IMPLANTABLE FLEXIBLE-COILED WIRELESS INTRAOCULAR PRESSURE SENSOR

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ABSTRACT

This work presents an implantable wireless passive pressure sensor for long-range continuous intraocular pressure (IOP) monitoring of glaucoma patients. The sensor is microfabricated with use of parylene C (poly-chloro-p-xylylene) to create a flexible coil substrate that can be folded during implantation for suture-less minimally invasive surgery, while stretched back without damage for enhanced inductive sensor-reader coil coupling and the corresponding sensing signal. Extensive device characterizations including on-bench testing and *in vivo* and *ex vivo* animal studies verify the device feasibility in both engineering (1 mmHg pressure sensing accuracy and 2 cm sensing distance) and surgical (robust fixation to the iris and long-term biocompatibility in the intraocular environment) aspects, all meeting specifications for future practical implementation of such IOP sensing technology.

INTRODUCTION

Passive telemetric sensing has been widely used as one of the viable methods to accomplish continuous and accurate non-contact IOP measurements of glaucoma patients [1, 2]. It enables straightforward IOP sensing by utilizing a transensor implant that registers environmental pressure variations inside the eye, so that the IOP can be directly measured by using an external reader wirelessly interrogating the implant. As illustrated in Fig. 1, this sensing methodology requires an external reader to interrogate IOP variations electrically registered by an implanted sensor through a wireless inductive coupling link. Accordingly, long sensing distance between sensor and reader coils in reasonable arrangements is crucial for practical IOP measurements. Previously, we developed a miniaturized implantable IOP sensor for preliminary feasibility study [3]. In spite of successful wireless sensing demonstration with achieving high pressure sensitivity, the sensing distance of the entire telemetric system was unsatisfactory (~2 mm) due to low quality factor and dimensional constraints of the sensor. This fact seriously hinders its application especially when considering the glasses-to-iris distance (1.5-2 cm) in practice, and thus needs further improvement.

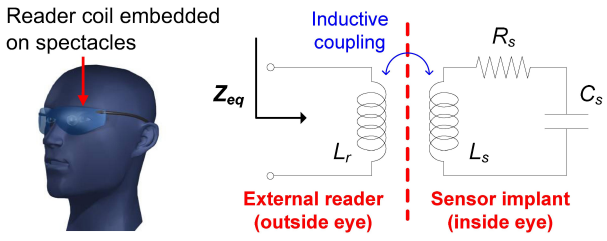

Figure 1. *Proposed IOP monitoring in practice: (left) Continuous sensing using the glasses reader paradigm; (right) equivalent circuit schematic of the sensing system.*

Based on applying the impedance phase-dip technique as the wireless measurement method [1-3], the sensor implant is designed to have a pressure-sensitive electrical LC-tank resonant circuit with a corresponding resonant frequency represented as

$$f_s = \frac{1}{2\pi}\sqrt{\frac{1}{L_s C_s} - \frac{R_s^2}{L_s^2}} \cong \frac{1}{2\pi\sqrt{L_s C_s}} \quad \text{if } R_s^2 << \frac{L_s}{C_s},$$

where L_s, C_s, and R_s are respectively the inductance, capacitance, and resistance of the sensor. When the sensor is excited at resonance, the phase of the equivalent impedance Z_{eq} to be measured drops to the minimum with a difference approximated as

$$\Delta\phi \cong \tan^{-1}\left(k^2 Q_s\right),$$

where k is the coupling coefficient of the inductive link totally dependent on physical geometries such as the planar size of the sensor and reader coils and the separation distance between the coils, and $Q_s = R_s^{-1}(L_s C_s^{-1})^{1/2}$ the quality factor of the sensor at resonance. As long as the impedance phase dip is detectable in the frequency scan, the resonant frequency of the sensor varied by pressure conditions can be accurately characterized, and the resultant IOP can be obtained in real time. Therefore, the objective of this work is to develop a microfabricated implantable wireless pressure sensor with improved electromagnetic coil coupling and enhanced quality factor in order to increase the signal strength with more distinguishable phase dip, so that the overall sensing distance can be increased for necessarily longer-range IOP detection, which eventually accommodates the iris-to-glasses distance for appropriate implementation of the glasses-type reader in the future.

DESIGN

It is deduced from the aforementioned description that both the integrated coil size and quality factor of the LC-tank should be increased as much as possible in order to increase the k^2Q factor. On the other hand, the entire device needs to be in a small form factor suitable for minimally invasive implantation in order to minimize associated surgical difficulty and complications. As a result, the proposed wireless IOP microsensor incorporates the flexible coil paradigm reported in the literature [4] to best meet the both requirements. Fig. 2 shows design of the microsensor comprising a pressure-sensitive parallel-plate variable capacitor embedded in a deformable diaphragm chamber, a spiral metal wire to serve as a planar inductor, and a flexible/foldable disk substrate to support the coil. The disk diameter is designed to be 4 mm to accommodate a substantially large coil while still fitting the iris rim width in normal conditions. The disk is also designed to have with sufficient mechanical flexibility so as to maintain a

small required incision (< 2 mm) during device implantation. These structures are integrated along with a rigid piece having air/gas cavity to provide pressure reference. The width of the backing piece is predetermined 1.5 cm so that the coiled disk can be folded to smaller than 4 mm × 2 mm for suture-less intraocular implantation as well as for ease of realization and handling of the parallel-plate variable capacitor. Because this prototype also needs another attachment piece to create the pressure reference in gauge pressure sensing, surgical anchoring features are directly created on the non-electronic sealing silicon piece for suture-less implant fixation on the iris. Electrical/mechanical design, material selection, and micromachining processes of the pressure-sensitive resonant circuit structures are analogous to those in the previous prototype [3]. The mechanical behavior of the parallel-plate variable capacitor is designed specifically in the small deflection regime to better estimate the pressure-sensitive performance of the transensor. All involving materials in the fabrication processes are in implantable grade. Parylene C is selected as the diaphragm and disk substrate material because of its flexibility (Young's modulus ~4 GPa), CMOS/MEMS processes compatibility, and biocompatibility (USP Class VI grade). Additionally, its low water permeability (0.08 g-mm/m^2-day) and low water absorption (< 0.06% after 24 hr) favor stable behavior of such device when immersed in the aqueous humor of the eye after implantation. Moreover, besides being used to create the top parallel capacitor plate, the second metal layer is arranged to be with all boundaries of the pressure-sensitive parylene diaphragm chamber to act as a strong barrier to transmissions/permeations of water vapor and gas in between the encapsulated air/gas and the ambience of the device. This inclusion can effectively prevent the sensor implant from substantial performance drift, which supports their long-term use in the intraocular environment.

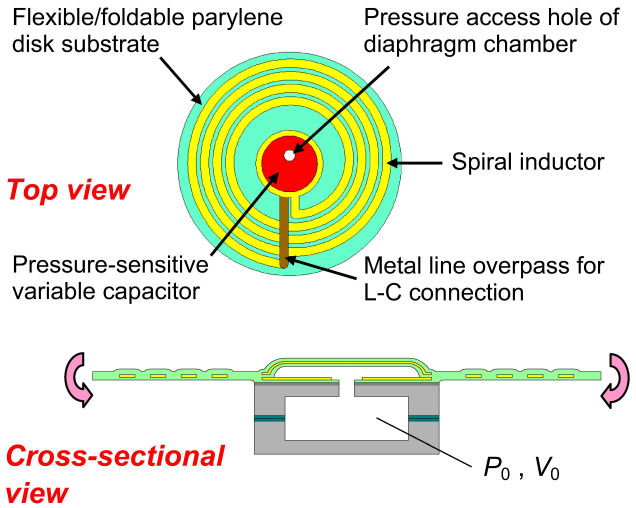

Figure 2. *Pressure sensor design schematics.*

FABRICATION

The sensor is monolithically microfabricated as depicted in Fig. 3 facilitated by low-temperature multi-layer parylene micromachining and deep silicon etching technologies. The fabrication processes started by thermally growing and patterning 2 µm oxide on a double-side-polished silicon wafer. Deep reactive-ion etching (DRIE) was performed on the backside of the wafer to define device release boundaries and access hole of the pressure diaphragm chamber until leaving approximately 50 µm silicon for ease of through-wafer etching using the remaining oxide as the mask. In frontside processes, a photoresist layer was created not only as a sacrificial layer for coil disk release, but also as a mask to gas-phase XeF_2 silicon roughening for physically strengthened parylene-silicon adhesion of the device. Afterwards, multiple parylene and metal layers were deposited and patterned to create the flexible-coiled pressure sensor structures along with using another sacrificial photoresist layer to define the free-standing pressure diaphragm chamber. The bottom parylene layer mechanically supports the metal coil windings and electrically isolates the other device layers from the substrate. The metals were e-beam-evaporated for better material quality purposes while thick deposition was required to obtain low overall resistance from the metal lines. Two thick titanium/gold layers (200 Å/3 µm and 200 Å/0.5 µm) were patterned using standard metal etching techniques. As previously stated, the sandwiched parylene-metal-parylene layers were arranged at the chamber sidewalls to minimize liquid/gas permeation from/to the encapsulated air cavity. In fact, this metal layer extended to the surrounding of the diaphragm chamber to contribute additional capacitance by interaction with the underneath parylene-metal layers, which facilitates control the device resonant frequency falling into reader scan range of interest. Devices were finally released with a backside recess for larger closed volume of pressure reference after performing another DRIE followed by photoresist stripping with acetone. Fig. 4 shows the air-dried microfabricated sensor before device packaging.

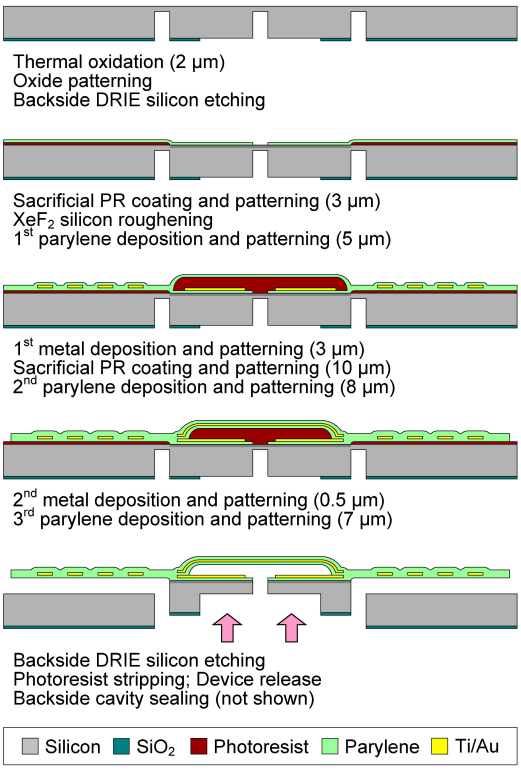

Figure 3. *Fabrication process flow. The arrows indicate the outcome of device release after fabrication processes.*

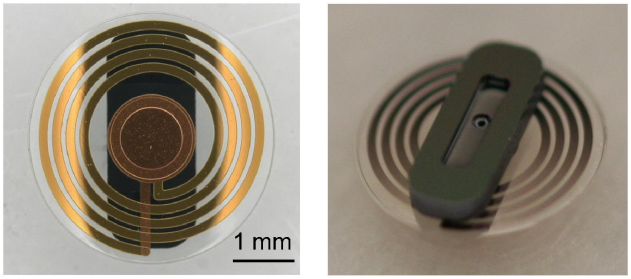

Figure 4. *Full-scale photographs of the microfabricated with its top (left) and bottom (right) views before packaged. The diameter of the flexible coil disk is 4 mm.*

The post-microfabrication sensor packaging was conducted in air under atmospheric pressure at room temperature as the conditions of the encapsulated air. A non-electronic piece was attached to the bottom of the microfabricated sensor using epoxy to form an air cavity inside the device for pressure reference in gauge pressure sensing. The overall size was measured at ϕ4 mm × 1 mm and reduced to a form factor of 4 mm × 1.5 mm × 1 mm by folding the coil disk as shown in Fig. 5, suitable for minimally invasive intraocular implantation. Given the high yield strain (~3%) characteristic of parylene C, the flexible disk can be stretched back to its original circular shape without severe permanent deformation or other damages after this extent of folding, and the inductor characteristics were hence unvaried.

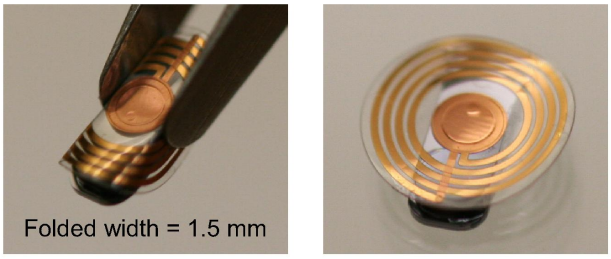

Figure 5. *Device flexibility demonstration: (left) Coil disk folding; (right) Coil disk stretched back after folding.*

RESULTS

Device testing was conducted using a hand-wound coil connected to a HP 4195A network/spectrum analyzer to serve as the external reader for electrical measurements. Electrical parameters of the fabricated microsensor were first obtained by analyzing the measurement data from both the actual device with the external wireless readout method and several test structures with on-chip probing. Table I lists the experimental results which were in good agreement with device design estimates.

Table I *Electrical parameters of the fabricated sensor*

Parameters	Values
Inductance	57 nH
Capacitance	3.6 pF
Resistance	4.2 Ω
Resonant frequency	~350 MHz
Quality factor	~30

In on-bench wireless pressure sensing test, the device was placed inside a customized chamber connected to a pressurization setup to simulate the environmental pressure variation surrounding the device. The wireless pressure sensing behavior of the device was characterized with the measured phase-dip curves as shown in Fig. 6 with an approximately 455 ppm/mmHg sensitivity analyzed using the derived pressure response of the normalized resonant frequency [3] as

$$\frac{f_{\min}(\Delta P)}{f_{\min}(\Delta P=0)} = \frac{\dfrac{1}{2\pi\sqrt{L_s(C_s+\Delta C_s)}}}{\dfrac{1}{2\pi\sqrt{L_s C_s}}} \cong (1-\alpha\Delta P)^{1/2},$$

where α is the fitting parameter. In order to meet the IOP sensing requirement, the allowed frequency fluctuation in measurements must be lower than the shift contributed by 1 mmHg pressure difference. Consequently, a supportive data-processed readout method [5] was utilized to achieve low-noise, high signal-to-noise ratio (SNR) phase-dip detections associated with long-range pressure sensing. Testing results indicate that SNR > 10 is the criterion of controlling the frequency shift noise lower than 400 ppm for applicable measurements. Given the minimally obtained $\Delta\phi_{\text{noise}} \sim 0.001°$ using the developed readout method, the maximum sensing distance was confirmed to be 2 cm using a 2.2-cm-diameter external reading coil, appropriate for the proposed glasses-type reader paradigm in practical wireless IOP monitoring with 1 mmHg pressure sensing accuracy. These investigations verify the device feasibility in engineering aspect.

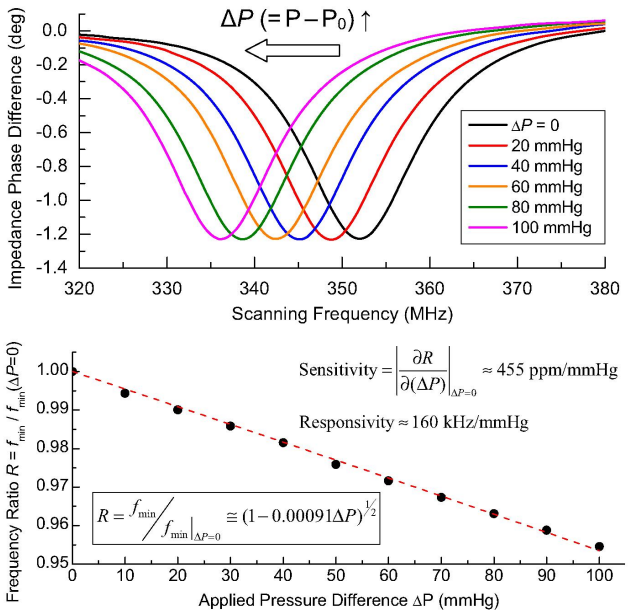

Figure 6. *On-bench wireless pressure sensing test: (top) Overlay plot of impedance phase-dip curves; (bottom) Pressure response characterization.*

In surgical aspect, a commercially available flexible ophthalmic iris retractor (Alcon/Grieshaber AG, Schaffhausen, Switzerland) was modified using a razor blade and then attached to the non-electronic sealing piece using epoxy as shown in Fig. 7 to serve as the tissue anchor for suture-less implant fixation. This surgical attachment

and the microfabricated sensor were assembled as the complete packaged device. After being introduced to the anterior chamber, the tapered feature at the end of the retractor hook penetrates the iris stratum to provide sufficient anchoring force to the device. This anchoring process is reversible if the implant needs to be removed from the eye. The packaged device could be conformally coated by a thin parylene layer to ensure its long-term biocompatibility in the intraocular environment.

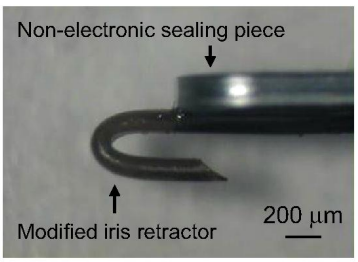

Figure 7. *Representative iris anchor assembly result (side view). The tapered retractor can hook the iris stratum to enable minimally invasive device fixation inside the eye.*

Chronic animal study was conducted with live rabbit model as shown in Fig. 8 to investigate surgical/biological compatibility of the implant. The entire surgery was remarkably completed within 15 min given its minimally invasive nature. In addition, the specific implant location has a tremendous advantage in aligning sensor and reader coils so that signal loss through coil misalignment can be minimized. Observation confirms that no device dislocation or post-operative complications (e.g., inflammatory response, tissue encapsulation/fibrosis, etc.) were found over 4 months, verifying surgical feasibility and bioefficacy of the device. Follow-up study is still in progress to collect long-term (e.g., 6-month) data.

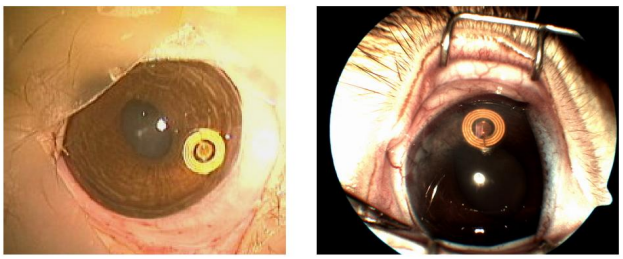

Figure 8. *Surgical feasibility test: (left) Implanted sensor inside the rabbit eye model as observed through the cornea; (right) Fundus photograph showing no device dislocation or post-operative complications in the intraocular environment after 3-month follow-up study.*

Finally, acute animal study was conducted to demonstrate *in vivo* wireless pressure sensing using the sensor implant inside a rabbit eye with the setup as shown in Fig. 9. *Ex vivo* testing using an enucleated porcine eye with the same setup was also accomplished to obtain quantitative results of sensor characterization in the simulated intraocular environment. A medical manometer was used in the infusion-based pressurization setup of this experiment to achieve precise IOP measurements as compared with the electrical readouts from the sensor. The wireless sensing results were analyzed and confirmed in good agreement with those in on-bench testing as shown in Fig. 6, indicating that the pressure response of the sensor was consistent when situated in different environments, regardless of different electrical performance (e.g., quality factor drop when the sensor was inside the eye) due to the medium effect which needs further study. Advanced surgical protocols and tools more suitable for such implant paradigm will also be investigated to better meet the future requirements in practice.

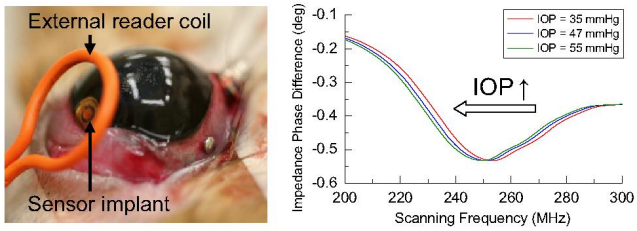

Figure 9. *In vivo wireless pressure sensing test: (left) Experimental setup. (right) Overlay plot of measured impedance phase-dip curves.*

CONCLUSION

An implantable wireless pressure sensor implementing passive telemetric sensing technology has been successfully developed as a solution to IOP measurements. Featuring a parylene-based flexible coil disk, the sensor achieves a satisfactory sensing distance suitable for practical glasses-type reader realization, as well as maintains a small form factor suitable for minimally invasive implantation. Engineering and surgical/biological performance of the sensor were characterized in a complete suite of on-bench, *ex vivo*, and *in vivo* experiments, and the results provide substantial evidence that the sensor has great potential for fulfilling continuous, real-time, reliable, and convenient IOP monitoring of glaucoma patients.

ACKNOWLEDGEMENTS

This work was supported in part by Bausch and Lomb. The authors especially thank Dr. Wen Li for her assistance on data acquisition of electrical impedance measurements, Dr. Damien Roger for his comments on surgical procedures and pressure testing with animal models, and Mr. Trevor Roper for his fabrication assistance.

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