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A Miniaturized Implantable Glucose Sensor Based on CMOS Line Sensor Using Glucose-Responsive Fluorescent Hydrogel

Toshikazu Kawamura[1], Masayuki Takahashi[2], Keita Masuda[1], Toshihiko Noda[1], Kiyotaka Sasagawa[1], Takashi Tokuda[1], Teru Okitsu[3], Shoji Takeuchi[3], and Jun Ohta[1]

[1] Nara Institute of Science and Technology
8916-5 Takayama-cho, Ikoma, Nara, 630-0192, Japan
Phone: +81-0743-72-6054 E-mail: ohta@ms.naist.jp
[2] BEANS Laboratory
4-6-1 Komaba, Meguro-ku, Tokyo 153-8505, Japan
[3] The University of Tokyo
4-6-1 Komaba, Meguro-ku, Tokyo 153-8505, Japan

Abstract

We present a CMOS line sensor dedicated for an implantable glucose sensor. The CMOS line sensor was designed to measure fluorescence of glucose-responsive fluorescent hydrogel. The size of the CMOS line sensor is approximately 0.3 mm × 0.8 mm and the sensitivity of the sensor is 6-times larger than our previous sensor. We also present an assembled glucose sensor and result of *in vitro* operation.

1. Introduction

Diabetes mellitus is a disease with maintained high level blood glucose. The high blood glucose level causes various complications and degrades quality of life. Diabetic patients have to control their blood glucose in their daily life, such as diet, exercise and insulin injection. They need a glucose monitoring technology to check their blood glucose level. Currently, CGM (Continuous Glucose Monitoring) [1] is focused on and studied. Because it has an advantage of high-frequency (with an interval of 1~5 min.). However, CGM has a limited lifetime of the sensor (typically within a week). The main reason of the lifetime is attributed to lifetime of enzymes for glucose detection, such as glucoseoxidase. As one of solutions, glucose-responsive fluorescent hydrogel was proposed and demonstrated [2].

We have developed implantable CMOS image sensors for *in vivo* brain imaging applications [3]. Based on the technology, we have proposed a glucose sensor based on the implantable CMOS image sensor and the fluorescent hydrogel. We assembled a prototype glucose sensor and confirmed transition of blood glucose can be measured. In this report, we present a CMOS line sensor dedicated for the implantable glucose sensing technology for reducing the size and improving the sensitivity of the sensor.

2. Implantable glucose sensor using glucose-responsive fluorescent hydrogel

Concept of a fully-implantable glucose sensor is shown in Fig.1. The glucose sensor measures transitions of glucose concentration based on fluorescence intensity of the glucose-responsive fluorescent hydrogel. In an application stage, the implantable sensor should be wirelessly operated and as small as it can be injected using an injection needle. Fig. 2 shows a sensing part of the glucose sensor, which was developed in a previous preliminary study [4]. An LED with a peak wavelength at 400 nm was mounted next to the CMOS image sensor as an excitation light source. The fluorescent hydrogel which emits fluorescence with 488 nm peak wavelength was placed on the CMOS image sensor. CMOS image sensor measures fluorescence through a filter that suppress scattered excitation light.

A typical fluorescent profile measured by the CMOS image sensor is shown in Fig.2 (b) [4]. The signal obtained from pixels close to the LED is larger than that from the pixels at the opposite side. We take advantage of this distribution in fluorescence intensity to perform simultaneous multi-sensitivity measurements. We expect that a wider measurement range can be realized based on the concept of the simultaneous multi-sensitivity measurements.

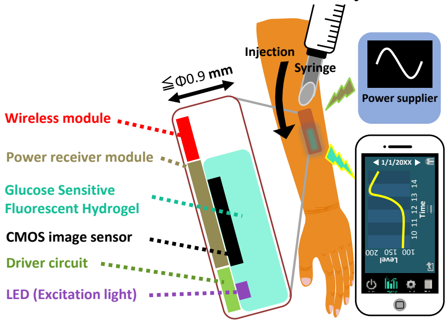

Fig. 1.Concept of our glucose sensor

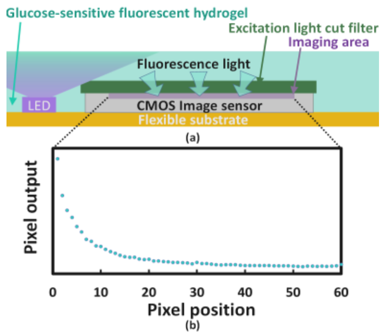

Fig. 2. (a) Configuration of proposed glucose sensor
(b) Typical fluorescent profile [4]

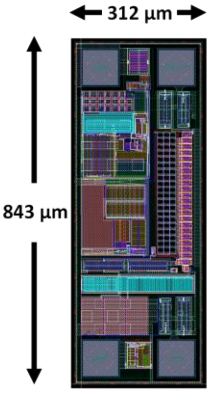

Table1 Specification of CMOS line sensor

Technology	0.35-µm 2-poly 4-metal standard CMOS Process
Operating voltage	3.3 V
Chip size	312 µm × 843 µm
Pixel Array	1×20
Type	4-Transistor Active Pixel Sensor
Photodiode	n-well – p-sub
Pixel size	15×15 µm^2
Fill factor	59.7%

(Left) Fig. 3. Layout of 1×20 pixels CMOS line sensor
(Right) Table 1 Specification of CMOS line sensor

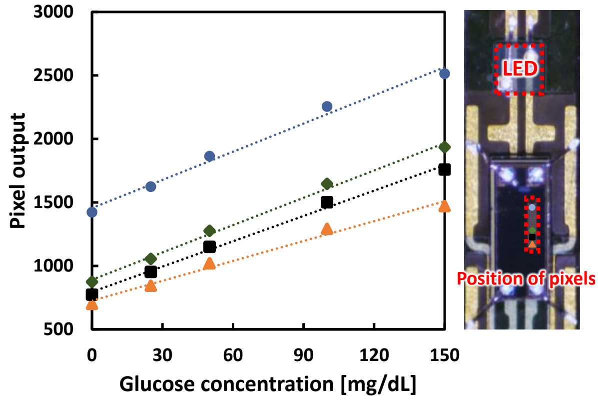

Fig. 5 (Left) Result of *in vitro* experiment
(Right) Position of measurement

3. CMOS line sensor for implantable glucose sensor

For the implantable glucose sensor using fluorescent hydrogel, a small-sized CMOS sensor is required. For downsizing CMOS sensor keeping the merit of the wide range measurement, we designed a CMOS line sensor using 0.35 µm 2-poly, 4-metal standard CMOS technology. Fig. 3 shows a layout of the sensor, and Table 1 shows specifications of the sensor. 4-transistor active pixel sensor (4Tr-APS) was used as pixel circuitry. The size of the pixel is 15 µm ×15 µm and fill factor is 59.7%. Photodiode was designed using n-well/p-sub structure in the CMOS process. With 4Tr-APS circuitry, we obtained approximately 6.6 times higher sensitivity than 3Tr-APS that we used in the previous work [4]. The CMOS line sensor can be operated with four I/Os; Vdd (3.3 V), Gnd, Clk, Vout. Timings of pixel select, signal read and pixel reset are internally generated in the CMOS line sensor.

4. Structure and fabrication process of the implantable glucose sensor

Fig. 4 shows structure and fabrication process of a wired implantable glucose sensor. The CMOS line sensor and a GaInN LED chip (λ=400 nm) were mounted on a polyimide flexible substrate. The excitation light cut filter was attached on imaging area of the CMOS line sensor. Epoxy resin was used to mold the device. The sensor head was mounted on a stainless-steel tube for mechanical strength. Parylene film was deposited on the sensor in the stainless-steel tube for waterproofness and biocompatibility. Finally, hydrogel was filled in the stainless-steel tube.

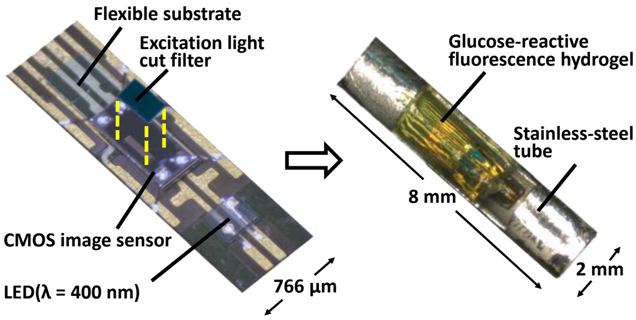

Fig. 4. Process flow of the glucose sensor

5. *In vitro* experiment using our glucose sensor

To confirm the capability of glucose sensing, we performed an *in vitro* experiment. We dipped the sensor in saline solution and varied the glucose concentration from 0 mg/dL to 150 mg/dL. Fig.5 shows results of the *in vitro* experiment. We successfully observed the fluorescence intensity that shows a linear increase accordingly to the glucose concentration. The advantage of multi-sensitivity measurement is available with the line sensor architecture, too. It should be also mentioned that the LED was operated with a current of 0.6 mA, which is lower than our previous work [4]. This decrease of the excitation intensity is due to the improved sensitivity of the pixels, and leads to a longer life of the fluorescent hydrogel.

6. Conclusions

A CMOS line sensor for implantable glucose sensing system was presented. Glucose-responsive fluorescent hydrogel was used as mediator for glucose sensing. The CMOS line sensor has features of small size, small number of I/Os for operation (4 wires), and improved light sensitivity. We assembled a wired implantable glucose sensor with the CMOS line sensor, and other components. Through *in vitro* experiment, we confirmed that our glucose sensor has a capability of the glucose sensing. The advantage of the multi-sensitivity measurement was kept from the previously developed sensor. Furthermore, the improved sensitivity allows us to use a smaller LED operation current, which will be effective for longer lifetime of the fluorescent hydrogel.

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