its applications," *Proc. IEEE Conference on Prospective Technologies and Methods in MEMS Design*, Polyana, Ukraine, pp. 29-36, 2007.
3. S. E. Lyshevski, V. P. Shmerko and S. N. Yanushkevich, "Benchmarking performance and physical limits on processing electronic device and systems: Solid-state, molecular and *natural* processing paradigms," *Proc. NanoTech Conference*, Boston, MA, vol. 3, pp. 31-34, 2008.

ACKNOWLEDGEMENTS

The author sincerely acknowledges a support from the US Department of Energy under the contracts DE-FG02-06 *Three-Dimensional Biomolecular Computing Architectures*.

Appendix F

Development of course work.

1. **Introduction to Nano-Science and Nano-Technology** **3cr.**

Instructor: Dr. Amir Fariborz, Associate Professor
Department of Mathematics and Science,SUNYIT..

Course description:

This course covers a broad range of introductory topics on nano-science and nano-technology and lays out the foundation for continuation to more advanced and technical courses on various aspects of nano-science and nano-technology. Approximately one half of the course is devoted to the mathematics and science foundations, and one half is devoted to selected topics on applications and technology. The foundation will include a review of basic mathematics, basic structure of atoms, molecules and solids, as well as properties of light and its interaction with matter. Selected topics on applications and technology will be included. The course evaluation will be based on two class tests, regular home assignments & the final examination.

Prerequisites: None.

Text Book:
No specific textbook has been assigned to the course. However, the course will heavily depend on the bibliography shown below.

Topics:

Week 1: Review of basic mathematics

Week 2: Review of basic mathematics

Week 3: Structure of atoms, molecules and solids

Week 4: Structure of atoms, molecules and solids

Week 5: Light and its interaction with matter

Week 6: Light and its interaction with matter

Week 7: Review/Midterm exam

Week 8-14: Applications: Carbon Nano-Tube, Buckyballs & Nano-Wires.

Week 15: Review/ Final Exam.

Bibliography:

1. Understanding Nanotechnology, Scientific American.
   Nanotechnology For Dummies by Richard D. Booker and
   Earl Boysen (Paperback - Aug 8, 2005)

2. Introduction to Nanotechnology(Hardcover)
   by Charles P., Jr. Poole (Author), Frank J. Owens (Author)

3. Nanotechnology: Understanding Small Systems by Ben
   Rogers, Sumita Pennathur, and Jesse Adams (Hardcover -
   Nov 29, 2007)

4. Nano-Hype: The Truth Behind the Nanotechnology Buzz by
   David M. Berube (Hardcover - Dec 30, 2005)

5. Principles of Nanotechnology: Molecular-Based Study Of Condensed Matter
   In Small Systems by G Ali Mansoori (Paperback - Mar 3, 2005)

6. Nanotechnology: Science, Innovation, and Opportunity by Lynn E. Foster
   (Hardcover - Dec 31, 2005)

2. Introduction to Nanotechnology

Instructor: Dr .Daniel K. Jones 3cr.
Associate Professor
MET & IET Department, SUNYIT

Course Description

An undergraduate course introducing the field of nanotechnology from the perspective of mechanical engineering. Topics include mechanics of materials, fabrication, and sensing at the micro- and nano-scales. Students will apply concepts from engineering, mathematics, physics, chemistry, and biology.

Prerequisites

Physics I, Calculus I, Chemistry

Topics

Units, scales, and dimensional analysis
Micro Electro Mechanical Systems (MEMS)
    Electromechanical concepts, piezoresistivity, magnetism, sensing, actuation
    Microfabrication, silicon-based technology, lithography, micromachining
Nano Electro Mechanical Systems (NEMS)
    Nano-scale materials, nano-electronics
    Cellular biology, E. Coli Bacteria
    Trans-disciplines: mechanical, fluid, chemical, biological, thermal, electromagnetic systems
    Motion, Nanoactuators
    Newtonian mechanics, Lagrange and Hamilton methods
Practical applications
        Gyroscopes, accelerometers
        Instrumentation, microscopy
        Thin films, micro-motors, turbines

Bibliography

"Foundations of MEMS," C. Liu, Pearson/Prentice Hall, 2006.
"Nano- and Micro-Electromechanical Systems: Fundamentals of Nano- and Microengineering," 2nd Edition, S.E. Lyshevski, CRC Press, 2005.
"Nanostructured Materials: Processing, Properties, and Applications," 2nd Edition, ed C.C. Koch, William Andrew Publishing, 2007.
"Nanotechnology: Science, Innovation, and Opportunity," L.E. Foster, Prentice Hall, 2006.
"Nanoscale Energy Transport and Conversion: A Parallel Treatment of Electrons, Molecules, Phonons, and Photons," G. Chen, Oxford University Press, 2005.

Selected Reading

"Fantastic Voyages: Nanodevices in development today promise to give medicine capabilities that were once purely in the realm of fiction," P. Decuzzi and M. Ferrari, Mechanical Engineering, Oct 2007, pp. 24-27
"A glossary of cellular components," Ned S. Wingreen, Physics Today, Sept 2006, pp. 80-81.
"Good conduct: A research says that a new membrane textured on the nanoscale will let fuel cells triple the current they can carry," Michael Abrams, Mechanical Engineering, Aug 2007, pp. 28-29.
Nanotechnology, Institute of Physics weekly journal, http://www.iop.org/EJ/journal/Nano
"Power Points: Nanoscale materials may soon revolutionize energy storage," Jeffrey Winters, Mechanical Engineering, Aug 2007, pp. 22-24.

"Nanotubular Gains," Jeffrey Winters, Mechanical Engineering, Aug 2007, pp. 10-11.
http://www.nanotechweb.org
"MEMS from the Nanoscale Up," A.C. Ratzel III, Mechanical Engineering, Mar 2007, pp. 24-33.
"No small risk: As nanotech products race to the marketplace, researchers are still trying to determine if they could endanger human health," J. Winters, Mechanical Engineering, Sept 2006, pp. 30-33.
"Nano-scale armor: molecular hinges, electrorheological fluids – will they protect tomorrow's infantry?" M. Abrams, Mechanical Engineering, Sept 2006, pp. 34-37.

3. **Introduction to Carbon Nanotubes**

Instructor: 3cr.

Dr. S. Qazi
Professor EET Department, SUNYIT.

Catalog Description: This course introduces the student with the emerging field of carbon nanotube, applications and fabrications. Topics will include the principle of carbon nanotubes, methods of fabrication, applications, visualization and challenges of implementing in different applications. **Prerequisite**: One course in Physics or the approval of the Instructor

Objectives/Goals:

- To review the fundamentals of nanotechnology and carbon nanotubes
- To study the principle of fabrications of nanotubes
- To study various applications of carbon nanotube

Text Book: No textbook is assigned. Handouts from journal and books will be provided. Use of Internet and simulation software for relevant material will also be made.

Tentative Topics:

- Introduction to the field of nanotechnology and carbon nanotubes (CNTs), new trends, applications and challenges
- Form of carbon , history and types of carbon nanotubes
- Single wall and multiple wall carbon nanotubes, structure of carbon nanotubes, arm chair, zigzag and chiral nanotubes
- Mechanical, electrical and optical properties of carbon nanotubes
- Unique properties of carbon nanotubes and applications

- Applications of carbon nanotubes in nanoelectronics, carbon nanotube based electronics, advantages of carbon nanotube field-effect transistors over Silicon CMOS
- Carbon nanotube and optoelectronics
- Biomedical applications of carbon nanotubes
- Microfluidcs, Fuel cells
- Method of fabrication of carbon nanotubes, arc discharge method, laser ablation method, chemical vapor deposition
- Large scale synthesis of single wall nanotubes, ultra fast pulses from a free electron laser method, continuous wave laser power method
- Electrokinetic tools for fabrication of carbon nanotubes, dielectrophoresis
- Large scale integration of carbon nanotubes, alignment and dispersion of carbon nanotubes
- Location and visualization of nanotubes, manipulation of carbon nanotubes
- Scanning tunneling microscope, Atomic force microscope, modes of AFM, tip –sample interaction of AFM modes
- Study of carbon nanotubes using simulation tools, nanotube modeler and nanohub

Recommended Reading**:**

1. Springer Handbook of Nanotechnology, Editor Bharat Bhushan 2004.
2. Michael Daenen, "Wondrous World of Carbon Nanotubes," 2003. http://students.chem.tue.nl/ifp03/synthesis.htmi
3. Michael Berger, "Carbonnanotube to the rescue of Moore's law," http://www.nanowerk.com/spotlight/spotid=1934.php
4. Niraj Sinha and John T.W. Yeow, "Carbon Nanotubes for Biomedical Applications," IEEE Transactions on Nanobioscience, Vol.4.No.2, June 2005.
5. K.Tsukagoshi et al, "Carbon nanotube devices for nanoelectronics, Science Direct, April 2002. http://www.sciencedirect.com/science
6. Phaedon Avouris and Jia Chen, "Nanotube electronics and Optoelectronics," Materialtoday, Volume 9, Issue 10, October 2006.
7. R. Martel et al, "Carbon Nanotube Field-Effect Transistors and Logic Circuits," DAC 2002, June 10-14, 2002, New Orleans, LA.
8. Joe Alper, "Nanotube Poisedto Help Cancer Patients,"NCI Alliance for Nanotechnology in Cancer, January/February 2006.
9. P.A. Williams, et al, "Controlled Placment of an Individual Carbon Nanotube Onto a Microelectromechaqnical Structures," Applied Physics Letters, April2002.
10. Nanotube Modeler, Generation of Nanogeometries, Copyright J Crystal Soft, 2005-2008. http://www.jcrystal.com/products/wincnt
11. http://www.nanohub.edu

Term/Research Paper:

Each student is required to submit a research/term paper on a topic chosen from the field of carbon nanotubes. The average length of paper may vary between 1200 and 1600 words and should conform to an established written format. The material for the paper should be

referenced from the recent Journal and technical magazines only. The instructor must approve all the topics.

Grading Criteria:

Mid term exam	33%
Final examination	33%
Research paper or simulation project and home work	33%

Important: Students are reminded to study and follow the code of academic conduct as given in SUNYIT Students Handbook

4. BIO 270 Cell Biology. 3 Cr.

Instructor: Dr. Michael L. Hochberg

Professor, Biology, SUNYIT.

Course Description:

A survey of modern cell biology which includes the chemistry of cellular molecules, structure, functions and specializations of cells and organelles. Four hours of lecture each week. Prerequisite: BIO 102, BIO 103 (One Year Introduction to Biology or consent of Instructor)

Learner Objectives:

Students will

1. understand the relationship between molecular structure and function
2. demonstrate knowledge of the dynamic character of cellular organelles
3. be familiar with the process of macromolecular biosynthesis
4. demonstrate knowledge of the use of chemical energy in running cellular activities
5. understand the nature of cellular regulation and relate it to the development of cancer
6. be able to relate topics of cell biology to physiological processes in plants and animals

Course Textbook:

Alberts et al. 2002. Molecular Biology of the Cell, 4th Edition. Garland Publishing. ISBN: 0815332181

Selected References:

Books:

Alberts et al. 2004. Essential Cell Biology, 2nd Edition. Garland Science/Taylor & Francis Group

Gall, R. and J. McIntosh. 2000. Landmark Papers in Cell Biology: selected research articles celebrating forty years of The American Society for Cell Biology. Cold Spring Harbor Laboratory Press

Lehninger, A. L., Nelson, D. C. and Cox, M. 2004. Lehninger Principles of Biochemistry. W.H. Freeman

Scott et al. 2003. Molecular Cell Biology, 5th Edition. W.H. Freeman

Watson et al. 2003. Molecular Biology of the Gene, 5th Edition. Benjamin Cummings

Journals:

American Journal of Respiratory Cell and Molecular Biology

Cell Structure and Function

Cell Stress & Chaperones

Molecular and Cell Biology

Nature

Science

Course Schedule:

Week	Topic
1	Cell and Genomes; Cell chemistry and Biosynthesis
2	Proteins; DNA and Chromosomes
3	DNA replication; Protein Synthesis
4	Gene Expression; Manipulating proteins, DNA and RNA
5	Manipulating proteins, DNA and RNA; Visualizing Cells
6	Membrane Structure and Membrane Transport
7	Intracellular Compartments and Protein Sorting; Vesicular Traffic.
8	Energy conversion: mitochondria and chloroplasts

9	Cell Communication; Cytoskeleton
10	Cell cycle; Cell Division
11	Cell Junctions, Adhesion and Extracellular Matrix
12	Germs, Cells & Fertilization; Multicellular development
13	Histology and Cancer
14	Adaptive Immune System; Pathogens, Infection and Immunity

Student Evaluation:

Exams (3)	70%	
Assignments	30%	100%

5. MA 380 Biomolecular Mathematics **3Cr.**

Instructor: Dr. Anthony Macula
Dept. of Mathematics
SUNY- Geneseo**.**

Course Description:

This course introduces the student to mathematical models and applications in biomolecular dynamics. The main focus is on combinatorial and statistical models used in the development of DNA based nanotechnology. Mathematical concepts mostly come combinatorics and probability, but no prerequisite knowledge of these areas will be assumed. Some calculus and linear algebra will be included. Instruction in Maple programming will be given.

Prerequisites: Completion of five courses toward the major in Mathematics or permission of instructor.

Topics:

1. DNA
2. Biomolecular Computing
3. Sequences, Subsequences and Secondary Structures
4. Dynamic Programming
5. Maple Programming
6. DNA Statistics
7. Combinatorial DNA Models
8. Statistical Thermodynamics
8. DNA Codes
10. Group Testing and DNA

Reading:

1. (TEXT) Theoretical and Experimental DNA Computation Martyn Amos

2. (REF) An Introduction to Bioinformatics Algorithms (Computational Molecular Biology Neil C. Jones , Pavel A. Pevzner

3. (REF) Algorithms on Strings, Trees and Sequences: Computer Science and Computational Biology, Dan Gusfield

4. (REQ) Group Testing to Annihilate Pairs Applied to DNA Cross-Hybridization Elimination Using SYBR Green I, Morgan Bishop, Anthony J. Macula, Kayla Nimmo, Lauren Wood, Wendy K. Pogozelski, Thomas E. Renz . Journal of Computational Biology. 2007, 14(1): 84-96.

5. (REQ) New t-Gap Insertion-Deletion-Like Metrics for DNA Hybridization Thermodynamic Modeling. Arkadii G. D'yachkov, Anthony J. Macula, Wendy K. Pogozelski, Thomas E. Renz, Vyacheslav V. Rykov, David C. Torney
Journal of Computational Biology. 2006, 13(4): 866-881.

6. (REQ) Free Energy Gap and Statistical Thermodynamic Fidelity of DNA Codes, Arkadii G. D'yachkov, Anthony J. Macula, Thomas E. Renz, Vyacheslav V. Rykov, Journal of Computational Biology, to appear

7. (REQ) Hypothesis Group Testing, Morgan Bishop, Anthony Macula, Thomas Renz, Vladimir Ufimtsev, Journal of Combinatorial Optimization, to appear

Grading:

Three exams and problem sets (which will include mathematical programming).

Outcomes:

1. Students will learn how mathematics is used to describe DNA molecular dynamics.

2. Students will learn how mathematics is used to design and optimize experiments.

3. Students will learn how information is stored, retrieved and processed by synthetically produced biomolecules

4. Students will learn how to write mathematical programs in Maple.

6. MAT 455 Membrane Computing 3 Cr.

Instructor: Dr. Edmond Rusjan
Associate Professor
Department of Mathematics and Science, SUNYIT.

Course Description:

This course is an introduction to membrane computing, a branch of natural computing, which abstracts from the structure and the functioning of the living cell. Membrane systems, also called P systems, are distributed parallel computing devices, processing multi-sets of objects, synchronously, in compartments delimited by the membrane structure. This computing model has been proposed in 1998 and has quickly gained wide attention and acceptance. Four hours of lecture per week. Prerequisites: MAT 381 or equivalent or permission of instructor.

Text Book:

Membrane Computing, G. Paun, Springer**.**

Bibliography:

1) "Computing with Cells and Atoms", Calude, C.S., Taylor and Francis.
2) "Membrane Computing", G. Paun, Springer.
3) "Membrane Computing: International Workshop", C. Martin-Vide., Springer.
4) "Membrane Computing: 6th International Workshop, WMC2005", R. Freund, Springer.
5) "Membrane Computing: WMC2004", G. Mauri, Springer.
6) "Aspects of Molecular Computing", N. Jonoska, Springer.
7) "Emergent Computation", M. Simon, Springer.
8) "Cellular Computing", M. Amos, Oxford University Press.
9) "Computation in Living Cells", A. Ehrenfeucht, Springer.

Goals / Objectives:

1) To gain knowledge of the basic principles of membrane computing;
2) To become familiar with the techniques of membrane computing and with recent results in the field of membrane computing.

Course Plan:

Week 1 Introduction to Membrane Computing

Weeks 2-3 Elements of Computability

Weeks 4-5 Membrane Systems with Symbol-Objects – Test I

Week 6 Evolution Rules Priorities

Week 7 Priority and Synchronization

.

Week 8 Controlling the Permeability of Membranes

Week 9 Promoters and Inhibitors

Week 10-11 Evolution Versus Communication – Test II

Week 12 Structuring the Objects

Week 13 Networks of Membranes

Week 14 Special Topics in Membrane Computing

Week 15 Review - Final Examination.

Student Assignment:

The final grading of each student will be based on the following:

1. Home Assignments (Solving problems).
2. Two Class Tests,
3. Final Examination.

Computer Usage:
Limited use of the computer for problem solving is encouraged.

Modern Algebra Usage:
Modern algebra principles are applied in the course.

Library Usage:
Students are encouraged to use Library Facilities.

COURSE ADVISEMENT STATUS:
ISET Elective and Applied Mathematics Elective

Prepared By: Edmond Rusjan

7. BIOL 312 DNA Laboratory *3 Cr.*

***Instructor**: Dr. Nancy J. Bachman*

Dept. of Biology, Suny-Oneonta.

Course description: Introduction to DNA laboratory methods applicable to the study of gene structure and function, forensic analysis, genetic testing,

bioinformatics, genome analysis and nano-biology. Course will review DNA chemistry and highlight topics of interest featuring DNA. Project-based labs will provide experience with DNA isolation, polymerase chain reaction, gel electrophoresis, DNA sequencing, DNA analysis software and reporter gene detection**.**

Offered alternate years

Pre-Requisite*:* BIOL 212.

Lecture topics to be covered:

Properties of DNA, information flow (3 lectures)

Gene regulation, reporter genes (3 lectures)

Recombinant DNA and polymerase chain reaction (4 lectures)

Eukaryotic genes: findings from the genome projects (4 lectures)

Gene transfer technologies (2 lectures)

DNA sequencing technologies (4 lectures)

Bioinformatics (2 lectures)

DNA diagnostics: genetic diseases and cancer (4 lectures)

DNA fingerprinting and forensics (2 lectures)

DNA computing and nanobiology (2 lectures)

Lab Facility: DNA Lab at SUNY- Oneonta

Appendix G

Published Conference Papers.

SUNYIT:

New York Nano-Bio-Molecular Information Technology (NYNBIT) Incubator

Digendra K Das
Professor
Department of Mechanical & Industrial Engineering Technology
Director
New York Nano-Bio-Molecular Information Technology (NYNBIT) Incubator.
SUNY Institute of Technology
P.O. Box 3050
Utica, NY 13504-3050

Abstract

This paper presents the outcome of an effort made by a consortium of six universities in the State of New York to develop a Center for Advanced Technology (CAT) in the emerging field of Nano Bio-Molecular Information Technology. The effort consists of activities such as organization of the NYNBIT incubator, collaborative research projects, development of courses, an educational program for high schools, and commercial start-up programs.

Introduction

Six New York Universities met in the Fall of 2004 at a workshop held at the SUNY Institute of Technology (SUNYIT), Utica, NY, and explored the possibility of establishing a Center for Advanced Technology (CAT) in the emerging field of Nano and Bio Information Technology. All the participants agreed that in order to achieve this goal an initial organization would have to be formed for a period of two years, which would be located at SUNYIT, Utica, NY, and named "New York Nano-Bio-Molecular Information Technology (NYNBIT) Incubator".

The mission and purpose of this organization is to set up a plan to establish a Center for Advanced Technology (CAT) focused on fostering an environment of research, development and education and creating a new industrial base in New York State in this unique technology area.

The collaborating Institutions are:

7. SUNYIT
8. SUNY- Geneseo
9. SUNY-Binghamton
10. SUNY-Oneonta
11. Rochester Institute of Technology (RIT)
12. New York University (NYU)

The activities of the NYNBIT incubator are as follows:

1. Organization of the NYNBIT Incubator
2. Collaborative Research Projects
3. Development of course work
4. High School Educational Program
5. Commercial start-up program.

These are briefly described in the following sections:

Organization of the NYNBIT Incubator

The participating institutions selected a Director for the NYNBIT Incubator, who was given the charge of setting up the organization and exploring possible sources of funding. This involved the following tasks leading to the current structure of the organization:

i) Select a proper location for the office of the NYNBIT incubator at SUNYIT.
j) Procure office furniture and computers, printers and other peripherals.
k) Set up the furniture and the computers and its peripherals in the office and establish the net work connections.
l) Identify and select the members for an Executive Advisory Board. Initially the board was constituted with four members selected from the federal government, local industries and the small business development center (SBDC). One of the members acted as the chairman of the board. The board advised the director of the NYNBIT incubator in all aspects of the project.
m) A Research and Development Advisory Committee was formed with representative from all the participating Institutions. The committee advised the director in various aspects of the research and development projects.
n) An Industrial Liaison officer was hired to identify possible commercial partners for the incubator and also to help the Director in the various aspects of the daily operations of the NYNBIT office.

o) An organizational consultant was hired to advise the Director in various aspects of the organization.
p) A work study student assistant was hired to assist in the daily operations of the NYNBIT office.

The fund raising efforts of the organization were spread over approximately two years. The NYNBIT project is now funded by the US Department of Energy for an amount at three quarter of a million dollars for a period of two years.

Collaborative Research Projects

One of the major objectives of the NYNBIT Incubator has been to develop collaborative research projects amongst the participating institutions and explore the possibility of commercial start- ups. In the first year of the operation of NYNBIT, all six institutions have participated in this collaboration; each project has been led by a principal investigator from the respective campus and there has been active participation by other faculty members and graduate students. However, senior undergraduate students have also been strongly encouraged to participate in these research projects. The titles of the projects and the participating institutions are shown below:

a) SUNYIT, Utica, "Designing a Web-based P System Simulator with Query Facilities."
b) SUNY- Geneseo, "Bio-molecular Computing Technologies."
c) SUNY-Binghamton. "New technologies to measure cancer and human pathogen proteins."
d) SUNY- Oneonta, "Molecular Quantum-Dot Cellular Automata and Nano-wires: Nano-scale charge transfer characterization for information processing".
e) Rochester Institute of Technology, Rochester, "Nanobiocomputing Architectures and Molecular Electronics."
f) New York University, New York, "GRIN: Technology combining Genomics, Robotics, Informatics and Nanotechnology for Single Molecule Analysis."
g) New York University, New York, "Self-Assembled DNA Arrays and Devices for Diverse Structural Patterning."

The research experience level of the participating principal investigators (PI) is in the range of ten to thirty years. All PIs have published extensively and two of them are endowed full professors.

All the projects mentioned above were funded by the NYNBIT incubator and are close to a successful completion and several papers are being prepared for publication. Some of the recent publications[1, 2, 3] by the participating faculty and student investigators are shown in the bibliography.

Development of course work

One of the important objectives of the NYNBIT has been the development of educational packages for the work force in the field of Nano-Bio-Information Technology. In the first year of the operation of the NYNBIT incubator, eight courses were developed at the baccalaureate (B.S.) level on various aspects of Nano-Bio-Information Technology. These courses will be used toward a concentration in nano-technology within the B.S. degree program in Mechanical Engineering Technology at SUNYIT. The courses will also be available, on-line, as electives for students in the collaborating institutions. The names of the courses are shown below:

i) Introduction to Nano-Bio-Molecular information technology: 3 Cr.
ii) Material Science Aspects of the Nanotechnology: 3 Cr.
iii) Nano-Micro-Electromechanical Systems (NEMS/MEMS): 3 Cr.
iv) Carbon Nanotube Technology: 3 Cr.
v) Molecular Biology of the Cell: 3 Cr.
vi) DNA Computing: 3 Cr.
vii) Membrane Computing: 3 Cr.
viii) DNA Laboratory: 3 Cr.

Several faculty members from the participating institutions with five to twenty years of teaching and research experience in these fields were actively involved in the development of these under-graduate level courses.

Two labs were developed to support the courses mentioned above. These labs are located at the SUNY Oneonta Campus. The names of the labs are:

3) Thin Film Lab
4) DNA Lab.

Another federal grant in the amount of a quarter of a million dollars was awarded to equip the DNA lab with the state of the art lab equipments.

High School Educational Program

A high school level educational package was developed based on the courses mentioned in the previous section. The intended audience for this package is high school students in the sophomore, junior and senior grades. All the faculty members involved in the development of college level courses, shown in the previous section, were actively involved in the development of this package.

The educational package was presented to a selected audience in two summer camps in the summer of 2007 at the SUNYIT campus. Field trips were organized for the participants to visit the Thin film lab and DNA lab at SUNY-Oneonta campus. A total of twenty high school students and ten high school Math, Science and Technology teachers attended the summer camps. The student's participation in the summer camps was free

and the participating teachers were awarded appropriate stipends to attend the summer camps.

Commercial start-up program.

One of the major objective of the NYNBIT incubator project was to transfer the know how of this emerging technology to the interested local industries of the New York state. The activities to achieve this goal are indicated below:

e) An Industrial Liaison Officer (ILO) was hired and his responsibility was to take all the actions necessary to establish a link between the local industries and the NYNBIT incubator under the supervision of the director. The ILO was also responsible for helping the director in the daily operation of the incubator office.
f) A data base of the local industries (initially Mohawk Valley region) was created with the help of the Small Business Development Center (SBDC, currently located at the SUNYIT campus).
g) In the first year of the operation of the incubator about ten local industries were identified for possible commercial collaboration with the incubator.
h) Currently plans and discussions are in progress to identify possible application projects and exploratory attempts are being made to identify sources of funds such as SBIR grants.

Plans for the future and concluding remarks.

The main objective of the NYNBIT incubator project was to establish a Center for Advanced Technology (CAT) in the emerging field of Nano & Bio Information Technology. The activities described in the previous sections were all focused on achieving that goal. The outcome of the activities in the first year of operation of the NYNBIT incubator has been positive and very encouraging. In the second year of the NYNBIT project, plans are in progress for creation of a CAT and possibility of acquiring funding from state sources are being explored. It is anticipated that the CAT will be located at the SUNYIT campus in the next couple of years.

Acknowledgement

The author would like to thank the U.S. Department of Energy for supporting the NYNBIT incubator project with a grant. The author would also like to thank the faculty /staff and the graduate / undergraduate students of the six Institutions for actively participating in the project.

Bibliography

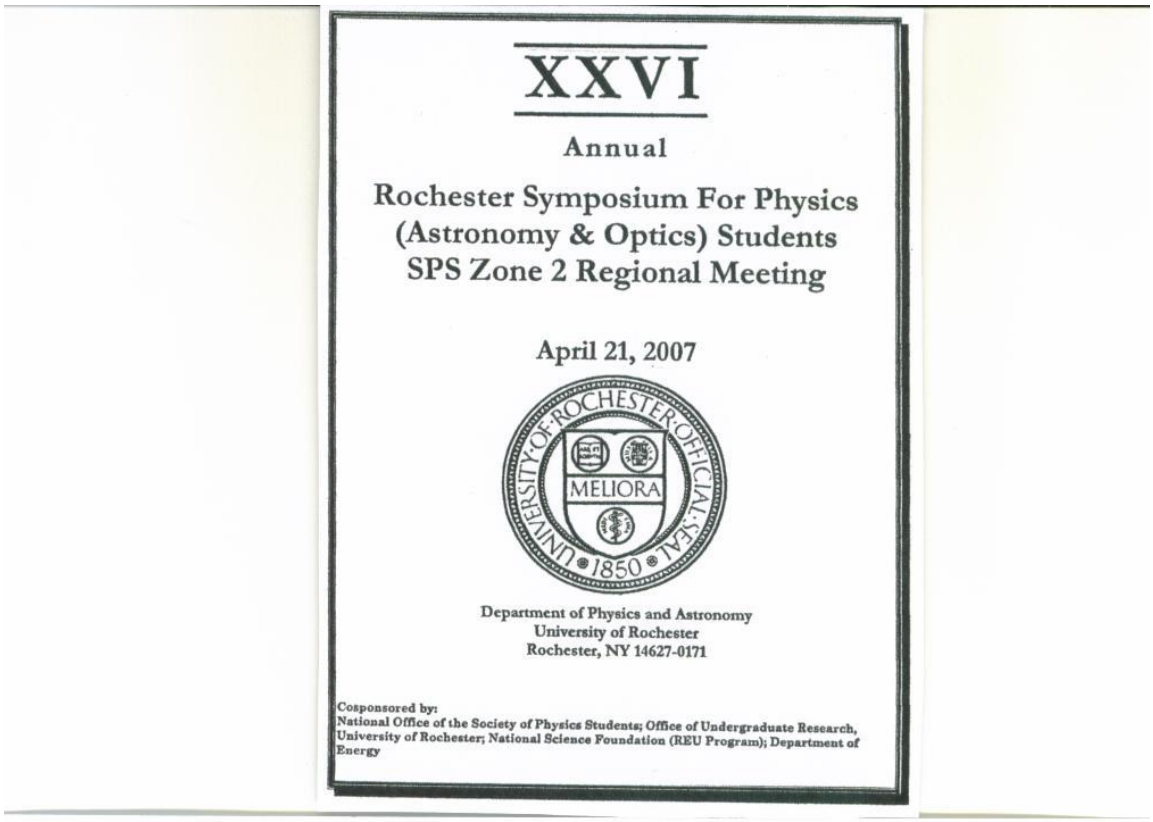
1. Baoquan Ding and Nadrian C. Seeman, "Operation of a DNA Robot Arm Inserted into a 2D DNA Crystalline Substrate." Science Vol 314 PP 1583 – 1585, 8 December 2006.
2. Digendra K. Das and Thomas Renz, "A Simulation model for P systems with active membranes." NanoSingapore 2006, IEEE conference on Emerging Technologies- Nanoelectronics. 10-13 January, 2006, Singapore.

3. Corey Lemley (Faculty advisor: Monisha Kamala Mahanta), "Synthesis of Nano-structures", The Twenty-six Rochester Symposium for Physics Students, SPS Zone 2 Regional Meeting held at Rochester University on April 21, 2007.

Presented at:

ASEE Annual Conference & Exposition
June 22 – 25, 2008, Pittsburgh, PA

SUNY- Oneonta:



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Annual

Rochester Symposium For Physics (Astronomy & Optics) Students SPS Zone 2 Regional Meeting

April 21, 2007

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Synthesis of Nano-Structures: A Feasibility Study

Corey Lemley, State University of New York at Oneonta
Advisor: Prof. Monisha Mahanta, State University of New York at Oneonta

Nanostructure synthesis and nanophotonics are some of the current focus areas of research in the field of nanotechnology. SUNY Oneonta is exploring these concepts on a Department of Energy (DOE)/NY Nano-Bio Molecular Information Technology (NYNBIT) Incubator project. The research is to determine the feasibility of synthesizing the growth of ZnO, InP, and/or GaN nano-wires using the thermal evaporation equipment available at SUNY Oneonta and chemical vapor deposition techniques cited in the literature, subject to the availability of equipment. The experimentation has the potential for involving the use of helical laser profiles, developed by Dr. Mahanta for the Air Force Research lab at Rome, NY during her senior fellowship from the National Academy of the Sciences. According to the nano-wire literature we have reviewed, such profiles have demonstrated the ability to move and manipulate nano-scale wires and particles due to their inherent orbital angular momentum.

We are also exploring localized tunneling by creating 'islands' of metal or molecular material on a substrate to assess the feasibility of using the available resources for the groundwork on quantum cellular automata for logic circuits and looking into how to create these island structures by depositing an ultra-thin, discontinuous layer of metal or molecular material and subsequently characterize their behavior.