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Much More than Moore – a journey from VLSI to disease biomarkers

The Infosys Prize 2018 for Engineering and Computer Science has been awarded to **Dr Navakanta Bhat**, Professor and Chairperson, Centre for Nano Science and Engineering, Indian Institute of Science (IISc), Bengaluru, for his work on the design of novel biosensors based on his research in biochemistry, and gas sensors that push the performance limits of existing metal-oxide sensors. The prize recognizes his efforts to build state-of-the-art infrastructure for research and talent training in nanoscale systems, and for developing technologies for space, atomic energy, and national security applications.

Bhat obtained the B E degree in Electronics and Communication in Mysuru (1989) and the M Tech degree in Microelectronics from IIT Bombay in 1992. He then entered Ph D program at Stanford University, where he worked under the guidance of Krishna Saraswat, one of the leading experts in semiconductor physics and technology. After graduating from Stanford in 1996, Bhat worked on sub-micron VLSI device and process design at the R&D facility of the Motorola Company, in Austin, Texas. He returned to India in 1999 to a faculty position in the Department of Electrical Communication Engineering (ECE), IISc and began his work in the Microelectronics Laboratory in the small annexe to the ECE building.

When he joined IISc faculty, Bhat knew that the Institute had no facilities to fabricate microelectronic devices of the kind that he had made and studied at Stanford or the kind produced by Motorola. Even devices of *circa* 1970 could not be made with the facilities available: India had famously missed the 'microelectronics bus' and, now, nanoelectronics and nanotechnology were on the horizon. Determined not to miss the bus again, Bhat and Rudra Pratap (then of the Department of Mechanical Engineering) led an interdisciplinary group of kindred spirits among the faculty and began discussions on establishing a state-of-the-art facility for fabricating and studying micro- and nano-electronic devices, which would also be the enabler of R&D into the emerging domains of nanoscience/technology, including nanomaterials, microelectromechanical systems (MEMS), and biology. It was an opportune time and the idea found resonance with R. Chidambaram, the then Principal Scientific Advisor to the Govt of India. With his advice and encouragement, a proposal to establish Centres of Excellence in Nanoelectronics at the IISc and IIT Bombay was submitted to the Department of Electronics and Information Technology, DeitY. With the proposal funded, Bhat tapped his Stanford and Motorola experience to design a nanofabrication facility in the new structure built expressly for it, empowered by strong support from Balaram (then Director, IISc, and funding from the DST also. Determined and dedicated team effort ensured that the facility could be benchmarked against the best in the world in academia. Fully operational in 2011, the National Nanofabrication Centre (NNfC) has won plaudits from experts from around the world and is presently the largest and most versatile such facility in an academic setting anywhere. NNfC became the anchor of the Centre for Nano Science and Engineering (CeNSE), a new academic unit established in 2010.

From the very beginning, it was the intent of DeitY and the team led by Bhat and Pratap that the unique and expensive NNfC should truly be 'national', accessible to researchers from across India. The Indian Nanoelectronics Users Program (INUP), also funded by DeitY, was designed to meet this goal and, over two five-year phases since 2008, has enabled training and project work of thousands of academic researchers from the farthest parts of the country. It has been hailed as one of the most successful academic R&D projects in the country for sharing advanced facilities, with Bhat presently as its leader at the IISc. NNfC has of course, been crucial to advanced in-house research projects on developing devices and technology based on gallium nitride, MEMS and NEMS devices, silicon photonics, aspects of 5G technology, and 3D integrated electronic systems.

Anticipating the importance of detecting gases with sensitivity, Bhat led from the front, the effort at CeNSE in designing, developing and fabricating gas sensors for monitoring hazardous gases, such as NO_2, SO_2, CO and H_2S. Detecting these gases is crucial to air pollution monitoring, but is important also to strategic agencies like ISRO, where, for example, monitoring the pre-launch level of NO_2 is critical. Toward this end, Bhat's group has been working closely with ISRO, DRDO and the DAE. Deploying the full processing capability of the NNfC, the group has recently designed and developed a metal oxide-based 'single-chip gas sensor array' capable of simultaneous, sensitive detection of CO, CO_2, NO_2 and SO_2; the array can be integrated with a CMOS-based platform. In collaboration with a multinational company, Bhat's group has developed a device that can sense H_2S at parts-per-billion (ppb) level, potentially enabling medical diagnosis based on breath analysis. In a related effort, a device for sensing NO_2 at ppb levels has been developed, with the study demonstrating that optimization of sensing material and sensing conditions can lead to stable and selective sensors useful to air quality monitoring, both indoor and outdoor.

The improbable and deep engagement of Bhat, a semiconductor scientist, with biochemical sensors, which led to his becoming an entrepreneur, is the stuff of movies. In 2004, Balaram introduced Bhat to P. R. Krishnaswamy, a biochemist and IISc alumnus, who had been the Chief of Pathology at Jaslok Hospital, Mumbai. The dialogue with Krishnaswamy led Bhat to develop interest in working on diabetes, an illness that was already a major public health problem in the country, straining severely the resources of patients, the medical establishment, and the nation.

As is well known, diabetes is a 'silent killer'. If uncontrolled, it affects blood vessels, eyes, heart and the kidneys, progressively. However, with timely detection and regular monitoring, diabetes can be controlled effectively. In 2008, Bhat embarked on an effort, with help from two faculty colleagues, to develop an electrochemical alternative to the standard HbA1c lab test that measures the amount of glucose bound to haemoglobin (Hb), and is a marker for diabetes that is much more useful than the measure of blood glucose provided by the common handheld glucometer. In addition to Bhat becoming familiar with the relevant techniques and issues, one of the outcomes of the work was the isolation of haemoglobin through a novel approach.

'Chance favours the prepared mind', as Pasteur has said. In late 2012, Bhat received an e-mail from Vinay Kumar, an engineer in a software firm in Gurgaon, seeking opportunity to work on a project related to diabetes. Vinay Kumar is a Type-1 diabetic who grew up in rural UP without discovering his diabetic condition until he was a teenager. A brilliant student, he went on to obtain M Tech degree in Electronics and to work in a Gurgaon firm. But, his condition led to a life-threatening crisis, after which he wrote to the institutions around the country seeking an opportunity to work on diabetes. Vinay Kumar's e-mail elicited immediate response from Bhat, who offered him a research associateship. On a mission, Vinay Kumar began immediately to dig deep into the issues of diabetes, given the access he now had to a vast trove of published literature. He qualified for admission to the Ph D programme in CeNSE in 2013 and began working formally as Bhat's student.

No point-of-care (PoC) device except the glucometer was then available to monitor diabetes, and markers like HbA1c could only be measured by complex and expensive lab tests. The desirability of frequent monitoring makes such tests unaffordable to most patients. Other important markers, such as albumin, also called for complex lab tests. Human serum albumin is either a lone, or associative, biomarker in several chronic diseases like necrosis, nephrosis, hepatitis, malnutrition, immune disorders and diabetes. In pathology laboratories, the serum albumin is usually tested on serum samples and not in whole blood samples. Since albumin is not a metalloprotein, it had been difficult to develop an electrochemical PoC biosensor for it.

The receptor in a biosensor should be specific to the biomolecule of interest amidst a pool of bio-fluid and should give a signal through an appropriate transduction. Antibodies and enzymes have been the first choice as receptor molecules in PoC biosensors. Though these biological receptors are highly sensitive and selective when used with analysers in a pathology lab, their use in PoC biosensors has significant limitations, because, the stability of antibodies and enzymes, after functionalization on disposable strips, is a serious issue. Moreover, accuracy is affected also by ambient temperature, humidity and pH variations.

Learning the relevant biochemistry together (I suspect), Vinay Kumar and Bhat first worked on sensing Hb. They learned that direct-electron-transfer biosensors, with direct communication between the biomolecule of interest and electrode surface, are preferable to enzymatic and mediator-based sensors. Although haemoglobin contains four redox-active iron centres, direct detection is not possible due to inaccessibility of iron centres and formation of dimers, blocking electron transfer. They soon found that, through the coordination of iron with aza-heterocyclic receptors – pyridine and imidazole – a cost-effective, highly sensitive, and simple electrochemical Hb sensor using cyclic voltametry and chrono-amperometry was possible. The receptor could be either in the form of liquid micro-droplets mixed with blood, or a 'dry chemistry' embedded in paper membrane on screen-printed carbon electrodes, enabling a PoC device.

Next to be tackled by the duo was albumin. They developed a novel technique for the electrochemical detection of serum albumin in whole blood samples, by exploiting its binding property with redox-active copper salts. Accuracy of the technique was verified on both real human blood plasma as well as whole blood samples. Glycated albumin – the glycated form of serum albumin – is emerging as a novel biomarker for diabetes management, as it gives the average blood glucose value over 15–20 days. It is extremely useful for chronic kidney disease patients and patients with hemoglobinopathies, in whom HbA1c can give erroneous results. Combining 'copper chemistry' with the boronic affinity principle resulted in the first-ever demonstration of glycated albumin sensing.

Creatinine followed. It is a nitrogen compound formed by the non-enzymatic cyclization of creatinine in muscle tissue. Creatinine levels in biological fluids are routinely tested in clinical labs for different conditions including renal function, muscle damage, nutritional status and thyroid function. The rate of urinary creatinine excretion has been used as a reliable marker of kidney functioning and to assess muscular damage. In clinical labs, detecting creatinine is done by spectrophotometry, which is affected by numerous metabolites and drugs found in biological samples, such as glucose, fructose, ketone bodies, etc. Electrochemical detection of creatinine either involves sophisticated steps of functionalizing electrodes,or depends on enzymatic detection of creatinine. Neither is suitable for a PoC device. Working with Krishnaswamy and Vinay Kumar, Bhat developed a highly accurate urine creatinine biosensor using iron(III) receptor membrane-coated electrode surface, where redox current depends on the formation of Fe(III)–creatinine complex. The method is simple and suitable for handheld PoC biosensing of urine creatinine.

All this work had been completed in *less than* two years. With results in hand, Bhat's group visited the labs of companies developing biosensors, to learn where things stood. The visit convinced Vinay Kumar to remark that 'CeNSE technology' was advanced enough for establishing a company to develop a multi-analyte PoC device of great utility. Bhat was soon persuaded, and incubated 'PathShodh' as a start-up company on IISc campus in July 2015, and went on a one-year sabbatical.

The rest, as they say, is history. Within a year, PathShodh developed the world's first multi-analyte PoC diagnostic device, called 'anuPath', to perform 5 blood tests (Hb, HbA1c, serum albumin, glycated albumin, glucose) and 3 urine tests (microalbuminuria, urine creatinine, and albumin-to-creatinine ratio, ACR) for the early diagnosis of multiple chronic diseases. For anemia and malnutrition, this Lab-on-Palm enables simultaneous measurement of Hb and serum albumin. For diabetes management, the simultaneous measurement of glucose, glycated albumin and HbA1c provides first-of-its-kind time-differential glycemic indexing. For early diagnosis of kidney disease, measuring microalbuminuria, urine creatinine and ACR on the same device provides unparalleled differentiation. The technology has been protected by multiple international patent filings. The rich features of the anuPath device, including novel non-enzymatic and hence robust disposable test strips; minimally invasive finger-prick testing; extremely low sample volume (micro-litre); user-friendly, touch-sensitive GUI customizable to any language, capability to store up to 100,000 test results on the device; Bluetooth connectivity to smartphones and the cloud, Android app enabling data storage and analytics on the cloud, together make it an ideal candidate to enable front-end interface for Digital Health platforms across the country. Another unique feature of anuPath is that all the test results of individuals can be mapped to the Aadhar number, thereby enabling a revolutionary health repository to help in data mining and analytics.

The innovative technology has brought many awards to Vinay Kumar and Bhat, as well as to PathShodh. More importantly, it has caught the attention of Govt agencies, which have recognized its transformative potential for improving public health through preventive care and mitigation of complications due to chronic disease. The Tata Trust has started using this technology in its massive national rural telemedicine programme. After a rigorous due diligence, the anuPath device has now been deployed in the mobile clinics in several villages in Andhra Pradesh and Uttar Pradesh. This programme will soon be expanded to other states.

Based on these experiences, the PathShodh technology is well poised for introduction in resource-challenged regions in other parts of the world. It is likely to play a game-changing role in enabling massive healthcare intervention for large-scale screening and early diagnosis and management of multiple chronic diseases. Given the rich analytical capabilities provided by anuPath, it is likely to serve well in mapping population dynamics and disease hotspots across the world.

Bhat hopes to expand on the Lab-on-Palm idea so that many more crucial diagnostic tests can be done on a single PoC platform to bridge the healthcare divide, to revolutionize healthcare, the way cell phones did for communication. He also hopes for 'serendipity to strike', taking him in an unexpected direction (again).

Even as the state-of-the-art NNfC was being launched, Bhat expressed more than once to me his concerns about the monetary and environmental cost of maintaining such a facility. He also mused about making R&D efforts that would not depend on expensive nanotechnology, but would make a difference to society at large and to India in particular. I therefore see the founding of PathShodh as a fitting outcome of Bhat's work and, indeed, the fulfilment of a vision. Though the R&D work that led to PathShodh was carried out at CeNSE, its unique and versatile point-of-care products are today being made in a simple, sterilized facility on a busy street in Bengaluru.

One last word: Bhat's accomplishments in diverse domains are such that a very significant one does not even find a mention in the Citation. Working with MoS_2, the new-fangled 2D semiconductor, his group has developed a dual-gated field-effect transistor (DGFET) with independent gate control, which overcomes the 'Boltzmann limit' on the so-called sub-threshold slope (SS) that determines the abruptness with which a transistor switches between ON and OFF states. Low-power operation, demanded by the ever-greater cramming of transistors on a chip, depends on abrupt switching, which is enabled by transcending the Boltzmann limit on the SS. The lower SS achieved in the MoS_2 DGFET means more abrupt switching, making it possible to operate with supply voltage as low as 0.5 V, much lower than possible in silicon MOSFETs.

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A short note on Sendhil Mullainathan's contributions to development economics

Dr Sendhil Mullainathan, winner of the 2018 Infosys Prize for Social Sciences is presently the University Professor at Booth School of Business, University of Chicago. He completed his BA (Computer Science, Mathematics and Economics) in 1993 from Cornell University and Ph D in Economics from Harvard in 1998. He was on the faculty of MIT until 2004, after which he moved to Harvard University as Professor of Economics. He joined the University of Chicago in 2018. He is a recipient of the 2002 MacArthur Fellowship and has been designated as 'Young Global Leader' by the World Economic Forum.

Starting off as a wunderkind in the MIT Economics Department, Sendhil Mullainathan has had a prolific career that reflects his vast array of interests in corporate finance, labour markets, behavioural economics and finance and more recently, machine learning applications in public policy and health care. His