Ultrathin and Robust Micro–Nano Composite Coating for Implantable Pressure Sensor Encapsulation

Jialin Yao, Wenjiang Qiang, Hao Wei, Yan Xu, Bo Wang, Yushuang Zheng, Xizi Wang, Zequn Miao, Lejin Wang, Song Wang, and Xing Yang*

ABSTRACT: Implantable pressure sensors enable more accurate disease diagnosis and real-time monitoring. Their widespread usage is dependent on a reliable encapsulation to protect them from corrosion of body fluids, yet not increasing their sizes or impairing their sensing functions during their lifespans. To realize the above requirements, an ultrathin, flexible, waterproof while robust micro–nano composite coating for encapsulation of an implantable pressure sensor is designed. The composite coating is composed of a nanolayer of silane-coupled molecules and a microlayer of parylene polymers. The mechanism and principle of the composite encapsulation coating with high adhesion are elucidated. Experimental results show that the error of the sensors after encapsulation is less than 2 mmHg, after working continuously for equivalently over 434 days in a simulated body fluid environment. The effects of the coating thickness on the waterproof time and the error of the sensor are also studied. The encapsulated sensor is implanted in an isolated porcine eye and a living rabbit eye, exhibiting excellent performances. Therefore, the micro–nano composite encapsulation coating would have an appealing application in micro–nano-device protections, especially for implantable biomedical devices.

1. INTRODUCTION

The development of implantable intraocular,1−4 blood,5,6 bladder,7,8 intracranial,9,10 and gastrointestinal tract11 micro-electromechanical system (MEMS) pressure sensors is important for disease diagnosis, monitoring, and adjuvant therapy. Compared with other types of pressure sensors, implantable MEMS sensors have small errors,12 small sizes,12,13 and high sensitivities,14,15 making them particularly suitable for such applications. For example, the range of regular human intraocular pressure is 9−21 mmHg (corresponding to 1.200−2.800 kPa). The error of measurement is required to be approximately 1−2 mmHg (corresponding to 0.133−0.267 kPa),16,17 and the volume of implantable intraocular sensors should be milliliters. However, the prevention from corrosion of body fluids and robustness are still challenging, which will limit the use of implantable MEMS pressure sensors.18

Proper encapsulation is essential to guarantee that implantable MEMS pressure sensors function in vivo with robustness, reliability, biocompatibility, and minimal performance decline.19 Encapsulation of MEMS sensors within a thin coating or cladding is a commonly used protection method.16,20−29 This involves the application of an ultrathin nonmetallic or metallic coating, including ceramic materials, alloys, and polymers (e.g., parylene, polyimide, and polydimethylsiloxane). For example, in 2018, Tai’s group proposed an encapsulation method based on a combination of parylene and silicon oil coating.16,21,22 They immersed the encapsulated pressure sensor with a zero-drift error of ∼2 mmHg in saline solution at 77 °C for 106 days, while the encapsulation is ∼0.8 mm thick, not negligible compared to the sensor size of ∼2.5 × 2.5 × 0.8 mm³. In 2015, Wen and co-workers reported an encapsulation method based on parylene, silica gel, and epoxy resin coating.23 Their encapsulated sensor yielded an output after immersion in saline solution at 85 °C for 160 days (the equivalent is 12.2 years at 37 °C). However, their encapsulation is as thick as ∼1.5 mm, added onto the sensor made from a ∼2 mm tall, ∼4 mm diameter cylinder.

In the aforementioned studies, the encapsulation thickness was relatively large (i.e., millimeters), and the encapsulation process was complex. For example, these studies reported improved waterproof performance by adding silica gel or
silicone oil while making the parylene coating. However, this increases the encapsulation thickness, and the process procedures are more cumbersome, leading to a risk of silicone oil leakage. Besides, most previous studies have not reported the accuracy and precision of the devices after encapsulation. For these reasons, an ultrathin and accuracy preserved encapsulated coating for implantable MEMS pressure sensors with a simple manufacturing method should be developed.

The expected encapsulation should be as thin and flexible as a “skin” to the sensor. Serving as the robust barrier between the internal and external environments of the body, human skin could effectively isolate hazardous substances from the ambient environment without adding restrictions to joint movements nor sensory reception. Similarly, we hope that encapsulation can give long-term, stable protection to the sensor without impeding the movement of the sensing component in the sensor. Based on challenges and problems in current studies, we summarized five requirements for the encapsulation of implantable pressure sensors.

1. Ultrathin: an encapsulation layer on the micro- or nanoscale with a small Young’s modulus can avoid the sensitivity30 loss of the sensor and cause trauma and difficulty in surgery.

2. Resistant to corrosion by body fluids.20,21

3. Robust: under cycling loading during operation, both the sensor and encapsulation material undergo deformation. Therefore, the encapsulation coating should have high robustness to avoid delamination, fatigue failure, and other problems.21,22,32

4. Biocompatible with human bodies.16,34–36

5. Minimal effect on the sensor performances: the measurement error and sensitivity of the sensor should be almost intact after encapsulation.2,23–25,37–41

Herein, an ultrathin and flexible micro−nano composite coating encapsulation for implantable MEMS pressure sensors is proposed. After analyzing the failure mechanical model of the sensor with the parylene-only coating, we summarize the design principles of the micro−nano composite encapsulation coating. The micro−nano composite encapsulation structure can meet the five requirements to guarantee the long-term performance of the in vivo device. As shown in Figure 1a, our ultrathin and flexible encapsulation coating, which can be seen as “micro−nano composite skin”, is adhesively coated on the surface of the implantable pressure sensor, and we studied the effect of coating thickness on the accuracy and lifespan of the encapsulated sensor. The encapsulated sensor was then implanted into the eyes of animals to verify the feasibility of the proposed encapsulation methods for implantable applications.

2. RESULTS AND DISCUSSION

The encapsulation of an implantable MEMS pressure sensor with the movable and sensing component working in an in vivo environment must fulfill five requirements: ultrathin, resistant to corrosion by body fluids, high robustness, good biocompatibility, and a minimal effect on the sensor performances. Our simple, flexible “micro−nano composite skin” encapsulation coating is designed to meet these criteria. Parylene is a conventional material for medical devices coating, but parylene-only coating cannot meet the encapsulation requirements of the implantable pressure sensor with the movable and sensing component. Accordingly, we analyze the mechanical model of the sensor only coated with parylene to find out the problems we should overcome in this model.

2.1. Mechanical Analysis and Failure Analysis.
Parylene has been used to coat medical devices that have demonstrated good biocompatibility. However, some literature had reported that only parylene as a coating cannot meet the encapsulation requirements of implantable pressure sensors with the movable and sensing component.20 So it is necessary to study the failure mechanism in the encapsulation of only parylene as a coating, which is also important in developing new encapsulation methods for implantable pressure sensors.

To analyze the failure mechanism of the encapsulation of only parylene as a coating, we simulated the implantable MEMS pressure sensor with the movable and sensing component using finite element calculations. The distribution of stress across the sensors before and after coating with a single layer parylene was visualized, as shown in Figure 2. In this simulation, we assumed the MEMS sensor was under a uniform pressure load in the body. Finite element analysis was conducted by taking only one-quarter of the pressure sensor chip as the mechanical model. This is a simplification for studying a whole inverted square silicon cup symmetric at its four vertexes.

In the simulation (described in Experimental Section), the maximum deflection variation of the movable and sensing component was almost unchanged after encapsulation (Figure 2a,b). The stress concentration points without encapsulation appear in the middle points of the four edges of the square silicon component above the cavity of the silicon cup. As shown in Figure 2c, when the pressure sensor was subjected to a uniform load of 0.12 MPa, the maximum normal stress was ∼5.13 MPa. The normal stress distribution simulation results of the encapsulated sensor are shown in Figure 2d. When subjected to a uniform load of 0.12 MPa, which is the top bound of a human normal blood pressure of 140 mmHg, the stress quantity and distribution of the encapsulated sensor was almost the same as that of the unencapsulated pressure sensor; thus, the microlayer parylene coating was loaded very slightly.
(showing blue in Figure 2d) and not appreciably influencing the sensitivity of the sensor. The stress concentration points in the square silicon component in the encapsulated pressure sensor chip still appear in the middle points of its four edges above the cavity of the silicon cup. The maximum normal stress was $\sim 5.16$ MPa, and the maximum stress on the encapsulation material was $\sim 0.0058$ MPa, which is almost negligible. Furthermore, the simulation results of the shear stress distribution of the encapsulated sensor are shown in Figure 2e. When the encapsulated sensor was subjected to stress, the largest shear stress between the encapsulation and sensor materials was computed as approximately 1.10 MPa.

According to the above simulation results, there is a strong friction shear stress between the parylene coating and the sensor surface. Given the large difference in Young’s modulus between the parylene and the sensor materials and the
changing load in real case, a strong friction shear stress was produced under repeated deformation. This stress easily leads to delamination and slippage failure of the parylene-only coatings, which would allow water molecules to diffuse through interface voids. As a result, the sensor materials, including electrodes, terminals, and other materials, commonly experience corrosion failure.

Moreover, repeated deformation also accelerates fatigue failure at the stress concentration points (the middle points of the four edges of the square component). This may lead to fracture of the parylene and sensor materials, rendering the sensor unusable. Besides, during device fabrication, structural defects (e.g. the deviations from the lattice arrangement of atoms or molecules) are introduced into the sensor material, through material nonuniformity and manufacturing errors. Such defects decrease the accuracy and precision of the device. The defects increase as a result of fatigue. Thus, the failure mechanism of the parylene-only encapsulation of the implantable MEMS pressure sensor is delamination, fatigue, or structural defects. In other words, because of the existence of strong shear stress, the parylene-only coating cannot meet the requirements of implantable pressure sensor encapsulation with movable components.

Therefore, according to the above analysis, to ensure long-term, accurate, stable, in vivo operation, ultrathin encapsulation materials with low Young’s modulus are necessary to the pressure sensor with the movable and sensing component. More importantly, strong adhesion is critical not only in preventing delamination and slippage failure between the coating and sensor materials but also in delaying the fatigue failure by compensating for structural defects between the coating and sensor materials. Consequently, we propose a micro–nano composite coating with low Young’s modulus and strong adhesion, which can withstand the shear stress between layers and slow down the fatigue failure. We believe it can meet the encapsulation requirements of implantable pressure sensors.

2.2. Design of the Micro–Nano Composite Coating. According to the above failure mechanism analysis, we propose a micro–nano composite encapsulation coating which is adhesively attached to the surface of the sensor with the movable and sensing component, similar to wearing a “human skin” on the pressure sensor. Human skin fits the body surface well without adding considerable volume or impeding joint movements. Such features would be ideal for the encapsulation of pressure sensors, which require an ultrathin, corrosion resistant, robust, deformable barrier between the internal and external environments. Addressing this objective, the design principles of our micro–nano composite coating are as follows:

(1) Structure: to avoid the three failure modes detailed above, we need to add one adhesive layer to enhance the strength of bonding between the coating and the device surface. Accordingly, the schematic of the proposed micro–nano composite encapsulation structure is shown in Figure 1b; a waterproof microscale layer directly protects the device from body fluids, while an adhesive nanoscale layer bonds to the microscale layer and the device firmly like many small hands, eliminating failure due to delamination, fatigue, or structural defects. (More related process will be described later.) In this way, our two-layer micro–nano composite encapsulation guarantees the long-term performance of the in vivo device.

(2) Materials: in view of the functions of the micro–nano composite structure, we chose parylene as the microscale membrane for waterproofing and the silane coupling agent A-174 (3-methacryloxypropyltrimethoxysilane) as the adhesive nanolayer. Parylene is a compact and biocompatible encapsulation material with low permeability to water molecules. The silane coupling agent can improve the interfacial properties between inorganic and organic substances by forming covalent or hydrogen bonds and effectively enhance the adhesion strength between the sensor material and parylene polymer.42 Besides, the micro–nano composite coating can reduce the notch sensitivity by making up for structural defects between the coating and sensor materials and improve the fatigue toughness.

(3) Process: we developed a two-step manufacturing process that is simple and stable. The silane coupling agent molecular layer and parylene layer were deposited successively to form the micro–nano composite coating. The nanomolecular layer of the silane coupling agent A-174 combines with the surface of the MEMS sensor to form a strong chemical bond, thereby helping to improve the surface adhesion ability of parylene mechanical properties. The chemical reaction between the silane A-174 molecule and the surface of the MEMS sensor is shown in Figure 3. In this figure, the hydroxyl group on the surface of the MEMS sensor is preformed by its reaction with the adsorbed water molecules in the air. After the coating of silane A-174, the monomers of parylene C would copolymerize with the methacryloxy tail of A-174 via a free radical addition reaction and deposit as a microthin polymer layer.43–47 The detailed method can be found in the Experimental Section.

After the design and process, this study focused on three areas: characteristics of the micro–nano composite coating; performances of the pressure sensor after encapsulation; and the results of implantable intraocular pressure measurement.

2.3. Properties of the Micro–Nano Composite Coating. 2.3.1. Adhesion of the Coatings. According to the
analysis above, good adhesion between the encapsulation coating and the base material is a precondition for implantable pressure sensors to achieve robust coating, high accuracy, and precision. We tested the characteristics of adhesion between the encapsulation coating and the base material. The adhesion of the encapsulation coating refers to the bonding strength between the coating and the base material and is the perpendicular force required per unit area of the coating to peel off the base surface.

We compared the adhesion of the proposed strongly adhesive micro–nano composite coating with a coating of only parylene. As shown in Figure 4a, when the coating was broken or peeled by the scriber of the nanoscratch tester and the slope of the lateral force curve would change, the friction coefficient would also change greatly. Through the dashed line, the load at this time was the critical load of the coating. The critical load for the shedding of the parylene coating (0.93 μm-thick) from the silicon slice after silanization was 225.27 ± 44.60 mN. The critical load for shedding of the coating (0.95 μm-thick) without silanization was 84.03 ± 5.33 mN (the results of one sample are shown in Figure 4b). Thus, the adhesion of the coating after silanization increased by ∼168.1% (Figure 4c).

The molecular layer of the silane coupling agent acts like a strong and powerful hand that pulls the parylene molecular layer, thus effectively increasing the adhesion between the parylene coating and the sensor surface. Meanwhile the lightweight micro–nano composite coating slightly affects the thickness of the coating on the sensors by measuring the thickness of the coating on the silicon slice.

To verify the effect of encapsulation thicknesses on the error of measurement of the sensor, the micro–nano composite coating deposition was conducted for thicknesses of 1.0, 3.8, 4.2, 8.4, and 12.3 μm, in which the thickness of the silane coupling agent coating on the silicon slices and devices was 0.4 nm, as measured using an ellipsometer (detailed in Experimental Section).

2.4. Performances of the Pressure Sensor after the Coating. 2.4.1. Effect of Coating Thickness on the Error of Measurement. According to the error theory, the error of pressure sensors was calculated as the square root of the sum which combines the squared maximum nonlinearity error, squared maximum hysteresis error, and squared maximum nonreproducibility error. The rate of change of the error of measurement before and after encapsulation is shown in Figure 4d. The influence of the coating on the sensor’s error increases with the increase of the thickness. The dashed line in Figure 4d shows that the influence of the coating on the sensor error increases monotonously with the thickness and has good linearity. For example, for a thickness of 1.0 μm, the average error (from nine devices) reduced by 29.4%. The sensitivity was only slightly affected, with an average decrease of 0.8%. For a thickness of 3.8 μm, the error of measurement of devices increased by 28.2% compared with that before encapsulation, meanwhile the sensitivity was decreased by 4.2%. The average accuracy and precision of all coated sensors were not impaired significantly and even improved with the strongly adhesive micro–nano composite coatings.

The molecular layer of the silane coupling agent acts like a strong and powerful hand that pulls the parylene molecular layer, thus effectively increasing the adhesion between the parylene coating and the sensor surface. Meanwhile the lightweight micro–nano composite coating slightly affects the thickness of the coating on the sensors by measuring the thickness of the coating on the silicon slice.

![Figure 4.](https://dx.doi.org/10.1021/acsomega.0c02897)
the flexibility of the movable and sensing component of the pressure sensor, resulting in a lower error of measurement output.

2.4.2. Effect of Different Encapsulation Techniques on the Waterproof Time. In accordance with the requirements of implantable MEMS pressure sensors, if the error exceeds 2 mmHg, the device is considered to be defective. Accordingly, we compared the waterproof effect of the parylene-coated sensors with and without the silane layer.

The waterproof time is an important indicator of the working life of the sensor, which can be assessed by accelerated aging. The aging rate is increased at elevated temperatures. For commonly used polymer encapsulation materials, this is generally tested based on a 10° principle. The aging rate is increased by a single raise in the temperature for an accelerated aging waterproof time. The acceleration factor is expressed as follows

\[ f = 2^{T - T_{ref}/10} \]  

where \( T \) is the accelerated aging temperature, and \( T_{ref} \) is the reference temperature. The aging speed can be doubled by increasing the accelerated aging temperature 10 °C higher than the reference temperature. The thermal expansion coefficients of the polymer encapsulation materials and sensor materials are different. As such, a high aging temperature increases the thermal stress of the polymer, resulting in its slippage and dropping. Therefore, 67 °C was chosen to be the accelerated aging temperature. The encapsulated implantable MEMS pressure sensor was placed in normal saline at a constant temperature of 67 °C. The aging rate can be increased by eight times in contrast to that at 37 °C in vivo. Besides, the pressure sensor placed in the saline solution was regularly recorded to evaluate its long-term stability.

The measurement results are as follows. Devices cladded with a 3.8 μm micro–nano composite coating (parylene after silanization) maintained good accuracy and precision after immersion in the simulated body fluid [saline solution at 67 °C, which is equivalent to body temperature (37 °C) for 434 days] with an error of less than 2 mmHg. Figure 5a shows (1) the measurement error of the two devices cladded with the 3.8 μm micro–nano composite coating (devices 1 and 2) changed with time and (2) the output of device 1 immersed for 410 days. Here, the nonlinear error of the characteristic curve of the piezoresistive linear pressure sensor is expressed by the maximum standard deviation, which is 0.018 mmHg. The slope represents the sensitivity of the device.

The morphologies of the implantable sensor before and after micro–nano composite encapsulation are shown in Figure 5b,c. The surface morphology is almost unchanged because of the ultrathin coating. The scanning electron micrographs taken near the position of the gold wire of the pressure sensor (near the middle point of the movable and sensing square component, Figure 5d) reveal that the micro–nano composite encapsulation coating (3.8 μm thick) is compact and uniform without surface defects. The device still worked after 72 days of immersion in the simulated body fluid. Electron micrographs also demonstrated that although there were some small wrinkles on the surface of the encapsulation coating (Figure 5e), it was still very dense and had no obvious defects. The coating still worked well as a waterproof barrier, which proved that the proposed encapsulation coating had good waterproof performance. After the device is immersed in the simulated body fluid, the device will be in the periodical pressure test until the device fails. So the longer the immersion life of the device, the more the pressure test. Therefore, the composite coating is more robust than the parylene coating.

By contrast, the devices encapsulated with only the parylene coating (4.0 μm thick) as the control experiment failed after only 72 days of immersion in the simulated body fluid. Because the lead wire and coating of the device would be damaged in the process of sample preparation, so we cannot further test. The electron micrographs in Figure 5f show that the surface of the coating at the position of the gold wire of the pressure sensor (near the middle point of the movable and sensing square component) aged, producing cracks. These also illustrate the importance of silanized nanolayers and adhesion, validating the encapsulation model and its failure analysis.

2.5. Implantable Intraocular Pressure Measurement. Our ultimate goal is to implant the sensor to monitor the body’s fluid pressure. We simulated this in two animal experiments: isolated porcine and living rabbit eyes.
2.5.1. Isolated Porcine Eye Measurement. The isolated porcine eye measurement and control system (Figure 6a) consisted of the implantable pressure measurement unit, an isolated porcine eye, a pressure control unit, and an electrical measurement unit (detailed in Experimental Section). The pressure sensor encapsulated with the micro−nano composite coating was implanted in the anterior chamber of an isolated porcine eye. By adjusting the height of the bottle of the pressure control unit, data were recorded every 10 cm. The results after an implantation time of ∼12 h are shown in Figure 6b. The intraocular pressure sensors encapsulated with our micro−nano composite coating accurately monitored the changes in intraocular pressure in real time.

2.5.2. Living Rabbit Eye Measurement. After the isolated porcine eye measurement, we also verified the feasibility of using the implantable pressure sensor with the proposed micro−nano composite coating in living animals (i.e., rabbits). As shown in Figure 6c, the sensor was connected with the electrical measurement unit to measure the intraocular pressure of the rabbit in real time (detailed in the Experimental Section). We monitored the output of the pressure sensor in real time after controllably injecting a certain volume of saline into the eye of the living rabbit to change the intraocular pressure. The results after sensor implantation in the living rabbit eye for ∼6 h are shown in Figure 6d, revealing good performance in this animal model. The linear relationship between the output of the sensor and the volume of the injected water shows that the sensor can accurately monitor intraocular pressure in vivo.

2.6. Comparative Analysis. The performance comparison of the aforementioned studies in implantable MEMS pressure sensors is summarized in Table 1.16,20−27 In contrast with the existing methods, our micro−nano composite coating exhibits the following merits: (1) ultrathin encapsulation layer: the average thickness of our micro−nano composite coating is about 3.8 μm, which is much thinner than those in the reported literature, and enables to decrease trauma and burden of implantation targets and difficulty in surgery; (2) good resistance toward corrosion from body fluids and better robustness: the sensors encapsulated by our micro−nano composite coating worked properly in saline solution after an equivalent body temperature implantation time of 434 days with long-term stability, which could reduce the need for a secondary operation; (3) minimal influence on device performances, such as error or sensitivity: for a thickness of 1.0 μm, the measurement error of the MEMS pressure sensors after our micro−nano composite coating is less than 1 mmHg. The sensitivity was only slightly affected and (4) a facile and economical fabrication process: the two-step method, which is simple, efficient, and low-cost, for coating the pressure sensors with our micro−nano composite coating has desirable application prospects in industrial production of biomedical sensors.

Table 1. Performances Comparison of Implantable MEMS Pressure Sensors Encapsulated with Different Coating Methods

| thickness of encapsulated layer | methods | measurement error after encapsulation | species | change rate of sensitivity after encapsulation | references |
|--------------------------------|---------|---------------------------------------|---------|-----------------------------------------------|------------|
| ~0.8 mm                        | casting and CVD | no report | porcine | <1% degradation | 16,21,22 |
| ~1.5 mm                        | casting and CVD | no report | rat | no report | 23 |
| ~1 mm                          | casting and CVD | no report | sheep | >10% degradation | 24,25 |
| ~1 mm                          | casting and CVD | no report | no report | 20% degradation | 20 |
| ~1 mm                          | casting | no report | rabbit | no report | 26,29 |
| ~1 mm                          | casting | no report | no report | no report | 27 |
| ≤3.8 μm                        | CVD | <1 mmHg | porcine and rabbit | <5% degradation | this work |

Figure 6. (a) Diagram of the isolated porcine eye measurement and control system. (b) Output of the intraocular pressure measurement unit after implantation in the isolated porcine eye. (c) Diagram of living rabbit eye measurement. A multimeter monitors the change in the intraocular pressure in the rabbit. The aqueous humor pressure in the anterior chamber of the eye is transmitted to the implantable MEMS pressure sensor through a 24G catheter. (d) Output of the intraocular pressure measurement unit after implantation in the living rabbit eye.

https://dx.doi.org/10.1021/acsomega.0c02897
ACS Omega 2020, 5, 23129−23139
pressure sensor (Silicon Microstructures, Inc. Milpitas, CA, USA) with an absolute pressure range of 0–15 psi was used for the experiments. The encapsulation materials were dichloro-paracyclophane C-type parylene (Specialty Coating Systems, Inc., Indianapolis, IN, USA) as the microlayer and silane coupling agent A-174 (Sigma-Aldrich Corporation, St. Louis, MO, USA) as the nanolayer.

4.2. Finite Element Calculations. The parameters of the sensors and encapsulation material in the model are as follows. The pressure sensor chip size is 0.65 × 0.65 × 0.65 mm³. The thickness and area of the movable and sensing silicon component were 20 μm and 100 μm × 100 μm, respectively; the Young’s modulus and Poisson’s ratio were 130,000 MPa and 0.28, respectively. The thickness of parylene was 1 μm, and its Young’s modulus and Poisson’s ratio were 2757 MPa and 0.4, respectively. The boundary condition of the pressure was a uniform load of 0.12 MPa.

4.3. Encapsulation Method. We established two experiments to verify how the proposed encapsulation model affects the robustness and resistance to corrosion by body fluids.

Experiment 1: for the control experiment, parylene was coated on the sensor surface. This was coated onto the sensor in a vacuum deposition chamber of a parylene special coating system PDS2010 (Specialty Coating Systems, Inc., Indianapolis, IN, USA). Parylene was heated when the pressure in the vacuum chamber reached 10 mTorr; parylene sublimated at 175 °C. The gaseous feedstock obtained through sublimation entered the pyrolysis chamber. When the temperature of the pyrolysis chamber reached 690 °C, the feedstock gas was split into its monomers, which entered the deposition chamber and deposited on the surface of the sensor to polymerize parylene.

Experiment 2: for the micro–nano composite coating, we first added the silane coupling agent (A-174) in a vacuum deposition chamber of a parylene special coating system PDS2010 to clad a silane coupling agent (A-174) molecular layer. Then, parylene was coated on the sensor surface.

For both experiments, epoxy (Devcon, Inc., Danvers, MA, USA) was coated on the immovable parts of the sensors to avoid circuit failure caused by the solder joints and wires.

4.4. Adhesion Measurement of the Coating. We measured the adhesion on three randomly selected lines on two parylene-coated silicon slices (with and without silanization, respectively) using a G200 Nano Scratch tester (Keysight Technologies Inc. Santa Rosa, CA, USA). The adhesion of the coating was determined by obtaining the critical load at which the coating material peeled from the surface of the silicon slice.55

4.5. Thickness Measurement and Morphological Characterization. The thickness of the micro–nano composite encapsulation coating was measured using the Dektak XT step profiler (Bruker Corporation, Billerica, MA, USA). First, the coating on the silicon slice was cut and peeled with a scalpel. Then, the contact needle of the step profiler was allowed to slide across the surface of the silicon slice with or without the micro–nano composite coating. The needle moved up and down depending on the height of the surface, allowing the thickness of the coating to be obtained.

Ellipsometry (HORIBA Jobin Yvon, Stow, Massachusetts, USA) is an optical measurement technique for determining film thickness of the nanolayer of the silane coupling agent. The refractive index of the silane-layer model (n = 1.5) was assumed to be the same as that of native oxide on the silicon model. The difference between the thicknesses of the
nanolayer-coated film and uncoated film was taken as the silane-layer thickness.\textsuperscript{16–58}

We observed the sensor before and after encapsulation and after being placed in a simulated body fluid using scanning electron microscopy Sirion 200 (FEI Company, Hillsboro, Oregon, USA). The failure modes of the implantable encapsulation coatings were further analyzed.

4.6. Measurement Error of the Pressure Sensors. Based on the previous work,\textsuperscript{59} the pressure sensor test system was established to measure the error of the pressure sensor. At room temperature (25 $\pm$ 1°C), the pressure sensor was placed in a sealed pressurized chamber and pre-pressed at least three times. Then, six points were uniformly selected in the whole range of the upper and lower limits of the sensor, at which the output was recorded. The pressure measurement range was from 0 to 75 mmHg of the gauge pressure and in increments of 15 mmHg. The measurement of each pressure sensor was repeated three times. Then, we determined the change in the measurement error after encapsulation.

4.7. Isolated Porcine Eye Experiment. First, a pressure control unit, which was mainly composed of a normal saline bottle, a bottle rack, and an infusion tube, was constructed. Second, a catheter filled with saline was implanted into the anterior chamber incision of the porcine eye. Then, the intraocular pressure of the porcine eye was modified by changing the height of the saline bottle. We then designed and prepared the implantable intraocular pressure measurement unit, which consisted of the pressure sensor (which was encapsulated with our ultrathin micro–nano composite coating) and a diversion device. The diversion tube was used to pierce into the anterior chamber in the porcine eye to guide the intraocular pressure to the sensitive component of the sensor. Finally, an electrical measurement unit, consisting of a multimeter and a power supply, was constructed, which connected the implantable intraocular pressure measurement unit with the electrical measurement unit. Thus, the implantable intraocular pressure measurement unit can monitor the change in the aqueous humor pressure in the porcine eye. The implantable intraocular pressure measurement unit was tested by adjusting the height of the bottle rack and the bottle in the pressure control unit. Data are recorded once every 10 cm.

4.8. Living Rabbit Eye Experiment. The research received institutional approval by the Ethical Committee and Institutional Review Board of Peking University People’s Hospital (Approval no. 2019PHE037). The study conformed to the Declaration of Helsinki and was carried out in accordance with institutional guidelines. The rabbit was initially fixed and anesthetized to facilitate the operation. Next, the anterior chamber was incised with a scalpel blade. The size of the incision was equal to the diameter of the diversion tube. The infusion tube of the pressure control unit was subsequently pierced into the anterior chamber of the eye. Finally, the sensor was connected with the electrical measurement unit to measure the intraocular pressure in real time.

### Author Information

**Corresponding Author**

Xing Yang — The State Key Laboratory of Precision Measurement Technology and Instruments, Department of Precision Instrument, Tsinghua University, Beijing 100084, People’s Republic of China; orcid.org/0000-0002-1249-3602; Email: yangxing@tsinghua.edu.cn

### Authors

**Jialin Yao** — School of Materials Science and Engineering, University of Science and Technology Beijing, Beijing 100083, People’s Republic of China; orcid.org/0000-0001-6797-0747

**Wenjiang Qiang** — School of Materials Science and Engineering, University of Science and Technology Beijing, Beijing 100083, People’s Republic of China

**Hao Wei** — School of Materials Science and Engineering, University of Science and Technology Beijing, Beijing 100083, People’s Republic of China

**Yan Xu** — School of Materials Science and Engineering, University of Science and Technology Beijing, Beijing 100083, People’s Republic of China

**Bo Wang** — School of Mechanical and Electrical Engineering, Yantai University, Yantai 264005, People’s Republic of China

**Yushuang Zheng** — School of Materials Science and Engineering, University of Science and Technology Beijing, Beijing 100083, People’s Republic of China

**Xizi Wang** — School of Materials Science and Engineering, University of Science and Technology Beijing, Beijing 100083, People’s Republic of China

**Zequn Miao** — Center of Optometry, Department of Ophthalmology, Peking University People’s Hospital, Beijing 100044, People’s Republic of China; Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroid Diseases, Beijing 100044, People’s Republic of China

**Lejin Wang** — Center of Optometry, Department of Ophthalmology, Peking University People’s Hospital, Beijing 100044, People’s Republic of China; Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroid Diseases, Beijing 100044, People’s Republic of China

**Song Wang** — The State Key Laboratory of Precision Measurement Technology and Instruments, Department of Precision Instrument, Tsinghua University, Beijing 100084, People’s Republic of China

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c02897

### Notes

The authors declare no competing financial interest.

### Acknowledgments

This work was financially supported by the National Natural Science Foundation of China Project (grant nos. 61671271 and 31427801) and the Capital Transformational Medicine Project (grant no. 2018-ZZ-4086). The authors would like to thank Dr. Yixu Wang and Dr. Hualai Dong for his comments and suggestions. We also acknowledge the micro–nano Electronic Facilities of Tsinghua University for ellipsometric measurement (Dr. Yalu Chen).

### References

(1) Araci, I. E.; Su, B.; Quake, S. R.; Mandel, Y. An implantable microfluidic device for self-monitoring of intraocular pressure. Nat. Med. 2014, 20, 1074–1078.

(2) Lee, J. O.; Park, H.; Du, J.; Balakrishna, A.; Chen, O.; Sretavan, D.; Chou, H. A microscale optical implant for continuous in vivo monitoring of intraocular pressure. Microsyst. Nanoeng. 2017, 3, 17057.

(3) Kim, J.; Kim, J.; Ku, M.; Cha, E.; Ju, S.; Park, W. Y.; Kim, K. H.; Kim, D. W.; Berggren, P.-O.; Park, J.-U. Intraocular Pressure
Monitoring Following Islet Transplantation to the Anterior Chamber of the Eye. Nano Lett. 2020, 20, 1517−1525.

(4) Zou, R.; Shan, S.; Huang, L.; Chen, Z.; Lawson, T.; Lin, M.; Yan, L.; Liu, Y. High-Performance Intraocular Biosensors from Chitosan-Functionalized Nitrogen-Containing Graphene for the Detection of Glucose. ACS Biomater. Sci. Eng. 2020, 6, 673−679.

(5) Shin, J.; Yan, Y.; Bae, W.; Xue, X.; Gamble, P.; Tian, L.; Kandela, J.; Flaxman, C. B.; Speev, W.; Lee, Y.; Choi, M.; Ko, J.; Ryu, H.; Chang, J.-K.; Pezhothou, M.; Kang, S.-K.; Won, S. M.; Yu, K. J.; Zhao, L. Y.; Lee, Y. K.; MacEwan, M. R.; Song, S.-K.; Huang, Y.; Ray, W. Z.; Rogers, J. A. Bioreabsorbable sensor protections with thermally grown silicon dioxide for the monitoring of chronic diseases and healing processes. Nat. Biomed. Eng. 2019, 3, 37−46.

(6) Ma, Y.; Zheng, Q.; Liu, Y.; Shi, B.; Xue, X.; Ji, W.; Liu, Z.; Jin, Y.; Zou, Y.; An, Z.; Zhang, W.; Wang, X.; Jiang, W.; Xu, Z.; Wang, Z. L.; Li, Z.; Zhang, H. Self-Powered, One-Step, and Multifunctional Implantable Triboelectric Active Sensor for Real-Time Biomedical Monitoring. Nano Lett. 2016, 16, 6042−6051.

(7) Abelson, B.; Majerus, S.; Sun, D.; Gill, B. C.; Versi, E.; Damaser, M. S. Ambulatory urodynamic monitoring: state of the art and future directions. Nat. Rev. Urol. 2019, 16, 291−301.

(8) Mickle, A. D.; Won, S. M.; Noh, K. N.; Yoon, J.; Meacham, K. W.; Xue, Y.; McIlvried, L. A.; Copits, B. A.; Samieni, V. K.; Crawford, K. E.; Kim, D. H.; Srivastava, P.; Kim, B. H.; Min, S.; Shiuian, Y.; Yun, Y.; Payne, M. A.; Zhang, J.; Jung, H.; Li, Y.; Lai, H. H.; Huang, Y.; Park, S.-I.; Gereau, R. W.; Rogers, J. A. A wireless closed-loop system for optogenetic peripheral neuromodulation. Nature 2019, 565, 361−365.

(9) Kang, S.-K.; Murphy, R. K. J.; Hwang, S.-W.; Lee, S. M.; Harburg, D. V.; Krueger, N. A.; Shin, J.; Gamble, P.; Cheng, H.; Yu, S.; Liu, Z.; McCall, J. G.; Stephen, M.; Ying, H.; Kim, J.; Park, G.; Webb, R. C.; Lee, C. H.; Chung, S.; Wie, D. S.; Gujjar, A. D.; Vemalupallli, B.; Kim, A. H.; Lee, K.-M.; Cheng, J.; Huang, Y.; Lee, S. H.; Braun, P. V.; Ray, W. Z.; Rogers, J. A. Bioreabsorbable silicon electronic sensors for the brain. Nature 2016, 536, 71−76.

(10) Hou, C.; Xu, Z.; Qiu, W.; Wu, R.; Wang, Y.; Xu, Z.; Qiu, L.; Liu, X. Y.; Guo, W. A Biodegradable and Stretchable Protein-Based Sensor as Artificial Electronic Skin for Human Motion Detection. Small 2019, 15, 1805084.

(11) Beardslee, L. A.; Banis, G. E.; Chu, S.; Liu, S.; Chapin, A. A.; Stine, J. M.; Pasricha, P. J.; Ghodssi, R. Ingestible Sensors and Sensing Systems for Minimally Invasive Diagnosis and Monitoring: The Next Frontier in Minimally Invasive Screening. ACS Sens. 2020, 5, 891−910.

(12) Clausen, I.; Glott, T. Development of Clinically Relevant Implantable Pressure Sensors: Perspectives and Challenges. Sensors 2014, 14, 17686−17702.

(13) Oelßner, W.; Zosel, J.; Guth, U.; Pechtstein, T.; Babel, W.; Connyer, J. G.; Deumuth, C.; Ganssey, M. G.; Verburg, J. B. Encapsulation of ISFET sensor chips. Sens. Actuators, B 2005, 105, 104−117.

(14) Sang, Z.; Ke, K.; Manas-Zloczower, I. Design Strategy for Porous Composites Aimed at Pressure Sensor Application. Small 2019, 15, 1903487.

(15) Kim, M.-g.; Alrowais, H.; Brand, O. 3D-Integrated and Multifunctional All-Soft Photonic Microsystems Based on Liquid Metal for Electronic Skin Applications. Adv. Electron. Mater. 2018, 4, 1700434.

(16) Agarwal, A.; Shapero, A.; Rodger, D.; Humayun, M.; Tai, Y.; Emami, A. A wireless, low-drift, implantable intraocular pressure sensor with parylene-on-oil encapsulation. IEEE Custom Integrated Circuits Conference, 2018, p. 1.

(17) Nazarov, A.; Kayazer, B.; Lifshitz, T.; Schartzman, M. Z.; Abdulhamil, I. Assessment of intraocular pressure sensing using an implanted reflective flexible membrane. J. Biomed. Opt. 2017, 22, 047001.

(18) Chen, P.-J.; Rodger, D. C.; Saati, S.; Humayun, M. S.; Tai, Y.-C. Microfabricated Implantable Parylene-Based Wireless Passive Intraocular Pressure Sensors. J. Microelectromech. Syst. 2008, 17, 1342−1351.

(19) Qin, Y.; Howlader, M. M. R.; Deen, M. J.; Haddara, Y. M.; Selvaganapathy, P. R. Polymer integration for packaging of implantable sensors. Sens. Actuators, B 2014, 202, 758−778.

(20) Chen, X.; Young, D. Robust implantable blood pressure sensor packaging for long-term laboratory animals monitoring. 2016 IEEE Sensors, Orlando, FL, 2016; p. 1.

(21) Shapero, A. M.; Liu, Y.; Tai, Y. Parylene-on-oil packaging for long-term implantable pressure sensors. Biomed. Microdevices 2016, 18, 66.

(22) Shapero, A.; Tai, Y.-C. Parylene-encapsulated low-drift implantable pressure sensors. 2018 IEEE Micro Electro Mechanical Systems, 2018.

(23) Wang, P.; Majerus, S. J. A.; Karam, R.; Hanzlicek, B.; Wen, H. K. Long-term evaluation of a non-hermetic micropackage technology for MEMS-based, implantable pressure sensors. 2015 Transducers—2015 18th International Conference on Solid-State Sensors, Actuators and Microsystems, 2015.

(24) Brancato, L.; Keulemans, G.; Verbelen, T.; Meyens, B.; Puers, R. An Implantable Intravascular Pressure Sensor for a Ventricular Assist Device. Micromachines 2016, 7, 135.

(25) Brancato, L.; Weydt, T.; Oosterlinck, W. Packaging of implantable accelerometers to monitor epicardial and endocardial wall motion. Biomed. Microdevices 2017, 19, 52.

(26) Mariacher, S.; Ebner, M.; Januschowski, K.; Hurst, J.; Schnichels, S.; Szurman, P. Investigation of a novel implantable suprachoroidal pressure transducer for telemetric intraocular pressure monitoring. Exp. Eye Res. 2016, 151, 54−60.

(27) Siwapornsathan, E.; Lal, A.; Binard, J. In A Telemetry and Sensor Platform for Ambulatory Urodynamic; Dittmar, A., Beebee, D., Eds.; IEEE, 2002.

(28) Ha, D.; de Vries, W. N.; John, S. W. M.; Irazoqui, P. P.; Chappell, W. J. Polymer-based miniature flexible capacitive pressure sensor for intraocular pressure (IOP) monitoring inside a mouse eye. Biomed. Microdevices 2012, 14, 207−215.

(29) Mariacher, S.; Ebner, M.; Hurst, J.; Szurman, P.; Januschowski, K. Implantation and testing of a novel episcleral pressure transducer: A new approach to telemetric intraocular pressure monitoring. Exp. Eye Res. 2018, 166, 84−90.

(30) Choi, C.; Lee, Y.; Cho, K. W.; Koo, J. H.; Kim, D.-H. Wearable and Implantable Soft Bioelectronics Using Two-Dimensional Materials. Acc. Chem. Res. 2019, 52, 73−81.

(31) Song, E.; Fang, H.; Jin, X.; Zhao; J.; Jiang, C.; Yu, K.; Zhong, Y.; Xu, D.; Li, J.; Fang; G.; Du, H.; Zhang; J.; Park, J. M.; Huang, Y.; Alam, M. A.; Mei, Y.; Rogers, J. A. Thin, Transferred Layers of Silicon Dioxide and Silicon Nitride as Water and Ion Barriers for Implantable Flexible Electronic Systems. Adv. Electron. Mater. 2017, 3, 1700077.

(32) Wang, G.-J. N.; Gasperini, A.; Bao, Z. Stretchable Polymer Semiconductors for Plastic Electronics. Adv. Electron. Mater. 2018, 4, 1700429.

(33) Yazici, H.; O’Neill, M. B.; Karac, T.; Wilson, B. R.; Oren, E. E.; Sarikaya, M.; Tamerler, C. Engineered Chimeric Peptides as Antimicrobial Surface Coating Agents toward Infection-Free Implants. ACS Appl. Mater. Interfaces 2016, 8, 5070.

(34) Zhang, S.; Li, Y.; Tomasello, G.; Anthonisen, M.; Li, X.; Mazzeo, M.; Genco, A.; Christen, P.; Cicoira, F. Tuning the Molecular Wall Motion. Exp. Eye Res. 2016, 14, 52−67.

(35) Golda-Cepa, M.; Chorylek, A.; Chytrosz, P.; Brzychczy-Wloch, M.; Jaworska, J.; Kasperczyk, J.; Hakkarainen, M.; Engvall, K.; Selvaganapathy, P. R. Polymer integration for packaging of implantable sensors. Sens. Actuators, B 2019, 221, 106269.
(37) Kwak, Y. H.; Kim, W.; Park, K. B.; Kim, K.; Seo, S. Flexible heartbeat sensor for wearable device. Biosens. Bioelectron. 2017, 94, 250–255.

(38) Kim, H.; Kim, G.; Kim, T.; Lee, S.; Kang, D.; Hwang, M.-S.; Chae, Y.; Kang, S.; Lee, H.; Park, H.-G.; Shim, W. Transparent, Flexible, Conformal Capacitive Pressure Sensors with Nanoparticles. Small 2018, 14, 1703432.

(39) Montazerian, H.; Rashidi, A.; Dalili, A.; Najjaran, H.; Milani, A. S.; Hoorfar, M. Graphene-Coated Spandex Sensors Embedded into Silicone Sheath for Composites Health Monitoring and Wearable Applications. Small 2019, IS, 1804991.

(40) Shao, L.; Li, Y.; Ma, Z.; Bai, Y.; Wang, J.; Zeng, P.; Gong, P.; Shi, F.; Ji, Z.; Qiao, Y. Highly Sensitive Strain Sensor Based on a Stretchable and Conductive Poly(vinyl alcohol)/Phytic Acid/NH2-POSS Hydrogel with a 3D Microporous Structure. ACS Appl. Mater. Interfaces 2020, 12, 26496.

(41) Ding, L.; Wang, Y.; Sun, C.; Shu, Q.; Hu, T.; Xuan, S.; Gong, X. 3D-Structured Dual-mode Flexible Sensors for Highly Sensitive Tactile-perception and Non-contact Sensing. ACS Appl. Mater. Interfaces 2020, 12, 20955–20964.

(42) Heriyanto; Palievani, F.; Sahajwalla, V. Effect of different waste filler and silane coupling agent on the mechanical properties of polyester resin composite. J. Cleaner Prod. 2019, 224, 946–956.

(43) Hasler, C.; von Metzen, R. P.; Ruther, P.; Steiglitz, T. Characterization of parylene C as an encapsulation material for implanted neural prostheses. J. Biomed. Mater. Res., Part B 2010, 93, 266–274.

(44) Gao, J.; Chen, T.; Dong, C.; Jia, Y.; Mak, P.-I.; Vai, M.-L.; Martins, R. P. Adhesion promoter for a multi-dielectric-layer on a digital microfluidic chip. RSC Adv. 2015, 5, 48626–48630.

(45) Specialty Coating Systems Inc. Technical Papers. Advances in Adhesion Solutions for Medical Applications. https://scscoatings.com/wp-content/uploads/2015/09/adhesion_solutions.pdf (accessed July 20, 2020).

(46) Azkés, B. Tailoring Surfaces with Silanes. Chemtech 1977, 7, 766–778.

(47) Gelest Inc. Handbook, Silane Coupling Agents. https://www.gelest.com/wp-content/uploads/Goods-PDF-brochures-couplingagents.pdf (accessed July 20, 2020).

(48) Grkov, Z. International Vocabulary of Basic and General Terms in Metrology (VIM); The Bureau of Standardization and Metrology Press, 1998, ISBN 9989-868-00-X.

(49) Starr, P.; Bartels, K.; Agrawal, C. M.; Bailey, S. A thin-film pressure transducer for implantable and intravascular blood pressure sensing. Sens. Actuators, A 2016, 248, 38–45.

(50) Webster, J. Medical Instrumentation: Application and Design; John Wiley & Sons, 2009, ISBN 978-0-471-67600-3.

(51) Kulite Pressure Transducer Handbook, in Section 3, Performance Characteristics. http://www.kulitesensors.com.cn/reference/Handbook/section3.pdf (accessed July 20, 2020).

(52) Hukins, D. W. L.; Mahomed, A.; Kukureka, S. N. Accelerated aging for testing polymeric biomaterials and medical devices. Med. Eng. Phys. 2008, 30, 1270–1274.

(53) Specialty Coating Systems Inc. Technical Papers. SCS Electronics Coatings. https://scscoatings.com/ (accessed July 20, 2020).

(54) Wang, T.; Huang, L.; Liu, Y.; Li, X.; Liu, C.; Handschu-Wang, S.; Xu, Y.; Zhao, Y.; Tang, Y. Robust Biomimetic Hierarchical Diamond Architecture with a Self-Cleaning, Antibacterial, and Antifouling Surface. ACS Appl. Mater. Interfaces 2020, 12, 24432–24441.

(55) Xu, N.; Han, W.; Wang, Y.; Li, J.; Shan, Z. Nanoscratching of copper surface by CeO2. Acta Mater. 2017, 124, 343–350.

(56) Yadav, A. R.; Sriram, R.; Carter, J. A.; Miller, B. L. Comparative study of solution—phase and vapor—phase deposition of aminosilanes on silicon dioxide surfaces. Mater. Sci. Eng. C 2014, 35, 283–290.

(57) Jung, I.; Vaupel, M.; Pelton, M.; Piner, R.; Dikin, D. A.; Stankovich, S.; An, J.; Ruoff, R. S. Characterization of Thermally Reduced Graphene Oxide by Imaging Ellipsometry. J. Phys. Chem. C 2008, 112, 8499–8506.

(58) Styrkas, D. A.; Keddie, J. L.; Lu, J. R.; Su, T. J.; Zhidan, P. A. Structure of self-assembled layers on silicon: Combined use of spectroscopic variable angle ellipsometry, neutron reflection, and atomic force microscopy. J. Appl. Phys. 1999, 85, 868.