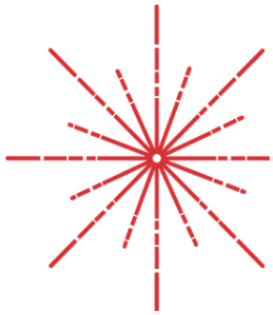

PhotoMedicine Labs

www.PhotoMedicineLabs.com

PROGRESS REPORT OF 2019

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Overview

The PhotoMedicine Labs (PML) is a research group within the Department of Systems Design Engineering at the University of Waterloo. Principle Investigator (PI), Professor Parsin Haji Reza, formed the PhotoMedicine Labs in September 2018, with the vision to nurture and grow this group into a major hub within the fields of biomedical optics and medical imaging. Throughout 2019, our lab has received significant notoriety and has been the source of several innovative discoveries.

We at the PhotoMedicine Labs are focused on designing and developing novel engineering systems for clinical and pre-clinical biomedical applications. These technologies aim to provide clinicians and researchers with novel tools and information which are presently difficult or impossible to obtain with existing techniques. Our philosophy involves translation of research from bench to bedside through investigations into fundamental biomedical imaging technologies with relevant real-world applications. Supported by our skilled interdisciplinary research team, we investigate, design, and develop our own in-house hardware and software systems.

This includes but not limited to research activities in state-of-the-art optical imaging systems, photoacoustic, nonlinear optics, optical sensing, fiber-optics, data acquisition, electronics, software development, image processing, machine learning, artificial intelligence, ultrasound, instrument control, analytical modeling and numerical modeling. We also design, perform and analyze significant pre-clinical and clinical experiments.

The PhotoMedicine Labs aim to offer innovative medical imaging techniques in the field of digital pathology, oncology, pre-clinical research, drug discovery, and ophthalmology. The central goal is to physically build, optimize, and characterize novel hardware and software imaging systems capable of recovering diagnostic cellular-scale information in-situ. The developed hardware and software systems will be used toward imaging in human tissues, including benign and malignant tumors, and imaging within the human eye. This will involve development from applications of fundamental physical phenomena into physical devices that are intended for use as a clinical tool. To progress along this path, we will continue to grow our extensive collection of interdisciplinary talents from graduate students, postdoctoral fellows, scientists, engineers, and clinicians.

2019 was an amazing year for the PhotoMedicine Labs. We have achieved ground-breaking accomplishments throughout the year and are blessed and honoured to have some of the most hardworking, dedicated, and talented students and staff on our team that makes what we do each and everyday possible. By January 2019, our first students were hired, and our lab was up and functioning. This year brough us a great deal of excitement as it was the start if our research program.

Currently, the PhotoMedicine Labs have two state-of-the-art optical and hardware design labs (the Discovery lab and the Imaging lab) and an image processing & machine learning lab. In addition, we have a pre-clinical imaging lab, in which we maintain our animals, perform cell culture studies and pre-clinical model studies. We have also established the necessary ethics approval to work on freshly resected human tissues (healthy and cancerous). To that end, we have also been working on extramural collaborations, securing lab spaces with major local hospitals such as Grand River Hospital in Kitchener, Ontario and Southlake Regional Health Centre in Newmarket, Ontario.

The track-record of the PhotoMedicine Labs over this last year has demonstrated that our team is on the right path to push the boundaries of biomedical optics and medical imaging. With the support of our donors, colleagues, department, and faculty, our lab will continue to focus on biomedical breakthroughs, and attract top talent in the field. Within this report you will discover the substantial progress that the PhotoMedicine Labs has made in 2019. If you wish to follow our process along the way, please check out our website (https://www.photomedicinelabs.com/) or follow us on our LinkedIn (https://www.linkedin.com/company/photomedicine-labs).

Research Accomplishments

In 2019, the PhotoMedicine Labs achieved some major research accomplishments.

- First label-free non-contact histology-like images of human breast, gastrointestinal, and skin tissues from formalin-fixed paraffin (embedded (FFPE) blocks and unstained thin slices.
- First near-one-to-one comparisons between brightfield microscopy images of H&E-stained tissue slides against PARS® images of adjacent unstained FFPE human tissue slides and unstained FFPE blocks.
- First volumetric PARS® scans of human FFPE blocks showing optical sectioning capabilities.
- First quantitative comparison between a PARS® acquisition and a brightfield microscopy image of an adjacent H&E-stained slide by tracking nuclear statistical information.
- First report of a non-contact multi wavelength microscope capable of label-free visualization of cellular morphology and hemoglobin.
- First report of a PARS® microscope which uses two distinct excitation sources consecutively.
- First report of a photoacoustic modality extracting hemoglobin contrast from FFPE samples.

The PhotoMedicine Labs Research Team

Our research team is made up of some of the best and brightest minds in the field. All the work that we accomplish would absolutely not be possible without each and every one of our staff and students paving the way for amazing research to take place. It is truly their hard work and dedication towards making the world a better place that makes PhotoMedicine Labs such a sought-after research lab to work for. The atmosphere in the group is full of passion and knowledge which welcomes everyone coming through its doors. There are always new changes and challenges taking place, and the team that we have built allows us to work through them together.

As the principal investigator, Parsin Haji Reza's strong desire to teach motivated him to create and grow the PhotoMedicine Labs to what it is today. Our lab aims to provide a unique research experience for all those who work with us. By doing so, we are able to assist everyone in discovering their strengths, help them to grow, and find purpose in life. We hold the teaching philosophy that learning can be impactful and can impart the desired knowledge and skills to students. We create a relationship with our team members that motivates them. Students should know what they have to learn, why they have to learn it and how they can apply their creativity.

In 2019, the PhotoMedicine Labs had the pleasure of working with eleven undergraduate research assistants, using the University of Waterloo's Undergraduate Research Assistantship (URA) program, which provides engineering students with the opportunity to gain first hand research experience working with a faculty member to further their knowledge in a field of interest. We accepted five co-op students and an international visiting scholar who ranked second in the Iran National Exam (which had more than 500,000 participants). Additionally, our lab brought on board four master's students and one Postdoc. These students found a research home with us to take an in-depth look at the world-class novel technologies that we are working with.

Here at the PhotoMedicine Labs, each team member is provided a defined specific project that delivers hands on work experience. While at the same time, the facility provides them with the necessary infrastructure and the PI offers daily guidance on their project.

We provide options for both software-based and hardware-based biomedical research opportunities, and we pride ourselves on accepting as many students as possible that we can, often receiving around 20 URA requests per term. We make it very clear that the expectation that we have on our students is to learn as much as they can, no questions are off the table. Students have full access to all of our labs. They are trained on how to perform experiments on all of our requisite state-of-the-art infrastructure. Many of our URAs experience the opportunity to contribute to our publications. This represents the great opportunity that the PhotoMedicine Labs provides for undergraduate students.

Awards

All of our amazing graduate students do work that is worthy of rewards. We are proud to recognize that two of our master's students received multiple awards and scholarships.

Our URA's are some of the top members of their cohort with GPA's of a least 80%. We get many applicants but can only select a handful of candidates. Many of our students received awards such as payment from the Dean's office or received the President's Research Award.

In 2019, we are proud to see the hard work and dedication of our team members recognized by these awards. Our lab members received a total of 12 rewards collectively.

Awards earned by our graduate students:

- Jasmine and Saad, our master's students both received the International Masters Student award.
- Jasmine and Saad, our master's students both received the University of Waterloo Graduate Scholarship.
- Saad, our master's student received the Graduate Research Studentship.

Awards earned by our undergraduate students:

- Four of our undergraduate students received the Undergraduate Research Assistantship (URA) provided by the Dean of Engineering.
- Two of our undergraduate students received the President's Research Award to work in the PhotoMedicine Labs.
- One of our undergraduate students received the Undergraduate Research Internship (URI) to work in PhotoMedicine labs.

News

In 2019, the PhotoMedicine Labs was highlighted in multiple news agencies including Systems Design Engineering New, University of Waterloo News, CTV News and more.

February 2019:

- Dr. Parsin Haji Reza is giving a cutting-edge research presentation exclusively for Systems Design Engineering alumni.

March 2019:

- The PhotoMedicine Labs awarded $420K from Mitacs Accelerate Program in collaboration with illumiSonics Inc.
- Dr. Haji Reza received John R. Evans Leaders Fund (CFI-JELF) grant for developing a new form of microscopy called Histological Photoacoustic Remote Sensing (hPARS®) microscopy.

September 2019:

- University of Waterloo researchers develop imaging tech that could 'revolutionize' cancer surgery (CTV News).
- Our recent discovery, "new imaging technology could 'revolutionize' cancer surgery," has been highlighted at several new agencies such as, CTVnews, Uwaterloo news, The Engineer, NCYT, The Medical News, MedicalXpress, ecancer, Scitech Daily, Pourquoi Docteur, ENN, PanARMENIAN, infowares, idigitalhealth, Exchange Magazine, Mindzilla, Ivao and many more.

November 2019:

- Our news story "UW researchers develop imaging technology that could 'revolutionize' cancer surgery" that was featured on CTV News has reached 12 million hits internationally and has been translated in several different countries. https://lnkd.in/ewkB8nT

October 2019:

- Dr. Parsin Haji Reza was featured in the weal (Waterloo Engineering Alumni Letter) magazine, October 2019 issue in the featured story: Ones to Watch: Seven researchers to keep an eye on as their soaring achievements continue to shake things up.
-

Grant Applications

The PhotoMedicine Labs has been fortunate to have access to some amazing funding that drives our research. In 2019, we were granted funding from a variety of organizations at the international, federal, provincial, and local levels. Our lab was awarded ~ $1.27M in cash and grants from sources including the Government of Ontario, CFI, NSERC, IRAP, MITACS and the University of Waterloo. This funding facilitates our timely throughput of high-impact research. Some examples are provided below.

Our project "Non-contact photoacoustic initial pressure imaging" was awarded the Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant. This grant program offers support to ongoing programs of research with long-term goals, while recognizing the recipient's creativity and innovation that are at the heart of all research advances.

Another major project that we are pioneering, histological photoacoustic remote sensing (PARS®) microscopy is a revolutionary technology that received the funding from the Canada Foundation for Innovation through the John R. Evans Leaders Fund (CFI-JELF). This fund helps exceptional researchers conduct their leading-edge work.

We at the PhotoMedicine Labs are fortunate to have a great partnership with a start-up company within the industry, illumiSonics Inc. This company develops, patents, and commercializes PARS® advanced optical imaging systems for a wide range of pre-clinical and clinical applications. IllumiSonics works with market leading partners to develop systems for specific applications. Our collaboration with this company involved expanding upon previous effort related to the design and research of the first combined optical coherence tomography and photoacoustic remote sensing device. It will also be used to research the system improvements for histology-like applications on human samples.

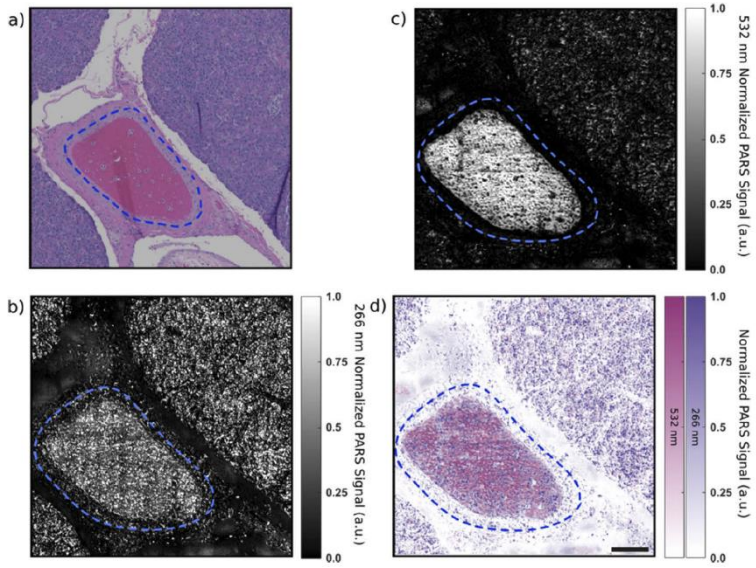
Our lab would be nothing without the support it receives from the University of Waterloo. Due in part to this incredible partnership, we were selected for the Centre for Biotechnology and Biotechnology (CBB) Seed Funding. PI Parsin Haji Reza, along with Optometry Professor Vivian Choh received the CBB Seed Funding for the project "Retinal oxygen metabolic rate extraction using a novel imaging method." This research will help develop a non-contact photoacoustic image to accurately evaluate retinal blood oxygen saturation and metabolic rate of oxygen consumption . Our PARS® technology, will represent the first non-contact photoacoustic imaging technique for recovery blood vessel networks within the eye. This research may prove critical for early detection of diseases such as diabetic retinopathy and age-related macular degeneration (AMD), while providing a more comprehensive picture of how glaucoma develops over time potentially leading to the development of novel and more effective treatments

Published Manuscripts

Peer reviewed publications are an important aspect of our labs work, providing valuable expert feedback from exterior academics. In 2019, the PhotoMedicine Labs had 3 publications in the field of biomedical optics and biophotonics within multiple reputable journals, such as Biomedical Optics Express, Scientific Reports, and Sensors. Each one of these published papers supports an incredible novelty and advancements in the field of Biomedical Imaging and our PARS® technology.

1. Saad Abbasi, Martin Le, Bazil Sonier, Kevan Bell, Deepak Dinakaran, Gilbert Bigras, John R. Mackey, and Parsin Haji Reza, "Chromophore selective multi-wavelength photoacoustic remote sensing of unstained human tissues," Biomed. Opt. Express 10, 5461-5469 (2019).
https://doi.org/10.1364/BOE.10.005461

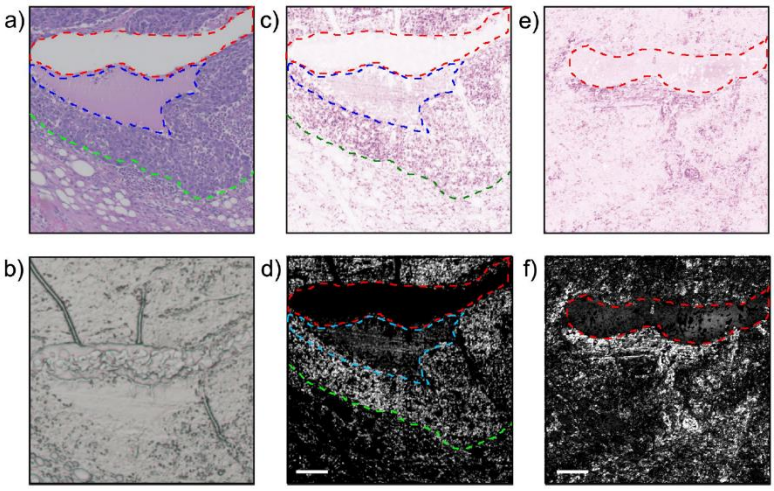
In this article we presented the first PARS® microscope capable of visualizing both nuclear contrast in tissue along with red blood cells (blood vessels) in the same system. This was accomplished through the implementation of ultraviolet (266 nm, targeting DNA) and green (532 nm, targeting hemoglobin) excitation sources. This dual-contrast PARS® device demonstrated its efficacy while visualizing unstained formalin-fixed paraffin-embedded (FFPE) slides of human pancreas and tonsil. The addition of the green excitation allowed for recovery of blood vessel structures which are otherwise poorly resolved while solely relying on ultraviolet excitation. This work paved the way for later efforts in 2020 which looked at further targeting broader hemeproteins such as cytochromes, facilitating visualization of cytoplasmic structure, a key aspect normally recovered by traditional histopathological processing.



(a) A standard H&E stained slide of a blood vessel (blue outline) within human pancreatic tissue imaged with a conventional brightfield microscope. (b) An adjacent unstained slide of the same specimen imaged with 266 nm excitation and (c) with 532 nm excitation. (d) A superimposed image of (b) and (c) with a histology-like colormap, DNA is colored purple, hemoglobin is colored red. Scale bar 100 µm.

2. Saad Abbasi, Martin Le, Bazil Sonier, Deepak Dinakaran, Gilbert Bigras, Kevan Bell, John R. Mackey, Parsin Haji Reza, "All-optical Reflection-mode Microscopic Histology of Unstained Human Tissues" Scientific Reports 9, 13392 (2019). https://doi.org/10.1038/s41598-019-49849-9

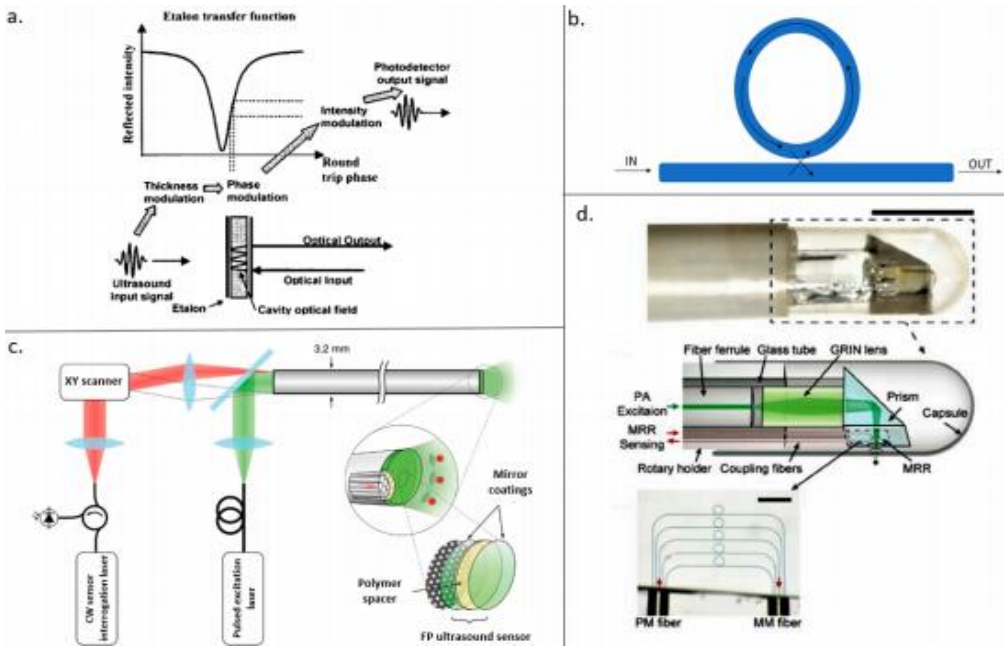
In this article we presented initial work on a PARS® microscope which is capable of visualizing nuclear contrast in human tissues. This was accomplished using an ultraviolet (266 nm, targeting DNA) excitation source. The work represents the first report of a non-contact photoacoustic microscope which is capable of visualizing sub cellular morphology from human tissues without the use of any exogenous contrast agents. Within the study are the first one-to-one comparisons between ultraviolet excitation PARS® imaging unstained formalin-fixed paraffin-embedded (FFPE) slides of human tissues and brightfield imaging of adjacent FFPE slides which had undergone conventional processing and staining. Comparisons were performed both from qualitative metrics (visual similarity between PARS® and traditional processing methods) and quantitative metrics by comparing key statistical sub cellular quantities. As the first published article from our new laboratory, this represented a huge milestone for all involved parties demonstrating the capabilities of the newly assembled research team and the new facility at the University of Waterloo.



A comparison between a PARS® images and (a) a bright field image at the of the same breast tissue sample with invasive ductal carcinoma. (b) an unstained slide imaged with a conventional bright field microscope. A PARS® acquisition of the regions is shown for the unstained tissue slide with (c) a false H&E colour map applied and a (d) logarithmic greyscale colour map applied. A PARS® acquisition of a FFPE block with (e) a false H&E colour map applied and (f) a logarithmic greyscale colour map applied. Green outline highlights a sharp delineation between a hypercellular region of tissue and healthy tissue, blue outline represents a high-grade malignancy with serosity and necrotic cells, the red outline represents an artifact present in the slides. Scale bar 100 µm.

3. Jasmine Chan, Zhou Zheng, Kevan Bell, Martin Le, Parsin Haji Reza, John T.W. Yeow, "Photoacoustic Imaging with Capacitive Micromachined Ultrasound Transducers: Principles and Developments." Sensors, 19(16), 3617 (2019). doi: 10.3390/s19163617

In this manuscript, a review is presented examining the use of capacitive micromachined ultrasound transducers (CMUTs) with focus on implications to their use in photoacoustic tomography (PAT, or PACT). Various potential benefits of CMUTs were compared against other acoustic transducers such as piezoelectric devices and optical resonators. Of note, some potential benefits listed include bandwidth range, device size/packaging flexibility, and sensitivity which would be well suited for use in PAT devices. This article represented a collaboration between the PhotoMedicine Labs and John Yeow's group at the University of Waterloo through Jasmine Chan who was co supervised between the two groups.



(a) Diagram of the working principle of Fabry–Perot interferometers (FPI). An incoming ultrasound wave causes a variation in thickness which in turn results in a phase modulation (Reproduced from [88], with the permission of AIP Publishing.); (b) schematic diagram of an micro ring resonators (MRR); (c) schematic diagram of a forward-viewing photoacoustic probe for endoscopy imaging used in [69]; (d) photoacoustic endoscopy with a MRR detector used in (Adapted with permission from ref [82],

International Scientific Conference Presentations

The PhotoMedicine Labs was honoured to present the World Molecular Imaging Congress (WMIC) in 2019.

WMIC ran from September 4-7, in Montreal, Québec, Canada. Each year, the WMIC bridges a range of disciplines including biology, chemistry, physics, and engineering. The theme for WMIC 2019 was “The Dynamics of Life: Integrating Molecular Imaging”. The World Molecular Imaging Congress (WMIC) is the only meeting that provides a unique platform for scientists and clinicians with very diverse backgrounds to interact, present, and follow cutting-edge advances in molecular imaging. In addition to the preclinical, basic sciences and translational coverage, much of the program is clinically driven, building a powerful bridge between the clinical and preclinical imaging.

A presentation was given on the following topic:

- Saad Abbasi*, Kevan Bell*, and Parsin Haji Reza, "Towards Non-Contact Microscopic Histology of Unstained Human Tissues" WMIC (2019). (Talk)

PhotoMedicine Labs – Group Photo

We at the PhotoMedicine Labs are committed to making the world a better place with our research. We are so proud of everyone who has had the honour of being a part of our team and are immensely excited to see what big things the future holds for us!