# CMOS Chip as Luminescent Sensor for Biochemical Reactions

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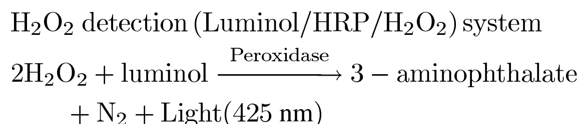
***Abstract*—We describe a novel biochemical sensing method and its potential new biosensing applications. A light-sensitive complementary metal oxide semiconductor (CMOS) chip prepared through a standard 0.5-$\mu$m CMOS process was developed for measuring biochemical reactions. A light producing enzymatic reaction catalyzed by horseradish peroxidase (HRP) was designed as a platform reaction to determine the concentration of hydrogen peroxide ($H_2O_2$) by the CMOS chip with a standard semiconductor parameter analyzer (HP4145). The kinetics of enzymatic reaction were determined and compared with a standard and sophisticated fluorometer (Hitachi F-4500) in a biochemical laboratory. Similar results were obtained by both instruments. Using glucose oxidase as an example, we further demonstrated that the HRP platform can be used to determine other $H_2O_2$ producing reactions with the CMOS system. The result points to an important application of the CMOS chip in biological measurements and in diagnosis of various health factors.**

## I. Introduction

RAPID advancement in modern biology has produced opportunities and needs in clinical diagnostics and many other biorelated measurements. To develop a high-throughput instrument with small size, low cost, ease of use, and high accuracy is becoming more and more important. Development of a suitable sensor for a variety of biochemical reactions is the key for this progress [1]. The small size of semiconductor sensors not only contributes to their potentially low cost, but also allows them to be integrated with microelectronic circuit, creating the so called integrated sensors, further enhancing their performance [2].

Optical instruments, such as UV-vis absorption spectrophotometer, fluorescence meters, and luminescence meters are routinely used to measure biochemical reactions, enabling bio- and chemiluminescence to become powerful tools for assaying a variety of biologically important molecules [3]. The photomultiplier tube (PMT) is the most common light sensor used in these spectrophotometers. PMT is an effective and sensitive light sensor, wherein one photon can induce approximately $10^6$ electrons in the photomultiplier tube. However, the need for high voltage (about 500 to 1000 V), the size, and the price of the PMT limit its application in a variety other fields such as personalized diagnosis kits.

The complementary metal oxide demiconductor (CMOS) process is the most commonly used procedure in semiconductor industry. A photodiode is basically a p-n junction operated under reverse bias. Free electron-hole pairs will be generated in photodiode when photodiode is illuminated by the photon, which contains energy higher than the band gap of photodiode [4]. CMOS photodiodes act as semiconductor light sensor with the advantages of low price, small size, and low power consumption as compares to that of PMT. These features make CMOS photodiodes easy to be a personalized healthy care instrument, and a high-throughput sensor. Recently, a CMOS photodiode has been used to monitor *Pseudomonas fluorescens 5RL* bacterial cells [5]. However, to our knowledge, there have been no reports in which a biochemical reaction has been coupled to CMOS photodiodes. We demonstrated a reaction (1) that can be used as the platform light emitting reaction to permit enzymatic activity to be observed



$$\mathrm{H_2O_2\ detection\ (Luminol/HRP/H_2O_2)\ system}$$
$$2\mathrm{H_2O_2} + \mathrm{luminol} \xrightarrow{\mathrm{Peroxidase}} 3-\mathrm{aminophthalate} + \mathrm{N_2} + \mathrm{Light}(425\ \mathrm{nm})$$

(1)

which shows the light emitting reaction catalyzed by horseradish peroxidase (HRP). Since many enzymes produce $H_2O_2$ (Table I and [6]), the HRP-luminol-$H_2O_2$ system should be a good platform reaction to couple and detect many other enzymatic reactions by luminescence. In a CMOS photodiode system, the chemiluminescence generated from the biochemical reaction produces current flow that corresponds to the rate of enzymatic-catalyzed reaction. By using this luminescent-coupled enzyme assay, we can easily translate the concentration of

Manuscript received May 12, 2002; revised February 14, 2003. This work was supported in part by a grant from Hong Wei Biotech and in part by the National Science Council (NSC), Taiwan, R.O.C., under Grant 90-2311-B-009-002. The associate editor coordinating the review of this paper and approving it for publication was Dr. Gerard L. Coté.

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Digital Object Identifier 10.1109/JSEN.2003.814653

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TABLE I
IMPORTANT BIOCHEMICALS THAT CAN BE DETERMINED BY HRP-luminol-$H_2O_2$ SYSTEM

| Target | Enzyme coupled | $H_2O_2$ producing reactions |
|---|---|---|
| Glucose | Glucose oxidase | $\text{Glucose} + O_2 + 2H_2O \xrightarrow{\text{Glucose Oxidase}} \text{Gluconic acid} + 2H_2O_2$ |
| Uric acid | Uricase | $\text{Uric acid} + O_2 + 2H_2O \xrightarrow{\text{Uricase}} \text{allantoin} + CO_2 + 2H_2O_2$ |
| Cholesterol | Cholesterol oxidase | $\text{Cholesterol} + O_2 \xrightarrow{\text{Cholesterol oxidase}} \text{cholesten-3-one} + H_2O_2$ |
| Lactate | Lactate oxidase | $\text{L-Lactate} + O_2 \xrightarrow{\text{Lactate oxidase}} \text{pyruvate} + H_2O_2$ |
| Phospholipids | Phospholipase/ Choline oxidase | $\text{Phospholipids} + H_2O \xrightarrow{\text{Phospholipase}} \text{Fatty acids} + \text{Choline}$<br>$\text{Choline} + H_2O + 2O_2 \xrightarrow{\text{Choline oxidase}} \text{betaine} + 2H_2O_2$ |
| Triglycerides / Lipase | Lipase/ Glycerol oxidase | $\text{Triglycerides} + 3H_2O \xrightarrow{\text{Lipase}} \text{Fatty acids} + \text{glycerol}$<br>$\text{Glycerol} + O_2 \xrightarrow{\text{Glycerol oxidase}} \text{glyceraldehyde} + H_2O_2$ |

specific compound to luminescence. In this paper, we choose glucose/glucose oxidase system [as seen in (2), at the bottom of the page] to demonstrate that a CMOS chip can be used to measure this frequently used clinical assay.

## II. EXPERIMENTAL

### A. Materials

D(+)−Glucose, horseradish peroxidase, luminol, and Bis-Tris propane were purchased from Sigma. $H_2O_2$ (30%, W/W) and $H_2KPO_4$ were purchased from Riedel-deHaën. Glucose oxidase (GOD, from *Aspergillus niger*) was purchased from Fluka. Tris-HCl buffer is purchased from Pharmacia Biotech. $K_2HPO_4$ was obtained from J. T. Baker.

### B. Photomultiplier Tube (PMT) Detection System

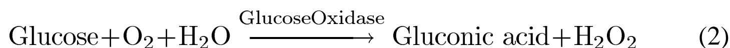
HITACHI F-4500 fluorescence spectrometer was used as control sensor for spectrophotometry in this study. To obtain comparable luminescent data between the fluorescence spectrometer and the CMOS photodiode, the instrumental parameters were set as follows: PMT voltage, 700 V; emission wavelength, 425 nm; and emission slit, 1 or 2.5 nm. The choice of emission slit was dependent on the strength of the luminescence observed. The emission slit at 2.5 nm observes 8 to 10 times luminescence compared with that of the 1-nm slit used.

### C. CMOS/HP4145 Detection System

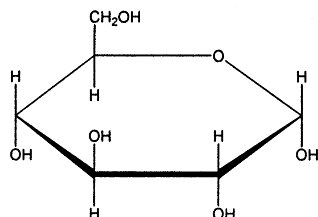
As shown in Fig. 1, the CMOS chip used for this study was manufactured by CMOS 0.5-$\mu$m standard process. The CMOS photodiode [Fig. 1(a)] and layout [Fig. 1(b) and (c)] diagram of $N^+/P$ well photodiodes array has 140 $\times$ 240 photodiodes with single pixel size 7.5 $\mu$m $\times$ 7.5 $\mu$m. The photodiode chip has no color filter, so it absorbs the full luminescence spectrum of chemical reaction (from 400 to 800 nm). The chemiluminescence-generated current of CMOS photodiodes was in pico ampere level, and a sensitive semiconductor parameter analyzer was needed to determine this small difference.

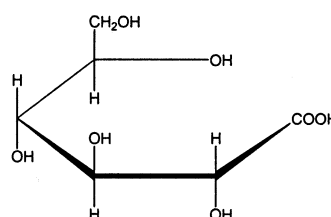
We used HP 4145 semiconductor parameter analyzer with a chip-fixing box HP 16058A test fixture to collect and analyze the chemiluminescence-generated current of $N^+/P$ well photodiodes. The structure diagram of the chemiluminescence-generated current monitoring system was shown in Fig. 2. A 3.3-V

$H_2O_2$generating (Glucose/Glucose Oxidase) system



$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{GlucoseOxidase}} \text{Gluconic acid} + H_2O_2 \quad (2)$$



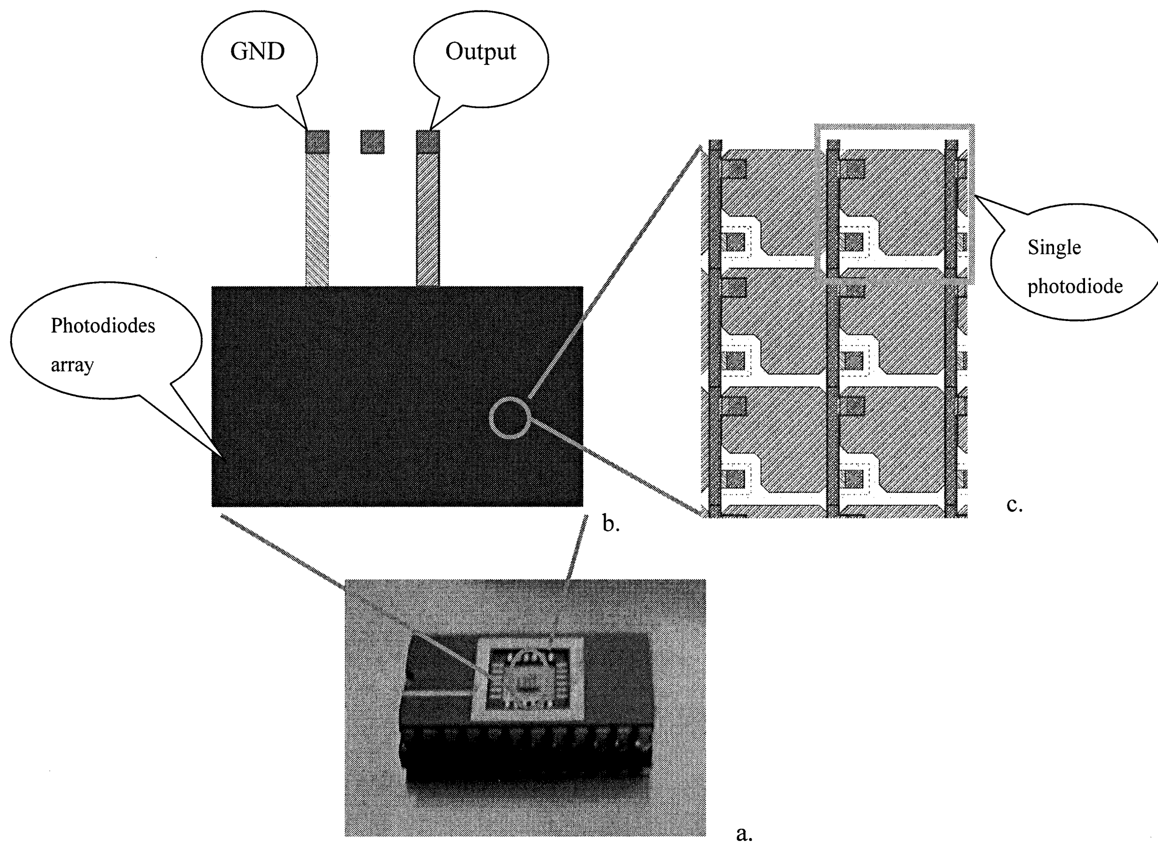



Fig. 1. CMOS photodiode as light sensor. (a) The CMOS photodiode manufactured by 0.5-$\mu$m standard process after packaging. (b) Layout of CMOS photodiodes. The photodiode array is 140*240. (c) The size of a single photodiode is $(7.5\ \mu\text{m})^2$.

reverse bias was given to CMOS photodiodes chip by HP 4145. The reaction condition was the same as that used by PMT detection system (Hitachi F4500) described later except that 0.2 unit of HRP is used.

### D. Preparation and Use of Enzymes

HRP powder (1 mg or 80 units) was dissolved in 1-ml Tris-HCl buffer (0.1 M at pH 8.6). The powder of Glucose oxidase (20 mg or 3000 units) was dissolved in 1 ml phosphate buffer (0.2 M at pH7.0). The stock enzyme solution was stored at $-80$ °C. The HRP and GOD solutions were melted in an ice bath just before use and were diluted with specified buffer. An aliquot amount of enzyme was added into the cuvette followed by the injection of all other necessary reagents and sample (as described later for reaction conditions) in order to make sure that all compounds were well mixed in cuvette without extra shaking and that the data can be collected in a short period of time. One unit of HRP means 1.0 mg of purpurogallin is formed from pyrogallol in 20 s at pH 6.0 at 20 °C as described by Sigma. One unit of GOD will oxidize 1-$\mu$mol glucose per minute at pH 7.0 and 25 °C as determined by Fluka.

### E. Reaction Condition of HRP-luminol-$H_2O_2$ System

The optimal condition for HRP-luminol-$H_2O_2$ system was determined, as shown in Figs. 3 and 4. Unless otherwise specified, the standard condition involved HRP-luminol-$H_2O_2$ system included luminol (1.5 mM,), $H_2O_2$ (3 mM), and Tris-HCl (100 mM at pH 8.6) and HRP (0.008 units) at 25 °C.

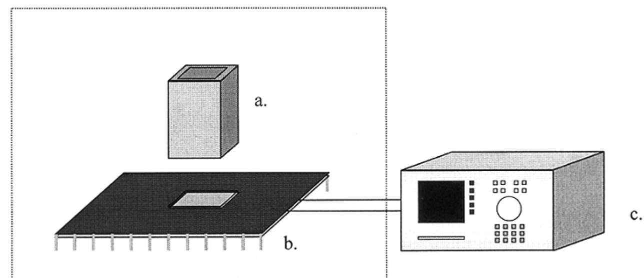



Fig. 2. Schematic diagram of the CMOS photodiodes/HP 4145 detection system. (a) Quartz cuvette (the reaction chamber) on the top of CMOS photodiode chip. (b) The CMOS photodiode was fixed on the HP 16058A test fixture which was connected to HP4145 semiconductor parameter analyzer. (c) HP4145 was used to collect and analyze the chemiluminescence generated current. Parts (a) and (b) were placed in a dark box.

For the coupled enzyme assay, $H_2O_2$ was omitted. Each data point was the average of three measurements. Luminescence of each measurement was obtained from the average of first 10 s in each reaction.

### F. Glucose Oxidase Coupled HRP-luminol-$H_2O_2$ System

The standard condition for this coupled enzyme system included 150 units GOD, 0.64 units HRP, 1 mM luminol, and 0.1 M Tris-HCl buffer (pH 8.6) in a final volume of 1 ml at room temperature. To start the measurement, the mixture of luminol, Tris-HCl buffer, glucose, and GOD that had been incubated for 10 min at room temperature was mixed with HRP. Each data

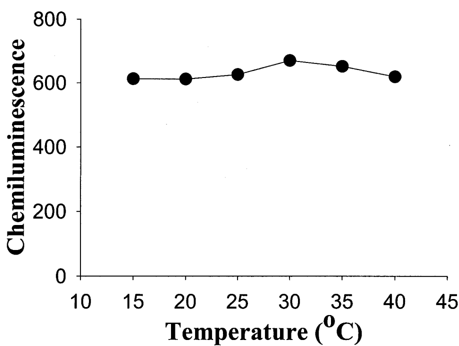



Fig. 3. Effect of temperature on HRP-luminol-$H_2O_2$ system. The mixture of luminol (1.5 mM,), $H_2O_2$ (3 mM), and Tris-HCl (100 mM) at pH 8.6 was added into HRP (0.008 unit) to start reaction. All reagents were incubated separately at desired temperature 5 min prior to reaction. Each data point was the average of three measurements.

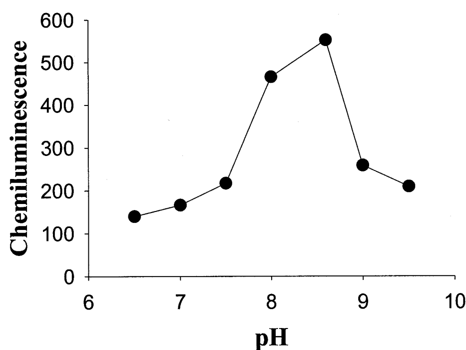



Fig. 4. pH profile of HRP-luminol-$H_2O_2$ system. The reaction condition was the same as described in Section II for HRP-luminol-$H_2O_2$ system except that 0.1 M Bis-tris propane buffer (pH 6.5, 7.0, 7.5, 8.0, 8.6, 9.0, or 9.5) was used to replace Tris-HCl. Each data point was the average of three measurements.

point was the average of three measurements. Luminescence of each measurement was obtained from the average of first three seconds in each reaction.

## III. Results and Discussion

### A. Biochemical Design

The HRP-luminol-$H_2O_2$ reaction system emits flash type chemiluminescence. The brightest chemiluminescence occurs at the initial steady state of the reaction, and may decay quickly. Reproducible measurements can be obtained according to the procedure described in Section II. The HRP-luminol-$H_2O_2$ system was impervious to temperature changes in the range of $15 \sim 40$ °C as shown in Fig. 3. However, changes in pH significantly affected the activity of HRP-luminol-$H_2O_2$ system (Fig. 4). According to the results shown in Figs. 3 and 4, pH 8.6 and $T = 25$ °C were chosen as the standard condition for HRP-luminol-$H_2O_2$ system. To use the same CMOS platform with enzymes from different sources or in a coupled enzyme system, the reaction condition can be easily modified with the established procedures.

### B. Control Data With PMT Measurement System

In addition to obtain control data, the PMT measurement system served as a tool to design the suitable reaction parameters for the novel CMOS detection system. For this purpose,

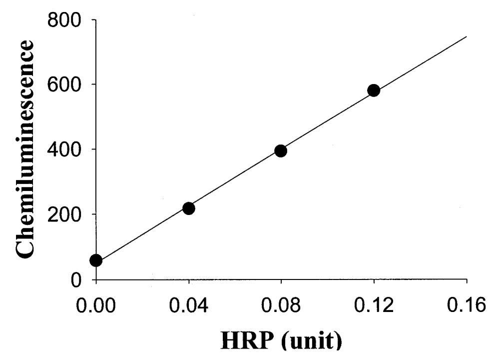



Fig. 5. Control of the HRP in an HRP-luminol-$H_2O_2$ system. The reaction mixture included $H_2O_2$ (2.7 mM), luminol (1.24 mM), Tris-HCl buffer (0.1 mM, pH 8.6), and 0∼0.12 unit HRP at room temperature. Each data point was the average of three measurements quantified by a fluorometer as described in Section II.

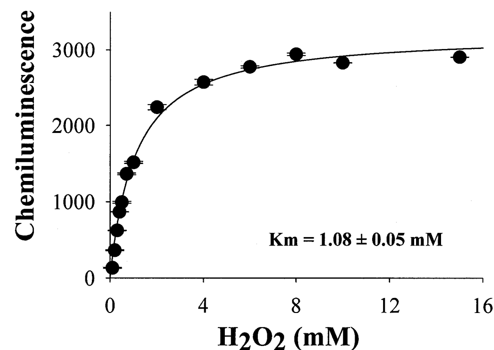



Fig. 6. Control of the variation of $H_2O_2$ concentration in an HRP-luminol-$H_2O_2$ system. Each data point was the average of three measurements determined by a fluorometer as described in Section II in a standard condition for HRP-luminol-$H_2O_2$ system except that 0.2 unit of HRP and 0.1 to 15 mM $H_2O_2$ were used.

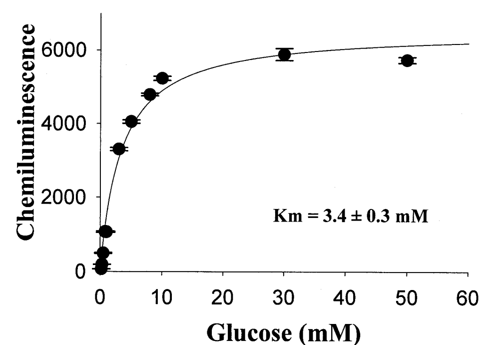



Fig. 7. Control of the variation of glucose concentration in a GOD-coupled HRP-luminol-$H_2O_2$ system. The glucose concentrations were varied from 0.2 to 50 mM. Each data point was the average of three measurements determined by a fluorometer as described in Section II.

the parameters of the PMT measurement system were adjusted so that comparable data can be obtained from both instrumentation in similar reaction conditions as described in Section II. The enzymatic reactions designed for PMT measurement system (by Hitachi F4500) as shown in Figs. 5–7 could then be compared with those obtained with CMOS/HP4145 detection system shown in Figs. 8–10.

To obtain a useful enzyme assay, a linear relationship between the amount of enzyme used and the enzymatic signal detected must be established. Data shown in Fig. 5 demonstrated

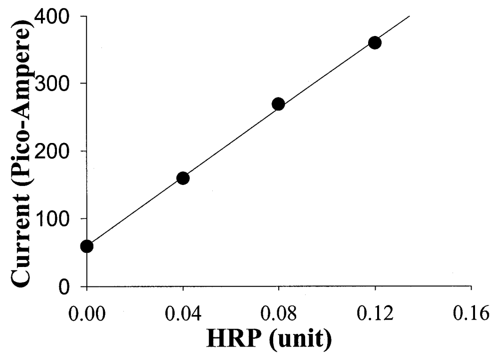



Fig. 8. Enzyme activities observed by CMOS photodiode. The reaction condition was the same as that used by the control detection system described in Fig. 5. Each data point was the average of three measurements.

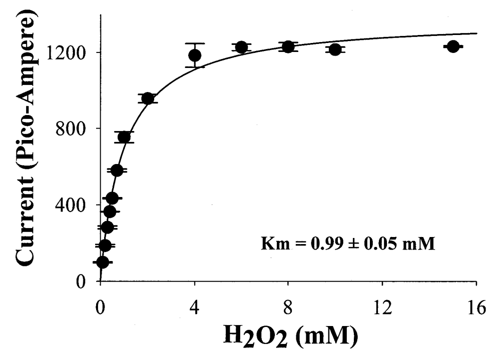



Fig. 9. Effect of $H_2O_2$ concentration on HRP-luminol-$H_2O_2$ system observed by CMOS photodiode. The reaction condition was the same as that used by the control detection system described in Fig. 6. Each data point was the average of three measurements.

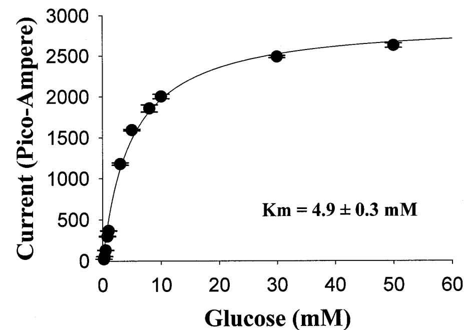



Fig. 10. Glucose concentration curve observed by CMOS photodiode. The reaction condition of the coupled enzyme system was the same as that used by control detection system described in Fig. 7. Each data point was the average of three measurements.

that chemiluminescence corresponded linearly to enzyme activity, so that the amount of light observed was a direct measurement for the quantity of active enzyme present. Fig. 6 gave the relationship of the substrate concentration, $[H_2O_2]$, and the HRP-luminol-$H_2O_2$ system. $K_m$ is a constant that describes this relationship and is defined by Michaelis–Menten equation, $v = V_{max}[H_2O_2]/(K_m + [H_2O_2])$. $V_{max}$ is the reaction rate measured at saturation of $[H_2O_2]$ and v is the reaction rate at each $[H_2O_2]$. Typical reaction profiles were obtained with the variation of substrates, $H_2O_2$ or glucose, as shown in Figs. 6 or 7, respectively. Fig. 7 describes the relationship of the glucose concentration and the coupled enzyme system. The concentration of $H_2O_2$ and glucose in an unknown sample can be determined according to Figs. 6 and 7, respectively.

### *C. Enzymatic Data Obtained From CMOS/4145 Detection System*

The rate of the enzymatic reaction obtained with CMOS/4145 detection system was described by the current in the range of picoampere to nanoampere (Figs. 8–10). Similar to that observed by the control PMT measurement system, the unit of the reaction rate measured should be considered as an arbitrary unit. The enzymatic signal can be magnified electronically and is dependent on the sensitivity of the instrument used. A linear relationship between the amount of HRP used and the current generated through the CMOS photodiode was obtained as shown in Fig. 8. A dark current at about 56 pA was also observed and was considered as a background that was substrated for the following reactions measured with CMOS photodiode. A typical reaction profile of HRP-luminol-$H_2O_2$ system with the variation of $[H_2O_2]$ was obtained and shown in Fig. 9. The $K_m$ of $H_2O_2$ determined with the CMOS photodiode was 1 mM. In a coupled enzyme system, monitored by CMOS/4145 detection system also gave a typical reaction profile. The $K_m$ of glucose was about 5 mM in the GOD coupled HRP-luminol-$H_2O_2$ system. The results shown in Figs. 8–10 all indicated that useful enzymatic data were obtained with CMOS/4145 detection system.

### *D. Comparison of Enzymatic Data Obtained From PMT and CMOS Photodiode*

The results shown in Figs. 8–10 were in excellent agreement with those shown in Figs. 5 and 7. Linear response of the enzyme used and signal observed by CMOS/4145 detection system (Fig. 8) was similar to that of PMT system (Fig. 5) and both gave satisfactory results. Differences in Kms obtained in both detection systems were in an acceptable range (Figs. 6 and 7 versus Figs. 9 and 10, respectively). Figs. 7 and 10 show that the activity of HRP-luminol-$H_2O_2$ system was dependent on the concentration of glucose. The $K_m$ of glucose was determined to be 3.4 ± 0.3 mM and 4.9 ± 0.3 mM with PMT instrument and CMOS photodiode, respectively. The concentration of glucose in biological samples (e.g., blood) is in the mM range. These results demonstrate that concentration of glucose can be determined with a GOD coupled HRP-luminol-$H_2O_2$ system by a CMOS photodiode.

## IV. Conclusion

1) We demonstrated that a CMOS photodiode manufactured by a standard CMOS process is useful for biochemical measurements. This result and the characteristics of CMOS (low price, small size, low power consumption, and short response time) may make CMOS photodiodes a very attractive sensor for clinical diagnostics.
2) We used glucose and GOD to show that CMOS photodiode and HRP-luminol-$H_2O_2$ system can be used as a platform for coupled enzyme assay to identify and quantify a variety of biochemicals (listed in Table I).

3) The sensitivity of this CMOS chip can be improved further to become a routine biochemical and enzyme sensor. PMT instrument is still a much more sensitive sensor (one hundred fold or more) than that of the CMOS diode. The preparation of a more responsive CMOS diode for biochemical sensing is now in progress.

## ACKNOWLEDGMENT

The authors wish to thank the reviewers for their suggestions.

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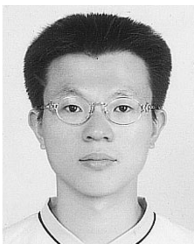


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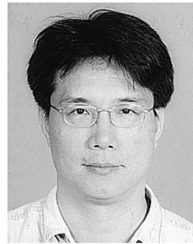


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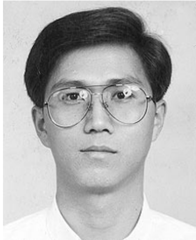

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