Design and Development of Integrated Sensor for Chemical Agent Detection

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ABSTRACT

Recent advances in nanotechnology promise considerable and realistic potential for the development of innovative and high performance sensing and diagnostic approaches in biomedical field. In particular, the microcantilever detection paradigm based on direct transduction of molecular binding induced surface stress into a nanomechanical motion of microcantilevers, has attracted considerable attention for label-free detection of biomolecules. As an alternative to the currently deployed optical, piezoresistive, and capacitance nanomechanical detection techniques, we introduce a new electronic transduction paradigm comprising two-dimensional microcantilever arrays with geometrically configured metal-oxide-semiconductor-field-effect-transistors (MOSFETs) embedded in the high stress region of the microcantilevers. We have shown that the deflection of the microcantilever induced by specific ligand-analyte binding events leads to a precise, measurable and reproducible change in the drain current of the MOSFET buried in the microcantilevers. High current sensitivity of MOSFET-embedded platform enables detecting nanoscale cantilever deflection from specific biomolecular binding events at very low concentration of analytes with sensitivity in the parts-per-trillion (ppt) range. We have shown ultra-sensitive detection of streptavidin-biotin based biomolecular interactions, atrazine antibody-antigen detection and biomarkers for cardiovascular diseases. This novel detection mechanism offers an excellent platform for variety of biomolecular sensing applications, from clinical diagnostics and environmental monitoring to drug discovery.

INTRODUCTION

Summary of Work Carried out under current NSF Award

Design, layout and Development of High Sensitive MOSFET embedded Cantilevers with New Geometries

We have been exploring methods to validate and enhance the MOSFET-embedded microcantilever detection scheme as a widely deployable microanalysis system. New designs of MOSFET cantilevers have been developed (Fig. 1A) and fabricated to achieve improvements in sensitivity and reliability of the platform. The device and process simulations were performed (Fig. 1B) to optimize the process parameters for fabrication and to determine the designs that are most sensitive to changes in cantilever surface stress with lower noise in signal while consuming less power for operation. After the fabrication of MOSFET cantilevers, their electrical behavior was characterized with pesticides such as atrazine antibody-antigen as well as biotin-streptavidin for both chemical and biosensing applications.

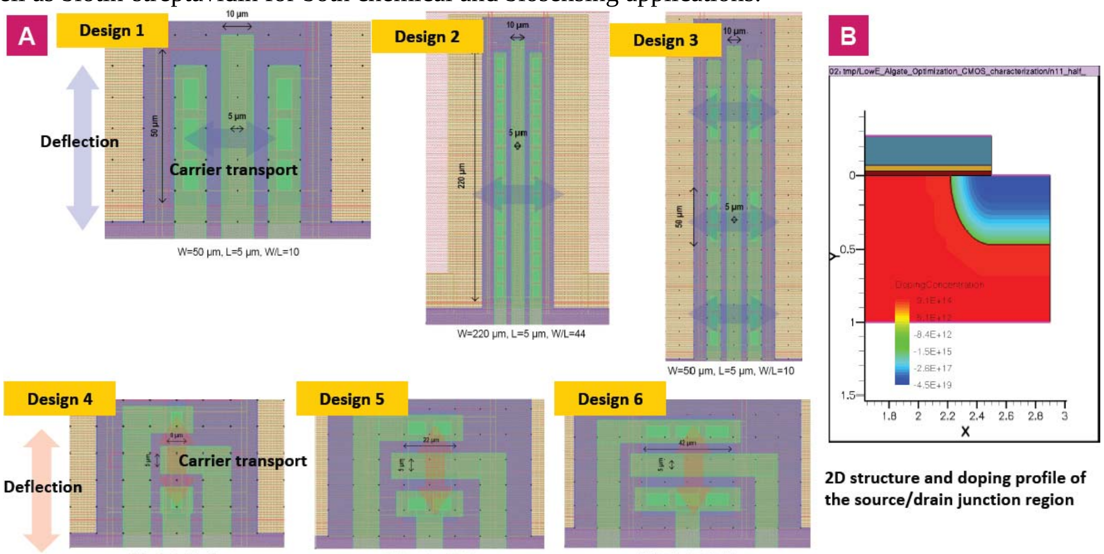

Figure 1. (A) Schematic showing various designs of MOSFETs embedded in the microcantilevers. The devices with different geometry are oriented in two different directions. (B) Process and device simulations provided optimum process conditions to create transistors with shallow junction depth and higher doping concentration to sensitively respond to surfaces stress change with large signal-to-noise ratio.

Rationale for International Cooperation Carried out under IREE

1. Highly International laboratories with most advanced biosensor and microfabrication facilities
2. English as an official language
3. Sufficient resources to conduct research
4. Our colleagues are working on similar areas and under IREE program, we were interested to utilize their expertise in microfabrication and novel receptor chemistries for biologicaland chemical sensing using our novel electronic readout based cantilever detection technologies.

Information about Host Laboratory and their Selection for IREE (Institute for Microbial technology-INDIA and central Electronics Engineering research Institute-INDIA)

IMTECH and CEERI are premier national research laboratories at the forefront of application oriented R&D. Ever since its inception, IMTECH has been formulating biotechnology research program's which have a short-term objective of capability generation and a long-term perspective of generating newer leads in the critical areas of its working, viz., molecular biology, protein engineering, fermentation technology etc. Most of the research programmes deal with the application of newer tools of molecular biology and genetic engineering to develop new technologies or improve upon the existing ones vital to their national needs. Currently IMTECH is developing specific receptors using aptamers based chemistry for selective detection of Atrazine, Heptane and RDX. The criteria for selecting IMTECH is two fold: (1) The current approach of using aptamers for robust receptors for IED's work on microcantilevers is similar to what we are developing with Thundat Group at ORNL. IMTECH is well recognized for developing specific antibodies and (2) Dr. Shekhawat ongoing efforts with IMTECH group in developing molecular sensors will tremendously help Northwestern to start new initiative with premier institute.

CEERI has been engaged in multiple major R & D programs, including advanced CMOS design, processing and device fabrication. The R&D programmes of the institute are responsive to the emerging needs of the country in the following areas:

- ***Microelectronics***: LSI/VLSI circuits, design and prototype fabrication of ASICs, power semiconductor devices, multilevel hybrid microcircuits etc. FET based integrated sensors.

- ***Microsystems*****:** Design and development of pressure sensors, micro valves and gratings. Biomedical applications of MEMS and 3D integration.

- ***Strategic Electronics*** (Semiconductor Devices): W-Band millimetre wave impatt diodes and GaAs devices; Microwave tubes - Design and prototype fabrication of power TWTs, magnetrons, crossed field amplifier, fast wave microwave tubes.

- ***Industrial electronics*** - Microprocessor- and PC-based control system for sugar, tea, leather, diary, pulp, paper and textile industry; energy-efficient drive and power electronic systems.

The criteria for selecting CEERI are also two fold: (1) CEERI is well established in microelectronics and have fully integrated CMOS processing and characterization laboratory and supports 6 inch MEMS facility as well. They are developing MEMS based pressure sensors and magnetic sensors based on microcantilevers. Both these devices are integrated with chip-based CMOS readout electronics. It falls with the scope of the work plan that we are executing here at Northwestern and (2) Dr. Shekhawat is an alumnus of CEERI and is well known researcher there. He is fully trained in their research network and has hands on expertise with all the CMOS processing capabilities at CEERI

<u>Selection Criteria for Best Qualitified Researchers (US)</u>

Dr. G.Shekhawat (US resident) is currently Co-PI on ECS award # 0330410 and developing integrated sensor program for last few years. He is actively involved and was chief architect of MOSFET embedded microcantilevers. He tested the functionality of that microcantilever with the combination of biotin-streptavidin, and various antibodies at ORNL (Thundat group). He is also developing molecular sensor program at Northwestern which can lead to detecting single antigen at a time. He has over a decade long expertise in micro fabrication, scanning probe microscopy and micromechanical devices. Dr. Shekhawat is also interacting with IMTECH and CEERI group for last few years and developing international program for integrated sensor development. He hosted Dr. Raman Suri from IMTECH last year. Being originally from India and alumni of CEERI, he has strong professional and personal relationship with members of both premier institutes and we hope that such strong relationship will be very fruitful for the success of this program.

Soo-Hyun Tark is graduate student and is actively involved in immobilization of receptors on microcantilevers for selectivity to specific antigen and also carrying out the numerical simulations of stress gradients across the cantilever. Dr. Raman Suri (IMTECH) was here as visiting scientist and he worked with S.Tark in developing site-specific immobilization of antibodies of Atrazine on microcantilever surface and measuring the binding constant of biomolecules. S. tark also visited Nanyang technological university under this program to carry out microcantilever fabrication with newer designs and studying the receptor chemistry.

Reserchers Visit under IREE

1. Gajendra Shekhawat, Research Assistant Professor
    a. IMTECH: December 1st to Dec. 29th , 2007
    b. CEERI: December 1st to Dec. 29th , 2007
    c. IMTECH: July 7th to July 20th , 2008
    d. Nanyang technological University, Singapore: Oct. 15th to Oct. 31st , 2008
2. Soo-Hyun Tark, Graduate Student
    a. Nanyang technological University: Sept. 1st to October 31st , 2007

RESEARCH ACTIVITIES AND ACCOMPLISHMENTS OF THE INTERNATIONAL COOPERATION

Objectives of Research Carried out during International research Experience

The proposed research objectives was successfully carried out in joint collaboration with IMTECH, CEERI and Nanyang technological Univerity

1. **Design, Simulation and Development of MOSFET Embedded Cantilevers With New Geometries.** We fabricated and optimized six different cantilever designs for high sensitiove deflection of probe-target binding interaction. The MOSFET-embedded cantilevers are being fabricated under our current ECS grant ((NSF#0330410).
2. **Receptors for improved selectivity for detection of Pesticides and Pathogens**: We explored highly specific anibodies for atrazine and insulin. These antibodies were designed and functionalized at IMTECH. Explored receptor molecules made of peptides and aptamers that are much more durable and robust than proteins (e.g. antibodies).

Collectively, we are working in very close collaboration with IMTECH, CEERI and NTU researchers and believe that new detection technologies will enable significant advances in science as well as engineering of biological and chemical detection system, and enable viable technologies based on sound fundamental underpinnings proposed in this work. The current ongoing work under the IREE is directly related with our current ECS grant (NSF#0330410), which is to develop integrated microcantilever based sensors for sensing biological and chemical agents.

Interaction between researcher and host laboratory under IREE program

1. During Dr. Shekhawat multiple visists to IMTECH, he interacted with both senior and junior researchers as well as students. Specifically Dr. Shekhawat worked with Dr. Raman Suri, our collaborator and biosensor laboratory director in exploring the robust peptides based receptor chemistries for bio-chem sensing as well as using antibodies. He worked with several students in Dr. Suri's lab. Nishima Wangoo, Sonu Ganghi and Jessica actively worked with Dr. Shekhawat and developed robust receptor chemistries for atazine and insulin molecules which were later utilized for cantilever sensing during Nishima Wangoo visist to NU in sept. 2008.
2. Dr. Shekhawat interacted with several of his colleabues at his former Institute CEERI and optimized the process flow for MOSFET embedded microcantilevers.
3. Soo-Hyun Tark (Graduate Student) interacted with Nishima Wangoo, Subodh Mhasailkar, Sok Yee and several other undergrad students at nanyang technological University-Singapore for fabricating newer cantilever geometries as well as molecular sensor development.

Accomplishments of Research under IREE Program

The new MOSFET cantilever platform was successfully fabricated with high yield (Fig. 2) and electrical behavior of these devices showed characteristics of a p-channel MOSFET with low-noise (Fig. 3) suitable for sensitive measurement of cantilever deflection in hundreds of nm to micron range. The magnitude and polarity of change in output drain current as a result of cantilever bend depended on the device geometry and orientation as demonstrated in the bending experiment results (Fig. 4) using an AFM. Devices with larger aspect ratio showed higher current sensitivity, and increase in current was observed with ones that have channel current flow perpendicular to cantilever bending. Biosensing experiments performed in an integrated fluidic cell using a model biotin-streptavidin binding system (Fig. 5) demonstrated the capability of the MOSFET cantilever platform to detect molecular interactions in fluids, in real time.

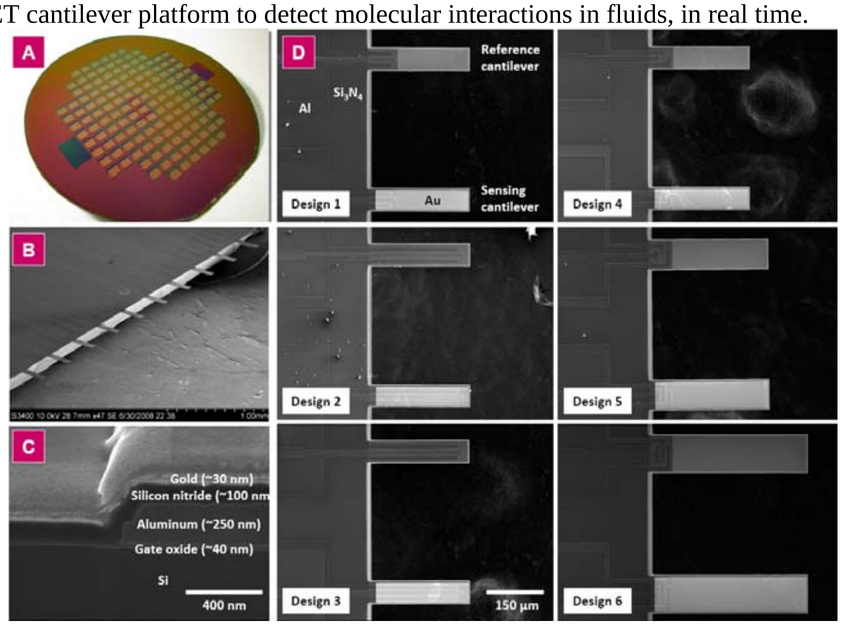

Figure 2. (A) 140 chips in 6 different designs were batch-fabricated on a 4-inch SOI wafer. (B) An array of 10 cantilevers after the completion of the fabrication process, and (C) cross-section of the embedded MOSFET. (D) Images of 6 different designs with reference (Si surface) and sensing (gold surface for receptor immobilization) cantilevers.

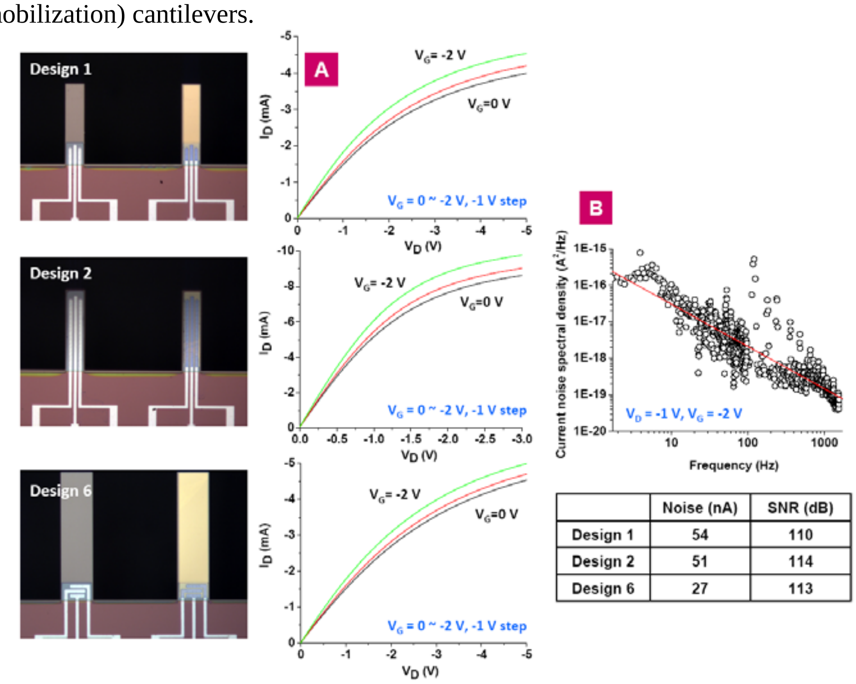

Figure 3. (A) Drain current vs. drain voltage (I-V) characteristics of embedded transistors showed p-channel MOSFET behavior. (B) Noise analysis and signal-to-noise measurements showed nA noise level in devices with high SNR to electrically measure cantilever deflection.

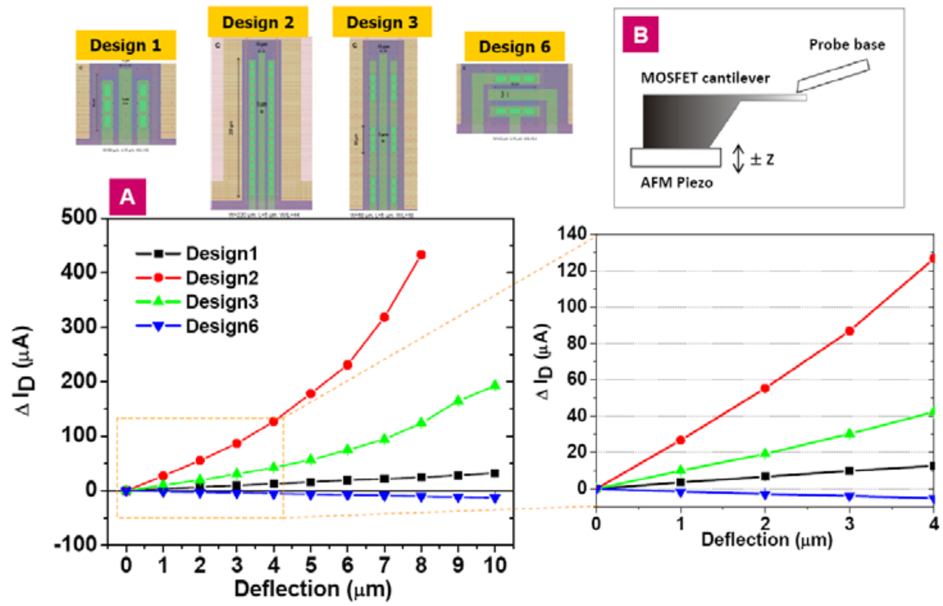

Figure 4. (A) Change in drain current as a results of cantilever bending in micron range using the setup shown in the schematic (B), demonstrated dependence on device geometry and orientation. Devices with larger aspect ratio showed larger current change per unit deflection. Devices with carrier transport direction perpendicular to cantilever deflection showed increase in current with increasing deflection while a device with current flow parallel to bending showed decrease in current.

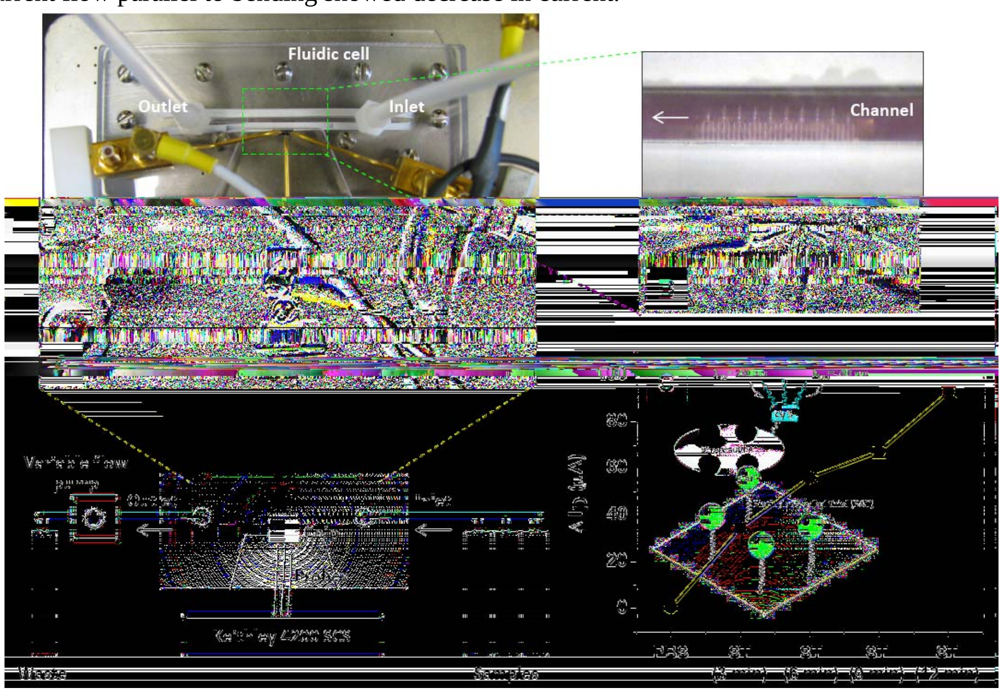

Figure 5. (A) Schematic and an image of a biosensing setup with integrated microfluidic cell and a micropump to control the flow of fluids. (B) Image shows a MOSFET cantilever chip placed in a channel with flowing buffer solution, and probes connected to contact pads to measure cantilever behavior with molecular binding on a cantilever surface. (C) Schematic of a model biomolecular system used for evaluating the sensing capability of the system. As a result of target streptavidin molecules binding to a

cantilever gold surface functionalized with thiolated biotin, drain current increased with time indicating deflection of the microcantilever.

BROADER IMPACT OF THE INTERNATIONAL COOPERATION

Diversity under IREE Program

The IREE supplemental award provides a foundation for our young research Dr. Shekhawat to innovate new cutting edge technologies by interacting his foreign collaborators having expertise in diverse research areas. For example, his interaction with Dr. Suri of IMTECH lead to development of peptides based molecues ultimate detection of antibody-antigen interaction. He met with several protein and genomic engineering experts at IMTECH to leverage their expertise that can be implemented on the current cantilever sensing technologies that we are developing. Some of the great advantages of such diversified opportunities for young researchers are:

1. Broadening the research perspectives
2. Improving the quality of innovation in research
3. Widens scope and range of applications for ongoing research
4. Expanding diverse global netwoks
5. Provide opportunity for faculty-student interaction working in diverse fields.

Expanding the scope of current NSF award

The objectives of the proposed work at collaborator's site about developing new MEMS based fabrication technologies of novel cantilever designs with embedded MOSFETs and developing newer and robust receptor chemistries under the IREE program falls well within the scope of the work we are carrying out using our existing ECS award # 0330410. The goal of this award was to develop electronic detection based MOSFET embedded micro cantilevers for highly selective and sensitive detection of biological and chemical threat agents. The interactions between NU young researcher, student with experts at IMTECH and CEERI helped NU to build program for integrated bio-chem sensing technologies with robust receptors with high selectivity.

IMTECH has already developed peptides based receptors for another dangerous molecule named Atrazine, which is an environmental carcinogen found around mid-west corn fields (pesticide). IMTECH is currently undertaking synthesis of peptides and aptamers based receptors that can accommodate a library of about 1000 residues (as opposed to 20 for amino acids).

Fosters closer future interaction between awardee institution and host instituion

Exchange of visitors between NU, IMTECH and NTU heled us to build a formidable international group for develoing new handheld sensor technologies. Several groups from diverse research areas and countires come together to share their expertise which laid down the foundation for future collaborative efforts which can be expanded to developed new technologies. Some of the important aspects of fostering closer interactions with host institutions are:

1. Fuels emergence of "best practices" effective in sustaining transcultural collaborations
2. Encourages the innovative development of shared work space to accommodate cultural difference
3. Develop research communities beyond US

Enhancing the International perspective of US researchers

1. Broadening their research skills and significantly expanded their portfolio.
2. Interaction with students, undergrads and young researchers working in diversified research areas
3. Minimal language/cultural barriers
4. Proposed research and educational activities were significantly overlapped.
5. Motivation for develoing new sensor based technologies.
6. Broader and diversified educational outreach accomplished under IREE program were:

   a. Sok Yee visisted NU from Nanyang Technological University-Singapore during July-Sept. 2008. She successfully carried out peptides based synthesis for molecular sensor development.
   b. Nishima Wangoo from IMTECH visisted NU during July-sept. 2008 and developed the protocols for surface immobilization of atrazine and diabetic antibodies on the cantilever as well as peptide synthesis.
7. Warm and sociable colleagues

DISCUSSION AND SUMMARY

Significant accomplishments

1. Design, simulation and microfabrication of cantilever with six different designs for significantly improving the current sensitivity.
2. Design and develop novel receptor chemistries using both antibodies and aptamers for high specificity. Antibodies of atrazine and glycated albumin have been successfully developed at IMTECH institute.
3. Genetically engineered polypeptides synthesis and patterning for molecular sensor applications.
4. Micro-fluidics for carrying out biomolecular interaction experiments in liquids.
5. Broader educational outreach with studentsand young researchers coming from diversdfied culture and research settings.

Recommendation for "best Practices" in futue operation of IREE program

Based on our exchange visists and copperatative research environments, we have few suggestions/recommendations for future administration of NSF-IREE program.

1. Maintain sustainability of the research project
2. More interaction between faculty of awardee and students of host institutions.
3. For broader educational outreach, it is very important that long-term relationship between institutions should be maintained as sometimes it is difficulty in rebuilding the relationships and plugging back into the flow.

ACKNOWLEDGEMENTS

The research and outreach activities are supported by NSF-EXP (Award #: 0731243), NSF-ECCS (Award #: 0330410) and NSF-OISE (Award #: 0352706) programs, administered by Drs. R. Khosla, M. Lueck at NSF.

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BRIEF BIOGRAPHIES OF SENIOR RESEARCHERS

Gajendra Shekhawat received the M.S. degree in Physics from the ML Sukhadia University in India in 1991. He received his Ph.D. degree in Physics and Material Science from University of rajasthan and Central Electronic Engineering research Institute (CEERI)-India in 1996. He joined CEERI as research scientist in 1996 working on semiconducting and superconducting devices . He worked over there and developed many MEMS and CMOS based devices and ASICs. He was a research scientist at State University of New york, Albany for 3 years and developed expertise in ultrasound microscopes as well as MEMS based devices. Since 2003, he has been an research Assistant Professor at Northwestern university and manger of the Nanoscale Integrated Fabrication and Instrumentation facility at NU, where he developed several innovative technologies sucs as microcantilever based detection technologies, molecular sensors using peptide based receptors and Ultrasound holography for sub-surface nano-metrology.

Vinayak P Dravid received his Bachelor of Technology (B.Tech.) in Metallurgical Engineering in 1984 from IIT Bombay, INDIA. He was awarded his PhD in Material Science and Engineering in 1990 from Lehigh University, after which he gathered his courage and ventured into academics, right away, at Northwestern University. Vinayak is now a professor of Materials Science & Engineering, and directs a multiple facility center called: NU*ANCE* (NU Atomic- and Nanoscale Characterization Experimental) Center. Vinayak's teaching and research interests revolve around nanoscale phenomena in materials. He is a member or an executive officer at several world-renowned NU research centers such as: International Institute for Nanotechnology (IIN), Nanoscale Science and Engineering Center (NSEC), Materials Research Center (MRC), Center for Cancer Nanotechnology Excellence (CCNE), Center for Catalysis and Surface Science (CCSS), Institute for Environmental Catalysis (IEC).