Microfluidics

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For enquiries, please contact :
Dr Chin Sai Kong
Head, Electronics
Science & Engineering Research Council
Agency for Science, Technology and Research (A*STAR)
1, Fusionopolis Way, #18-10 Connexis North
Singapore 138632
Email : CHIN_Sai_Kong@a-star.edu.sg

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SERC's Positioning in Microfluidics

AIM

1. This paper reviews current trends in microfluidics technology, highlights some microfluidic related activities at the RIs and universities, and discusses SERC's current positioning in this field going forward.

INTRODUCTION

2. Fluid flows in channels of cross sections at and below micro-meter scales behave qualitatively very different from those in bulk. These microfluids are more streamlined with fewer tendencies for mixing between steaming layers. The enhanced surface-to-volume ratio, mass and heat transfers, and surface tensions also mean that considerations very different from that of the bulk fluids are needed in understanding and controlling microfluids.

3. The study and application of collective technologies in physics, chemistry, engineering, and micro-fabrications, etc. that enable the manipulation of microfluids under physical confinements (typically channels between 1 mm to 1 μm) is called microfluidics. Subjecting microfluids to sensing through electrical, optical, magnetic means is also fast becoming an integrated part of the microfluidics study and development in recent years.

4. Microfluidics offer many potential advantages similar to the miniaturization in microelectronics: portability, scalability, and less material wastage, ease of automation, etc. The development of micro-machining in the 1970s, a linchpin technology underlying the Microelectromechanical systems (MEMS), also helps to spur the development of microfluidics.

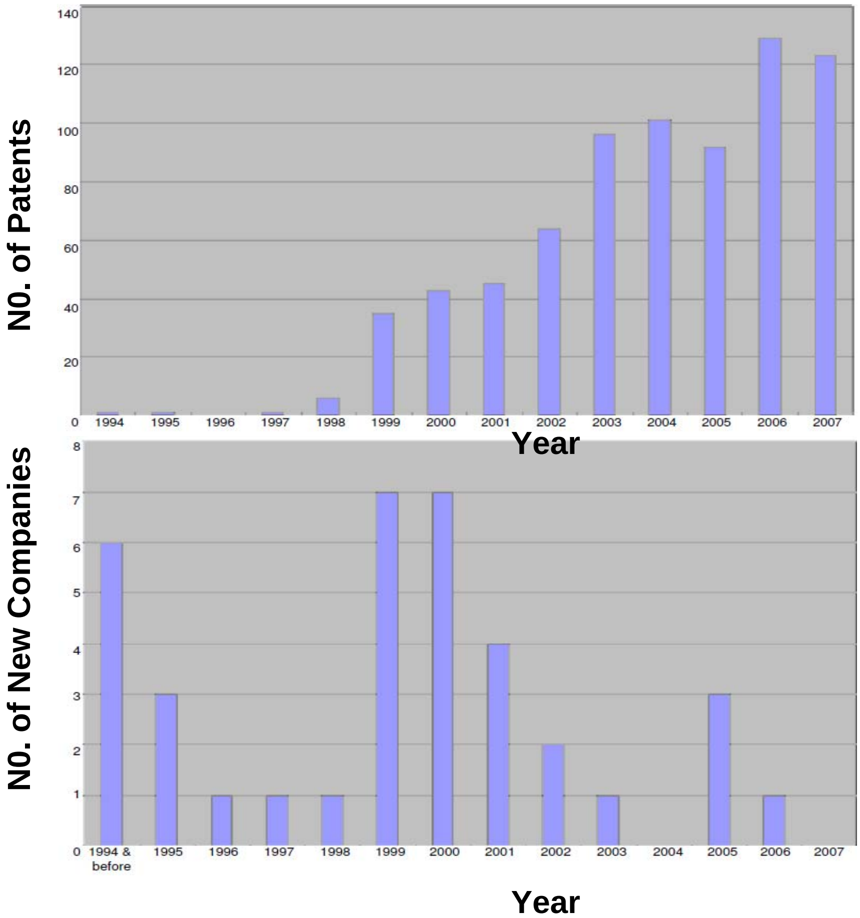
5. The first and perhaps still the most successful application of microfluidics is in the inkjet print head, pioneered by HP. There are two success factors of the print head devices. Firstly, the devices are fabricated on silicon platform, where the scalability of Moore's law can be exploited. Secondly, the very high level of integrations of the microfluidics, MEMS and other electronics components and circuitries enable ever more features and performance enhancement.

6. Besides the print head, biomedical diagnosis is biggest segment where microfluidics is under very active application development. The potential market for Microfluidics in life sciences is

estimated at US$2 billion in 2010 according to Yole Development [9]. Medical diagnoses are always performed in very limited quantities of liquids, required stringent precisions and control of contamination risks. Portability of microfluidics-based devices also promises much faster diagnoses and response time nearer to the patients. For example, the point-of-care diagnostic systems developed by IME can reduce diagnostic time for diseases from the typical 1-2 days to within a few hours with only a few drops of blood. Moreover, modular device design and disposability also place less technical demand on users, simplify usage cycle with minimum contamination risks or errors.

7. However, it is widely recognized that applied microfluidics are not taking off as fast as anticipated, especially outside of diagnostic devices segment, given its vast potential. Although the number of microfluidics-related U.S. patents granted has grown steadily from 1994 to 2007 for applications in many areas, the number of new microfluidics related companies has been sporadic over the same period (see Fig 1(a) & (b) below). This means that while the R&D investment and intellectual properties have been building up steadily, the adoption for commercial use has not been keeping pace with expectations.

Figure 1: (a) The number of microfluidics related patents and (b) new companies formed per year from 1994 to 2007 [9]



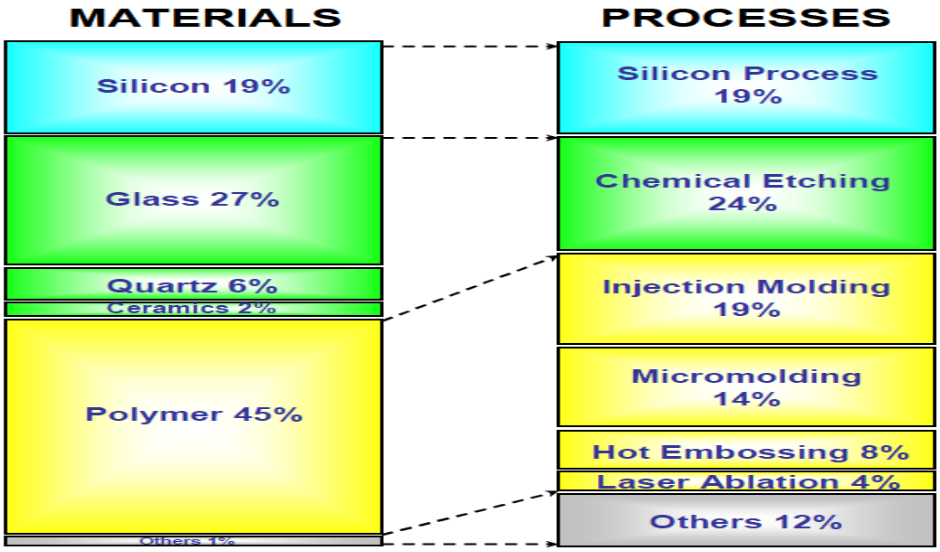
8. The main reason for the slow pace of commercialization of microfluidics, even in the diagnostic devices segment, is that microfluidics is just one of the many enabling technologies needed[1] to be integrated to functional system to solve real problems. For example, diagnostic applications need integration of microfluidics and the relevant electronic and optical sensing to be effective. For complex application development, issues like non-standard methodologies, accuracies of other components, and manufacturing scalability, cannot be solved by just improving microfluidics alone.

9. Outside of diagnosis, microfluidics has been applied in many areas like environmental monitoring, chemical synthesis, and phase separations, etc. However, commercial successes are still very elusive. It is generally recognized that microfluidics is a solution looking for a suitable problem.

Microfluidics: Technology Characteristics

10. There are three main wet components in a microfluidic device are: the substrate in which microchannels are formed, the cover for the channels, and an (optional) adhesive bonding the substrate and the cover. The cover is commonly made of glass or plastic to meet the needs for transparency, while a wide variety of materials are used for the substrate and bondings.

Figure 2. Common materials & processes for microfluidics



11. Polymers are currently the most common materials used for microfluidics because of their low costs, and the versatile and

cost effective range of methods that can process them for microfluidics use. Common polymers used include PMMA, PC and COC and the pervasive PDMS.

12. However, polymers still face many fabrication challenges before they can substitute their more expensive cousins like silicon and glass in biomedical applications because of the requirements of bio-compatibility and more narrow channels, typically at nanometer scales.

13. Although more expensive than polymer and glass, silicon is an attractive microfluidics substrate because of the potential in integrating and packaging microfluidics components together with other electronic components including sensing, signaling, and other interconnects in a device, and manufactured in a demonstrated scalable way. (See Fig. 2 for existing materials and processing means for microfluidics substrates.)

14. Most of the critical macrofluidic components and functions have analogs for microfluids. For example, a system of microscale pumps, valves, mixers, etc., can achieve common functions like fluid storage, transport, flow control, mixing separation, etc.

15. It should be noted that in most applications, it is usually not practical or necessary to achieve “lab-in-a-chip” setup. The crucial microfluidic components can be very small, but they are typically connected to macro-apparatus, especially for open systems involving stock feeds.

16. In recent years, greater emphases are placed on integrating microfluidics and other enabling technologies needed for specific applications like biomedical diagnoses. These adjacent technologies can include sensors of optical, electrical or magnetic, or plasmonic means, and MEMS. The great diversity and complexity of usage within biomedical diagnosis, from molecular to cell levels with diseases with different diagnostic methodologies and designs, demand heavy investment in vertically aligned and focus applications. This same situation also applies in emerging field like drug discovery, quantitative analysis in food and water safety, etc.

EXISTING SERC-funded Capabilities in the RIs and Universities

17. SERC has seeded many microfluidics capabilities in the universities and the RIs through intramural and extramural fundings. Given the current states of the field as discussed and the potential roles microfluidics plays in Singapore’s long term thrust to grow the water, environmental and biomedical industry,

it is timely that we takes stock of existing capabilities, review our strategies, and cast sights on future opportunities.

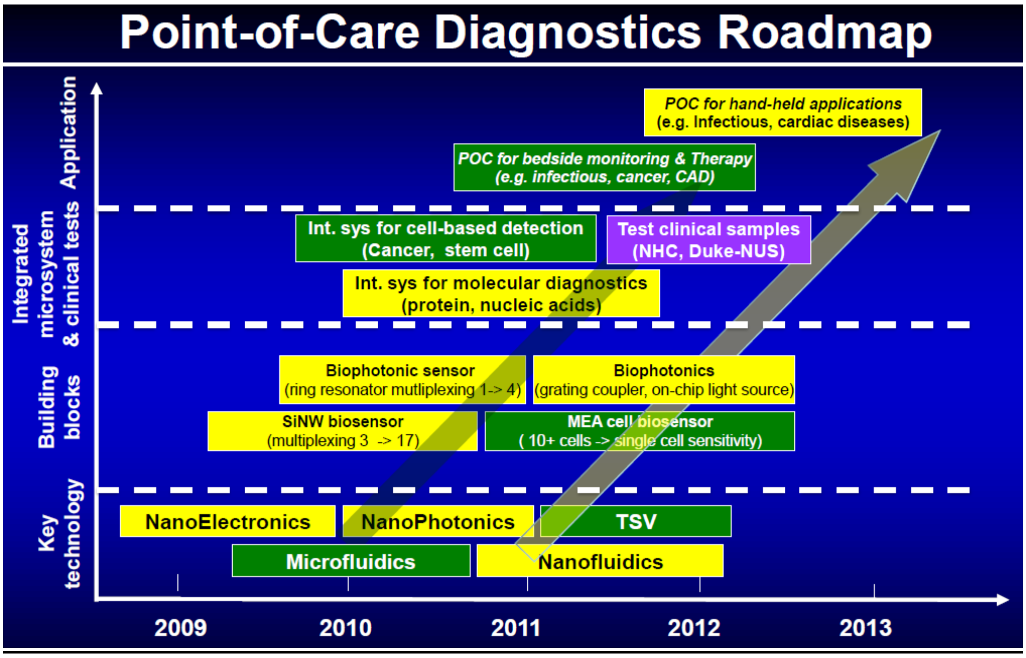
18. Since the late 1990s, SERC have been seeding microfluidics technologies (both componential and integrative in nature) at the SERC RIs and the universities.

19. The SERC RIs where major microfluidics works have been funded as core capabilities are IME, SIMTech, IMRE, and IHPC. Below is a short write up of the effort at respective RIs:

a. IME Equipped with the necessary micro-machining tools used for MEMS R&D, IME had already built up strong core capabilities in silicon-based microfluidic device design and fabrication by 2004 through biomedical application projects in collaboration with NUS biologists. In Jan 04, IME's tecnologies on micro Polymerase Chain reaction (µPCR) for DNA replication and micro Total Analysis Systems (µTAS) for DNA extraction and analysis were licensed to SiMEMS, a local spin-off SME providing BioMEMS solutions. It was the world's first DNA Lab-On-Chip at that time. Separately, in 2005, IME's related development of DNA/RNA diagnostic kits used to detect avian flu and other infectious diseases was licensed to Veredus Labs, a Singapore SME specializing in developing portable diagnostic toolkits.

In recent years, under their Bioelectronics Programme, IME have worked closely with local clinicians and industry partners and capitalized on their diverse suite of capabilties which include microfluidics, nanoelectronics, nanophotonics, MEMS, packaging, integrated circuits, etc. to develop silicon-based Point-Of-Care (POC) diagnostics devices which can detect infectious (dengue) and cardiovascular diseases as well as gastric cancer. These devices can dramatically reduce diagnosis time from 1-2 days to 45 mins-4 hours with only a few drops of blood.

Figure 3. IME Roadmap for POC Diagnostics



b. SIMTech had developed broad based competency in the enabling technologies for the rapid prototyping and mass production of low-cost polymer-based microfluidic BioMEMS devices by 2005. These technologies include lithography methodologies, laser process techniques, micro-molding and embossing methods.

Today, SIMTech's Microfluidics Manufacturing Programme (MMP) aims to spearhead innovations in polymer-based microfluidics devices manufacturing, including design, fabrication, integration, testing and characterization. Main polymers include PMMA, PC, COC & also the pervasive PDMS. The Microfluidics Research Foundry under the MMP also provides a testbed for rapid prototyping and pilot manufacturing. Besides biomedical applications, SIMTech's microfluidics devices have also been developed for industrial analysis applications, such as chemical synthesis and water quality monitoring.

c. IMRE: Through international collaboration with IMT of Switzerland as well as local partnership with NUS and NTU, IMRE had developed core capabilities in designing, fabricating (wet etching), packaging and characterizing/testing key microfluidic components such as microchannels (silicon & glass), micropumps, microneedles and microflow sensors by 2003.

Recently, Prof. Stephen Quake has been engaged as a consultant under the Visiting Investigator Pogramme (VIP) to spearhead Microfluidics System Biology (MSB) research in Singapore. Prof. Quake is an eminent researcher in the field of microfluidics technology. Under this research programme, a MSB Lab has been set up and the research will focus on the development of high-throughput microfluidics tools for the quantitative characterization and study of biology-related molecular interactions and reactions. This cross-disciplinary research in engineering and biology will deepen the links between the scientists and engineers from IMRE, SIMTech, IMCB, GIS, ETC, NITD, and Stanford University, where Prof. Quake is currently based.

Separately, IMRE is also developing Lab-On-Chip (LOC) prototypes of a portable electrophoretic analyzer based on capacitively coupling contactless conductor detection technology integrated with microfluidics.

d. IHPC had developed relevant modelling and simulation capabilities to support the design of microfluidic devices by 2003. Various computation tools and 2D/3D source codes were developed to simulate liquid flow and heat transfer in micro geometry, taking into account fluid/structure interactions. Simulations to predict the vibration behaviour of fluid conveying carbon nanotubes and nanowires were also performed.

Recently, IHPC have developed a PDMS-based microfluidic device for the purpose of ultrasound harvesting intracellular content of yeast using acoustic cavitation of air bubbles[5]. Simulation models have been developed in conjunction to help predict the behaviour of the collapsing bubble and its nearest cell. This proven technique is now being applied by BTI biologists to conduct gene therapy research in transferring genes into mouse / human Embryonic Stem Cells (ESC).

e. ICES Of late, in collaboration with a foreign partner, ICES have designed & fabricated a PDMS-based microfluidic crystallisation chip to study crystal nucleation and growth. Due to the transparent nature of PDMS, crystallization process can be observed in real time under a stereomicroscope.

20. The BMRC IBN also has significant effort in microfluidics related medical devices. An avian flu lab-on-a-chip test kit based on droplet microfluidics was successfully developed together with IMCB and GIS. In 2008, the technology was licensed to MP

Biomedicals, a global company specialized in diagnostic products. The kit is sensitive enough to detect avian flu directly from throat swab samples within 28 minutes, compared to about 4 hours that usually take by conventional commercial test kits, and yet the IBN kit can be cheaper by 50 times [3]. MP Biomedicals planned to use the technology to target global mass markets. Moreover, MP Biomedicals is making the VRC test kit at its Tuas facility in close collaboration with IBN.

21. Another notable successful diagnostic device developed by IBN is the all-in-one kit called MicroKit, which is a fully automated desktop system that integrated the RNA/DNA extraction and RRT-PCR detection in one platform [4] and can diagnose up to 3 infectious diseases (e.g., H1N1 swine flu) in 2.5 hours at the field, compared to about 7 hours in a lab. All the diagnostic reagents are sealed in a polymer cartridge and disposable after use, hence minimized risks of contaminations. Moreover, the MicroKit can be readily enhanced to detect potentially up to 25 diseases, such as the hand-foot-and-mouth diseases, dengue, HIV, etc. Due to its ease of usage, the Microkit can be deployed at the immigration and check points and outpatients clinics where rapid detections at sites are highly valued. The MicroKit has now been licensed to SG Molecular Diagnostics, a local spin-off from another local SME, Dyamed Biotech.

22. Over the last decade or so, NTU and NUS have also built up substantial capabilities in microfluidics

a. <u>NTU</u> N.T. Nguyen's Lab for Micro & Nanofluidics focuses on the development of micro/nano machining technologies, especially polymeric micromachining, and its applications in microfluidics. With the enabling technologies, NTU has fabricated devices and investigated fundamental fluidic effects in the micro scale such as convective/diffusive mixing, Taylor-Aris dispersion, viscoelasticity, fluid/structural coupling and optofluidic interactions. Functional microfluidic components such as microvalves, micropumps, micromixers, microdispensors, and microsensors have been fabricated and implemented in various handheld or desktop-based LOC platforms such as DNA amplifiers and chemical sensors.

b. <u>NUS</u> Pockets of microfluidics expertise reside in various engineering and science departments, ranging from bioengineering, chemical & biomolecular engineering, electrical engineering to chemistry and physics. Fundamental capabilities pertaining to modeling & simulation, design & fabrication technologies as well as the development of PDMS and glass-based diagnostics/POC devices have been built up in recent years.

23. SERC's TSRP on Integrated Nano-Photo-Bio Interface (iNPBi) was launched in Apr 2010 to develop and strengthen capabilities at the boundaries of science and engineering that encompasses the Nano-Photo-Bio regime, so as to complement existing application-driven programs in biological and medical areas. Under this TSRP, 3 microfluidics-related projects were approved.

a. In collaboration with IME, SIMTech, SBIC, NTU & NCCS/SGH, DSI is leading the development of an integrated optical-nanoantenna microfluidics system used for multiplexed protein sensing via Surface Enhanced Raman Scattering (SERS). This prototype system is to be used as a Proof-Of-Concept for detecting known protein biomarkers in bladder cancer. With the relevant background expertise, DSI is developing the optical nanoantenna (for detection) while IME and SIMTech are developing the microfluidics substrates (silicon & polymer respectively).

b. Collaborating with I2R, SIMTech, NTU and NCCS/SGH, DSI is also leading another development of an integrated fibre-optic microfluidic device for detecting and identifying known biomarkers in liver and pancreas cancer. With the relevant photonics expertise, DSI and I2R will jointly develop the fibre micro-channels while SIMTech is developing the polymer-based microfluidics substrate.

c. In collaboration with NUS and NUH, IMRE is developing a Quantum Dot (QD) microfluidic device to help clinicians in diagnosing the origins of flu-like symptoms, be it a virus, bacteria or allergy. This will be done via a single nasal swab and the PDMS-based large-scale integrated (LSI) microfluidic chip (fabricated by IMRE) will screen for a large range of viruses and bacteria. The semiconductor QD assay (developed by NUS) serves as the fluorescent label so that detection by the clinician's eye is enabled under UV light excitation. No expensive detectors are hence required.

CONCLUSION AND RECOMMENDATIONS

24. SERC has invested substantially in a myriad of capability development in microfluidics at the SERC RIs and the universities in terms of manpower, material processing, and equipment expertise.

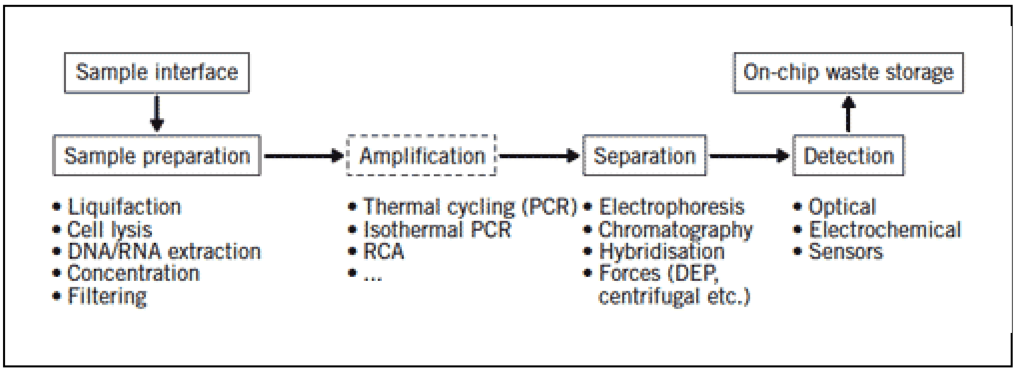
25. Relevant know-how pertaining to the design, fabrication, integration, testing, characterization and even mass manufacturing are largely in place and are ready not only to support conventional microfluidics-based applications like medical diagnostics and analyses, but also potentially other new and emerging applications in nascent areas.

26. Moreover, SERC's microfluidic capabilities are now consolidated and organized under umbrella programmes hosted by some of the RIs that are readily accessible by the industry. IME's bioelectronics POC programme and SIMTech MMMP are the flagship programmes for end users.

27. For new capability development in microfluidics, biomedical diagnosis remains the key vertical segment that SERC is actively investing in the short and long term. Today, in order to make commercial advancement in this field, integration of sensing technologies (especially optical) and microfluidics is the key. The Integrated Nano-Photo-Bio programme represents such focus today. Other promising sensing technologies that can be considered for future deep-integrations may include plasmonics, magnetic, nanowires, MEMS, etc.

28. In addition to integrating adjacent technologies with microfluidics, deep-integration from materials to systems remains a challenge. To date, there are numerous stand-alone ingenious devices but very few fully-vertically integrated systems available in the market. Focusing on tackling this challenge head on is the key towards all-in-one microfluidic-based application.

Figure 4. Schematic diagram of a typical diagnostic process flow in a microfluidic device.



29. Outside of biomedical diagnosis, there is scope for SERC to focus on application development that can realize the full potentials of existing capabilities. However, the stagnant state of microfluidics adoption today is a global phenomenon. Perhaps lessons from another enabling technology, MEMS, in 90s is

timely. In the 90s, MEMS was also struggling to look for adoption outside of inject print head business. Notable commercial success came only after MEMS-based accelerometer in automotive airbags were first identified and exploited by ST Microelectronics. When prices came down, adoption of MEMS-based motion sensors (gyroscopes, accelerometers, etc) spreaded to consumer electronics, which is now a $3 billion business whereas MEMS for automotive is about $400 million.

30. While preparing to a potential killer-application to emerge, Singapore has sufficient microfluidic capabilities and industry breadth to actively look out for and nurture nascent, unconventional microfliuidics usage, i.e., the airbag equivalent of microfluidics. The focus may be performance enhancement, but adoption in one area may cement and broaden to other local industry. Some examples of nascent areas not penetrated by microfluidics are chemical synthesis, food processing and monitoring, environmental and water monitoring, microscale cooling, etc. It is expected that the solutions, if identified, have to be very cost effective and manufacturing scalable.

31. Towards this end, there is a leadership scope for SERC to continue to promote and expand the industrial portfolio of existing capabilities through SIMTech's MMP and IME's Bioelectronics POC. Active engagement with the industry through consultations, showcasing and inspiring usage through workshops, and feedbacks of industry problems and trends will be critical for adjusting new positioning and spotting opportunities.

32. In sum, SERC is adequately positioned to realize the full potential of the suite of microfluidics capabilities that have been developed in the past years through on-going development that are industry-focus and problem-based.

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Written by : Mr Tan Hwee Feng, AH (Elec) SERC
Dr Chin Sai Kong, H (Elec), SERC

With inputs by : Dr Gary Ng, SIMTech
Dr Chan Yin Thai & Prof. W.F. Burkholder, IMRE
Dr Chen Yu & Dr Tushar Bansal, IME
Dr Tandiono & Dr Ohl Siew Wan, IHPC

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