# Embedded System Based Automated Drug Delivery Unit and MicroFluidics for drug discovery

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**ABSTRACT**: Drug dosing is a technique that is done to cure the diseases through proper prescription and control of drugs that have been identified to the corresponding disease based on diagnosis. Drug dosing is a very critical and challenging step that needs to be correctly monitored and prescribed by the doctor.  Drug dosing in human beings also depends upon size, area, weight and volume of the recipient. There are various ways of drug dosing, targeted therapies are the current state of the art and are probably the best predictor in terms of perceiving the dosing. Nanobio systems are used for targeted therapies. Food and Drug Administration (FDA) has recommended the use of nanobio systems for targeted therapy and drug dosing but they do not have many models. In reality very few exist. With limitations in availability of common platforms for development and validation of automated systems there is a need for a new methodology or integration of multiple platforms to integrate biosensors, expert system and drug diffusion unit. Prostate cancer is one of the major cancers that is affecting men in India. After lung cancer prostate cancer has caused large number of deaths in India. Nanowire is the biosensor used for detection of cancers. In this paper, we present a design of nanowire array sensor for prostate cancer detection. A sensor array of 8 x 8 elements is designed to capture the PSA present in the blood that helps in detecting the presence of prostate cancer. An experimental setup has been developed using the biosensors lab from Nanohub.org. Based on the experimental setup the nanowire sensor is characterized for PSA detection. The sensitivity of detection is increased by use of sensor array. The Automatic drug delivery system is based on bio sensors. However the bio sensors are not under the purview of this project. To create a real time model, the sensors were simulated. Employing Servo motors connected to a voltage divider network simulated sensors. Eight voltage dividers were employed wherein, in each of the dividers; a fixed resistor & a potentiometer were used. The servo motor moves the wiper of pot and thus varies the voltage output on the ADC channel.

*Keywords: Prostate specific antigen, bio sensors, nano wire sensors, Bio markers, DNA, Micro Fluidics*

## I.   INTRODUCTION

Cancer diagnosis and treatment are of great interest due to the widespread occurrence of the diseases, high death rate, and recurrence after treatment. Existing cancer screening methods include (1) the Papanicolau test for women for detection of cervical cancer and mammography for detection of breast cancer, (2) prostate-specific antigen (PSA) level detection in blood sample for men in detecting prostate cancer, (3) occult blood detection for colon cancer, and (4) endoscopy, CT scans, X-ray, ultrasound imaging and MRI for various other cancer detection. These traditional diagnostic methods however are not very powerful methods when it comes to cancer detection at very early stages. The screening methods are quite costly and therefore not easily available for ordinary citizens. Therefore, the development of technology that is specific and reliable for detecting cancers at early stages and easily accessible for functioning as the first-line guidance is of critical importance. Nanotechnology

has been developing rapidly during the past few years and with this, properties of nanomaterials are being extensively studied and many attempts are made to fabricate appropriate nanomaterials. Due to their unique optical, magnetic, mechanical, chemical and physical properties, nanomaterials have been used for more sensitive and precise cancer detection [1]. The Various nanowires that have been used in biomarker detection are silicon nanowires [2-5], $In_2O_3$ nanowires [6], gold nanowires [7,8], conducting polymer nanowires [9]. Silicon nanowires (SiNW) are semiconducting nanowires with exceptional physical, optical, electronic properties, and excellent biocompatibility [10-13]. Since silicon is a well studied material, the surface of the nanowires can be modified with well-known methods. This advantage makes itself a promising platform for sensitive detection of biomarkers [14-15]. In this paper, we propose biosensor for detection of prostate cancer, based on nanowire sensor array. Section II, presents discussion on nanostructured devices for prostate cancer detection, section III presents biomarkers and design of biomarkers. Section IV presents the analysis of various nanowire sensors and design of nanowire arrays for

cancer detection. Results and discussion is presented in section V.

## A. Nanostructured devices

Nanostructured devices, such as single-walled carbon nanotubes1 (SWNTs), silicon nanowires2 (Si NWs), or metal oxide nanowires3 (e.g., In2O3 NWs), are used in biosensors. Devices having very high surface-to-volume ratios are highly sensitive, thus nanotubes and nanowires are used in biosensors for disease detection [16-17]. In this paper, metal oxide NWs (e.g., In2O3 and SnO2), which are traditionally the key materials for sensing are used in detection of prostate cancer. PSA is an oncological marker for the presence of prostate cancer, which is the most prevalent diagnosed cancer among men in India (fourth major cancer among men) [18]. Despite its critical importance, detection of PSA using nanowires has not been reported. In this paper two major contributions have been carried out. An array of nanowires sensors have been designed to detect PSA density, The sensor array is designed with planar nanowires and spherical nanowires to increase the sensitivity of detection. Prostate cancer is diagnosed by identifying the presence of a protein called the Prostate Specific Antigen (PSA) [19]. PSA will be present in blood of a patient if the PSA level in the blood increases beyond certain levels. The patient is then diagnosed with prostate cancer.
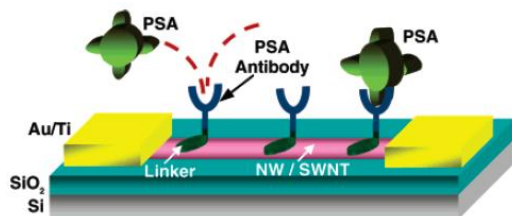


Figure 1 Nanowire sensor

The device structure of nanowire sensors is shown in Figure 1. An active channel made up of nanowires bridges the source and drain electrodes gold and the silicon substrate (silicon di oxide) is used as gate. Receptors placed on the channel are used to detect the target molecules (PSA in this case) and also called as biomarker. In a normal human being (men), PSA levels is between 0 - 4 ng/mL. If PSA levels exceed this level then it indicates abnormality and thus cancer is detected. PSA levels are converted from ng/mL to mmol/liter.

## B. Biomarker:

A biomarker is an indicator of a biological state of disease.

It is characteristic of a specific state and therefore can be used as a marker for a target disease. A biomarker can be a protein, DNA, or RNA-based. Biomarkers, specifically cancer biomarkers, are an indication of cancer and by detecting them the existence of that specific cancer can be verified. In this work, the biomarker designed by [19] is used to detect prostate cancer. Detection of PSA present in the blood is to functionalize the channel surface with anti-PSA antibody (PSA-AB), a specific ligand for PSA protein. In2O3 NW devices were first submerged in a solution of 3-phosphonopropionic acid, resulting in binding of the phosphonic acid to the indium oxide surface with the COOH groups. The COOH groups on the nanowire surface are subsequently converted to a carboxylate succinimidyl ester via incubation in *N*,*N*'-dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide5 and treated with a buffered saline solution of PSA-AB at 50 *u*M concentration. The antibody is thus anchored to the nanowire surface [19]. In this work, we have used nanowire sensor with PSA-AB setup for prostate cancer detection.

## C. Design of biosensors:

Biosensors that are developed in this work are very generic and are not defined for any particular disease. A basic understanding of units and dimensions that correlate the biological terms with the biosensor are discussed. A mole (mol) is the number of particles (molecules) in a substance. Regardless of the substance, 1 mole always expresses a number equivalent to the exact  number of particles. However, the number of grams in 1 mole may vary greatly from substance to substance. One mole equals the molecular (atomic) weight of a substance in grams. For example, the molecular weight of calcium is 40, and 1 mole of calcium equals 40 grams. Osmoles (Osm) and milliosmoles (mOsm) refer to the number of particles in a specific amount of liquid. Equivalents (Eq) and milliequivalents (mEq) measure a substance's ability to combine with another substance. A milliequivalent is roughly equivalent to a milliosmole. Formulas are used to convert a measurement from one unit to another. The same amount can be expressed in terms of different units. For example, the concentration of calcium in the Blood is normally about 10 milligrams in a deciliter (mg/dL), 2.5 millimoles in a liter (mmol/L), or 5 milliequivalents in a liter (mEq/L).

Based on the above discussions, for a biosensor the most important parameters that are required for detecting diseases are:
- Size of micro channel
- Flow rate of fluid in the channel

- Concentration of antigens in fluid
- Number of antigens through channel per hour
- Total area occupied by Antibodies
- Area of one Si NW occupied by Antibodies
- Target receptor conjugation
- Type of antigen
- Ratio between total occupied area and Si NW
- Mean time between one antigen reacts with one antibody on the Si NW

Based on the above design requirements, three different nanowire sensors are chosen and their performance characteristics are analyzed. Based on the results obtained, one of them is chosen for cancer detection.

## II.MICRO FLUIDICS FOR DRUG DISCOVERY

The process of drug discovery and development continues to pose a significant challenge because the biological hypothesis must ultimately be tested in humans [20]. In 2006, only 18 new molecular entities and 4 new biologic license applications were approved by the US Food and Drug Administration (FDA) [21, 22]. Recent developments, such as combinatorial chemistry, have greatly enhanced our ability to generate drug candidates. Furthermore, the sequencing of the human genome has opened new doors to understanding the nature of biological interactions in disease. Consequently, new drug candidates from the top ten pharmaceutical companies entering clinical trials increased by 52% from 1998–2002 to 2003–2005 [21]. Accordingly, investigational new drug (IND) applications to begin clinical testing increased by 45% from 2003 to 2005 [21]. Considering the time for drug candidates to develop successfully into new drugs takes more than ten years, the number of new drugs is expected to increase in the next few years. Despite this promise, the process of drug discovery is limited by a number of challenges, some of which include the need to analyze drug candidates in a more rapid and accurate manner. Therefore, there seems to be an emerging opportunity to develop new tools that may aid in the drug discovery and development process.
Microfluidic technologies are powerful tools for various applications for the drug discovery and development process. Microfluidic-based approaches have already made a significant impact in the area of chemical synthesis, protein crystallization, high throughput drug screening and drug delivery, because they address a number of limitations imposed by conventional macroscale methods including low throughput, expensive processes and large volume of reagents. In particular, microfluidic technologies have great potential in high-throughput studies involving target selection, lead compound generation, identification and

dosage design. However, despite exponential growth of microfluidics in the past few years, a number of challenges still need to be addressed. In particular, microfluidic devices must be simple and highly versatile to enable their use in both academic and industrial pharmaceutical laboratories. A standard microfluidic platform should be developed to enable easy coupling of extant microfluidic systems. More studies should be conducted to determine the reliability of microfluidic chips over hundreds of thousands of samples and months of constant use. Thus, much progress remains to be made to further enhance the use of microfluidics in addressing challenges of drug discovery and development studies.

Microfluidics is also useful for studying DNA and gene synthesis,which is potentially useful for biological drugs. A microfluidic DNA oligonucleotide synthesizer containing multiple on-chip valves was made by perfluoropolyether (PFPE) [23]. Using this device, 60 pmol of DNA oligonucleotides was synthesized while consuming less than 500 nl of phosphoramidite solution in each reaction. This device could be useful for screening small interfering RNA (siRNA) sequences and creating DNA nanostructures. Besides DNA synthesis, multiplex genes were also synthesized in a microfluidic device [24]. Genes that encoded the proteins of the E. coli30S ribosomal subunit (21 in total) were synthesized and optimized in a device. Rapid prototyping of individual genes can be useful for the synthesis of ribosomes in vitro.

## III AUTOMATIC DRUG DELIVERY SYSTEM

The Automatic drug delivery system is based on bio sensors. However the bio sensors are not under the purview of this project. To create a real time model, the sensors were simulated. Employing Servo motors connected to a voltage divider network simulated sensors. Eight voltage dividers were employed wherein, in each of the dividers; a fixed resistor & a potentiometer were used. The servo motor moves the wiper of pot and thus varies the voltage output on the ADC channel. The reason for selecting servo motors was that only 8 Microcontroller pins are required for accurately positioning & controlling these motors. If stepper motors were to be used, each of the motor would require 4 dedicated control lines. Ordinary dc motors cannot be used since they cannot be precisely stopped or started.

Automatic drug delivery system comprises of three sub systems. Each of the sub systems is powered by a dedicated microcontroller. A distributed architecture was selected for implementing this system as the complex process of diagnosing & administering drug for the patient requires

multiple process/tasks, scheduled & synchronized. When each entity can carry out the designated task and communicate with other systems without infringing on to the task of other processors/systems the overall goal is easily & efficiently realized.



Figure 2  Drug delivery model prototype

The blocks play a vital role in
1. Simulating the disease pattern
2. Building disease knowledge base
3. Reporting diagnosed disease as interpreted from the knowledge base.
4. The delivery of the prescribed drug in the required quantities

## IV HARDWARE MODEL BLOCK DIAGRAM

The prototype model developed consists of the blocks as shown in Figure 8.1, an input signal representing the sensor is applied to an ADC, the digitized data is compared with prerecorded data stored in look up table, based on the prerecorded data, decision unit chooses a suitable drug and suitable parameters are chosen from according to the disease and drug to be administered. The drug diffusion unit diffuses the drug and a feedback unit monitors the drug administered.
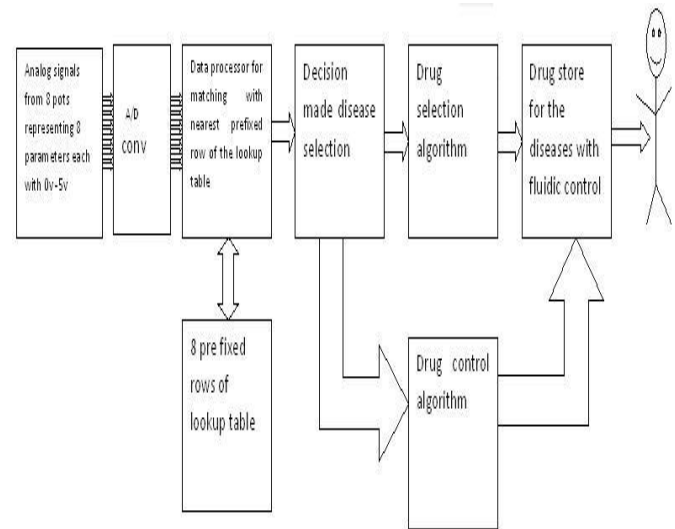


Figure 3  Block diagram of prototype model

### A.    Master Controller (The drug delivery system)

An ATMEL AVRM162 micro controller is the heart for this unit. The delivery of the drug is affected by a high precision peristaltic pump. A bank of solenoids is connected to different preloaded syringe systems which have drugs that can be administered by the system. These syringes are pressurized by a micro compressor which finally pushes the drug into the bottle. The Host micro controller commands the pump micro controller which regulates the speed of the pump which in turn regulates the amount of drug. The communication between the master and the pump controller is through serial interface RS232. A protocol controls the peristaltic pump speed in real time as per requirements. Figure 5.2 to Figure 5.4 shows the developed master controller unit modules.
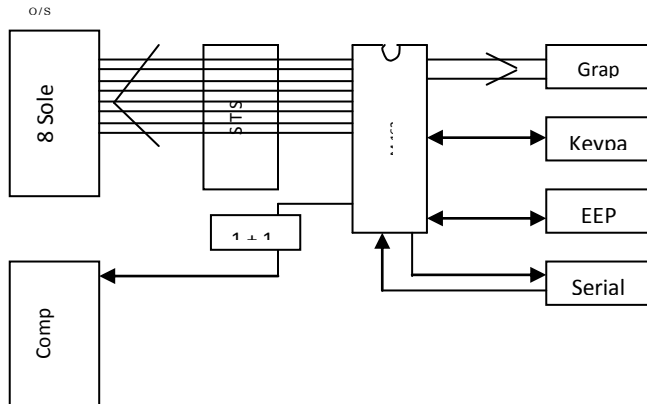


Figure 4.  Controller unit

Figure 5  Block diagram of master control unit

The Host controller is ATMEL ATM162.This controller interfaces the graphical LCD display module and the key board which provides a user interface for configuring and customizing the system. The graphic display and the key board forms a user interface which in real time displays the disease diagnosed, the drug selected for administration and the amount of drug to be administered. It also facilitates communication with the other sub systems.
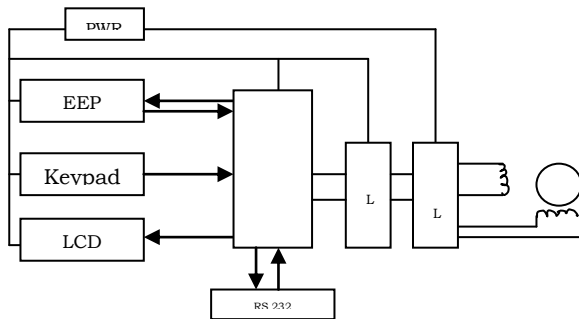


Figure 6  Pump control unit

## B) Disease Simulator &  Analyser (Biosensor simulator controller)

Eight potentiometers wired as voltage dividers are mechanically moved by servo motors with a real time feedback from the on-chip analog to digital converter simulating different diseases in run time mode. The servo motors randomly position the wipers to produce an analog voltage which is related to the voltage divider equation. The resultant voltages are adjusted in the range from 0-5 V. These voltages actually correspond to a disease parameter in such a way that the system has an upper and a lower boundary for the disease. The micro controller in real time measures the output of the pots, compares with the knowledge base and concludes at the probable disease. The system then analyses the intensity of the disease for administering the appropriate drug. Since real time sensors are not present, a special mode had to be created to generate a knowledge base which is done by controller AVR M32. The micro controller is commanded by the HOST controller through the selections made by the user for positioning the servos. The servos can be adjusted to produce different voltage patterns. Collection of 8 values from the potentiometers is stored under disease pattern. The system can be programmed for newer disease patterns through user interface. Figure 5.5 shows the developed disease simulator.



Figure 7 Prototype model of biosensor

## V RESULTS OF THE PROTOTYPE MODEL

Since real time sensors are not present in this system, a special mode had to be created to generate a knowledge base. This is done again by this controller [AVR M32]. The microcontroller is commanded by the host controller through the selections made by the user for positioning the servos. The servos can be adjusted with fine resolution to produce different voltage patterns. A collection of the 8 values from the potentio meters are stored under disease pattern. The system thus can be programmed for newer disease patterns by employing the knowledge base building mode selected through  the user interface.

Thus Knowledge Base is set for 6 Diseases is shown in Table 5.1.

The Low and High Values are set for each disease. It indicates the abnormal range which is used to detect that particular disease.

Table. 1. Knowledgebase for the automatic drug delivery unit

| Disease | Range | CH0 | CH1 | CH2 | CH3 | CH4 | CH5 | CH6 | CH7 |
|---------|-------|-----|-----|-----|-----|-----|-----|-----|-----|
| 1 | LOW | 44 | 150 | 95 | 70 | 127 | 67 | 108 | 117 |
| 1 | HIGH | 74 | 170 | 133 | 106 | 143 | 99 | 138 | 142 |
| 2 | LOW | 88 | 104 | 67 | 115 | 58 | 127 | 76 | 149 |
| 2 | HIGH | 117 | 129 | 93 | 138 | 81 | 149 | 99 | 170 |
| 3 | LOW | 104 | 90 | 72 | 111 | 68 | 117 | 79 | 126 |
| 3 | HIGH | 136 | 133 | 111 | 134 | 108 | 142 | 117 | 139 |
| 4 | LOW | 104 | 85 | 120 | 56 | 138 | 63 | 65 | 118 |
| 4 | HIGH | 140 | 118 | 170 | 122 | 170 | 108 | 90 | 140 |
| 5 | LOW | 134 | 95 | 65 | 55 | 79 | 63 | 65 | 118 |
| 5 | HIGH | 154 | 118 | 95 | 95 | 120 | 101 | 90 | 105 |
| 6 | LOW | 55 | 45 | 110 | 23 | 123 | 101 | 76 | 54 |
| 6 | HIGH | 95 | 92 | 150 | 63 | 173 | 143 | 117 | 95 |

By adjusting the potentiometers with the help of the servo motors, the input values are set and a disease pattern is created which is compared with the stored knowledge Base.

## VI CONCLUSION

In this paper, a PSA detector is designed using nanowire sensor and is characterized for various test cases. Based on the sensor designed a sensor array is developed consisting of 64 sensors. The sensor array is used in accurately detecting the PSA concentration in a given analyte, thus detecting prostate cancer. An experimental setup has been developed to model and simulate the nanowire sensor and sensor array for cancer detection. Sensor parameters are identified based on experimental test results. The biosensor is designed based on various parameters; the analyte concentration is identified corresponding to PSA levels. The test results obtained show that the array sensor has better sensitivity compared to single nanowire sensor. The sensors developed can be used for detection of various cancers by changing the biomarkers, based on the signatures obtained from the sensor. The sensor array output can be interfaced with expert system for disease detection and classification.

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### Biography

**Dr. Ushaa Eswaran** obtained her Bachelors Degree in Electronics and Instrumentation Engineering from the University of Annamalai in the year 1989 and her post graduation degree in Electronic Instrumentation Engineering from the University of Andhra, Vishakhapatnam in the year 2003. She completed her Doctoral degree from the Jawaharlal Nehru Technological University Hyderabad. She has obtained with distinction the International certificate for teachers and trainers being awarded by Cambridge University.

She has rich teaching experience having taught in various engineering colleges in the state of Andhra Pradesh. She is currently the Principal of Siddartha Institute of Science and Technology, Puttur.She was  the Vice-Principal, Professor and Head of Department, Electronics and Communication Engineering in Siddharth Institute of Engineering and Technology, Puttur earlier. She is also the Chief placement officer in the institution and takes care of the placement related activities.

Under her guidance, the college has successfully organized a number of on-campus and off-campus recruitment drives resulting in placement of a large number of students. She has been constantly monitoring the weaker students and provided them with additional academic and allied support so as to ensure their successful completion of course curriculum and their eventual absorption into an appropriate career in the corporate sector. She has trained students in developing communication and interpersonal skills followed by evaluation through conduct of mock interviews and detailed individual debriefs.

She has also contributed extensively towards the development of infrastructure in the institution in line with the AICTE and UGC directives. As project head, she has conceived and created technical facilities during the expansion activities. She has also created/coordinated training and performance appraisal programmes for teaching and non teaching staff. Her efforts, through constant monitoring and effective maintenance of documents and records have ensured ISO and AICTE accreditations of the institution.

She has undertaken planning and coordination of major seminars and symposiums in addition to handling day to day administration of institution and execution of special tasks. She has to her credit the streamlining of the placement cell activity and in creation of data bank of students and companies as sources for future reference.

She has been providing technical advice to college management on need of staff and equipments during college recruitment and expansion activities. She has facilitated outsourcing of services and conduct of technical negotiation in the equipment sourcing activities. She has been enthusiastic in organizing and conduct of national level intercollegiate student symposium including sourcing of corporate sponsors and publication of souvenir. She has been an effective relationship manager dealing with all stakeholders.

**Mrs.Sreelakshmi** completed her bachelor's degree in Electronics & Communication Engineering from leading Engineering College. She has vast teaching experience in various engineering colleges as Lecturer, Assistant Professor, in Andhra Pradesh. She is currently working as an Assistant Professor in the department of Electronics & Communication Engineering in Siddartha Institute of Science & Technology, Puttur. She guided several UG projects in the field of VLSI, Image Processing and Nano-Technology. She published various papers in the field of VLSI and Nano Technology in International Journals and conferences.

**Mr.Vivek Eswaran** is presently pursuing his Bachelors degree in Electronics and Communication Engineering from Anna University.

A Pre Final year student of RMK Engineering College, Vivek is an academically brilliant student having consistently securing distinction in all his previously held examinations. Vivek has always exhibited interest in topics that have potential for revolutionizing sciences. His electronic background has helped in conceiving and exploring mathematical models and simulation studies.