Chapter 10 Chemical Biosensor

- The functional status of an organ is determined by measuring the chemical input and output analytes of the cells
- A chemical biosensor is a sensor that produces an electrical signal proportional to the concentration of biochemical analytes.
- Important critical-care analytes: Table 10.1
- Central clinical laboratory
  - 30 min or more of delay ⇒ delay of the therapeutic intervention
  - potential errors in the origin of the sample
  - potential errors in sampling-handling techniques
- Decentralized clinical testing: stability, calibration, quality control, ease of use
  - In critical-care and surgical settings
  - Continuous monitoring of blood gases and electrolytes in operating room
  - Timely measurement of uric acid and other blood analytes in dialysis center
  - Self-contained, small, economical blood-chemistry unit in physician's office or patient's home
- Future development
  - In vivo, real-time measurements of body chemistry
  - Self-contained biosensor units for closed-loop systems
  - Closed-loop drug delivery system
  - Control of cardiac pacemaker and internal defibrillator
  - Regulation of anesthesia during operations
  - Control of insulin secretion from an artificial pancreas
  - Noninvasive measurement of biochemistry
    - Pulse oximetry: widely used now
    - Glucose, cholesterol, urea, electrolytes, etc.
10.1 Blood-Gas and Acid-Base Physiology

- Fast and accurate measurements of the blood levels of the partial pressure of O\(_2\) (\(P_{O_2}\)), the partial pressure of CO\(_2\) (\(P_{CO_2}\)), and the concentration of \([H^+]\) (pH) from arterial blood or aterialized venous samples from infants

- Saturation of O\(_2\), \(S_{O_2}(\%) = \left(\frac{HbO_2}{total\ Hb}\right) \times 100\), amount of O\(_2\) per unit of blood, usually 98% (2% is in plasma)

  - Oxyhemoglobin dissociation curve (ODC) in Fig. 10.1: \(P_{O_2}\) of 60 mmHg still provides 85% of \(S_{O_2}\)

- Arterial \(P_{O_2}\) : efficiency of alveolar ventilation, 90 ~ 100 mmHg (12 ~ 13.3 kPa) for young normal adults

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**Figure 10.1** The oxyhemoglobin dissociation curve, showing the effect of pH and temperature on the relationship between \(SO_2\) and \(PO_2\).
• Group 1: decreased overall ventilation (narcotic overdose or paralysis of the ventilation muscle), obstruction of major airways (aspirated foreign object or spasm of the airway muscles from asthma), filling of the alveoli and small airways with fluid (pneumonia or pulmonary edema) ⇒ decreased delivery of O₂ to the lung alveoli ⇒ decrease in \( P_{O₂} \)

• Group 2: congenital cardiac abnormalities (blood shunting, the Tetralogy of Fallot), obstruction of flow through the pulmonary vessels (pulmonary emboli) ⇒ decreased delivery of blood to the lung alveoli ⇒ decrease in \( P_{O₂} \)

• Group 3: emphysema and chronic bronchitis ⇒ decreased delivery of O₂ and blood to the lung alveoli ⇒ decrease in \( P_{O₂} \)

○ Arterial \( P_{CO₂} \) level: indication of the adequacy of ventilation, 35 ~ 40 mmHg (4.7 ~ 5.3 kPa) for young normal adults
  - Group 1: increased \( P_{CO₂} \)
  - Group 2: normal \( P_{CO₂} \)

○ Arterial pH: acid-base status of the blood by \([H^+]\) concentration, \( pH = -\log_{10}[H^+] \), 7.38 ~ 7.44 for the normal
  - Decreased rate of excretion of CO₂ (respiratory acidosis), increased production of fixed acid from diabetic ketoacidosis (metabolic acidosis), abnormal losses of bicarbonate (metabolic acidosis) ⇒ decreases in pH (increased quantity of \([H^+]\))
  - Increased rate of excretion of CO₂ (respiratory alkalosis), abnormal losses of acid from prolonged vomiting (metabolic alkalosis) ⇒ increases in pH (decreased quantity of \([H^+]\))

○ Classification of acid-base abnormality (Table 10.2): both \( P_{CO₂} \) (or bicarbonate level in blood) and pH measurements are required

10.2 Electrochemical Sensors
**Measurement of pH**

- Glass electrode (an ion-specific electrode) generates an electric potential when solutions of different pH are placed on the two sides of its membrane (Fig. 10.2).
- Sensitivity of the glass electrode = 60 mV/pH and range of physiological pH = 0.06 pH units ⇒ required accuracy = 0.1 mV
- Reference electrode: Ag/AgCl or saturated calomel electrode with salt bridge
- Reference solution with known pH: hydrochloric acid (HCl)
- Impedance of the pH electrode is 10 ~ 100 MΩ ⇒ pH meter must have an extremely high input impedance
- Temperature compensation
  - Use a water bath with 37 °C without temperature correction
  - Correction using temperature only or both temperature and \( P_{CO_2} \)
- Calibration using two solutions of known pH (6.8 and 7.9)

![Figure 10.2 pH electrode](From R. Hicks, J. R. Schenken, and M. A. Steinrau, *Laboratory Instrumentation*. Hagerstown, MD: Harper & Row, 1974. Used with permission of C. A. McWhorter.)

**Measurement of \( P_{CO_2} \)**

- Linear relationship between log \( P_{CO_2} \) and pH over 10 ~ 90 mmHg (1.3 ~ 12 kPa):

\[
\text{pH} = \log[\text{HCO}_3^-] - \log k - \log a - \log P_{CO_2}
\]

where \( a = 0.0301 \) mmol/liter per mmHg \( P_{CO_2} \)
• \( P_{CO_2} \) electrode in Fig. 10.3
  - pH electrode is bathed by a buffer solution of bicarbonate and NaCl
  - Semipermeable membrane: Teflon or silicone rubber, dissolved CO\(_2\) can pass through, charged particles (H\(^+\), HCO\(_3^-\)) are blocked
  - CO\(_2\) moves into (out of) the buffer solution \(\Rightarrow [H^+]\) increases (decreases)
  - Calibration before each use with two gases of known \( P_{CO_2} \)

![Figure 10.3 \( P_{CO_2} \) electrode](From R. Hicks, J. R. Schenken, and M. A. Steinrauf, *Laboratory Instrumentation*. Hagerstown, MD: Harper & Row, 1974. Used with permission of C. A. McWhorter.)

**The \( P_{O_2} \) Electrode**

• Clark-type polarographic electrode in Fig. 10.4
  - At the cathode (glass-coated Pt): exposed Pt electrode has a diameter of 20 \(\mu\)m

\[
\begin{align*}
O_2 + 2H_2O + 4e^- &\rightarrow 2H_2O_2 + 4e^- \rightarrow 4OH^- \\
4OH^- + 4KCl &\rightarrow 4KOH + 4Cl^-
\end{align*}
\] (reduction)

- At the anode (Ag/AgCl): 4Ag + 4Cl\(^-\) \(\rightarrow\) 4AgCl + 4e\(^-\) (oxidation)

• Polarogram in Fig. 10.5(a): plot of current vs. polarizing voltage
• Polarizing voltage of 600 ~ 800 mV using a mercury cell \(\Rightarrow\) linear relationship between O\(_2\) concentration and current in Fig. 10.5(b)
  - Background current: current when \( P_{O_2} \) is zero
  - Wait until stagnant equilibrium to avoid stirring effect
- Time to reach a equilibrium is a function of $P_{O_2}$: about 360 s for $P_{O_2}$ of 430 mmHg (57 kPa), faster measurement technique is available in some product (2 s)
- Semipermeable membrane: O$_2$ membrane, permeable to O$_2$ and other gases
  - Tradeoff between consumption of O$_2$ and the time for equilibrium: permeability $\uparrow$ ⇒ O$_2$ consumption $\uparrow$ and response time $\downarrow$, Polypropylene is preferable and is less permeable than Teflon
  - Thicker membrane ⇒ increased diffusion time and smaller current
- Calibration using two gases of known O$_2$ concentration
  - Fill the specimen chamber with water ⇒ CO$_2$-N$_2$ mixture (no O$_2$) is bubbled slowly ⇒ after about 90 s, the $P_{O_2}$ meter output is set to be zero
  - Use O$_2$-CO$_2$-N$_2$ mixture to determine the second point on the $P_{O_2}$-versus-electrode-current calibration scale
- Temperature compensation
  - Reaction is very sensitive to temperature ⇒ ±0.1 °C temperature control is required
  - Use water jacket or precision electric heat sources
  - Typical current through the meter: 10 nA/mmHg (75 nA/kPa)

**Figure 10.4** $P_{O_2}$ electrode (From R. Hicks, J. R. Schenken, and M. A. Steinrauf, *Laboratory Instrumentation*. Hagerstown, MD: Harper & Row, 1974. Used with permission of C. A. McWhorter.)
10.3 Chemical Fibrosensors

Chemical fibrosensor or optrode or optical fibrosensor or optical-fiber sensor

- **Advantages**
  - Small in size
  - Multiple sensors through a catheter for intracranial or intravascular measurement
  - No electric hazard to patients
  - Immune to external electric interference
  - No reference electrode
  - High flexibility, good thermal stability, low cost, disposal usage

- **Disadvantages**
  - Sensitive to ambient light
  - Modulation is often required
  - Limited dynamic range

Figure 10.5 (a) Current plotted against polarized voltage for a typical PO₂ electrode for the percents O₂ shown. (b) Electrode operation with a polarizing voltage of 0.68 V gives a linear relationship between current output and percent O₂.
Intravascular Measurements of Oxygen Saturation

- Intravascular fiber optic catheter (Swan-Ganz): a flow-directed fiber optic catheter into the right jugular → vein right atrium → pulmonary artery by balloon
- Measurements of mixed venous oxygen saturation ⇒ effectiveness of the cardiopulmonary system
- Abnormalities
  - High oxygen saturation in the right heart: congenital abnormalities of the heart and the major vessels, inability of tissue to metabolize oxygen
  - Low oxygen saturation in the left heart: reduced ability of the lungs to oxygenate the blood, reduced ability of the cardiopulmonary system to deliver oxygen to the lungs
  - Low oxygen saturation in the arterial system: compromised cardiac output, reduced oxygen carrying capacity of the blood
- Optical absorption spectra (Fig. 10.6)
  - Isosbestic wavelength: 805 nm, used to compensate for the scattering and normalize the signal with any changes in hemoglobin
  - Red: 660 nm, low absorption coefficient ⇒ long transmission of light
- Two-wavelength oximeter and dye dilution flow meter (Fig. 10.7)
  - Absorbance or optical density,
\[ A(\lambda) = WL[a_0(\lambda)C_0 + a_r(\lambda)C_r] \] with \( C_0 + C_r = 1 \) where \( W \) is the weight of Hb per unit volume, \( L \) is the optical path length, \( a_0(a_r) \) is the absorptivity of HbO_2 (Hb), and \( C_0(C_r) \) is the relative concentration of HbO_2 (Hb).

- At \( \lambda_2 = 805 \text{ nm} \), \( a_0(\lambda_2) = a_r(\lambda_2) = a(\lambda_2) \) and \( WL = \frac{A(\lambda_2)}{a(\lambda_2)} \)
- \( A(\lambda) = \frac{A(\lambda_2)}{a(\lambda_2)}[a_0(\lambda)C_0 + a_r(\lambda)C_r] \) and we measure \( A(\lambda_1) \) with \( \lambda_1 = 660 \text{ nm} \), then the oxygen saturation, \( C_0 = x + \frac{yA(\lambda_1)}{A(\lambda_2)} \)
- Hematocrit affects the measurements of \( S_O_2 \) below 80%.
- CO is also measured by dye dilution (Indo/cyanine/green) with 805 nm and 900 nm.
- Three wavelength oximeter (Fig. 10.8) measures the mixed venous \( S_O_2 \) and hematocrit simultaneously.

**Figure 10.7** The oximeter catheter system measures oxygen saturation *in vivo*, using red and infrared light emitting diodes (LEDs) and a photosensor. The red and infrared LEDs are alternately pulsed in order to use a single photosensor.
Reversible-Dye Optical Measurement of pH

- Metabolic and respiratory problem $\Rightarrow$ continuous monitoring of blood pH in a range of 7.0 to 7.6 pH units with a resolution of 0.01 pH unit
- pH sensor (Fig. 10.9): plastic optical fiber with a reversible colorimetric indicator system in an ion-permeable envelope, light-scattering microspheres mixed with the indicator dye optimizes the backscattering of light
- Reversible indicator dye: phenol red, pH-sensitive, optical characteristic changes with pH (Fig. 10.10 and 10.11) $\Rightarrow$ use green and red light

Figure 10.8 The catheter used with the Abbott Opticath Oximetry System transmits light to the blood through a transmitting optical fiber and returns the reflected light through a receiving optical fiber. The catheter is optically connected to the oximetry processor through the optical module. (From Abbott Critical Care Systems. Used by permission.)

Figure 10.10 The plot of absorbance against wavelength of phenol red (base form) increases with pH for green light but is constant for red light.

Figure 10.11 The ratio ($R$) of green to red light transmitted through phenol red for basic and acidic forms of the dye. $\Delta =$ deviation of pH from dye pK. (From J. I. Peterson, S. R. Goldstein, and R. V. Fitzgerald, "Fiber-optic pH probe for physiological use," *Anal. Chem.*, 1980, 51, 864-869. Used by permission.)
**Fluorescence Optical pH Sensor (Irreversible)**

- A single-fiber intravascular fluorescent pH sensor (Fig. 10.12) with pH sensitivity range of pKa ± 1
- pH-sensitive dye hydroxypyrene trisulfonic acid (HPTS): water-soluble fluorescent dye with a pKa of 7.0
- Fluorescent dye emits light energy at a wavelength different from that of the excitation wavelength (Fig. 10.13) ⇒ single optical fiber both for the delivery and reception of light
- Irreversible chemistry requires a long-lasting reagent or a continuous reagent delivery

![Diagram of a single-fiber intravascular blood-gas sensor](image)

**Figure 10.12** A single fiber intravascular blood-gas sensor excites fluorescent dye at one wavelength and detects emission at a different wavelength. The following modifications are made to the sensor tip:
- pH: Chemistry – pH-sensitive dye bound to hydrophilic matrix.
- PCO2: Chemistry – bicarbonate buffer containing pH-sensitive dye with silicone.
- PO2: Chemistry – Oxygen-sensitive dye in silicone.

**Fluorescence Optical $P_{CO_2}$ Sensor**

- Use pH-sensitive fluorescent dye (irreversible fluorescence optical pH sensor)
- Use the relationship between the pH change in a bicarbonate solution and the CO$_2$ concentration in that solution

**Fluorescence Optical $P_{O_2}$ Sensor**

- Fluorescent spectra of oxygen-sensitive dye (Fig. 10.14)
- Oxygen molecules provide collision paths and transfer of energy to oxygen molecules ⇒ the increasing loss of energy to oxygen decreases luminescence
- Fluorescent quenching dyes are irradiated by light at an appropriate wavelength ⇒ the period of dye fluorescence is inversely proportional to these partial pressure of oxygen
- Fiber-optic oxygen sensor (Fig. 10.15): blue and green light, PM tube

Figure 10.15 In a fiber-optic oxygen sensor, irradiation of dyes causes fluorescence that decreases with $P_{O_2}$. [From R. Kocache, "Oxygen analyzers," in J. G. Webster (ed.), Encyclopedia of Medical Devices and Instrumentation. New York: Wiley, 1988, pp. 2154-2161. Used by permission.]

Design of an Intravascular Blood-Gas Monitoring System

- Continuous monitoring of arterial pH, $P_{CO_2}$, and $P_{O_2}$ in critical-care and surgical setting
System design: radial-artery catheter with a fluorescence-based blood-gas probe, an optoelectronic instrument, and a probe calibration

Blood-gas probe design (Fig. 10.16)
- Operating temperature: 15 ~ 42 °C
- pH range: 6.8 ~ 7.8
- $P_{CO_2}$ range: 10 ~ 100 mmHg
- $P_{O_2}$ range: 20 ~ 300 (or 500) mmHg
- Simultaneous temperature and blood pressure measurement

Mechanical design
- Small enough for the radial artery insertion: 20-gage catheter, probe diameter of 600 μm, fiber diameter of 130 μm
- Blood-gas sample withdrawal
- Material: sterilizable and biocompatible, no carcinogenicity and no toxicity, nonthrombogenic and nonhemolytic blood-contact surface
- Should not be affected by naturally occurring substances such as proteins or any injected substances
- Must be immune to absorption of the components in the blood and to their deposition on the sensor surfaces

Fluorescence sensor design
- Single fiber for both the delivery and reception of light
- Nontoxic dye with appropriate absorption and emission characteristics, sufficient sensitivity, high fluorescent intensity
- No influence from drugs or other blood constituents
- Stability to maintain the accuracy up to three days
- Cost and shelf life of dye
- Fast enough dynamic response

Instrument design
- Configuration: analyzer module, patient interface module (PIM), and display
- Illuminator (20 Hz pulsating light source): a broadband xenon-arc lamp (350 ~ 750 nm), a collimating lens system, a filter wheel (flash rate of 20 Hz), a condensing lens
- Light energy from the illuminator travels along the fiber optics to PIM and is coupled by the graded index (GRIN) lens to the interfacing optics
- Maximizing the energy delivery: (1) minimal number of optical connections, (2)
minimal length of the fibers, (3) transduction of the light signal to an electrical signal at the distal end as rear as possible to the patient, (4) ADC and MUX in PIM and digital signal transmission to the analyzer through a cable (less than 4 m)

- Calibration device: fluid-filled calibration cuvette

![Diagram](image)


### 10.4 Ion-Sensitive Field-Effect Transistor (ISFET)

- Low cost microminiature sensor (Fig. 10.17)
- Fast measurements of multiple analytes on a single chip
- Sensors and signal processing IC's on a single chip
- Ion-selective membrane deposition on the gate: CO\textsubscript{2}, potassium (Fig. 10.18), calcium, pH, glucose, oxygen saturation, etc.
- Encapsulation is a challenging problem

### 10.5 Immunologically Sensitive Field-Effect Transistor (IMFET)

- Polarized solution-membrane interface: charged species cannot cross the membrane
- Antigen sensor: antibody is immobilized on the membrane that is attached to the insulator of a FET
- Antibody sensor: antigen is immobilized on the membrane
Figure 10.17 (a) In a chemically sensitive field-effect transistor, the ion-selective membrane modulates the current between the source and the drain. (b) A stretched ISFET maximizes the spacing between the "wet" sample region and the electric connections. (Part (b) from P. Rolfe, "In vivo chemical sensors for intensive-care monitoring," *Med. Biol. Eng. Comput.*, 1990, 28. Used by permission.)

Figure 10.18 Dependence of current on potassium ion activity for a potassium ion-sensitive field-effect transistor.
10.6 Noninvasive Blood-Gas Monitoring

- Efficiency of pulmonary gas exchange
- Adequacy of alveolar ventilation, blood-gas transport, and tissue oxygenation
- Simple, real-time, continuous, and noninvasive monitoring of arterial oxygen saturation ($S_{O_2}$), oxygen tension ($P_{O_2}$), and carbon dioxide tension ($P_{CO_2}$)

![Diagram of pulse oximeter analysis](image)


**Skin Characteristics**
- Thickness of 0.2 ~ 2 mm
- Three principal layers (Fig. 5.7)
  - Stratum corneum: nonliving, outer layer, supple and protective layer of dehydrated cells
  - Epidermis: nonvascular and living tissue with proteins, lipids, and melanin-forming cells (melanocytes), average thickness is 0.1 ~ 0.2 mm
  - Dermis: dense connective tissue, hair follicles, sweat glands, nerve endings, fat cells, profuse system of capillaries, vertical capillary loops about 200 ~ 400 μm in length
- Blood supply: large arteries (subcutaneous tissue) ⇒ arterioles (flat network parallel
to the skin surface below dermis) ⇒ capillaries ⇒ venules (upper and middle dermis) ⇒ large veins (subcutaneous tissue)

- Arteriovenous anastomoses (shunt)
  - Innervated by nerve fibers
  - In the dermis of the palms, ears, and face
  - Regulate blood flow through the skin in response to heat (increased blood flow of 30 times the basal level)

- Normal gas diffusion through the skin is low ⇒ with increased heat (40 °C or above), the skin becomes more permeable to gases

**Figure 10.20** (a) Noninvasive patient monitor capable of measuring ECG, noninvasive blood pressure (using automatic oscillometry), respiration (using impedance pneumography), transmission pulse oximetry, and temperature. (From Criticare Systems, Inc. Used by permission.) (b) Disposable transmission $S_{O_2}$ sensor in open position. Note the light sources and detector, which can be placed on each side of the finger. (From Datascopc Corporation. Used by permission.)

**Transcutaneous Arterial Oxygen Saturation Monitoring (Pulse Oximetry)**

- Light attenuation by tissue and blood absorption, refraction, and multiple scattering eight wavelength measurements
- Two-wavelength measurement: analysis of time-varying component of the light transmitted through the skin during the systolic phase of blood flow (Fig. 10.19)
- Transcutaneous reflectance or transmission oximeter: 2.5 % accuracy over 50 ~ 100 % $S_{O_2}$
- Transcutaneous sensor (Fig. 10.20): red (660 nm) LED, infrared (940 nm) LED, and photodiode
• Applications
  □ Administration of anesthesia
  □ Pulmonary function test
  □ Bronchoscopy
  □ Intensive care
  □ Oral surgery
  □ Neonatal monitoring
  □ Sleep apnea studies
  □ Aviation medicine
  □ Home monitoring for self-administered oxygen therapy

• Problems: poor signal with shock, interference from lights, interference from the presence of carboxyhemoglobin, poor trending of transients

Figure 10.21 Cross-sectional view of a transcutaneous oxygen sensor. Heating promotes arterialization. (From A. Huch and R. Huch, "Transcutaneous, noninvasive monitoring of $PO_2$," Hospital Practice, 1976, 6, 43-52. Used by permission.)

**Transcutaneous Arterial Oxygen Tension ($tcP_O_2$) Monitoring**

• Clark-type $tcP_O_2$ sensor (Fig. 10.21)
  □ Three glass-sealed Pt cathodes and one Ag/AgCl anode ring
Buffered KCl electrolyte
- Heating coil and a thermistor
- Two point calibration: (nitrogen and oxygen) or (sodium sulfite and ambient air)
- Drift: 1 ~ 2 mmHg/h
- Broken seal between the probe and the skin ⇒ output of 155 mmHg

- Heating of the skin between 43 and 44 °C
  - Hyperemia of the skin ⇒ (skin $P_{O_2}$) ≈ (arterial $P_{O_2}$)
  - Frequent sensor reposition to avoid burns (especially neonates): 2 ~ 6 h per site
  - Increased $O_2$ diffusion through the stratum corneum
  - Increased blood flow due to vasodiation of the dermal capillaries ⇒ increased $O_2$ supply

- Applications
  - Newborn infants with respiratory distress: $O_2$ administration without high arterial $P_{O_2}$ (high arterial $P_{O_2}$ ⇒ damage to retinal and pulmonary tissues)
  - Evaluating the adequacy of cutaneous circulation in patients with peripheral resuscitation
  - Hypothermia, acidermia, anemia, and shock ⇒ $tcP_{O_2} < P_{O_2}$
  - Not very accurate for adults (thick skin, even at 45 °C) ⇒ $tcP_{O_2} < P_{O_2}$

Transcutaneous Carbon Dioxide Tension ($tcP_{CO_2}$) Monitoring

- More accurate than $tcP_{CO_2}$ in adults
- Sensor (Fig. 10.22): based on Stow-Severinghaus principle
  - Glass pH electrode with a concentric Ag/AgCl reference electrode
  - Heating element and thermistor
  - Electrolyte (bicarbonate buffer)
  - $CO_2$-permeable Teflon membrane
  - One point calibration using a known $CO_2$ concentration solution
  - Longer time constant (in-vivo): 15, 7.5, 5, and 3.5 min at 37, 39, 41, and 44 °C, respectively
• Heating of the skin ⇒ (tcPCO₂) > (arterial PCO₂), but good correlation
  ◦ Decreased solubility of CO₂
  ◦ Increased local tissue metabolism
  ◦ Increased rate of CO₂ diffusion through the stratum corneum
• Applications
  ◦ Adults and neonates without shock
  ◦ Arterial PCO₂ varies linearly with alveolar ventilation ⇒ tcPCO₂ provides information about the effectiveness of spontaneous or mechanical ventilation
  ◦ Monitoring of the impaired tissue perfusion (circulation to the limb)
  ◦ Monitoring of the response to therapy

Figure 10.22 Cross-sectional view of a transcutaneous carbon dioxide sensor. Heating the skin promotes arterIALIZATION. (From A. Huch, D. W. Lübbers, and R. Huch, "Patientenüberwachung durch transcutane Pco₂-Messung bei gleichzeitiger kontrolle der relativen lokalen Perfusion," Anaesthesist, 1973, 22, 379. Used by permission.)

10.7 Blood-Glucose Sensors

◦ Diagnosis and long-term management of diabetes
◦ Normal fasting blood glucose: 80 ~ 90 mg/100mL (normoglycemia), insulin from beta cells in pancreas promotes glucose transport into skeletal muscle and adipose
tissue

- Diabetes mellitus: blood glucose of 300 ~ 700 mg/100mL (hyperglycemia)
- Closed-loop vs. open-loop insulin delivery system

**Figure 10.23** (a) In the enzyme electrode, when glucose is present it combines with $O_2$, so less $O_2$ arrives at the cathode. (b) In the dual-cathode enzyme electrode, one electrode senses only $O_2$, and the difference signal measures glucose independent of $O_2$ fluctuations. (From S. J. Updike and G. P. Hicks, "The enzyme electrode, a miniature chemical transducer using immobilized enzyme activity," *Nature*, 1967, 214, 986-988. Used by permission.)

**Electroenzymatic Approach**

- Glucose + $O_2 \xrightarrow{\text{Glucose oxidase}}$ Gluconic acid + $H_2O_2$
  - Decrease in $P_{O_2}$
  - Increase in pH
  - Production of hydrogen peroxide
- Glucose enzyme electrode (Fig. 10.23)
- Glucose oxidase immobilized on a membrane or a gel matrix
- Oxygen-sensitive polarographic electrode
- Dual-cathode enzyme electrode: to remove the effect of the oxygen in the solution itself
- Hydrophobic membrane over a glucose enzyme electrode ⇒ increases the linear response
- Instability of the immobilized enzyme and fouling of the membrane surface under physiological conditions ⇒ short operating time ⇒ need to develop a more highly selective membrane

**Optical Approach**

- Fluorescence-based affinity sensor (Fig. 10.24 and 25): monitoring of metabolites, especially glucose in blood plasma
  - Miniaturization is possible
  - Implantable through a needle
  - No electric connection
  - Lack of long-term stability of the agent
  - Slow response time
  - Dependence of the measured light intensity to the amount of the reagent

![Optical fiber diagram](image)

**Figure 10.24** The affinity sensor measures glucose concentration by detecting changes in fluorescent light intensity caused by competitive binding of a fluorescein-labeled indicator. (From J. S. Schultz, S. Manouri, *et al.*, "Affinity sensor: A new technique for developing Implantable sensors for glucose and other metabolites," *Diabetes Care*, 1982, 5, 245-253. Used by permission)

**Attenuated Total Reflection and Infrared Absorption Spectroscopy**

- Multiple infrared ATR spectroscopy
- Measured infrared spectra of the blood is independent of the sample thickness
- Laser light source (CO₂ laser) improves the sensitivity
- Advantageous in measuring the transmission of light in aqueous solutions to identify unknown biological substances

- Fingerprints (Fig. 10.26): specific resonance absorption peaks of each molecule due to vibrational and rotational oscillations of the molecule, usually overlap
  - Absorption-peak magnitude is directly related with the glucose concentration
  - Beer's law quantitative measurement of the glucose concentration

- Problems
  - Pure water has an intrinsic high background absorption in the IR region
  - Normal blood glucose (and other analytes) concentration is low (90 ~ 120 mg/dl or mg%)

10.8 Summary

- Implantable sensors in the chemically harsh environment of the body
- Biocompatibility
- Proper encapsulation
- Protection against high temperature and saline condition
- In situ calibration