CAREER: Development of Bio-MEMS for determining cell structure using microfluidics and bio impedance

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ABSTRACT: This report emphasizes the development of a single use microvalve for controlled drug release forming a part of automated implantable microsystem. Implementation of such a platform was built upon selective blistering in ultra-thin Si membrane implanted with inert gas species followed by on demand (subjected to external feedback) rupturing sequence. In this research investigation, H_2 was implanted into 2 µm Si membrane and then thermally actuated for valve action. As a part of collaborative research work leveraging host laboratory's expertise in ion beam techniques and nanophotonics, it was also found that silica nanowires synthesized at the parent institution proved to be an excellent sensitizing medium to enrich the optical activity of Er. A provisional patent has been applied to commercialize this technology that could revolutionize the telecommunication industry. These additional results facilitate further interaction with the host for future funding opportunities. The intellectual merit and broader impacts of this international visit have also been discussed. Insert a one-paragraph abstract of this report.

INTRODUCTION

The awardee institution for the current NSF grant is the University of South Florida (USF) in Tampa, Florida. Proposed objective was to develop a bioMEMS system for determining cell structure based on micro-fluidics, bio-impedance, and microelectronics. An automated cell mapping system for monitoring biophysiological events has been implemented. Impedance measurements have been carried out on optimized planar microelectrodes capable to identify cells based on their bio-impedance maps. The thematic focus of quantitative diagnosis in diverse environments could be extended to facilitate an integrated drug delivery platform.

The goal of the IREE research activity was to extend the scope of the investigator's NSF CAREER research by validating the feasibility of an automated drug delivery platform. Proposed approach would be used to deliver polymer microencapsulated drugs. In addition, the system will incorporate drug quantification capability and a unique single shot microfluidic valve for controlled drug release. Implementing a simple one shot microvalve will circumvent the problems of spatially discrete delivery system, inelegant integration and bulky nature of the final die. The process of implantation assisted exfoliation has recently been investigated on a variety of functional materials and/or substrates for novel material synthesis and applications. In particular, a plethora of information is available on implanted H^+/He induced "Smart Cut" process of customized SOI (Silicon-on-Insulator) fabrication. Adopting such a strategy would demand expertise in ion beam tools and techniques with knowledge in microsystems. This formed the basis of the international co-operation carried out under IREE with a unique synergy of expertise to solution for a complex problem. The objective of the proposed research is to develop a low power single shot microvalve for controlled and regulated drug release.

A critical feature in current state of the art implantable drug delivery systems is the use of active pumping schemes which utilize microfluidic pumps and valves. Presently conceived system designs are an inefficient coupling of stand-alone sampling systems and spatially discrete delivery systems. Moreover, such architectures when unified with unidirectional microneedle sampling array pose challenges on a seamless integration while limiting on achievable functionalities. All the abovementioned issues calls for a simple yet robust on-demand drug release strategy/scheme in compliance with microfabricated bioelectric interfaces. Anticipated research tasks of this exfoliation scheme include (a) to experimentally observe and understand the effect of implantation energy, dose and dose rate for H_2 on the blistering morphology and distribution upon an ultra thin (2 μm) Si membrane, (b) to identify the critical dose and implantation depth required for dense blister initiation and smooth exfoliation for each of the implanted species and (c) verify the role of substrate orientation on the blister kinetics and propagation.

The results of this research will translate into case studies in course modules and seminars rendered by the investigators/students. Various outcomes would be widely disseminated in the form of published articles. The importance of critical patient care systems cannot be manifested enough. Knowledge acquired from these research investigations is not only relevant in the US, but also in Australia and India with rising demand.

Through this proposal, the principal investigator at USF will partner with Dr. R.G. Elliman; Head of the Electronic Materials and Engineering Department (EME) at the Australian National University (ANU), Canberra. Dr.Elliman (http://wwwrsphysse.anu.edu.au/eme/profile.php/3) would continue to be the host and research collaborator. Research themes of ion beam modification of materials and advanced material characterization techniques at EME, ANU ideally suits the needs of the proposed research. Fundamental ion beam studies employ the department's state-of-the-art accelerator facilities that include, a low energy (150 KeV) ion implanter, a high-energy, high current ion-implanter (1.7 MeV terminal potential), and a separate tandem accelerator (1.7 MV terminal potential) for post beam analysis. Moreover, Dr.Elliman will be co-advising/supervising the graduate student from USF during the student's visit under IREE program. This is very critical for continued future collaboration and funding opportunities. The participating graduate student from US would be Praveen Sekhar from the BioMEMS and Microsystems Lab with traveling dates from March 15^{th} to July 3^{rd}, 2007.

RESEARCH ACTIVITIES AND ACCOMPLISHMENTS OF THE INTERNATIONAL COOPERATION

Figure 1 illustrates the thematic focus of the proposed approach. The initial vision was to extract the optimized implantation conditions to achieve the targeted depth of exfoliation around 1 µm. Implantation parameter space for early set of experimentation was chosen based on prior research investigations. Through a careful design of experiments, implantation variables (dose, energy, temperature, ambient) were optimized to achieve the targeted exfoliation depth and temperature. For a bulk Si substrate to exfoliate 1µm of the surface, H_2 was implanted at energy of 125 KV with a dose level of 3e17 ions/cm^2 at room temperature and thermally actuated at 350 C equivalent to 30 mA of electrical stimulus. These implantation values were successfully applied to rupture a 2 µm Si membrane. Exfoliation kinetics was studied using Nomarski Contrast. Various implantation schemes such as single and double side implantation were also explored to reduce the actuation temperature. Structural characterization of the ultra-thin Si membrane in the scanning and transmission electron microscopy reveals amorphization after implantation and re-crystallization upon thermal actuation. Based on preliminary investigation, recommendations are offered to lower the actuation temperature with a view to use electrical stimulus to rupture the membrane. The use of heavier gas species such as Ar in combination with multiple dose and energy implants would lead to lower thermal budget. There are various models governing the blister formation such as the gas pressure model which correlates the internal gas pressure and material rupture strength towards exfoliation of the latter. In brief, supersaturation of noble gases in the substrate lattice leads to the formation of the bubbles, distribution of which is influenced by the implantation parameters. A smooth exfoliation occurs following blister expansion upon thermal excitation.

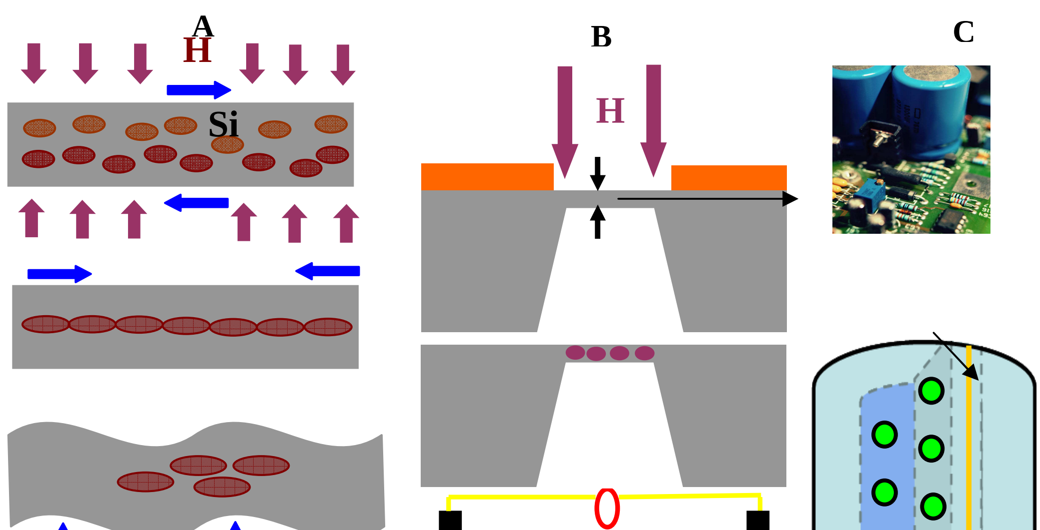

Figure 1. Thematic Illustration of Implantable Drug Delivery System with Single Shot Microvalve.
(A) Theoretical model explaining the kinetics of hydrogen implantation induced blistering and exfoliation of Si membrane upon continuous thermal stimulus. Expansion of gas in a constrained volume leads to explosion of the membrane. (B) Process sequence towards the fabrication of feedback controlled, single use regulator and (C) The envisioned unified therapeutic system with the sampling module (concentric hollow silicon microneedle, with the outer needle providing a pathway for analysis and the inner needle acting as a reservoir for drug delivery) attached to the microvalve driven by customized electronics.

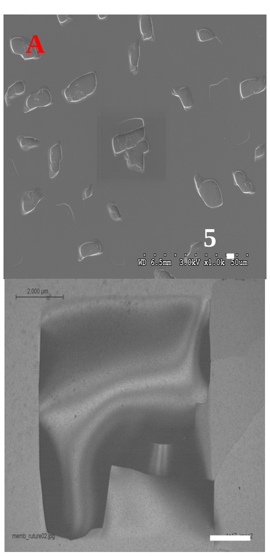

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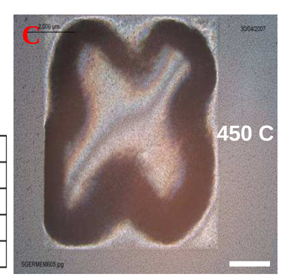
Table 1. Experimental Results of H_2 Implantation Based Si Exfoliation at 100 KeV

(×– Absence of Blistering/Exfoliation on Surface, β – Blister Formation on Surface, Φ – Layer Exfoliation)

Temperature (^{0}C)	H_2 Dose (ions/cm^2)			
	1E16	3E16	1E17	3E17
525	×	×	β Φ	Φ
625	×	×	β Φ	Φ
725	×	Φ β	β Φ	Φ



Tasks	Mar15th – May 15th	May15th – July 15th	Future
Identifying the optimal implantation parameters for controlled exfoliation of the membrane			
Structural characterization of the unimplanted, implanted and exfoliated surface to understand the rupturing kinetics			
Process development towards low temperature exfoliation of the membrane			
Valve Action: Thermal actuation to electrical stimulus			
Design of complete electronic circuitry for on-demand rupturing sequence			

Figure 2. Progress of the IREE Research
(A) SEM micrograph indicating 1 µm exfoliated depth, (B) Optimized Process Variables, (C) Study of exfoliation kinetics using Nomarski contrast, (D) SEM image of the exfoliated membrane at 650 C and (E) Research Milestones.

Reiterating, the aim of this project is to extend the scope of the investigator's NSF CAREER research by validating the feasibility of an automated drug delivery platform. A major goal of drug delivery platforms is to enable controlled or sustained release of drugs into the body. The use of polymeric microencapsulation of drugs has been identified as a part this solution. Our project aims to enhance the advantages obtained by polymeric encapsulated drugs by enabling precise control of the time and amount of microcapsule delivery. While the on-demand drug release (Figure 2) achieved through the development of one shot microvalve, regulated (quantification)/sustained delivery realized using the microelectrode module developed in-house capable of sensing the passage of a single microcapsule. The former research component was intended to be completed at the host institution under the guidance of Dr.Elliman. The interaction between researcher (graduate student) and host laboratory during the international research experience was very productive and mutual transfer of knowledge was evident from the results from nanophotonics (figure 3) based experiments as a supplement. Leveraging ion implantation as a generic tool, the researcher established selective growth of silica nanowires in ANU. Imparting a commercial usage, silica nanowire sensitized Er doped photonic systems were under implementation. The researcher was exposed to various research domains in the host department and subjected to weekly seminars and presentation. General interaction between the researcher and host laboratory led to active collaboration resulting in provisional patent disclosures. In addition, Dr.Elliman has accepted to co-advice the researcher in his doctoral studies. Research expertise from ANU, EME in ion beam tools & techniques, nanophotonics in tandem with the student's experience of handling microsystems at USF has been uniquely poised to accomplish the long term goals.

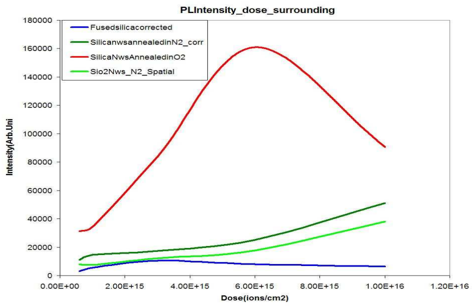


Figure .3 Photoluminescence Spectra: Silica Nanowires as Better Er Sensitizing Medium

The research will provide a basis for an integrated therapeutics tool for controlled and quantified drug release utilizing novel microvalve architectures. This is a major advance across fields. Proposed research also opens the gateway for using ion implantation as a general purpose nanoscale catalysis tool towards mass manufacturing bottom-up controlled nanosystems for wide variety of applications. The envisioned goals bring in unique synergy of broad disciplines such as material science, engineering, manufacturing, physics and biology to realize an application specific complex microcosm.

BROADER IMPACTS OF THE INTERNATIONAL TRAVEL

The international research collaboration promoted participation from diverse groups from the host institution trying to solve a common problem of clinical interest. It also fostered progressive discussions with ethnically variant student population as well as researchers assessing the current health care needs in their respective nations. Particularly the social implication of this is in aboriginal Australians, where urbanization has caused changes in their life style, and obesity, heart disease has become one of the major causes of concern. The success of this research will be critical in delivering cost-effective health care, reduce the dependence on nursing staff and allow first response in the golden hour, by delivering drugs as soon as the symptoms of an illness are detected. This supplemental award was instrumental in establishing the feasibility of an automated release system using a one shot microvalve. The initial results could be further refined to meet the application specific needs. Production of inexpensive single use but efficient devices will greatly increase the quality of lifestyle for the patients concurrent with the extended scope/objective of the current award.

The international visit in association with the outcomes of the research investigations fostered closer interaction between institutions via:-

- joint application for provisional patent disclosure
- manuscripts (four) under preparation with combined authorships
- involvement of Dr.Elliman as PhD committee examiner of the participant
- submission of IREE 2007 proposal to extend the current collaboration between ANU and USF
- Preparation for future funding opportunities such as ARC-NSF and ANN (NSF), 2007.

Teaching of learning skills and dissemination of information are increasingly becoming important in research to keep pace with societal and technological changes. The IREE participant was an invited speaker to the ‘Off the cuff’ seminar series rendering latest research trends across the globe. This opportunity facilitated the discussion of challenges and limitations of the proposed approach as well identify the researcher as a brand ambassador of USF. The researcher from USF had a flavor of the lingual variation, culture and business practices in Australia after touring visits to Sydney and Melbourne.

DISCUSSION AND SUMMARY

Through the IREE supplemental award facilitating research visit to the electronic materials engineering department at the Australian National University, the following were accomplished in terms of :-

Research

- Established the feasibility of implementing a single use microvalve for an automated drug delivery platform
- Explored the use of silica nanowires as efficient sensitizing medium to enhance optical activity of Er that could revolutionize the current telecommunication industry. Exposure to photoluminescence based optical concepts was a revelation to the IREE participant's research career.

Training

- Approved user status to operate the sophisticated ion beam equipments such as the ion-implanter (low and high) and Rutherford Backscattering Spectroscopy (RBS)
- Commissioning equipments related to photoluminescent based measurements
- Experience to operate transmission electron microscopy (TEM) and advanced scanning electron microscopy (SEM).

ACKNOWLEDGEMENTS

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BRIEF BIOGRAPHIES OF RESEARCHERS

Praveen Kumar Sekhar received BE in electrical and electronics engineering with distinction from Coimbatore Institute of Technology, Coimbatore, India (2001), MSEE in microelectronics from the Department of Electrical Engineering at the University of South Florida (USF), Tampa (2005) and currently pursuing his doctoral studies specializing in nanosensors at USF, Tampa, FL. His interests are in the areas of smart materials and their processing with emphasis on MEMS related applications. In addition, he also specializes in synthesizing silica nanowires harnessing their electrical, mechanical and optical properties for various sensor applications. He has been invited speaker to the several PASI (2006, 2007) conferences.