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"Point of Injury" Sampling Technology for Battlefield Molecular Diagnostics

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DARPA SBIR PHASE I OPTION REPORT: Point of Injury, Sampling Technology for Battlefield Molecular Diagnostics. W31P4Q-11-C-0222 (UNCLASSIFIED)

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Report Covers: October 22 to March 17, 2012 (option period)

Executive summary

Technology

- The overall aim of this project is to develop a diagnostic field test that can be used to detect traumatic brain injury and late stage shock from a drop of blood taken from a finger stick.
- For Phase I Option, the broad goal is to integrate the sample processing technology developed in Phase I with the nanoscale optical sensing array (NOSA) which will ultimately be used to carry out label-free detection of blood-borne markers.
- The technology should enable a portable system that can be set up in a remote location and enable clinical diagnosis of a variety of conditions. The system will be accompanied with disposable cassettes that are specific to the test.

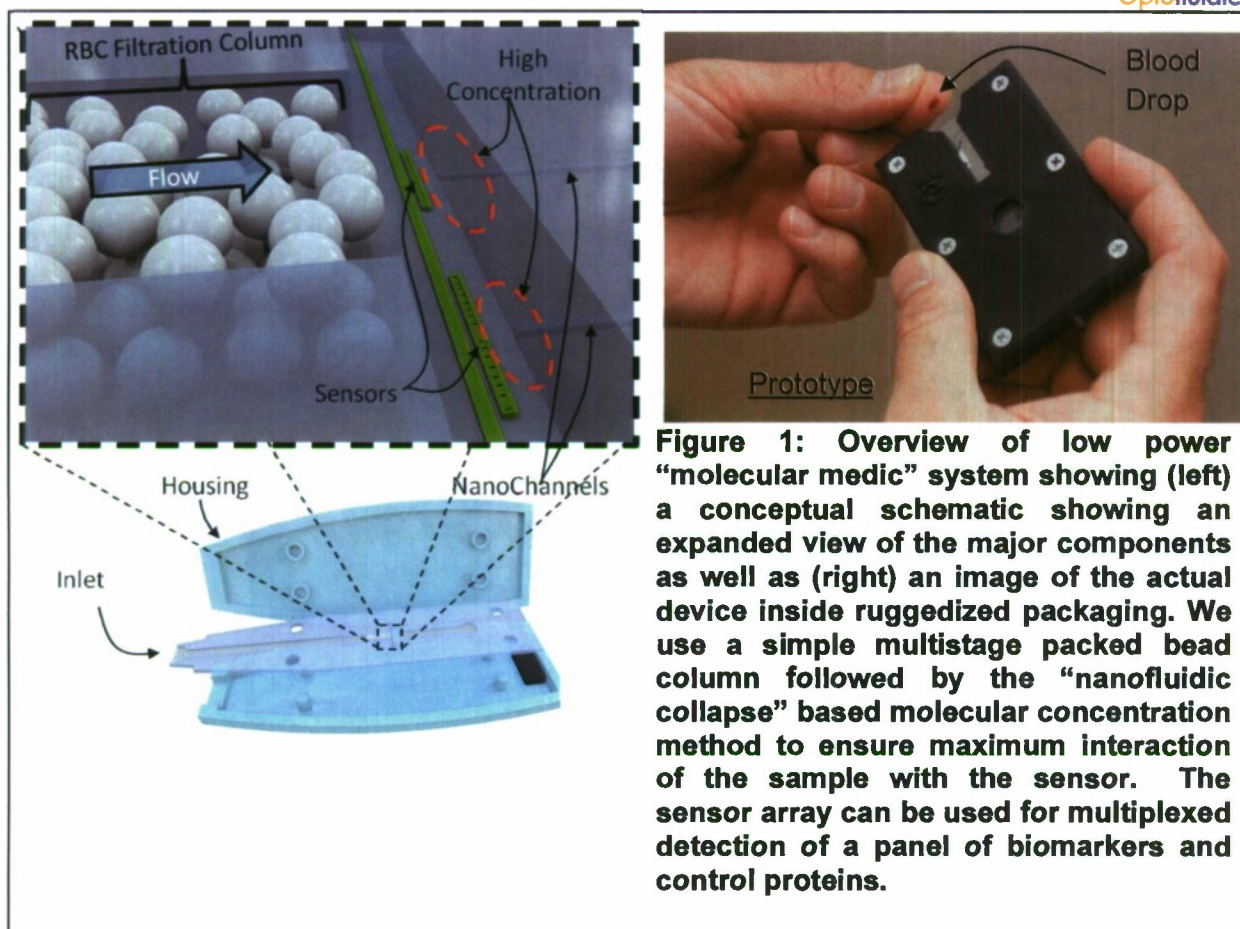
Accomplishments

Phase I Option

- Fabricated several sensor chips using nanofabrication techniques
- Constructed an alignment system that provides micron-precision integration of the sample prep module with the sensing module. This allows the sensors to be placed within the concentration zone of the NanoPrep sample processor.
- Several integrated molecular medic chips were built. (Each device consists of the self-driven blood filtration column, the nanochannel concentrator and the aligned sensing array)
- Developed an experimental apparatus consisting of a tunable laser, polarization optics, fiber alignment and optical power measurement

Phase II Work

- We have begun construction of an integrated reader instrument that will ultimately pair with the chips.
- Negotiations are underway with several optical instrument manufacturers to develop a professional Molecular Medic reader.
- Developed an automatic optical alignment system with robotic fiber launch stages and software that performs fiber-waveguide coupling.
- Programmed a graphical user interface and wavelength scanning software that captures sensor readings from Molecular Medic chips.
- Upgraded financial and accounting system to be in accordance with DCAA and FAR. We are four months in to the audit but expect a successful outcome soon.
- Negotiated the NOSA (sensing technology) license with Cornell. The license should become active in March 2012.



1. Summary Statement

In this project Optofluidics, Inc. proposes to develop a “CLIA waivable” sample collection method for the concentration and quantification of blood-borne biomarkers associated with late Phase hemorrhagic shock and traumatic brain injury. The overall goal for the Phase I option is to integrate the upstream sampling processing technology (NanoPrep) developed in Phase I of this project with the patented sensing array technology being licensed from Cornell. Together, the combined device will be capable of carrying out point-of-care diagnosis from whole blood. A conceptual overview is shown in Figure 1. This device will take raw blood and produce filtered, preconcentrated plasma that is ready for detection. During Phase I, we have developed sample processing technology that is based on (1) a finger prick based assay, (2) a multistage packed bead filtration system, and (3) a protein concentration technique relying on nanochannels that are fabricated with a novel “nanofluidic collapse” technique originally demonstrated by the Erickson lab at Cornell University, and recently published in the Proceedings of the National Academy of Sciences. In this Phase I option report, we will show how we have integrated this sample prep system with an array of optical sensors that can carry out multiplexed detection of biomarkers. In addition to the Phase I option work, we have made serious advanced progress for Phase II. This progress includes a nearly completed instrument that can read the chips, as well as initiated negotiations with optical instrument manufacturers to develop a professional device. Other Phase II activities include developing a variety of software and hardware that enables automatic optical fiber alignment for



fiber-chip coupling and reading of the sensors. Finally, a variety of company infrastructure advances were made that have direct and positive consequences for the DARPA Molecular Medic work. These include an upgrade of our financial accounting system for which we anticipate DCAA approval, the successful negotiation of a license from Cornell (effective this month) for the sensing array to be used in the Molecular Medic and (3) we have conducted interviews and initiated the hire of at least one employee that complements our technical team will play an important role on the DARPA Phase II effort. ***The overall goal of this project is to provide our devices to untrained personnel or first responders who could diagnose with better certainty the presence of these injuries and make more informed decisions regarding treatment, having a dramatic influence on outcomes following a traumatic event.***

The original Phase I option tasks are summarized below along with a brief description of our progress to date. In addition to the option tasks, we have carried out additional work not described in the original proposal but was left for Phase II.

1.1 Phase I Tasks

Task 1: Fabricate sensor chips: A key component of the Molecular Medic is designed, is a nanoscale optical sensor array. These sensors report a change in refractive index that occurs when biological material is captured (e.g. with an antibody). This goal of this first task was to nanofabricate several sensor chips that could be used for developing an integration scheme between the sensors and the sample preparation module developed in Phase I. **The sensor chips have been successfully fabricated.**

Task 2: Integration of the sensing and sample prep modules: The sample prep method developed in Phase I operates using channels and structures in PDMS. Phase I testing and development work was carried out on glass slides. The goal of this task is to integrate the sample prep system with a silicon chip that has the sensor array. The challenges are (1) to align the working parts of each piece so that they work in concert, (2) to protect the delicate nano-scale sensors from mechanical damage, (3) to load the device with the appropriate reagents in a way that does not disrupt the integrity of the entire chip bonding. ***This task was considered to be the most challenging and risky. It has been accomplished and a system and protocol for routine integration has been developed.***

Task 3: Detection experiments using the sensing array: After integrating the sample prep and sensing modules, this task focuses on the development of a system to measure the chips and the actual measurements themselves. An experimental apparatus was constructed and successful optical alignment was accomplished. Carrying out chemistry experiments will be left as future work during Phase II.

1.2 Phase II Tasks:

Task 4: Construction of a reader instrument: A Molecular Medic instrument will consist of a laser system and associated optics, an optical power meter and software. As part of a synergistic NSF effort to commercialize similar photonic chips and readers, we have begun development work on a reader instrument along two fronts. First, we have begun to package the individual instruments into a portable box so that off-site demos can be performed. Except



for an outer housing, this portable system was developed. This DARPA project will, at some point, require a similar instrument. Although additional design will be required, the in-house expertise and an existing system will greatly benefit and simplify this effort. Second, we have initiated negotiations with two optical instrument manufacturers in an effort to determine the cost, form and performance of a professional portable laser reading system.

Task 5: Automatic coupling and alignment: In order to measure the response of the sensors, a method for coupling light from a laser to the chip, needs to be developed. In an experimental setup, this process requires aligning a fiber optic with the waveguides on the chip using free space optics. In the future, this procedure will be obviated with industrial-scale coupling methods. However, in the absence of this robust industrial method, the work proposed for the Phase I option requires only non-sophisticated hand alignment. For this task, an automatic alignment and coupling system was developed. Robotic piezo XYZ stages were controlled with PC software which was developed in-house. **Using this software, an automatic and robust fiber alignment procedure was created.**

Task 6: Measurement software and GUI: A simple graphical user interface was developed that allows a user to measure multiple resonance peaks with greater precision than a manual method. The manual method would require the user to locate a resonance peak and then monitor the power output throughout the experiment. **The GUI no longer requires manual tuning of the laser and obtaining power readings. Instead, the system was automated using LabView software.**

Task 7: Financial Audit, Patent Licensing and Hiring: A variety of non-technical milestones were achieved during the Phase I option period that dramatically improve our viability as a company and are highly enabling for our Phase II work. In particular, (1) we have completely overhauled our accounting and bookkeeping systems to become compliant with DCAA and FAR (audit still underway). (2) We have also successfully negotiated an exclusive license with Cornell University for the key patent underlying the sensing technology behind the Molecular Medic. Finally, (3) we have initiated the hiring process for several employees that will play key technical roles in this DARPA Phase II project.

2. Phase I Option detailed progress

2.1 Task 1: Optical chip sensor manufacturing and design

We fabricated optical resonator devices shown in Figure 2 using standard photolithographic techniques. After making the optical mask, we spun 1.1 μ m of SU-8 photoresist on top of a 100mm diameter silicon wafer containing a 2 μ m LPCVD oxide cladding, following and after performing a 65°C, 95°C softbake, we UV exposed (Figure 2a) the desired structures using a stepper. After performing a post exposure bake at the same temperatures as mentioned above, we developed the features (Figure 2b) resulting in the desired optical structures consisting of polymer waveguides and ring resonator devices as shown in Figure 2c.

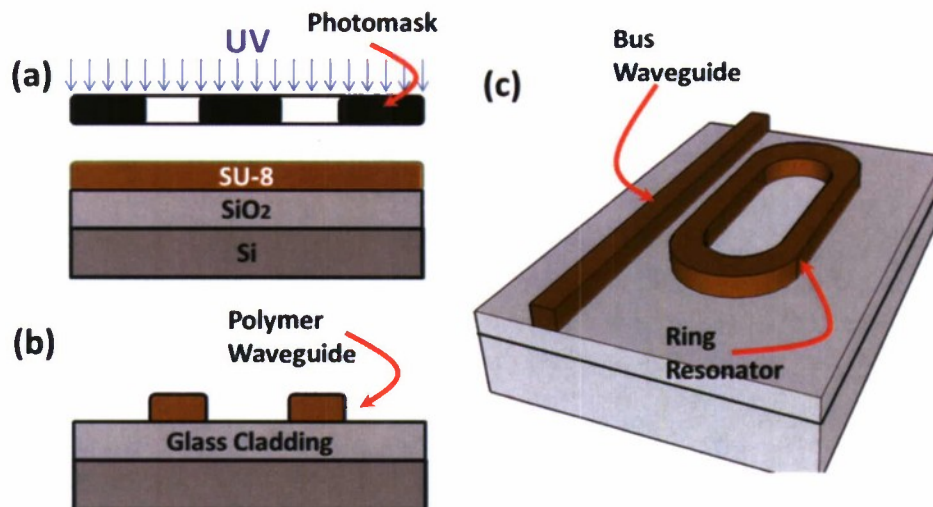


Figure 2: Fabrication process of optical chip sensors: (a) UV Exposure through photomask illuminating desired optical component features. This figure does not show heating stage to activate and dry resist. (b) Chemical development, resulting in the desired optical structures. (c) Resulting polymer waveguide and ring resonator devices.

The optical structure design, which determines the waveguide and resonator geometry as well as material choice, was based on previous work and optimizations by the Erickson group at Cornell University [1,2]. Briefly, the optical structures are made by a polymer core of refractive index 1.55 @ 1550nm, and are cladded by water ($n=1.33$) and an oxide ($n=1.45$) layer in order to allow IR light to be guided efficiently through the core. The waveguide and resonators were designed to preferentially support Transverse Electric (TE) mode, though the Erickson group has shown formats that allow for other mode configurations as well. In Figure 11 of the appendix, we show a finite-difference mode-solved simulation using COMSOL that shows the electric field distribution of around the waveguide. As shown in Figure 11, most of the energy is confined inside the polymer waveguide (though some light resides outside of it due to the lower index cladding), which in turn allows one deliver the energy effectively onto the sensors to generate effective sensors due to the high energy content. However, some of the energy resides outside of the core, which interacts with the outside environment and allows one to register positive binding events of up to attograms of matter by using custom devices and spectrographic techniques[2,3].

The resulting optical structures are shown in Figure 3 below. Figure 3a shows a ring resonator 100 μm in length on its major axis, while the cross sectional dimensions are 1.1 μm tall and 2 μm wide. Figure 3b shows the scale of an optical sensor chip containing 30 waveguide/resonator sensor sets. This number density can be easily increased 10-fold in this setup given that the waveguides are currently spaced at 100 μm distance, but there is little to no cross talk for waveguides spaced as close as 2 μm . In the actual NOSA devices, this number can be increased by a thousand-fold given the thin and low area coverage of each sensor. Also, we note that a significant portion of the chip area is designated to accommodate fit the input and output ports of the fluidic chip (not shown) which can also be scaled down. In the following



section, we describe the integration of this optical sensor chip with its fluidic delivery and sample preparation module.

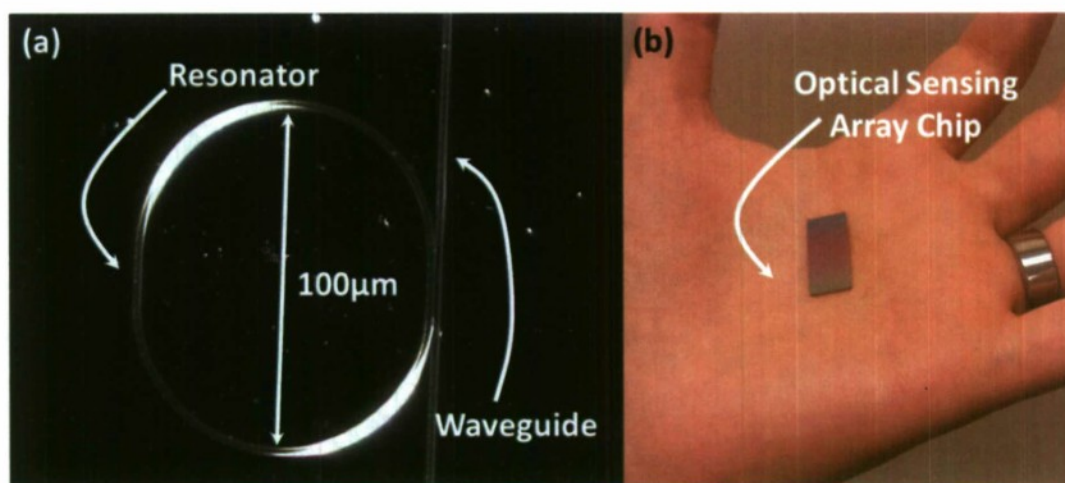


Figure 3: (a) Micro patterned optical ring resonator. Waveguide dimensions are 2µm wide by 1.1 µm tall. (b) Optical sensor scaled view.

We chose to use polymer waveguide sensors as opposed to our silicon on insulator based Nanoscale Optical Sensor Arrays (NOSA). The main reason for this shift is that the polymer waveguide fabrication process enabled us to build devices faster and cheaper. This in turn allowed us to perform more experiments to test the chips, integration and the instrumentation. Furthermore, it was also more cost effective to use the polymer waveguide chips during the irreversible alignment process. Given that we have optimized the integration and construction methods using these operational test-chips, we will transition back to the NOSA format during phase II. These NOSA chips have the advantages of greater sensitivity and mass producibility.

2.2 Task 2: Integration of the sensing and sample prep modules

Our next task is to integrate the optical sensor array with the microfluidic sample preparation component. In Phase I, we demonstrated our sample preparation and specific concentration system called “NanoPrep” shown in detail in Figure 1. The NanoPrep system works as follows: (1) Fabrication of a microchannel/ nanochannel interface using a custom but scalable fabrication strategy developed in the Erickson research group at Cornell. This technique allows one to generate nanoscale channels in PDMS from micro-patterned structures by using a roof collapse method described in detail in the Phase I report. (2) Forming a porous packed column of 15µm polystyrene microspheres at the microchannel/nanochannel interface to filter plasma from raw blood (3) Specific concentration of the target sample (we used fluorescent streptavidin/biotin as a model system). We quantified the concentration of streptavidin spiked in a plasma solution by registering its binding to biotinylated gold immobilized on a glass slide by employing two methods: (3-1) Using Fluorescence detection through FITC labeled streptavidin (3-2) Surface Enhanced Raman Spectroscopy (SERS) detection enabled by the plasmonic signal enhancement due to the aggregation of gold colloids. All of the above tasks were demonstrated in Phase I, but it is important to note that they were performed on a standard glass slides. In this option task, we seek to integrate our NanoPrep system with the optical detection chips to obtain

the envisioned multifunctional device. In the below, we describe our alignment system used to bring the fluidic and optical components as well as the resulting integrated chips.

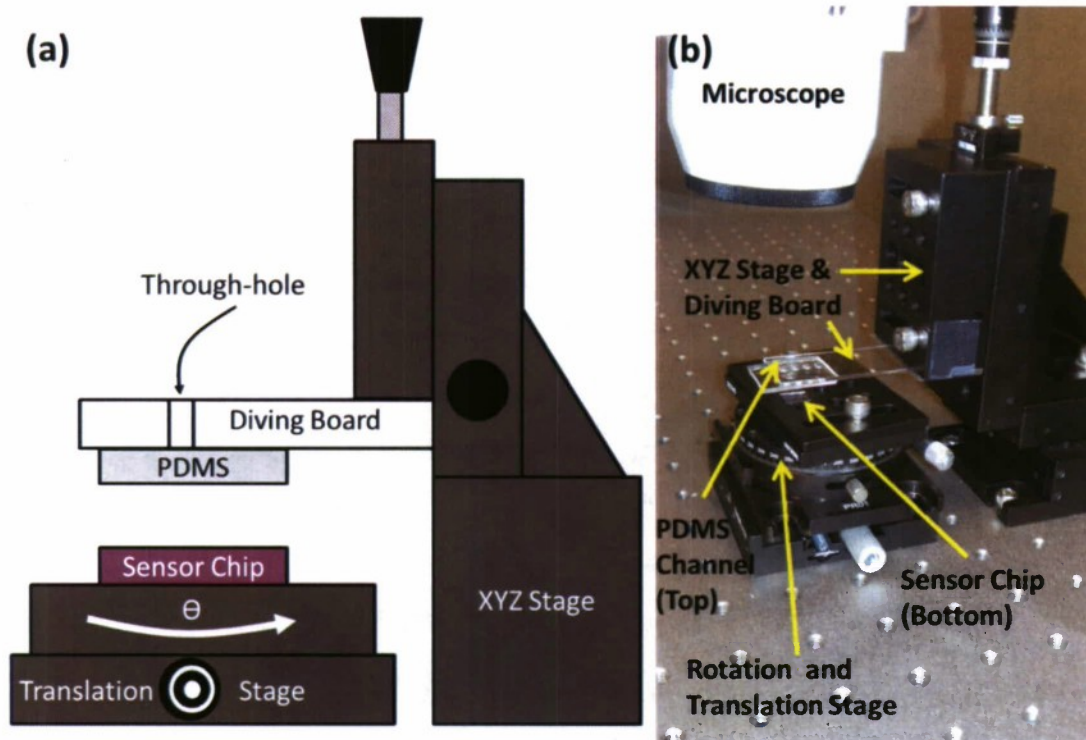


Figure 4: Alignment Stage System (a) Schematic of two stage mechanical alignment system. The optical chip is placed on a mechanical translation and rotation stage, and the fluidic chip suspended on an acrylic diving board. The two components are aligned and brought into contact and form an irreversible bond.

The alignment system: Our system, showed in detail in Figures 4a and 4b, uses two stages (1) A 1-D translation and rotation stage into which the optical sensor chip is placed and (2) an XYZ stage into which the fluidic chip is placed suspended on an acrylic springboard. After plasma treating both pieces, they are aligned and bonded as described below.

After placing the two components on the alignment system, the optical chip is laterally and rotationally aligned with its fluidic counterpart which initially lies above it (suspended on the acrylic springboard). The PDMS fluidic chip is then tightly aligned so that when bonding occurs, the resonators are in close proximity to the nanochannels. It is then lowered and brought in contact with the optical

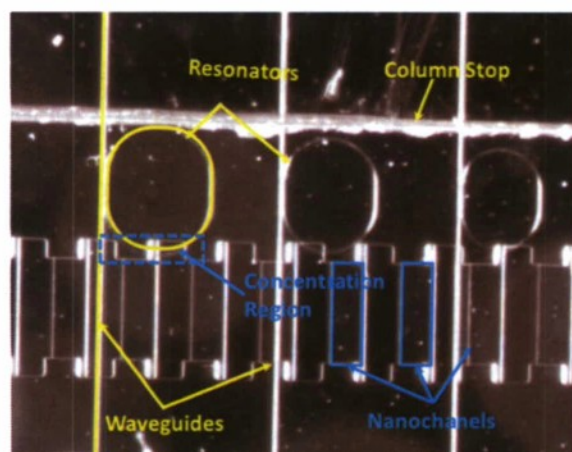


Figure 5: Aligned optical sensor and fluidic components. Part of the sensors are exposed to the sample concentration region.

chip. The acrylic springboard was fabricated using a laser cutter, and it has four 2 mm through holes which are used to dislodge the fluidic chip/optical assembly from the acrylic springboard by inserting a thin metal rod.

After successful alignment, the columns are packed by flowing in 15 μm polystyrene microspheres treated with Starting Block®. This reagent ensures hydrophilicity so that the blood wicks in quickly and is filtered into the sensor region. The column of beads was formed at the nanochannel interface as shown in Figure 6 to the right. Note that

there's a "free zone" between the columns and the nanochannels where the resonators sit. We did this intentionally to separate the beads from the sensor region, which could damage the sensors or foul the detection process.

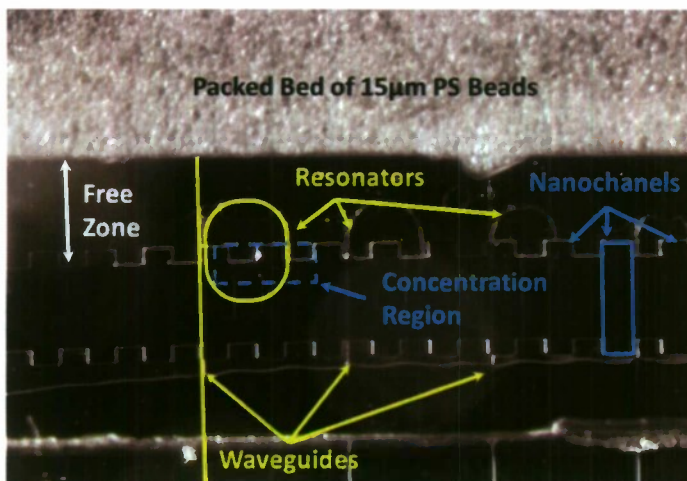


Figure 6 Packed bed of PS beads formed next to the optical sensor and nanochannel region

2.3 Task 3: Detection experiments using the sensing array

For task 3, several subtasks needed to be accomplished. First, an experimental apparatus needs to be constructed. Second, a method for coupling light onto the chip needs to be worked out. Third, once the infrastructure is in place, we can then measure resonance shifts. The experimental apparatus is shown in Figure 7.

Experimental Apparatus: A description of the optics portion of the experimental apparatus, starting from the light source, and ending with the light measurement is as follows. The light originates in an Agilent tunable laser, which produces light centered in the C band with a wavelength range of 1520-1560 nm. The laser is coupled to a fiber which runs through a set of polarization paddles which are adjusted to provide TE polarized light. The fiber itself is single-mode and lensed such that it has a 3 μm focal distance. The light is coupled from the fiber to a waveguide on the chip where it interacts with the resonators and then exits the chip at the waveguide outlet (in air). The exiting light is captured with a collimator, which directs the light through an adjustable polarization filter (TE/TM). Finally, the light is captured with an InGaAs power meter. The lensed fiber output is fitted onto an XYZ stage with sub-micron precision so that the fiber can be aligned to the waveguide on the chip. The chip is mounted on a stage that can rotate (yaw) and translate. Together, these allow for excellent alignment and coupling. The output optics (collimator, polarization filter and power meter) are all mounted on an XYZ stage as well.

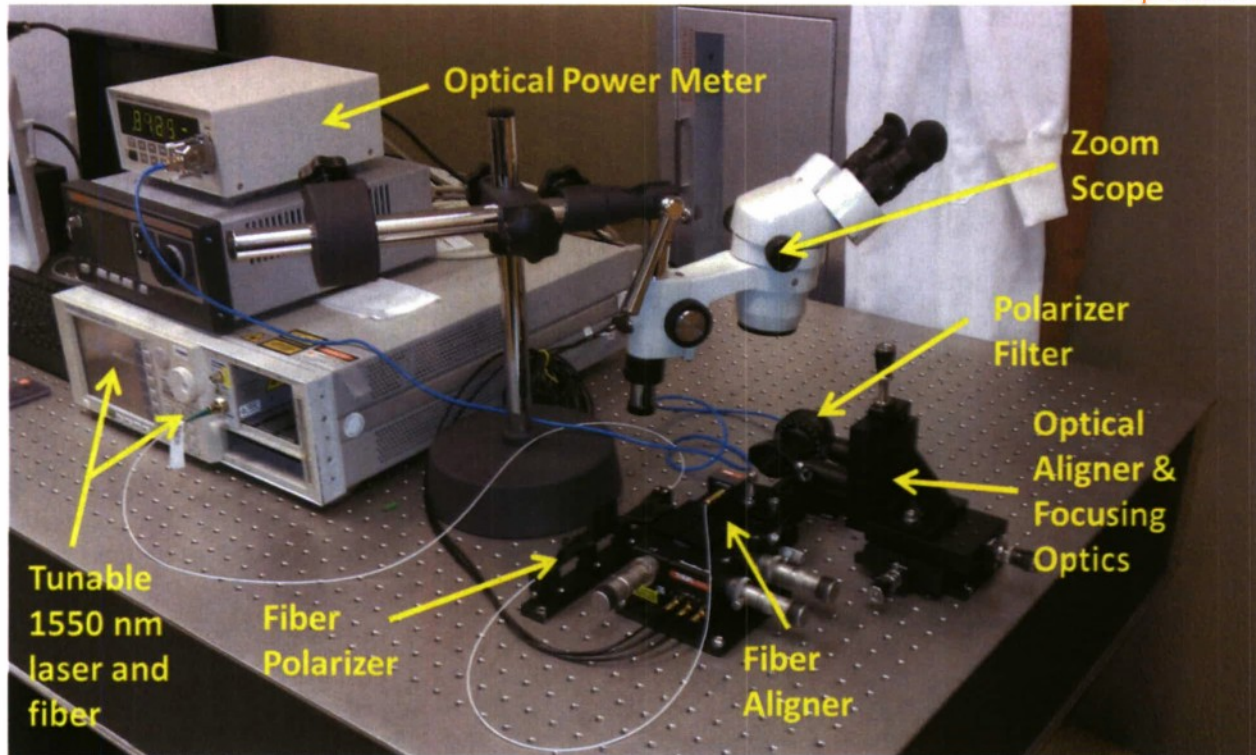


Figure 6: Experimental Apparatus

Optical alignment and coupling procedure: First, the output optics are aligned with the fiber so that the maximum amount of light can be captured. The light coming out of the fiber shows about 1dB losses (and varies slightly with different fibers). After the output optics are aligned, the yaw of the chip is adjusted so that the waveguides are made parallel to the fiber. Finally, the fiber is moved to the waveguide input. The waveguide is designed with an s-shaped bend so that the input is offset from the output (see Figure 8). In this way, scattered light aimed at the waveguide input does not flood the output optics, which are aligned with the waveguide output and thus are offset. The cross-sectional dimensions are approximately 1 μm thick and 2 μm wide. Therefore a high degree of translational precision and stability need to be built into the alignment stages. Our stages have sub-micron precision. Alignment is carried out manually in x, y, and z to maximize coupled light into the waveguide. Successfully coupled light shows about a 15-20 dB (power) loss.

Detection experiments were not yet attempted and are left as future work. Examples of detection carried out in the Erickson lab at Cornell using similar resonators are shown in the appendix.

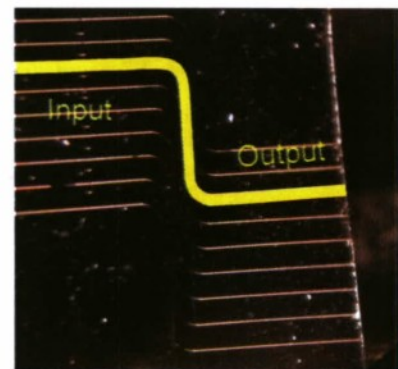


Figure 7: S-shaped bend in the waveguide

2.4 Task 4: Construction of a reader instrument

Optofluidics, Inc. is currently building an optical instrument under a synergistic NSF SBIR effort to commercialize chips that perform fluidic and optical operations for biomolecular research. As shown in Figure 9a below, this instrument consists of an IR laser with a single mode fiber output, associated optics to filter and polarize the light (a paddle polarizer and a fiber isolator), as well as an optical power meter and sensor that are used in tandem to ensure that light is effectively coupled into the photonic chips. We have recently built a portable package that houses separate instruments and components in a single unit as shown in Figures 7a and 7b. We are using this portable setup to perform tests outside of the lab environment. Through this work, we have de-risked the building of the Molecular Medic reader for this DARPA effort. The only major changes involve using a different tunable laser source, as well as slight changes in the housing and component packaging. Furthermore, we commenced negotiations with BWTek and AVO photonics, two industry leaders in developing original equipment manufacturer optical instruments. Our aim is to use our vision with their design expertise in order to transition our system from a bulky unit that contains several instruments and towards a smaller integrated instrument that only contains the most critical components and is touch screen controlled as shown in Figure 7c. This transition will allow us to reduce the costs, ensure mass production of the instrument and bring about a professionally designed, easy to use and ergonomic system.

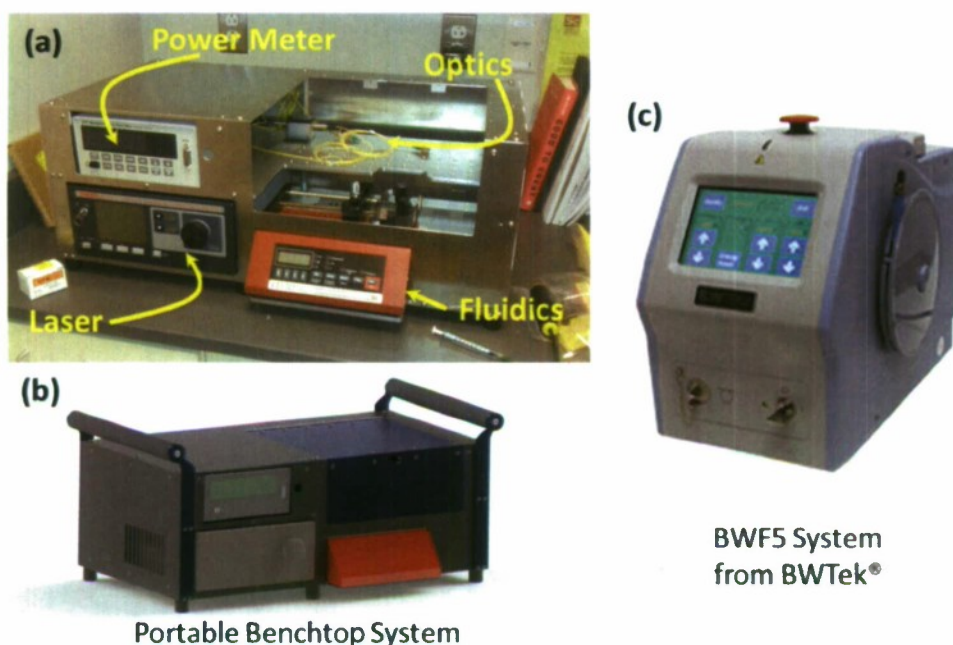


Figure 8: (a) Portable benchtop laser and optical power meter system (b) Schematic of (a). (c) Integrated optical OEM offered by BWTek which houses very similar components.

2.5 Task 5: Automatic coupling and alignment

Manual alignment of the optical fiber to the waveguide is sufficient for low numbers of experiments. However, it was apparent that Phase II would require many more experiments and a more user-friendly method for coupling would be needed. A software package was therefore designed to carry out auto-alignment of the fiber to the waveguide. The system is powered by LabView which communicates with two devices. The first device is the XYZ stage (Nanamax 300 – Thorlabs) and the second is an optical power meter (1830-R – Newport). Both instruments are connected to the PC.

A conceptual diagram of the alignment method is shown in Figure 10. The user is required to do a coarse alignment by eye and then initiate the alignment software. The software turns on the laser and the piezo XYZ stage then begins to raster over a $20\text{ }\mu\text{m}$ by $20\text{ }\mu\text{m}$ area. The system has incredible precision and can make steps as small as 20 nm . Manual adjustment, on the other hand, is somewhere near $1\text{ }\mu\text{m}$ of precision. Measurements are made for each XYZ position and a series of intensity maps are generated. Figure 10 (top) shows five intensity maps taken during an auto-alignment run. When the fiber is aligned perfectly with the waveguide, a spike in power is observed. This intensity peak can be clearly seen in Figure 10 (bottom).

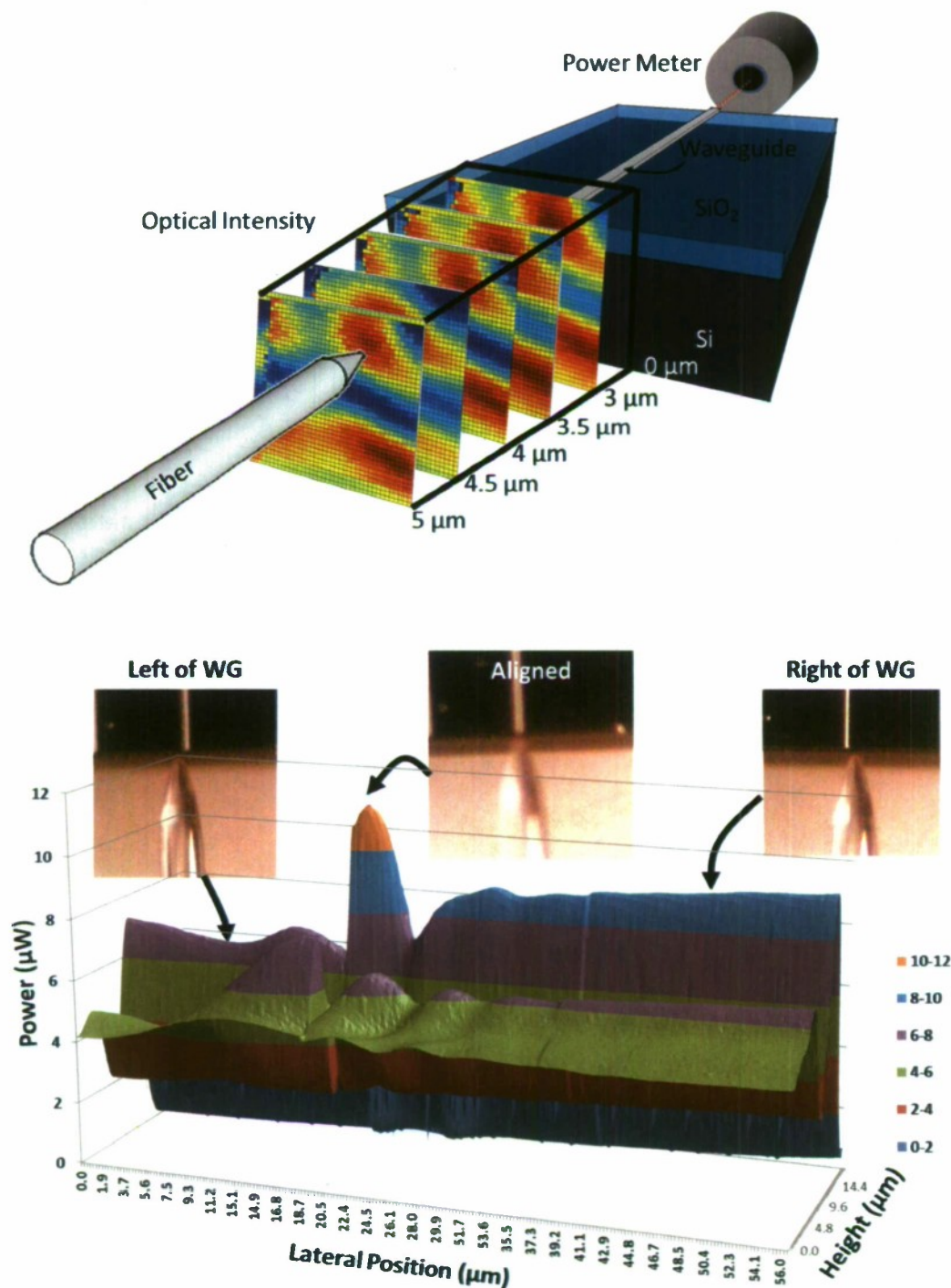


Figure 9:Top – conceptual diagram of the auto-alignment method. The fiber is positioned near a waveguide and then the computer automatically moves the fiber generating intensity maps and “searching” for a peak. Bottom – 3D surface plot of optical power taken over three scans in the lateral direction. The nice peak clearly indicates the aligned/coupled position of the fiber.

2.6 Task 6: Measurement software and GUI

Although cumbersome, an optical resonator sensor may be monitored manually by observing power shifts near resonance. In the case of the NOSA sensors and many other optical resonators, a wavelength scan will show distinct, sharp drops in power coming out of the waveguide. These drops or “valleys” represent the absorption of optical power in a resonator. A measurement of the resonance shift can be accomplished by finding the resonance wavelength and then monitoring the power throughout time. As the resonance valley shifts, the power will rise and this rise can be calibrated to provide an estimation of resonance shift, which can, in the case of a biosensor, be converted into mass of bound material. Although effective, this method works well for only a single sensor (not a whole array) and furthermore requires manual tuning of the laser to identify the exact resonance wavelength.

For Phase II of this DARPA project, and the Molecular Medic project as a whole, a sensing array will be used to detect markers in blood. In order to probe each sensor in this array, a manual method would be insufficient. An investment in more automation to automate sensor readings was therefore undertaken. For this task, a LabView program was developed to perform wavelength sweeps. The GUI along with some of the code is shown in Figure 11. In addition to offering the user with the ability to select a custom wavelength range and step-size, the code has built-in signal processing to reduce noise, time-stamping and automatic data backup.

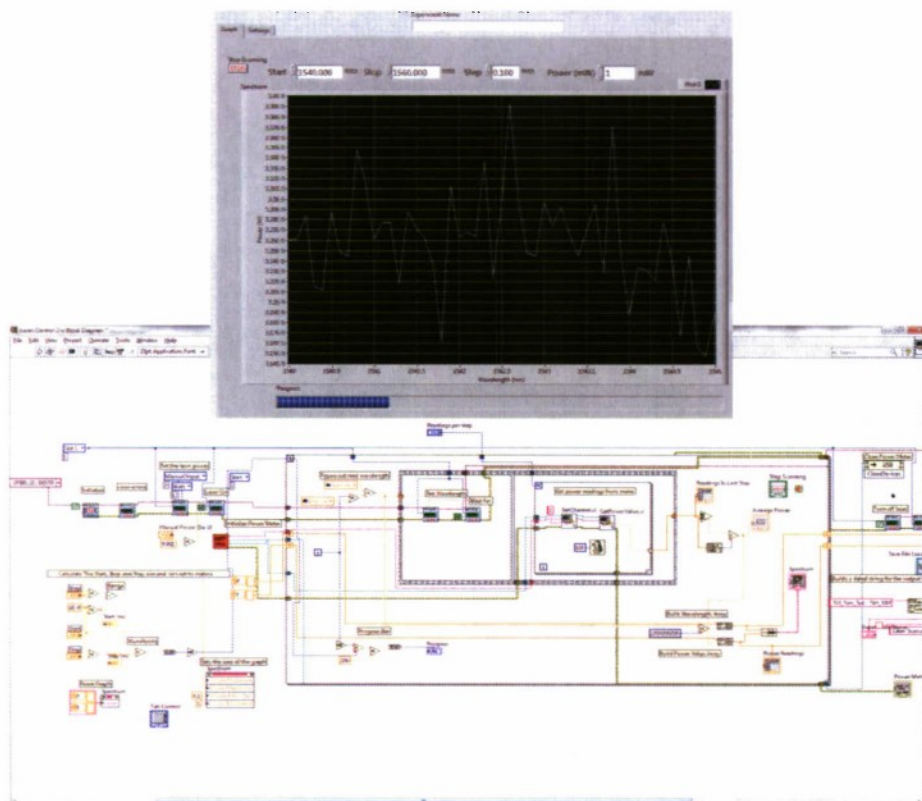


Figure 10: LabView GUI and block diagram showing the automatic measurement software for the Molecular Medic chips.

2.7 Task 7: Financial Audit, Patent Licensing and Hiring

In preparation for Phase II, numerous company infrastructure changes were made during this Phase I option period. Just a year old, Optofluidics consists of two full time employees. In order to interface with the DoD financial system a complete overhaul of our bookkeeping and accounting package took place. Whereas Phase I and Phase I option were firm fixed price contracts, Phase II will be a “cost plus” contract. In order to operate such a contract, we need DCAA approval. As such, we are currently undergoing both DCAA and DCMA audits. A new accounting firm was enlisted to make numerous upgrades in accordance with Federal Acquisition Regulation (FAR) and other DARPA requirements. The audit has taken approximately four months and we are awaiting the DCAA assessment, which should be completed within a week. After the financial system audit, the DCMA audit will take place to verify that our proposal is up to DoD standards as well.

Optofluidics has also successfully negotiated an exclusive license for the Nanoscale Optical Sensing Array (NOSA). The license deal, which took about a year to work out, is expected to take effect this month. This is a critical milestone for Optofluidics. Armed with this license, we may now freely operate within the field of medical diagnostics and also to reach out into the investment community. Without protected IP, we would not be able to attract investment partners, which we will need to commercialize the Molecular Medic.

Finally, in anticipation of the award, we have made several key hires that will take effect when the DARPA Phase II project starts. These hires will play critical roles on the DARPA Phase II project and have backgrounds that complement the existing team.

3. Conclusion

This Phase I option DARPA project made great strides in two critical areas – chip integration and infrastructure. After demonstrating the capabilities of the NanoPrep sample processing system in Phase I, the largest technical unknown was the ability to integrate the NanoPrep with the NOSA sensing array. After fabricating the chips, we have accomplished full integration and have shown the ability to fabricate integrated devices using an alignment system without destroying the sensors or disrupting the bonding between the pieces of the chip. This was the most important technical milestone of the option project and was a critical barrier to performing the Phase II work.

The other major accomplishments concerned developing the necessary infrastructure for a successful Phase II. The various infrastructural improvements include valuable software packages, the construction of the major experimental apparatus and systems that assist in constructing integrated chips and optical coupling. Without the experimental apparatus, no experiments could take place at all. But with the experimental apparatus alone, experiment throughput would be extremely slow and cumbersome. It is estimated that the automation investment produces at least an order of magnitude in experimental time savings and will enable much more rapid and productive experiments.



Optofluidics

These technical and infrastructure accomplishments, which have taken place over the course of four months, and with an extremely modest budget has produced a huge amount of value for DARPA. Most importantly, these milestones pave the way for a successful Phase II.

We believe the great strides taken in this Phase I option towards developing a point-of-care diagnostic that can be used by the military, first responders or in the general practitioner's office.

4. Appendix:

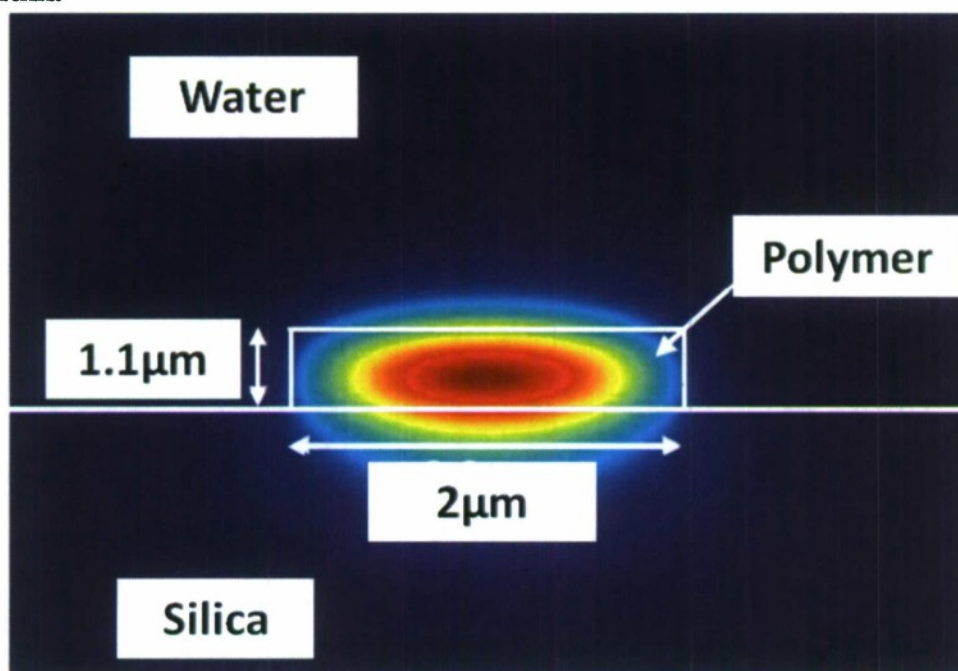


Figure 11: The electric field profile of TE mode on a polymer waveguide cladded by glass and water.

The Transverse electric mode profile of IR light traveling on a polymer waveguide. As shown in this figure, light is tightly confined in the core of the device, allowing most of the energy to be delivered to the sensor region. However, some of the energy resides outside of the core, which interacts with the outside material and allows one to register positive binding events by using custom spectrographic techniques. The Erickson group has ample expertise in polymer waveguide devices, with expertise ranging from optical waveguide sensors to waveguide particle manipulators. [1,2].

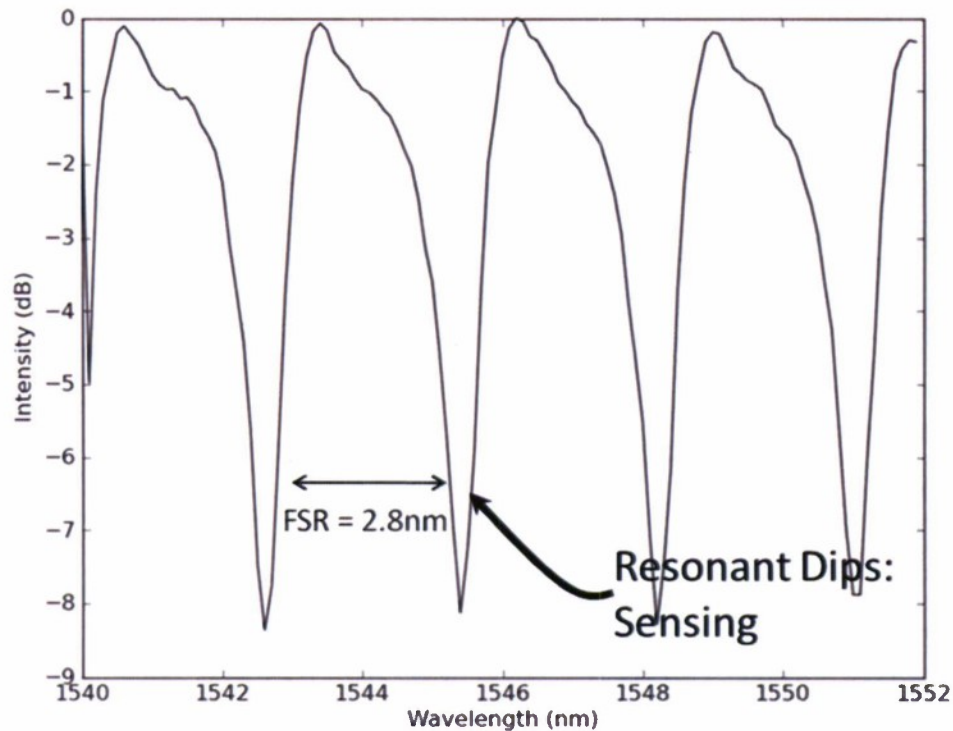


Figure 12: Resonant dips in a ring resonator

The optical ring resonators used here were based on a design by Mancusco et al. briefly, 1550nm is evanescently coupled into the ring resonator structures from the bus waveguide, and different wavelengths from the 1550nm light constructively and destructively interfere. The wavelengths that constructively interfere (those which form a standing wave on the race track shaped resonator) stay behind locked in the resonator. If taking a spectrographic readout of light coming out of the bus waveguide, these resonant wavelengths are observed as dips. The different resonant dips observed in this figure correspond only to 1 resonator. The reason is that one resonator supports multiple wavelength bands in the 1550nm region. In terms of performance, polymer waveguide devices made by the Erickson group have shown performance of dips as great as 9dB and a Free spectral range (distance between dips) of 3nm. [2]

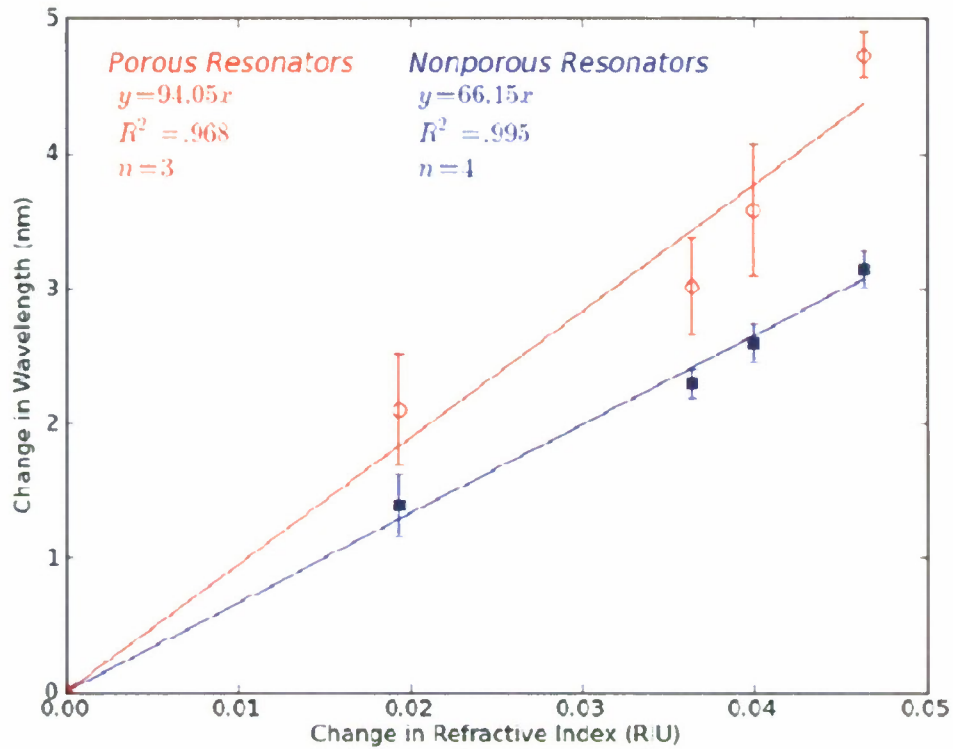


Figure 13: Polymer waveguide resonator performance

The Erickson group has made optical polymer resonators made out of different materials including SU-8, PMMA and porous PMMA and several geometric configurations [1,2]. The optical detection sensitivity for such devices has been as great as several nanometer changes in wavelength per unit of refractive index change, which meets the state of the art.

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