# AN INTERVENTIONAL FLEXIBLE MICRONEEDLE WITH THREE-ELECTRODE SYSTEM ON THE CAPILLARY FOR CONTINUOUS GLUCOSE MONITORING AND DRUG DELIVERY

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## ABSTRACT

A three-electrode system has been fabricated and integrated on the cylindrical polymer capillary surface by micromachining, which could be used as an interventional flexible microneedle for glucose sensor application in future. A UV-lithography system is improved to realize for the first time the multi-layer alignment exposure for cylindrical polymer capillary substrates based on our previous home-made lithography equipment. The ±1µm alignment precision has been realized on the polymer capillary surface with 330µm outer-diameter, on which the three-electrode structure consisting of two platinum electrodes and one Ag/AgCl reference electrode has been fabricated. The microneedle prototype with integrated three-electrode structure has been also characterized in 1mol/L KCl and 0.02mol/L $K_3Fe(CN)_6$ mix solution for obtaining its corresponding cyclic voltammetry curve. It shows that the prepared three-electrode system has a good redox property.

## KEYWORDS

Three-electrode; cylindrical surface micromachining; multi-layer alignment; microneedle; glucose sensor

## INTRODUCTION

Diabetes is a huge healthcare problem, and in particular the inability of diabetics to continuously monitor their glucose levels causes some of the most severe complications for this condition due to undetected hypoglycemic or hyperglycemic events. The traditional fingerstick test is an invasive, painful and inconvenient method of measuring glucose levels, and it often fails to detect rapidly fluctuating glucose levels. This manual method is also not conducive to identifying hypoglycemia or hyperglycemia during sleep. Recently, the microneedles based on micro-electro-mechanical systems (MEMS) process have been proposed and widely used as a painless interventional component for continuous glucose monitoring system and related medical applications.

However, most of these microneedles are fabricated on silicon by suing conventional micromachining process so that their structures are intrinsically brittle and fragile [1-2]. Those brittle microneedles could only be expected limited applications to some extent in biomedical fields. As a result, there have been being numerous efforts and reports on developing of non-silicon microneedles.

Several metal microneedles have been proposed and fabricated by electroplating deposition method [3-4], but their lengths are limited due to their photoresist-based moulds with limited heights, and their large stiffness also still leads to pain sometimes. In this respect, many researchers started to fabricate flexible microneedle systems by various polymer materials, such as acrylic, polyethylene terephthalate (PET), SU-8, PDMS, PMMA and so on [5-6]. As a matter of fact, those flexible microneedles are usually involved of complicated fabrication processes. The complex processes always cause a low yield and devices to easily failure. In particularly, the flexible microneedles are often subjected to damage during their peeling-off process from moulds. In addition, it's noteworthy is that both the abovementioned metal and flexible microneedles are generally fabricated as only an individual device or component, especially as a sampling part in a micro-total-analysis system (µTAS). Although several microneedle arrays have been fabricated and configured for special purposes [7], there is still no any functional unit integrated onto each individual microneedle. Therefore, the microneedles and their arrays have to be assembled and integrated with other external detection or measurement units (e. g. electrochemical three-electrode system) for finally realizing a total analysis function. This situation is not beneficial to miniaturization and also again increases the complexity of the total system.

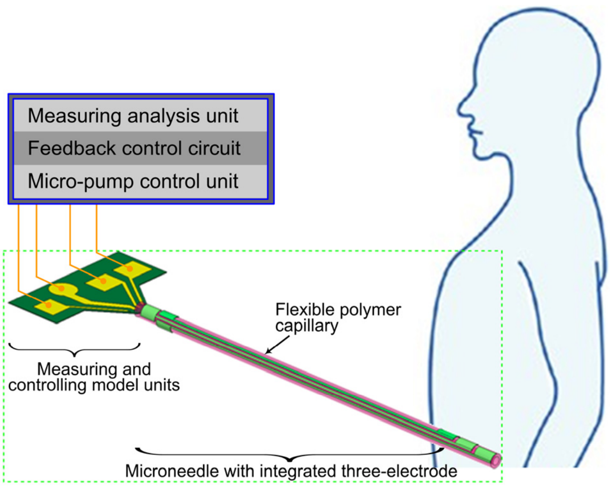


*Figure 1: Sketch of the interventional flexible microneedle on polymer capillary with drug delivery for continuous glucose monitoring.*

In the present work, we will use a very thin cylindrical polymer capillary as the substrate, on which a three-electrode structure will be directly microfabricated to realize a flexible and implantable microneedle with detecting function for glucose sensor application in future. In order to realize multi-layer alignment during the microfabrication, a new programmable UV-lithography system for cylindrical substrates would be improved based on our previous developed lithography equipment [8]. Using the lithography system, different kinds of functional materials could be patterned and integrated on the capillary surface. Finally, the basic cyclic voltammetry property of the fabricated three-electrode system in the microneedle will be also characterized.

## DESIGN AND PRINCIPLE

The three-electrode system consisting of different materials has been proposed and developed as a flexible interventional microneedle for possible glucose sensor application. The electrode structure was designed and fabricated on a cylindrical hollow polymer capillary surface based on the micromachining technology, which would be also beneficial to be used as a drug delivery component that could be integrated with other external medical systems in the future. The flexible microneedle design is shown in Figure 1, and it could be partly implanted into human body for glucose sensing and drug delivery during the medical interventional treatment. A three-electrode system is directly integrated with the flexible microneedle. The three-electrode system mainly consists of reference electrode (RE), working electrode (WE) and counter electrode (CE). Their distributions and main structural parameters are shown in Figure 2(a) and Figure 2(b), respectively. The outer diameter (OD) and inner diameter (ID) of the polymer capillary are 330µm and 250µm, respectively. The length and width of the electrode are *L*=630µm and *W*=280µm, respectively. Figure 2(c) shows the programmable pattern of three-electrode structure in the microneedle system. In the practical glucose sensor, the special enzyme still needs to be fixed onto the electrodes for realizing a chemical reaction with glucose in the blood. The test signal from three-electrode system will be obtained by measuring analysis unit as shown in Figure 1, and the feedback control unit will detect the glucose level in the human body and subsequently decide whether to inject the insulin (i.e., drug delivery) by micro-pump control unit or not. The proposed assay system including the microneedle with three-electrode structure is promising to realize painless and convenient continuous glucose monitoring and drug delivery.

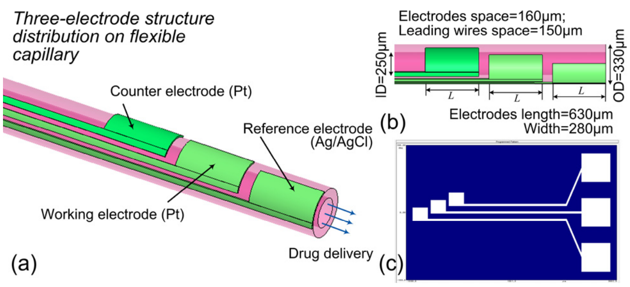


*Figure 2: Distribution (a) of the three-electrode system and (b) its main structural parameters; (c) programmable pattern of three-electrode structure during lithography.*

## FABRICATION

The microneedle device with three-electrode was fabricated based on surface micromachining by our previously developed UV-lithography system and process for cylindrical substrates [8-11]. The difference is that here the micropatterns of expected device can be executed by programmable controlling in the PC operation window, as shown in Figure 3. In order to realize the multi-layer alignment during the exposure fabrication, two CCD cameras are used to observe simultaneously the projected mask's patterns and those ever fabricated on the capillary substrate. This operation can be realized by real-timing alignment unit by software controlling. The whole lithography system includes multiple degree-of-freedoms (DOFs). The mask and the capillary substrate can be simultaneously driven along their corresponding DOFs. All motorized *XYZ-θ* stages and exposure time were automatically driven and precisely controlled, respectively. In the each axial direction, the movement accuracy was set to 0.1µm, and the rotation accuracy in the *θ*-direction was set to 0.01º, and these values were defined as the repeat positioning accuracy of the automatic stages used.

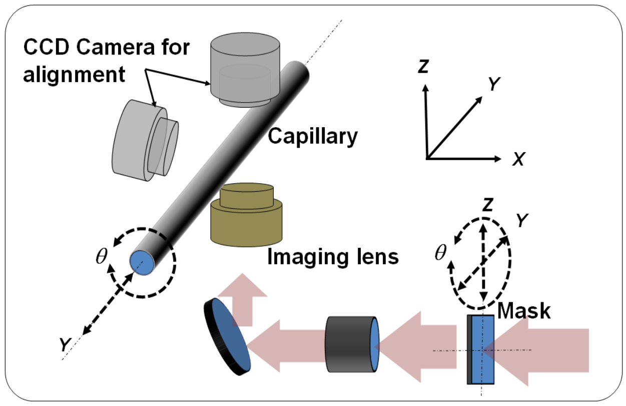


*Figure 3: Sketch of the home-made lithography equipment for cylindrical substrates with multi-layer alignment function.*

Figure 4 shows the basic fabrication process of the three-electrode system on the cylindrical flexible capillary surface. The photoresist solution used in the present work is prepared by a positive photoresist S1830 and a thinner AZ5200 in the weight ratio of 1:1. The former is from Shipley Company LLC, which is one of the most commonly used resists in our lab. The latter is from AZ Electronic Materials, which is mainly based on propylene glycol monomethyl ether acetate (PGMEA) that is also commonly used as a thinner for the direct coating process. The polymer capillary from Furukawa Electric Co., Ltd. was used as the microneedle substrate in this work because of its excellent and chemical properties. Especially, this capillary can withstand the temperature up to 200ºC. After the spray coating the photoresist film is always baked at 120ºC for 20min. The basic procedures are as follows:

Spray coating photoresist film ~2µm on the polymer capillary surface by our previously developed spray coating system. Before spray coating the capillary needs to be treated by a UV ozone treatment unit (VX-0200HK-002, AcingTec, Japan) for the surface modification.

a. Patterning the capillary with coated photoresist film according to the programmable micropattern of three-electrode using above lithography system.
b. Magnetron sputtering of 120nm-thcik platinum (Pt) film onto the capillary surface with patterned photoresist.

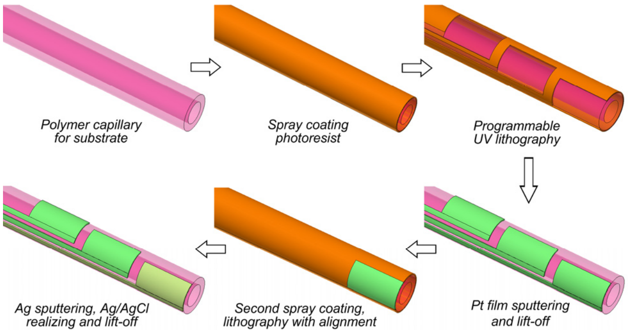


*Figure 4: Main fabrication process sketch of the flexible microneedle system on polymer capillary.*

c. Photoresist film was removed by lift-off process and obtaining the patterned Pt microstructures on the capillary surface.
d. Again spray coating of 2µm-thick photoresist film on the capillary with patterned Pt microstructures.
e. Secondary alignment, exposure and development were performed to pattern the photoresist film again.
f. 500nm-thick Ag film was deposited by magnetron sputtering, and then one of the electrodes partly transformed to AgCl by soaking in the 0.4mol/L KCl solution for 2 hours. As a result, the Ag/AgCl was formed to be used as RE in the three-electrode system.
g. Again lift-off, removing the residual photoresist film, and obtaining the flexible microneedle with three-electrode structure consisting of different materials (CE and WE: Pt, and RE: Ag/AgCl).

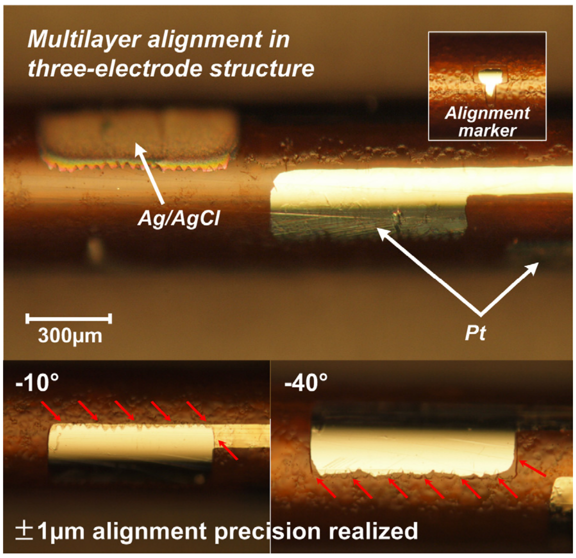


*Figure 5: Three-electrode system obtained by multi-layer alignment. Close-ups are photoresist boundaries in -10º and -40º views after the secondary alignment lithography.*

During the secondary alignment and exposure, the capillary substrate must be slowly rotated and adjusted to make sure its alignment mark to be overlapped with the exposure window in the mask image, and this state is defined as the starting position at this time. Subsequently, the second layer photoresist film will be patterned in the expected areas according to the programed micropatterns.

Figure 5 clearly shows the alignment boundaries in -10º and -40º views and final fabricated three-electrode structure on the polymer capillary. Up to now, the ±1µm alignment precision has been realized in our improved programmable lithography system. In addition, in our practical microfabrication experiments the 5µm feature line width has been also obtained utilizing the present lithography system.

The scanning electron microscope (SEM) of the fabricated flexible microneedle with integrated three-electrode system is also shown in Figure 6. It can be seen that the whole thin microneedle has a good compliance and flexibility, which could be easily used as an implantable component in such as glucose monitoring, medical interventional treatment and mini-invasive drug delivery, etc. Compared with other reported microneedle devices [2-7], the present developed one has better flexibility and compliant performance, and its inherent hollow structure could be conveniently used as a drug delivery channel in future. What's more important is that the microneedle device itself directly integrates with the three-electrode structure, which will greatly simplify subsequent external integration and miniaturization.

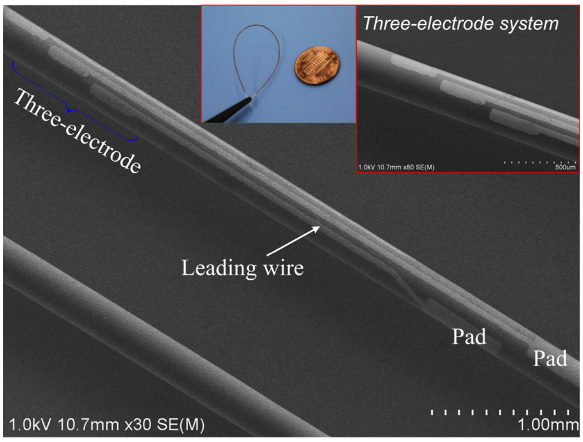


*Figure 6: SEM of the fabricated flexible microneedle with three-electrode system and its flexibility performance.*

## CHARACTERIZATION

We used the cyclic voltammetry method to evaluate the basic electrochemical properties of the fabricated three-electrode structure in the flexible microneedle device. An electrochemical analyzer (ALS/CHI 600E, CH. Instruments Inc., USA) was used to test the cyclic voltammetry curve of the three-electrode structure. The experiment was performed in the solution consisting of 1mol/L KCl and 0.02mol/L $K_3Fe(CN)_6$ without stir at the room temperature. The pH value of the solution is 8. A slower scan rate, 10mV/s, was used in the test for obtaining its property in the steady state as possible.

The measured cyclic voltammetry curve of the three-electrode system is shown in Figure 7. It can be seen that our fabricated three-electrode structure directly integrated on the capillary as a flexible microneedle generally shows a good redox property although the current peaks are not so evident. This situation is mainly due to that the areas of reaction electrodes fabricated on the capillary surface are very small and the sputtered films are also not perfect and stable as standard bulk materials. Even so, based on the test result, the calculated peak current density of the three-electrode of the flexible microneedle is about 0.8mA/dm$^2$, which is generally sufficient for subsequent circuit signal processing in the glucose sensor application. In addition, the flexible microneedle device could be more easily implanted into the objects compared to other reported ones [2-7].

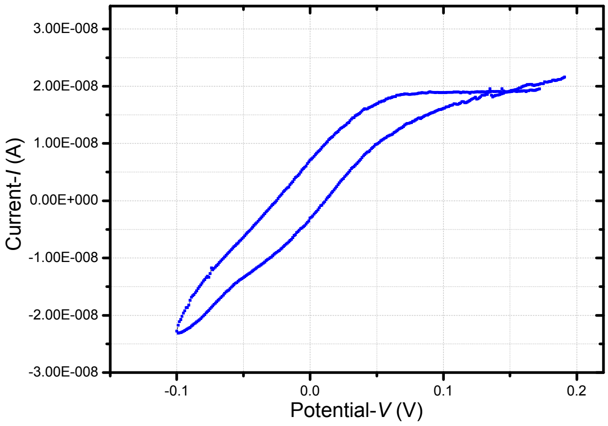


*Figure 7: Measured cyclic voltammetry curve of the three-electrode on the fabricated prototype microneedle.*

In the further work, we will try to fix the glucose oxidase onto the three-electrode structure for evaluating its electrochemical properties and response performances in the glucose sensing. In addition, the external feedback circuit and micro-pump also need to be developed in order to be integrated with the fabricated microneedle for realizing an intact glucose monitoring and drug delivery closed-loop system in the future.

# CONCLUSION

An interventional and flexible microneedle with integrated three-electrode system has been proposed for glucose monitoring application in future. An improved UV-lithography system with programmable and multi-layer alignment functions is developed for the cylindrical capillary substrate. The multi-layer alignment and exposure of the capillary with coated photoresist film is successfully realized for the first time by the lithography system. This lithography system has achieved up to ±1µm alignment precision and 5µm feature line width. Based on above lithography system, the three-electrode structure consisting of different materials has been fabricated on the capillary surface as a flexible microneedle. The cyclic voltammetry curve of the three-electrode structure is tested and generally shows a good redox property. The proposed microneedle device shows a good flexibility and is promising various medical interventional treatments, glucose sensors, mini-invasive drug delivery applications and so on.


# ACKNOWLEDGEMENTS

One of the authors, Z. Yang appreciates the Japan Society for the Promotion of Science (JSPS) for offering a fellowship.


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