Next-Generation Point-of-Care Multiplexing Blood Analyzers using High Sensitivity NanoPhotonic Devices

under the aegis of the Ontario Research Fund – Research Excellence program

Newsletter 2022 (issued May 2023)

www.sensing.utphotonics.ca

Inside this Issue

About *Sensing*

This newsletter is published as part of the Ontario Research Fund – Research Excellence (ORF-RE) project, "Next-Generation Point-of-Care Multiplexing Blood Analyzers using High Sensitivity NanoPhotonic Devices". The 4th issue of the *Sensing* newsletter provides an overview of the research developments, outreach activities, and the actions taken for technology demonstration during 2022. The newsletter also highlights key events and research progress that have served to advance the R&D objectives and milestones of year 3 of the project.

Project Overview

The focus of this project is to research, develop, prototype and commercialize high sensitivity multiplexing rapid blood analyzers which can be deployed at the point-of-care. This project involves four research thrusts that are expected to culminate in the development and integration of key technology elements comprising of: NPS (nanophotonic sensing) elements, state-of-the- art microfluidic devices for blood processing, portable optical imaging systems and spectrometers all packaged in a portable instrument with an intuitive user interface. The four thrusts and the corresponding objectives are summarized below:

- Developing integrated nanophotonic-microfluidic devices
- Developing on-chip whole blood processing devices
- Prototyping hand-held integrated nanophotonic-microfluidic multiplexing blood analyzers
- Technology demonstration, preliminary validation and commercialization

Research Highlights

Congratulations to all sensing team members on the publication of their research results in high quality journals, and for presenting their work at international/national conferences in 2022 - highlighted on Page 2.

Some of these research results are highlighted on Pages 3 - 4.

New Funding

Congratulations to the team on the receipt of new academic and industrial project awards, further spurring advanced R&D activities and technology translation - highlighted on Page 4 & 7.

Sensing Outreach

Inspiring outreach activities on sensing and light-based sciences were delivered to young students via summer program at the University of Toronto - highlighted on Page 6.

Technology Development

SERS and AI have been applied for (i) detection of pathogens in water samples, and (ii) biomarkers in blood serum pertaining to cardiovascular disease - highlighted on Page 5.

Research Highlights

2022 Patents

- C. L. Ren, R. Z. Gao, “Air microfluidics and air minifluidics enabled active compression device, apparel, and method”, U.S. Patent Application US17/620,921, 2022.
- J. S. Aitchison, L. Chen, JJ. Dou, RK Nayyar, ”Method and system for portable cell detection and analysis using microfluidic technology”, CA. patent App 2.828, 487 A.

2022 Journal Articles

1. J. Y. Y. Loh, A. Zeineddine, M. Shayegannia, R. McNeil, L. McRae & N. P. Kherani, "A one-step tunable method of selective reactive sputter deposition as a wrinkling approach for silver/polydimethylsiloxane for electrically conductive pliable surfaces”, *Nature Microsystems & Nanoengineering*, 8(89), 2022.
2. X. Yuan, T. Darcie, Z. Wei, J. S. Aitchison, “Microchip imaging cytometer: making healthcare available, accessible, and affordable”, *Opto-Electronic Advances,* 5(11) 2022.
3. Law, J. H, Wang, X., Luo, M. X., Xin, L. M., Du, X. Z., Dou, W. K., Wang, T. C., Shan, G. Q., Song, P., Huang, X, Yu, J. F., & Sun, Y, “Microrobotic swarms for selective embolization”, *Science Advances*, 8(29), 2022
4. W.K. Dou, M. Malhi, T. Cui, M.Y. Wang, T.C. Wang, G.Q. Shan, J.H. Law, Z.Y. Gong, J. Plakhotnik, T. Filleter, R.K. Li, C.A. Simmons, J.T. Maynes, and Y. Sun, "A carbon-based biosensing platform for simultaneously measuring the contraction and electrophysiology of iPSC-cardiomyocyte monolayers," *ACS Nano*,16(7), 2022.
5. X. Wang, J.F. Yu, T.C. Wang, X. Chen, J.H. Law, G.Q. Shan, Z.Y. Gong, W.T. Tang, C.H. Ru, X. Huang, and Y. Sun, "Microrobotic swarms for intracellular measurement with enhanced signal-to-noise ratio," *ACS Nano,* 16, pp. 10824-39, 2022.
6. S. Shariari & P.R. Selvaganapathy, “Integration of hydrogels into microfluidic devices with porous membranes as scaffolds enables their drying and reconstitution”, *Biomicrofluidics*, 16(5), 2022.
7. S. Damodara, J. Arora, D.J. Dwivedi, P.C. Liaw, A.E. Fox-Robichaud, P.R. Selvaganapathy, “Microfluidic device for single step measurement of protein C in plasma samples for sepsis prognosis”, *Lab on a Chip*, 22, 2566 – 2577, 2022.
8. S. Damodara, J. Arora, P.C. Liaw, A.E. Fox-Robichaud, P. Ravi Selvaganapathy, “Single-step measurement of cell free DNA for sepsis prognosis using a thread-based microfluidic device”, *Microchimica Acta*, 189, (4), 2022.
9. S. Sayed & P.R. Selvaganapathy, “High resolution fabrication of nano patterns by multi-step iterative miniaturization of hot embossed pre-stressed polymer films and constrained shrinking”, *Microsystems and Nanoengineering*, 8(20), 2022.
10. W. Cui, Z. Abbasi, C. L. Ren, ”Crosstalk analysis and optimization in a compact microwave-microfluidic device towards simultaneous sensing and heating of individual droplets”, *J. Micromechanics and Microengineering,* 32(9), 2022.
11. W. Cui, Z. Ren, Y. Song, C. L. Ren, ”Development and potential for point-of-care heavy metal sensing using microfluidic systems: A brief review”, *Sensors and Actuators A: Physical,* 344, 2022.
12. S. Kashyap, Z. Almutairi, N. Qin, P. Zhao, S. Bedi, D. Johnson, C. L. Ren, ”Effects of surfactant size and concentration on the internal flow fields of moving slug and Disk-like droplets via μ-PIV”, *Chemical Engineering Science,* 255, 2022.
13. M. Hebert, J. Huissoon, C. L. Ren, ”A quantitative study of the dynamic response of compliant microfluidic chips in a microfluidics context”, *J. Micromechanics & Microengineering,* 32(8), 2022.
14. W. Cui, P. Zhao, J. Wang, N. Qin, E. A. Ho, C. L. Ren, “Reagent free detection of SARS-CoV-2 using an antibody-based microwave sensor in a microfluidic platform”, *Lab on a chip*, 22, 2022.
15. X. Liu, D. Esser, B. Wagstaff, A. Zavodni, N. Matsuura, J. Kelly, E. Diller, “Capsule robot pose and mechanism state detection in ultrasound using attention-based hierarchical deep learning”, *Scientific Reports,*12(21130), 2022.
16. M. A. Bomben, A. R. Moody, J. M. Drake, N. Matsuura, ” Fabrication of Customizable Intraplaque Hemorrhage Phantoms for Magnetic Resonance Imaging”, *Molecular Imaging & Biology*, 24, 2022.


Joel Loh


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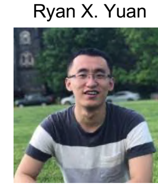
Wenkun Dou


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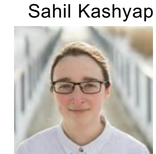
Marie Hebert

Research Project Highlights

Reagent free detection of SARS-CoV-2 using an antibody-based microwave sensor in a microfluidic platform

Dr. Ren's team developed a novel microfluidic microwave sensing method for Point-of-care diagnosis of the SARS-CoV-2 virus. This method relies on the antibody being immobilized on the microwave sensor, thereby selectively capturing and concentrating the SARS-CoV-2 antigen/virus present in the buffer solution flowing through the sensor region in a microchannel. The capturing of the SARS-CoV-2 antigen/virus results in a change in the permittivity of the medium near the sensor region, thus leading to a resonance frequency shift which is used for detection. The use of microchannels offers precise control of sample volume while continuous flow nature presents the potential to monitor the dynamic capturing process.

A Carbon-Based Biosensing Platform for Simultaneously Measuring the Contraction and Electrophysiology of iPSC-Cardiomyocyte Monolayers

Dr. Sun's team developed a biosensing platform for on-chip and simultaneous measurement of contractility and electrophysiology of human induced pluripotent stem-cell-derived cardiomyocyte (iPSC-CM) monolayers. This platform integrates with a flexible thin-film cantilever embedded with a carbon black-PDMS strain sensor for high-sensitivity contraction measurement and four pure carbon nanotube electrodes for the detection of extracellular field potentials with low electrode impedance. Cardiac functional properties were evaluated to quantify iPSC-CM responses to common cardiotropic agents. Drug-induced cardiac arrhythmia was also modeled *in vitro* to validate the platform for disease modeling and drug testing.

Frequency shift probe-based surface enhanced Raman spectroscopy immunoassay for C-reactive protein sensing

Dr. Kherani's team developed a single-step label-free sensing modality using surface enhanced Raman spectroscopy frequency shift – specifically, showing the detection of C-reactive protein (CRP). The CRP is indirectly detected by measuring the frequency shift of a *Raman probe* which binds betwixt the immunoassay platform and the antibody-antigen. Results here indicate that successful detection of CRP over a broad quantitative range down to 10 nM is possible; an enhancement factor of 10^5 shows high sensitivity, while variability of only 4% displays high specificity and repeatability. It is noteworthy that the absence of a secondary antibody reduces the reaction times which in turn greatly increases rapidity in sensing.

Microfluidic device for single step measurement of protein C in plasma samples for sepsis prognosis

Dr. Selvaganapathy's team demonstrated a low cost, single step assay for detection of protein C in blood plasma by combining isoelectric gates with barium-immobilized metal affinity trapping. COMSOL simulation was used to optimize the electric field for use with immobilized metal affinity. The integrated device was tested with samples containing buffered protein C, protein C in the presence of high concentration bovine serum albumin and alpha 1-proteinase inhibitor, and in blood plasma with spiked protein C. Results showed that the device could be used to distinguish a reduction in protein C from 4.46 μg mL^{-1} to 1.96 μg mL^{-1} with over 98% confidence (in plasma) making it suitable for sepsis prognosis.

Research Project Highlights

Multi-Objective Optimization of all-Dielectric Metasurfaces Using 2D RCWA Algorithm For Sensing Applications

Dr. Aitchison's team proposed an evolutionary algorithm-based multi-objective optimization method of all-dielectric metasurfaces for sensing using Rigorous-Coupled-Wave-Analysis (RCWA). Here, they optimized a Si nano-dimer. Simulation results show a Fano resonance with a quality factor of 53570 at 1500nm wavelength and sensitivity of 292 nm/RIU.

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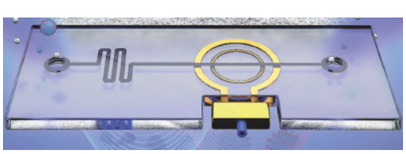
Ultrasound Image-Guided, High-Intensity Focused Ultrasound for Remote Controlled Modification of Polylactic Acid Films

Dr. Matsuura's team developed an ultrasound-guided, high-intensity focused ultrasound as a remote and precise means to modify the mechanical properties of biodegradable polylactic acid films to induce stent failure. This development enables future implants to be removed at time points tailored to meet the requirements of their end applications.

Academic and Industrial Highlights

Rapid detection of E.coli in water system using microfluidic microwave sensor (Academic)

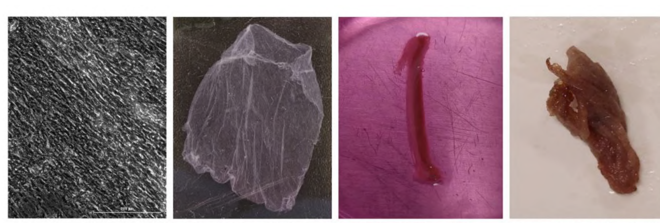
Dr. Ren received a Seed grant from Water Institute (WI) and the Waterloo Institute for Nanotechnology (WIN) to explore the potential of a novel microwave-based biosensor for rapid detection of the E. coli strain STEC within water samples.



Dr. Ren's microwave-based biosensor

Biotech Startup received new funding from Industry

Evolved meat, a startup founded by Alireza Shahid (CEO), former PhD student and PDF from Dr. Selvaganapthy's group, received funding from Garage Capital and Maple Leaf Foods to recreate meat in a way that is identical to nature by bio-fabricating functional muscle tissues and capturing the entire muscle to meat transition.



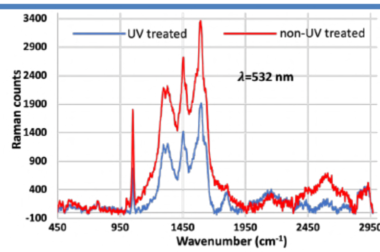
Aligned cells | **Scaffoled-free cell sheet** | **Marbled cultivated meat** | **Fibrous, cooked cultivated meat**

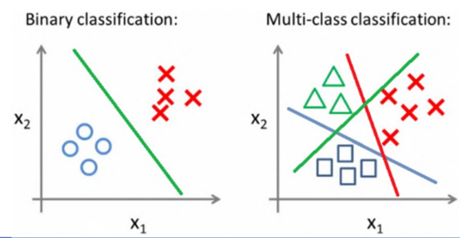
Evolved meat biofabrication of meat tissue

Technology demonstration

Using SERS to screen quality of UV-treatment of water samples

Dr. Kherani's team employed sputtered random nanoparticles as a platform for surface enhanced Raman spectroscopy (SERS) to differentiate between UV-treated and non-UV treated water samples. The water samples were filled with various bacteria and viral pathogens. Preliminary results appear to corroborate with microbial plating where UV treated sample shows lower SERS signals than non-UV treated samples. In addition, presence of peaks in multiwavelength SERS suggest certain bacteria in the UV-treated water sample are still alive and able to reproduce. Further experiments are underway.





Using SERS and AI for classification of CVD biomarkers within blood plasma samples

Dr. Kherani's team employed sputtered random nanoparticles as a platform for Surface Enhanced Raman spectroscopy (SERS) to detect 5 key biomarkers - related to cardiovascular diseases (CVD) - in blood serum plasma at various concentrations, indicative of physiological and pathological conditions. Machine learning algorithms (support vector machines and random forest classification) were used for binary classification of the samples into pathological vs physiological with over 90% accuracy. In addition, regression methods (linear regression, k-nearest neighbors and random forest regression) were used for detecting the exact concentration of the biomarkers with the relative squared error of 20% for LDL biomarker. To further improve the results, Machine Learning classification methods (support vector machines, deep neural networks, k-nearest neighbors and random forest classification) were implemented for multi-class classification of data in order to predict the concentration range of these biomarkers with over 70% accuracy. These results indicate potential for integrated SERS-AI sensing platform to detect biomarkers with quantifiable range of biomarker concentrations.

Research and invited talks

Name of presenter	Type of presentation	Title	Venue
Dr. Naomi Matsuura	Keynote speaker	Targeted in vivo drug delivery with focused ultrasound	Nanotechnology in Medicine, Italy
Dr. Naomi Matsuura	Invited speaker	Ultrasound-stimulated, drug-loaded bubbles for cancer therapy	Acoustical Society of America Annual Meeting, USA
Dr. Mikhail Shapiro	Invited speaker by Dr. Matsuura	Biomolecular ultrasound for noninvasive imaging and control of cellular function	Department of Biomedical Engineering, University of Toronto
Dr. Pietro Valdastri	Invited speaker by Dr. Sun	Robotic Flexible Endoscopy	Robotics Institute, University of Toronto
Dr. Rajni Patel	Invited speaker by Dr. Sun	Teleoperation, Haptics and Control Issues in Medical Robotics Applications	Robotics Institute, University of Toronto

Research Talk Highlight

Targeted in vivo drug delivery with focused ultrasound

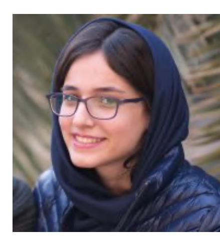
Dr. Matsuura was invited as a keynote speaker at the Nanotechnology in Medicine III: Enabling Next Generation Therapies which was held in Italy during May 2022.

The Abstract of her talk is reproduced here:

Non-invasive, focused ultrasound in combination with microbubbles have previously been used for targeted drug delivery. Focused ultrasound-stimulated microbubbles can increase local tumour blood vessel permeability such that co-injected chemotherapeutics can diffuse preferentially into tumour tissue. Focused ultrasound and microbubbles have also been used to initiate other local bioeffects, for example, to damage tumour vessels for mechanically induced vascular disruption therapy, which can profoundly increase the efficacy of a variety of anticancer drugs. In this talk, the development of new acoustically-active bubbles that are capable of carrying and releasing therapeutic concentrations of hydrophobic and hydrophilic chemotherapeutic drugs will be introduced. Agents that are entirely composed of FDA-approved components are preferred as they may permit expedited translation into clinical use. Trade-offs among size, stability, drug-loading, and *in vivo* performance between bubble variants will be overviewed. Challenges and opportunities identified through recent efforts towards achieving cancer therapy potentiation in small animal cancer models will also be discussed.

Summer Outreach Activity

From Lenses to Lasers:The Science and Engineering of Optics
Presented at The Da Vinci Engineering Enrichment Program (DEEP) Summer Academy



Saba Ale Ebrahim from Kherani's group delivered a multi-week course to grade 10 international high school students during the DEEP Summer Academy 2022. The course was titled "From Lenses to Lasers: The Science and Engineering of Optics". Students were exposed to fundamental physics of light, and existing cutting-edge photonic health technologies, through theoretical lectures, practical laboratory experiments, and fun activities.

Awards, Achievements and Grants

Faculty Awards & Recognition

Congratulations to:

- Prof. Yu Sun for wining the 2022 IEEE EMBS Technical Achievement Award

- Prof. Carolyn Ren for becoming the new Canada Research Chair in Microfluidic Technologies.

- Prof. Naomi Matsuura for wining the Mid-Career Leadership Award. Women In Molecular Imaging Network

- Katelyn Dixon (Kherani's group, UofT) successfully defended her PhD dissertation and graduated. She is now an industry PDF at Quantum Valley Ideas Lab

- Wenkun Dou and Kaiwen Zhang (Sun's group, UofT) successfully defended their PhD and MASc dissertation, respectively. Wenkun is now a PDF at the Hospital for Sick Children.

- Kierdra Dowling and Amanda Ricketts (Matsuura's group, UofT) successfully defended their MASc dissertations.

New Funding

- Prof. Carolyn Ren Received WI/WIN Seed Grant for "Rapid detection of E.coli in water system using microfluidic microwave sensor".

- Prof. Stewart Aitchison Received NSERC discovery grant for "Functional silicon photonics".

- Prof. Ravi Selvaganapathy Received NSERC discovery grant for "Microfabrication technologies for soft biomaterials and their applications".

The Sensing Team

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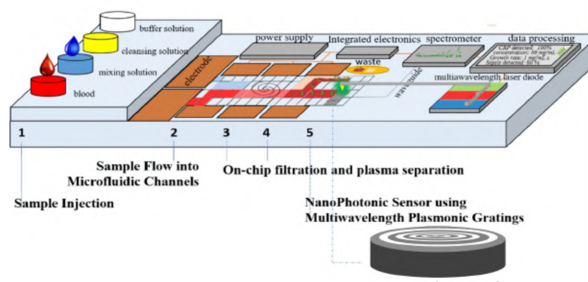
Towards Lab-on-a-Chip Platform for PoC Diagnosis

Infectious diseases are a major cause of morbidity and mortality world-wide due to lack of point-of-care (POC) reliable diagnostic instruments to quickly identify and treat them. We aim to develop POC blood analyzers for multiplexing quantification of pathogens and biomarkers towards advancement of personalized medicine and healthcare, and beyond.

In particular, we aim to further develop and integrate:

- Sensing technologies (using SERS, SEF, SEIRA, Cell counting)
- Blood processing/separation technologies
- Surface functionalization technologies



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Schematic of a lab-on-a-chip point of care system with plasmonics bull's eye nano grating sensor (Team Kherani).

Selvaganapathy Group

Kherani Group

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