COMPARISON BETWEEN OUTPUT LINEARITIES OF OXYGEN DETECTOR AND HYDROGEN PEROXIDE DETECTOR FOR AMPEROMETRIC GLUCOSE SENSORS

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The amperometric determination of glucose concentration is classified into two types, oxygen and hydrogen peroxide detector types. The differences in output response of these two detectors are ascribed to the difference of the electrode reaction. Oxygen is reduced to water on the oxygen electrode, while hydrogen peroxide is oxidized to proton and oxygen on the hydrogen peroxide electrode. Since those reaction products, proton and oxygen, relate with the GOD reaction, the sensor current of the hydrogen peroxide detector is considered to be affected by the electrode reaction itself. Theoretical analysis for a rotating-disk electrode covered with an immobilized-enzyme membrane could simulate well experimental outputs of oxygen and hydrogen peroxide electrodes. The output current of the oxygen detector showed asymptotical saturation as glucose concentration increased for the Thiele modulus, M_G , rather than unity. The detection limit of glucose concentration, $C_{G,lim}$ increased with increasing concentration of the dissolved oxygen, C_O . Oxidation products of hydrogen peroxide affected dominantly with output currents of more than $300 \text{ mA}\cdot\text{m}^{-2}$. The $C_{G,lim}$ value of the hydrogen peroxide detector was found to be larger than that of the oxygen detector except for the high C_O range at $M_G = 1$.

Introduction

There are two types of electrodes for the amperometric determination of glucose using immobilized glucose oxidase membrane. One detector is an electrode monitoring oxygen consumed, and the other is an electrode monitoring hydrogen peroxide produced by the glucose oxidase (GOD) reaction. The products of the electrode reaction on these electrodes might affect the enzyme reaction. Oxygen is reduced electrochemically to water on the oxygen electrode. Hydrogen peroxide is oxidized to proton and oxygen on the hydrogen peroxide electrode. Since products such as proton and oxygen relate with the reaction catalyzed by GOD, the current of the hydrogen peroxide electrode is considered to be affected by the electrode reaction itself.

The improvement of output linearity of a glucose sensor was examined experimentally by using a membrane with high permselectivity of oxygen to glucose (Genshaw and Jones, 1989; Nakagawa and Uchida, 1987), a membrane covered with a hydrophobic film (Romette *et al.*, 1979), and a high-loaded enzyme membrane (Thevenot *et al.*, 1978). A few studies have been reported on a theoretical modeling including comprehensive treatments applicable to the general sensor. Mell and Maloy (1975) developed a model of an amperometric glucose sensor with

iodine mediator, to which one-substrate enzyme kinetics was applied. They concluded that the linearity extended to concentrations greater than the intrinsic Michaelis constant in the case of diffusion control for the high-loaded enzyme membrane. Leyboldt and Gough (1984) developed a mathematical model of a two-substrate enzyme electrode for a glucose-specific sensor. They analysed the steady-state current on the oxygen electrode and indicated the advantages of limited immobilization of enzyme in order to control the range of glucose detectability. Shichiri *et al.* (1983) compared both types of glucose monitoring experimentally, and reported that the hydrogen peroxide monitor was less affected by oxygen tension than the oxygen monitor. The detection limit of the glucose concentration by the hydrogen peroxide monitor was found to be higher than that by the oxygen monitor (Asperger *et al.*, 1987; Shichiri *et al.*, 1983). In our previous papers (Sudoh *et al.*, 1991a; Sudoh *et al.*, 1991b), permeation properties of membrane supports for the immobilized-enzyme membrane were estimated by using a rotating-disk electrode covered with the membrane to be examined. The effect of electrochemical reaction of the hydrogen peroxide electrode on the sensor current was examined experimentally and was found to become significant at higher concentrations of glucose and also for higher loaded-enzyme membrane.

The purpose of this paper is to compare the output linearity of the oxygen detector and that of the hydrogen peroxide detector as a glucose sensor experimentally and

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Hydrogen Peroxide Detector

Oxygen Detector

Fig. 1 Schematic comparison between hydrogen peroxide and oxygen detectors of glucose sensor

theoretically, and also to propose the criteria for designing a glucose sensor with extended linearity.

1. Theory

Figure 1 shows a schematic comparison of the enzyme and electrode reactions in the immobilized enzyme membrane using hydrogen peroxide and oxygen monitors. The symbols G and GL in Fig. 1 denote glucose and gluconolactone, respectively. Glucose oxidase and catalase were abbreviated as GOD and CAT, respectively.

The GOD reaction was described as follows.

$$r_{Gm} = \frac{k_G C_{EG}}{1 + K_{MG} / C_{GM} + K_{MO} / C_{Om}} \quad (2)$$

$$r_{Cm} = \frac{k_c C_{EC}}{1 + K_{MP} / C_{Pm}} \quad (4)$$

The theoretical calculation is based on the model considering the diffusion and enzyme reaction within the membrane, and also electrode reaction. Material balance equations of the glucose (G), the hydrogen peroxide (P), the oxygen (O) and the hydrogen ion (H) within the membrane at the steady-state were given as follows:

$$D_{im} \frac{d^2 C_{im}}{dx^2} + s_{Gi} r_{Gm} + s_{Ci} r_{Cm} = 0 \quad (5)$$

($i = G, O, P, H$)

where s_{Gi} and s_{Ci} were stoichiometric coefficients of the

reactions (1) and (3), respectively, and were positive for production and negative for consumption.

The oxygen balance equation was described by a simple form with assumption of limited (full or no) activities of catalase.

$$D_{Om} \frac{d^2 C_{Om}}{dx^2} - v_O r_{Gm} = 0 \quad (6)$$

where $v_O = 1$ for no catalase and $1/2$ for full activity of catalase in the membrane.

On the hydrogen peroxide electrode,

On the oxygen electrode,

The boundary conditions for Eqs. (5) and (6) were given as follows.

By assuming fast reaction rates of the hydrogen peroxide and oxygen electrodes, the surface concentration of each reactant was assumed to be zero.

$$C_{im} \Big|_{x=\delta} = 0 \quad (i = O \text{ or } P) \quad (9)$$

The mole flux j of the reactant transferred on the electrode surface is related to the current density and also corresponds to a diffusional flux at a membrane/electrode interface.

$$j = \frac{I_i}{n_i F S} = -D_{im} \frac{dC_{im}}{dx} \Big|_{x=\delta} \quad (10)$$

The diffusional flux of the species except the reactant, adjacent to the electrode, was equivalent to the production or consumption rate of the reaction (7) or (8).

$$-D_{im} \frac{dC_{im}}{dx} \Big|_{x=\delta} = s_{ei}j \quad (i = G, H, O \text{ or } P) \quad (11)$$

The boundary condition at a membrane/solution interface was given by the following equation.

$$-D_{im} \frac{dC_{im}}{dx} \Big|_{x=0} = k_{Li} \left(C_i - \frac{C_{im}}{K_{pi}} \right) \quad (12)$$

($i = G, O, P, H$)

1.1 Special conditions

By neglecting the effect of catalase activity and assuming constant values of enzyme kinetics, k_G , K_{MG} , and K_{MO} through the membrane, the sensor current for the hydrogen peroxide anode is theoretically given as follows (Gough and Leypoldt, 1981; Sudoh *et al.*, 1991b):

$$I_P = \frac{n_p F S K_{pG} D_{Gm} C_G}{\delta (1 + B_{iP}^{-1})} \phi_P \quad (13)$$

The sensor current for the oxygen cathode is theoretically given as follows by using the current I_{O_i} for $C_G = 0$.

$$I_{O_i} - I_O = \frac{n_O v_O F S K_{pG} D_{Gm} C_G}{\delta (1 + B_{iO}^{-1})} \phi_O \quad (14)$$

where the I_{O_i} corresponds to the limiting current of oxygen permeated through the membrane without any enzyme reactions.

$$I_{O_i} = \frac{n_O v_O F S K_{pO} D_{Om} C_O}{\delta (1 + B_{iO}^{-1})} \quad (15)$$

where $n_O = 4$ and $n_P = 2$ in the above equations. Now the dimensionless factor ϕ_i ($i = O, P$) will be introduced as follows by using the effectiveness factor η , the modulus M_G of the immobilized enzyme membrane and the Biot numbers.

$$\phi_i = 1 - \frac{C_{Gm}(\delta)}{K_{pG} C_G} + \frac{K_{MG}}{K_{pG} C_G} \eta M_G^2 (B_{iG}^{-1} - B_{iG}^{-1}) \quad (16)$$

where the effectiveness factor η is given by the following equations.

$$\eta = \frac{\int_0^\delta r_{Gm} dx}{k_{EG} \delta} = \left(\frac{K_{pG} C_G}{K_{MG}} \right) \left(\frac{B_{iG}}{M_G^2} \right) \left(1 - \frac{C_{Gm}(0)}{K_{pG} C_G} \right) \quad (17)$$

1.2 Culcation procedure

Material balance equations of the four substances glucose, oxygen, hydrogen peroxide and proton were written in finite difference form using linearization of the non-linear term of enzyme reaction rate and solved by a modified Newton-Raphson method of a BAND(J) algorithm developed by Newman (1991). The following conditions were used for calculations; no activity of catalase, pH 5.6 for initial pH through the membrane, and temperature of 308 K.

Table 1 Properties of immobilized enzyme membranes

δ	=	100 μm
Water content	=	0.45
M_G	=	3.3
B_{iO}	=	7.6
B_{iP}	=	13.0
B_{iG}	=	35.0
$K_{pO} D_{Om}$	=	$4.9 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$
$K_{pP} D_{Pm}$	=	$2.5 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$
$K_{pG} D_{Dm}$	=	$0.47 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$

Table 2 Rate constants of the enzyme reaction (1)

$k_{G(pH=5.6)}$	=	1870 s^{-1}
$K_{MG(pH=5.6)}$	=	$75.5 \text{ mol} \cdot \text{m}^{-3}$
$K_{MO(pH=5.6)}$	=	$0.549 \text{ mol} \cdot \text{m}^{-3}$
$k_{G(pH=5.6)}^k$	=	$\exp\{-0.42(pH-5.6)^2\}$
$K_{MG}^k K_{MG(pH=5.6)}$	=	$\exp\{-0.33(pH-5.6)^2\}$
$K_{MO}^k K_{MO(pH=5.6)}$	=	$\exp\{-0.33(pH-5.6)^2\}$

Fig. 2 Theoretical results of concentration profiles of glucose, oxygen and hydrogen peroxide within membrane for oxygen and hydrogen peroxide detectors

2. Experimental

A rotating-disk electrode was employed as the electrode of the glucose sensor. The Pt circular disk 2 cm in diameter was covered by the immobilized enzyme membrane. The membrane was a proteinic one where bovine serum albumin was mixed with glucose oxidase (BMV grade II) followed by crosslinking with glutaraldehyde. The rotating speed was 100 rpm in most experimental runs. The electrolyte was 0.1 $\text{kmol} \cdot \text{m}^{-3}$ phosphate buffer solution. The electrochemical cell of 500 cm^3 in volume was thermostated at 308 K and was equipped with a rotating-disk electrode, a counter electrode of Pt plate and a reference electrode. The concentrations of the glucose and the dissolved oxygen in the electrolyte were in the range of 0.1 - 100 $\text{mol} \cdot \text{m}^{-3}$, and 0.2 - 1 $\text{mol} \cdot \text{m}^{-3}$, respectively. The potential of the working electrode was controlled at -0.6 V for the oxygen cathode and 0.7 V for the hydrogen

Fig. 3 Comparison between output currents calculated for oxygen and hydrogen peroxide detectors at $M_G = 0.1$

Fig. 4 Comparison between output currents calculated for oxygen and hydrogen peroxide detectors at $M_G = 1$

peroxide electrode with respect to the Ag/AgCl reference electrode.

3. Results and Discussion

Permeation properties of oxygen, hydrogen peroxide and glucose through the membrane were estimated by permeability experiments using potential step chronoamperometry and a diffusion cell (Sudoh *et al.*, 1991b). The properties were correlated with water content of the membrane. The Michaelis constants of enzyme kinetics were obtained as functions of pH. The activity of immobilized enzyme was estimated from the linear relationship between output current and glucose concentration under the condition of uniform reaction rates across the membrane, and was evaluated to be close to the activity of native enzyme used for membrane preparation (Sudoh *et al.*, 1991a). The mass-transfer coefficient in the liquid film was

Fig. 5 Comparison between output currents calculated for oxygen and hydrogen peroxide detectors at $M_G = 5$

Fig. 6 Comparison between output currents measured experimentally with oxygen and hydrogen peroxide detectors at different concentrations of glucose and oxygen

estimated by a Levich relationship (Levich, 1962). **Table 1** lists the physical properties, GOD activity of the membrane and the Bi values for the experimental conditions. **Table 2** lists the rate constants (Sudoh *et al.*, 1991b) of glucose oxidase kinetics used for calculation.

Figure 2 shows a theoretical result of concentration profiles within the membrane. For the oxygen detector, the oxygen concentration within the membrane was calculated to be zero in the vicinity of the electrode, and the reaction rate within the membrane was considered to be governed by the diffusion of oxygen. For the hydrogen peroxide electrode, the reaction rate of GOD in the vicinity of the electrode was enhanced by oxygen generated by the electrode reaction, and then the glucose near the electrode was decreased in its concentration.

Figures 3-5 show a comparison between the theoretical results of sensor currents of oxygen and hydrogen

Fig. 7 Schematic diagram of determination of detection limit of glucose concentration for hydrogen peroxide detector

peroxide detectors for $M_G = 0.1, 1$ and 5 , respectively. In these figures, the concentration of the dissolved oxygen was changed as $0.99, 0.21$ and $0.05 \text{ mol} \cdot \text{m}^{-3}$, the values which corresponded to the saturated concentration of pure oxygen, air in the electrolyte and the subcutaneous environment of human beings at 308 K . When C_G was below $1 \text{ mol} \cdot \text{m}^{-3}$, the sensor currents, $I_{O_i} - I_O$ and I_p were linear to the concentration C_G , and $I_{O_i} - I_O$ were about 2 times larger than I_p , as seen from the relationships of Eq.(13) and Eq.(14) with $\phi_i = 1$.

$$\frac{I_{O_i} - I_O}{I_p} = \frac{n_O v_O (1 + Bi_p^{-1})}{n_p (1 + Bi_i^{-1})} \quad (18)$$

When the modulus M_G is larger than 1.0 , the current ($I_{O_i} - I_O$) indicated markedly a saturated curve with respect to the glucose concentration. The dependency of the oxygen concentration on the sensor current was prolonged for the oxygen detector rather than the hydrogen peroxide detector. The sensor current became large with increasing M_G value.

Figure 6 shows the experimental results of the relations between the sensor current and the glucose concentration measured by using oxygen or hydrogen peroxide detectors with the immobilized enzyme membrane. The dependency of the oxygen concentration on the output current was less apparent when using the hydrogen peroxide detector rather than the oxygen detector. The experimental outputs were well simulated by the calculated results according to theoretical considerations, as shown in the solid and broken lines in Fig. 6. The difference between oxygen and hydrogen peroxide detectors was due to the difference of the products of electrode reactions. Oxygen produced on the hydrogen peroxide anode was considered to promote the enzyme reaction. The effect of electrode reaction on output current became dominant at over $300 \text{ mA} \cdot \text{m}^{-2}$ and output current showed a tendency of asymptotical saturation as glucose concentration increased.

Fig. 8 Comparison between detection limits of glucose concentration for oxygen and hydrogen peroxide detectors as a function of oxygen concentration at different M_G

The detection limit of glucose concentration $C_{G,lim}$ by the oxygen detector is defined as the cross point between the saturated current and the linear current of the glucose concentration. When the current is linear to the glucose concentration, the reaction is governed by the enzyme reaction.

$$I_{O_i} - I_O = \frac{n_O v_O F S K_{pG} D_{Gm} C_G}{\delta (1 + Bi_O^{-1})} \phi_O \quad (19)$$

where the ϕ_O value is given as follows (Sudoh *et al.*, 1991b):

$$\phi_O = (1 - \frac{Bi_G}{M_G \tanh M_G + Bi_G}) (\frac{Bi_G}{Bi_O} - 1) + (1 - \frac{Bi_G}{M_G \sinh M_G + Bi_G \cosh M_G}) \quad (20)$$

When oxygen diffusion through the membrane governs the reaction, the current I_O approached a saturated value of zero.

$$I_{O_i} - I_O = \frac{n_O v_O F S K_{pO} D_{Om} C_O}{\delta (1 + Bi_O^{-1})} \quad (21)$$

From the relationship that Eq. (19) = Eq. (21),

$$C_{G,lim} = \frac{K_{pO} D_{Om} C_O}{K_{pG} D_{Gm} \phi_O} \quad (22)$$

ϕ_O given as an analytical form at the extreme condition.

At low M_G values ($M_G \ll 1$),

$$\phi_O = \frac{M_G^2}{2} (1 + \frac{2}{Bi_G}) \quad (23)$$

At high M_G values and larger Bi_G than M_G ($Bi_G \gg M_G \gg 1$),

$$\phi_O = \frac{Bi_G}{Bi_O} \quad (24)$$

Fig. 9 Effect of Biot number on detection limit of glucose concentration by oxygen and hydrogen peroxide detectors

When the Biot numbers and the modulus M_G were constant, ϕ_O became constant. Then $C_{G,lim}$ was proportional to C_O .

Figure 7 shows a schematic diagram for determination of the detection limit by the hydrogen peroxide detector. The detection limit of glucose $C_{G,lim}$ was estimated as the glucose concentration at which the current deviated to 70% of the linear relationship between output current and the glucose concentration.

Figure 8 shows the theoretical comparison of the $C_{G,lim}$ between oxygen and hydrogen peroxide detectors as a function of C_O for different values of M_G . The membrane properties shown in Table 1 were used for calculation. The $C_{G,lim}$ value of the hydrogen peroxide detector was larger than that of the oxygen detector except for the high C_O range at $M_G = 1$. The small deviation for $M_G = 1$ is considered to be due to the difference between estimation methods of the detection limit for the two detectors.

Figure 9 shows the theoretical effect of the Biot number on the detection limit of glucose concentration by oxygen and hydrogen peroxide detectors at $M_G = 1$. The Biot numbers were changed by some magnifications of the reference numbers listed in Table 1. Since ϕ_O in Eq. (22) was a function of the Biot number, $C_{G,lim}$ was affected by the Biot number. The Biot number decreased with decreasing liquid-film resistance. Then the surface concentration of the dissolved oxygen decreased with decreasing Bi_O number. The $C_{G,lim}$ for the oxygen detector described by Eq. (22) had a tendency to decrease with decreasing Bi_O number. Meanwhile, for the hydrogen peroxide detector, the dependency of the Biot number was found not to be so large. Similarly, the detection limit of the hydrogen peroxide anode was larger than that of the oxygen cathode for the low concentration of the dissolved oxygen.

This paper dealt with a fundamental analysis based on a homogeneous membrane for a glucose sensor. A composite membrane having different functions was used

for a needle-type glucose sensor implanted in a subcutaneous tissue. The design for the composite membrane will be discussed in a separate paper.

Conclusions

The sensor current observed experimentally with the hydrogen peroxide detector was less affected by the oxygen concentration than with the oxygen detector. The effect of electrochemical reaction of the hydrogen peroxide electrode on the output current became dominant at more than $300 \text{ mA} \cdot \text{m}^{-2}$. The output current of the oxygen detector showed asymptotical saturation as glucose concentration increased when the modulus M_G was more than unity. The sensor currents were well simulated according to the theoretical consideration for the oxygen and hydrogen peroxide detectors. The glucose concentration of the detection limit $C_{G,lim}$ increased with increasing concentration of dissolved oxygen. The detection limit of glucose, on $C_{G,lim}$ value of the hydrogen peroxide detector, was larger than that of the oxygen detector except for the high C_O range at $M_G = 1$.

Nomenclature

Bi	$= k_L \delta / (D_m K_p)$, Biot number	[-]
C	$=$ concentration	$[\text{mol} \cdot \text{m}^{-3}]$
C_E	$=$ enzyme concentration	$[\text{mol} \cdot \text{m}^{-3}]$
$C_{G,lim}$	$=$ detection limit of glucose concentration	$[\text{mol} \cdot \text{m}^{-3}]$
D	$=$ diffusivity	$[\text{m}^2 \cdot \text{s}^{-1}]$
F	$=$ Faraday's constant	$[\text{C} \cdot \text{mol}^{-1}]$
k	$=$ rate constant of enzyme reaction	$[\text{s}^{-1}]$
I	$=$ current	$[\text{A}]$
j	$=$ diffusional flux of electro-active substance	$[\text{mol} \cdot \text{m}^{-2} \cdot \text{s}^{-1}]$
K_M	$=$ Michaelis constant	$[\text{mol} \cdot \text{m}^{-3}]$
K_p	$=$ distribution coefficient	[-]
k_L	$=$ mass transfer coefficient in liquid film	$[\text{m} \cdot \text{s}^{-1}]$
M_G	$= (k_G C_{EG} \delta^2 / D_{GM} K_{MG})^{0.5}$, Thiele modulus	[-]
n	$=$ electron charge number	[-]
r	$=$ reaction rate of enzyme	$[\text{mol} \cdot \text{m}^{-3} \cdot \text{s}^{-1}]$
S	$=$ surface area of electrode	$[\text{m}^2]$
s	$=$ stoichiometric coefficient of enzyme reaction	[-]
s_e	$=$ stoichiometric coefficient of electrode reaction	[-]
δ	$=$ membrane thickness	$[\text{m}]$
η	$=$ effectiveness factor	[-]
ν_O	$=$ stoichiometric coefficient of net oxygen consumption	[-]
ϕ	$=$ dimensionless parameter defined by Eq. (16)	[-]
<Subscripts>		
C	$=$ catalase	
G	$=$ glucose or glucose oxidase	
H	$=$ hydrogen ion	
m	$=$ membrane	
O	$=$ oxygen	
P	$=$ hydrogen peroxide	

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