1. Introduction

1.1 Definition and Classification of Biomedical Sensor

1.1.1 Basic Concept of Sensors

The sensor is a kind of special electronic device which can transfer the various non-electrical quantities to easy detecting electrical quantities.

1.1.2 Classification of Biomedical Sensors

The biomedical sensor is a kind of special electronic device which can transfer the various non-electrical quantities in biomedical fields to easy detecting electrical quantities.

- Physical sensors: for detecting and monitoring of the blood pressure, breath, body temperature, heart sounds, heart electrical signal, blood viscidity, velocity of flow and flux etc. physical quantities;
- Chemical sensors: for detecting and monitoring of the odor molecular and ion e.g. pH values of body liquids, as blood, sudoral eruptions and urine etc. oxygen and carbon dioxide $(P_{O_2}, P_{CO_2}), Na^+, K^+, Ca^{2+}, Cl^-$ and heavy metal ions etc.
- Biosensors: for detecting and monitoring of the tissue, cells, enzyme, antigen, antibody, hormone, sour of gallbladder, acetylcholine, 5-HT and DNA, RNA etc.

1.2 Biomedical Measurement Technology

- Biomedical measurement technologies are more complex and rigid than common industrial detection technology.
- Biomedical measurement technologies have a direct affect on the design and application of sensors and medical instruments.
- Biomedical measurement technology involves the detection of physical, chemical and biological signals in different levels of organisms.
- Nowadays the measurement of physical signals has been popularized and many measurements of chemical signals have practical applications.

1.2.1 Bioelectrical Signal Detection

- The detection of physiological quantities in the circulatory system and nervous system develop relatively early and rapidly.
- Many researchers are still working on automatic extraction and discriminating arrhythmia(心律不齐) information from ECG under strong interference. In addition, the detection of the P wave, research on obtaining an ECG of a fetus from a mother’s body surface, research on high frequency ECG, research on body surface real-time detection and late potential detection have been improved to different extents.

1.2.2 Biomagnetic Signal Detection

- The biomagnetic field comes from the in vivo human body with biological electrical activities, such as MCG（magnetocadiogram, 心磁图）, MEG （脑磁图）, MMG（Mammography,乳腺摄影术）etc.
- For MCG, the detection system does not directly come in contact with the organism, the detecting signals come from a certain spot or place rather than the difference between two points and a location measurement can take place.

1.2.3 Other Physiological and Biomedical Parameter Detection

- It has become a common practice to use sensors noninvasively to detect noninvasive blood pressure, blood flow, breath, pulse, body temperature and cardiac sounds.
- The trend is to develop new noninvasive or slightly invasive detecting methods and use one sensor once to detect multiple physiological parameters.
- Non-contact and long-distance detection are also current development trends.
- Noninvasive and slightly invasive biochemical parameter detecting methods have received great attention.

1.3 Characteristics of Biomedical Sensors and Measurement

1.3.1 Features of Biomedical Sensor and Measurement

- Interdisciplinary Research
- Basic research and technological innovation
- Sensitive materials and film formation technology
- Knowledge-intensive
- High reliability
- Fine technology

1.3.2 Special Requirement of Biomedical Sensor and Measurement

biomedical sensors design --> biocompatibility --> Hemocompatibility and Histocompatibility

material selection --> experiments on animals and clinical trials --> evaluate the host response by biological method

1.4 Development of Biomedical Sensors and Measurement

- Biomedical sensors and measurements have been developing rapidly over the past 30 years.
- The development of the medical sensor has basically changed the traditional mode and achieved some technical breakthroughs.
- Other new types of sensors such as DNA sensors, fiber sensors, and biological tissue sensors are also being developed.

1.4.1 Invasive and Noninvasive Detection

- Miniaturization of sensors makes direct and continuous monitoring of vascular parameters (such as blood pressure, temperature, and flow rate) possible.
- Chemical and biological sensor technology plays an important role in the field of

  public health. Because it has the characteristics of rapid detection, high sensitivity and expertise.
- A lot of effort is being made in this respect, using chemical and biological sensors to expand into non-traditional clinical chemistry analysis.

Noninvasive Detection

Noninvasive detecting sensors should have a higher sensibility, accuracy, anti-interference and signal-to-noise rate.

Nondestructive monitoring

- Nondestructive monitoring is the most receptive monitoring method to the patient ; it is the current biomedical sensor technology by the practical problems of common concern.
- At present the progress made in a non-destructive are percutaneous(经皮) blood gas sensor monitoring blood gas sensor(P_{O_2}、P_{CO_2}), the use of non-blood measuring to monitor blood glucose, urea, etc.

1.4.2 Multi-Parameters Detection

Serial operation is hard to overcome when using discrete sensors for monitoring different parameters, which has low efficiency, and can not meet the simultaneous requirements in terms of time and space. Integrated technology creates conditions for multiparameter sensors. At the beginning of 1980s', Researchers invented

integrated blood electrolyte sensor which monitors 5 parameters (Na^+, K^+, Ca^{2+}, Cl^- and pH).

1.4.3 In Vitro and In Vivo Detection

- In vivo detection is a technology that detects the structure and function of living humans or animals while in vitro detection is a technology that detects the blood,

  urine, living tissues or pathological specimens in vitro.
- In vitro analysis and detection of tissue slices and blood or gas samples aim to quantitatively analyze the composition and quantity of those substances and evaluate whether they are normal or whether there are some pathological microorganisms.
- In vitro detection requires high detection accuracy and precision and quick response. Because of the variety of detection categories, multiple kinds of automatic detection are required to make the most of the samples and testing reagents.

Improved Technological Fields

- conventional clinical analysis detection
- minim and tracing element detection
- super minim hormone detection
- molecular level and cellular level detecting technology

- biosensor micro system development and applications
- cancer cells self-recognition
- chromosome automatic classification
- DNA automatic analysis
- detection of olfactory and taste quantities

Improved Technological Fields

- As with the increase in the importance of clinical biochemical analysis and the amount of analyzing samples and contents, in vitro detection is becoming multi-functional, continuous and automatic.
- All different kinds of automatic biochemical detecting devices, using the methods of optical analysis and electrochemical analysis, will rapidly improve with the development of computer automated recognition and analysis technology.

Monitoring in vivo

- Monitoring in vivo can be done as observing physiological and pathological processes in real-time, fixed-point in a long time. In vivo monitoring of the information provided is unmatched.
- Implanted sensor can transmute or launch the information from inner to outer; the catheter sensor can sense gas / ion in intravascular blood or heart continuously.
- The main problem of in vivo monitoring is how to improve the compatibility between the organs and the sensors.

Brain-computer interface (BCI)

- A direct communication pathway between a brain and an external device.
- Aimed at assisting, augmenting(扩张) or repairing human cognitive or sensory-motor functions.
- Neuro prosthetics(修复) is an area of neuroscience concerned with neural prostheses, using artificial devices to replace the function of impaired nervous systems or sensory organs.

Sensor in a Molecular System

- The sensor in a molecular system can identify proteins.
- The processor can ascertain the structure of the gene and the actuator can cut or unite the gene, which is the molecular system that can control and modify the gene and affect the life course（生命历程）.
- The design and synthesis of molecular systems is a new task for medicine and pharmacology.
- Achievements in two respects:
    - The first is the property of all magnetic waves and infrared light passing through skin and human tissue.
    - The second is the coupling method of internal and external information.

1.4.4 Intelligent Artificial Viscera(脏器)

- The invention of an intelligent artificial pancreas(胰腺) provides a reference to intelligent artificial organs.
- Intelligent artificial viscera, which are equipped with a sensor system, microsystems or a molecular system, are intended to have all the functions of normal organs.
- Xenotransplantation(异种器官移植) is faced with problems of insurmountable rejection(难避免排异), so it will be an effective way to equip an anti-rejection molecular system on the transplanted organs(移植).

Bedside Detecting

- The usual sampling, submitted to the report, the fastest speed also need more than half an hour, which is highly disadvantageous to save time and do a good surgery in critically ill patients(危重病人).
- To solve the above issues, bedside monitoring sensors have been developed, bedside monitoring sensors should be simple, robust, strong, light and can be continuous or semicontinuous operation, easy-as medical operation.

Fabric-based Sensors

- Wearable devices developed quickly in recent years.
- Smart textiles(纺织) using fabric-based sensors have been utilized in biomedical applications, such as monitoring gesture, posture(姿态) or respiration.
- Most of fabric-based sensors were fabricated by either coating piezo-resistive materials on a fabric or directly knitting conductive fibers into fabrics.
- The sensors used are generally physical sensors like resistance sensors, capacitance sensors and inductance sensors in biomonitoring, rehabilitation, and telemedicine.

1.4.5 Micro-Nano Systems

- Attributing to silicon technology, it is realizable to integrated CPU and miniature sensor on the same silicon chip, which promotes the intelligent microsensor technology.
- Microsystem is a silicon chip integrated of microsensor, microprocessor and micro controller. One typical application is intellectual pills for on-line detection in vivo.

Micro-Sensors

This is the molecular biomedical era, in the level of system, organs, tissues, cells and macromolecules, sensor detection types are changing with the development of life science research, from mechanical sensors, physical sensors, chemical sensors, biological sensors to molecular sensors.

Nano-technology

- Involves many disciplines across advanced technologies that study the structure and property of substances at the level of 1-100 nanometers.
- Molecular production process: how to make molecules produce substances and how to control the process.

1.4.6 Biochips and Microfluidics

Currently, the various biochemical analysis apparatus equipped for the clinical laboratory in hospital are bulky and expensive, the majority rely on imports.

Early diagnosis can not hope too much to imaging equipment, biochemical changes occur before changes in the quality, the sensor to sensing immune can realized a rapid detection to virus

Gene Sensors

- The gene controls cell activities and the process of men's life, gene detection is viewed as one of the core of the technique in modern life science.
- The gene detection uses the traditional biochemical methods and gene probe at present. The disadvantages of these method are complicated operation and low efficiency, DNA, RNA sensors are an efficient way to solve these problem and proceeding actively.

Monitoring in cells

- Human cells are the basic unit of human body. It is a hot topic in biomedical sensors to monitoring ion incident and the molecular events in cells.
- The ion-selective microelectrode technology which is used to monitoring ion incident. The ion-selective microelectrode technology which is used to monitoring molecular events is developing.

1.4.7 Biomimetic Sensors

Human body is the place that concentrates various sensors， these human body sensors have good features such as high sensitivity, good selectivity, high density, the development of biomimetic sensors is an important.

2 Basics of Sensors and Measurement

2.1 Introduction

- This chapter introduces basic sensor microfabrication technology, characteristics of sensors and measurement technology as well as common measuring methods and systems.
- Moreover, the serious concern about devices that comes from direct contact with the human body, which termed as“biocompatibility”, will be discussed here.

2.2 Sensor Characteristics and Terminology

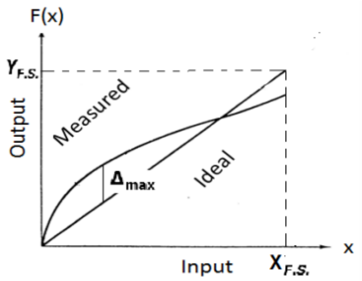
2.2.1 Static Characteristics

- Since a sensor influences the characteristics of the whole measurement system, it is important to describe its performance.
- The characteristics of a sensor may be classified as being either static or dynamic, and these parameters are essential in describing its behavior.
- Static characteristics can be measured after all transient effects have stabilized to their final or steady state.
- Dynamic characteristics describe the sensor's transient properties, and they can be measured in the sensor's responses to the time-varying inputs.

Linearity

Linearity is the closeness of a sensor's calibration curve to a specified straight line, and the specified straight line usually is the sensor's theoretical behavior or its leastsquares fit. Linearity is expressed as a percent of the fullscale output (YF.S.), which is the maximum deviation (Δmax) of any calibration point from the corresponding point on the specified straight line, and it is usually denoted the maximum relative error as ε :

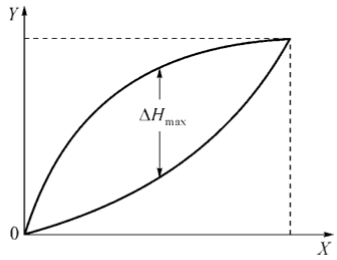
$$\varepsilon = \frac{\pm\Delta_{\max}}{Y_{F.S.}} \times 100\%$$



Hysteresis

Hysteresis(迟滞) is the maximum difference in output ΔHmax at any measured value within the specified range, when the value is approached first with an increasing and then a decreasing measured, which is shown in Fig. 2.2. It is also given in the percentage of maximum deviation and full range that is Hysteresis

$$\delta_H = \pm\Delta H_{\max} / Y_{F.S.} \times 100\%$$



2.2.2 Dynamic Characteristics

The relationship between the input and output of any linear time invariant measuring system can be written as:

$$a_n \frac{d^n y(t)}{dt^n} + a_{n-1} \frac{d^{n-1} y(t)}{dt^{n-1}} + \ldots + a_1 \frac{dy(t)}{dt} + a_0 y(t)$$
$$= b_m \frac{d^m x(t)}{dt^m} + b_{m-1} \frac{d^{m-1} x(t)}{dt^{m-1}} + \ldots + b_1 \frac{dx(t)}{dt} + b_0 x(t)$$

Zero-order sensors

The differential equation of zero-order system is:

$$a_0 y(t) = b_0 x(t)$$

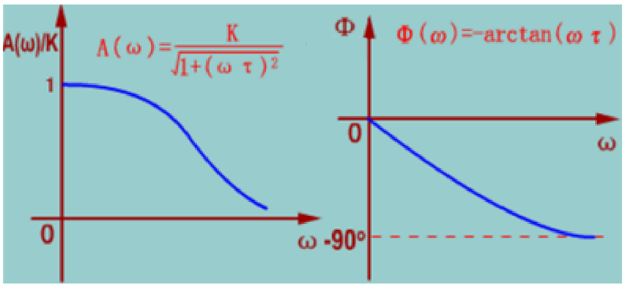
and the transfer function is:

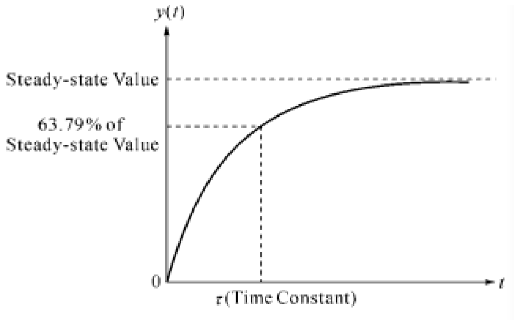
$$H(s) = b_0 / a_0 = K$$

First-order sensors

They can be represented by such differential equations:

$$a_1\frac{dy(t)}{dt}+a_0y(t)=b_0x(t)$$
$$\tau\frac{dy(t)}{dt}+y(t)=Kx(t)$$
$$H(s)=K/(1+\tau s)$$





Second-order sensors

The representation of a second-order system can be defined either as

$$a_2\frac{d^2y(t)}{dt^2}+a_1\frac{dy(t)}{dt}+a_0y(t)=b_0x(t)$$
$$H(s)=\frac{\omega_0^2K}{s^2+2\xi\omega_0s+\omega_0^2}$$
$$A(\omega)=\frac{K}{\sqrt{[1-(\omega/\omega_0)^2]^2+4\xi^2(\omega/\omega_0)^2}}$$
$$\Phi(\omega)=-\arctan\left[\frac{2\xi(\omega/\omega_0)}{1-(\omega/\omega_0)^2}\right]$$

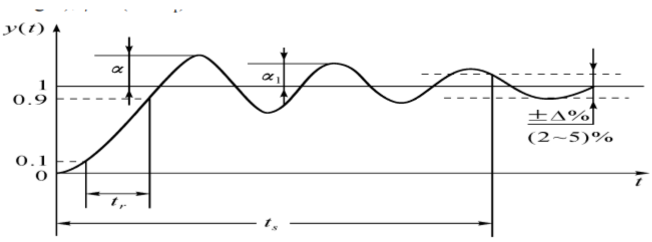
Rise time t_r : the required time that the steady-state value rises from 10% to 90%.

Response time t_s : the required time that the output response maintains stability in the ± Δ% error tolerances.

Overshoot(过冲) α: the value that the maximum output exceeds the steady-state value.

Delay time t_o : the required time that the output first reaches 50% of steady-state value.

Attenuation(衰减) ψ: the percentage of height decline between two adjacent peaks (or troughs), ψ = (α - α1)/α×100%.



2.3 Sensor Measurement Technology

- According to different kinds of classifications, the measurement methods can be classified as direct and indirect, active and passive, invasive and noninvasive, wired and wireless.

- A sensor system should include the sensor interface, signal preprocessing circuits, as well as other computer-aided digital signal processing hardware and software and so on.
- Sometimes, in some specific environments, it is difficult for a sensor system to detect signals. In this case, some other methods are implemented to improve the performance of the sensor system.

2.3.1 Measurement Methods

- Direct and Indirect Measurement
  - The direct measurement method uses the outputs of instruments as the results.

    > A schematic configuration for airflow monitoring

  - The indirect measurement method uses the calculated results of some measured parameters as the final ones.

    > A schematic configuration for airflow monitoring

- Active and Passive Measurement

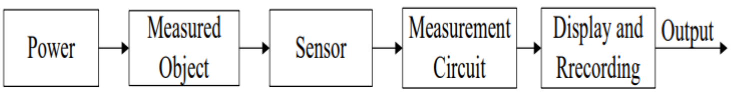


Fig. 2.7. Active measurement system

  -

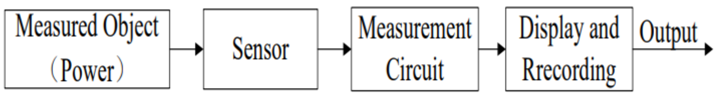


Fig. 2.8 Passive measurement system

- Invasive and Noninvasive Measurement
  - Invasive measurement uses methods that would influence or even injure the objects while the
  - Noninvasive measurement would have no influences on the objects.
- Wired and Wireless Measurement
  - In recent years, wireless measurement has developed very fast and is being used in more and more fields such as communication technology, biomedical fields and so on.
  - For example, an RFID-Based Closed-Loop Wireless Power Transmission System has been used in the biomedical field, especially for inductively powering implantable biomedical devices.
  - In this system, the transmitter and receiver coils are in a wireless power transmission.
  - This system can be used on the implanted chips to better detect diseases.

2.3.2 Sensor Measurement System

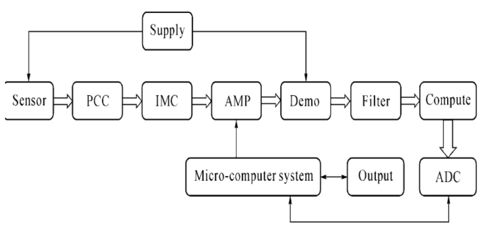


Fig. 2.3.3 Fundamental composition of sensor detecting system

PCC: Parameter Converting Circuits, IMC: Impedance Convertor Circuits

Circuits

- Parameter Converting Circuits
- Impedance Convertor Circuits
- Computing Circuits
- Ratio computing
- Analogue Filter Circuit
- DAC and ADC interface circuits
- Digital Signal Processing

2.3.3 Signal Modulation and Demodulation

- output values are relatively small
- the noise would result in serious measuring errors
- output signal is modulated in a parametric conversion circuit
- narrow-band filter demodulation and the relevant demodulation

  ### Signal Modulation Demodulation or Detection

  - Amplitude modulation
  - Frequency modulation
  - Phase modulation
  - Pulse-width-modulation
  - Envelope detection
  - Full-wave linear detection
  - Phase-sensitive detection

2.3.4 Improvement of Sensor Measurement System

- The overall errors in the sensor detecting system are integrated by the errors of three basic parts.
- The sensor is the first input of a detection system, improving the accuracy of the sensor is of vital importance.
- The design of sensors is the integration of mechanics, electricity, chemistry, biology, materials science and many other aspects.

  ### How to improve

  - Choosing proper sensors
  - Stabilization technology
  - Linearization Technology
  - Averaging technique

2.4 Biocompatibility Design of Sensors

- The term 'biocompatibility' is used extensively within biomaterial science.
- Sensors used for biological detection and medical diagnosis must seriously consider biocompatibility in order to avoid hemo(血液)- or histo(组织)- problems with direct contact.
- invasive sensors for implanting and monitoring physiological environment in vivo and sensors for monitoring cell or tissue in vitro.

2.4.1 Concept and Principle of Biocompatibility

Biocompatibility

- A serous problem with all devices used in contact with tissue is that of biocompatibility, especially hemocompatibility when they are used in contact with blood.
- Since biocompatibility is a special issue of biomedicine, the present description is restricted only to some special problems of sensor applications.

  #### Factors Should be Considered

  - Sensors are not supposed to be corroded or toxic.
  - The shape, size and structure of sensors.
  - Sensors must be solid enough & electrically insulated.
  - Sensors can neither give physical activities a burden, nor should they interfere with the normal physiological function.
  - The in vivo sensors used for long term implantation should not cause any vegetation.
  - The structure of the sensor should be easily disinfected.

Classification of Biocompatibility

- Blood compatibility: Biomedical sensors used in the cardiovascular system are in direct contact with blood, thus, the reactions between them should be carefully considered.
- Histocompatibility: Biomedical sensors implanted out of cardiovascular system are mainly focused on the interaction between the materials and the tissues or organs.

Evaluation of Biocompatibility

- Contact tissues: body surface and body tissues, bones, teeth, blood;
- Contact means: direct contact and indirect contact;
- Contact time: Temporary contact is less than 24 hours, short and medium-term exposure is longer than 24 hours but shorter than 30 days, and longterm exposure is more than 30 days;
- Purpose: general function, reproductive and embryonic development （胚胎发育）, biodegradation （降解）.

2.4.2 Biocompatibility for Implantable Biomedical Sensors

The biocompatibility design for biomedical sensors in vivo involves several problems: surface materials, device morphology, infection, toxicology and host response affections toward the responses of the device. An optic micropressure sensor for evaluating its biocompatibility using the International Organization for Standardization (ISO) test standard.

Biocompatibility for Implantable Biomedical Sensors

Twelve healthy white rabbits were divided into three groups for different 2 Basics of Sensors and Measurement 38 implantation periods (1, 4 and 12 weeks), with four animals tested during each time period.

2.4.3 Biocompatibility for in Vitro Biomedical Sensors

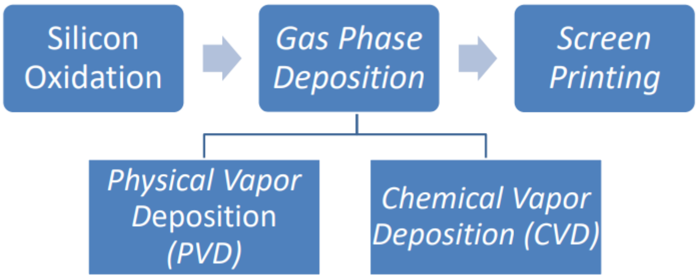
- Biocompatibility of the biomedical materials on sensor surfaces must be enhanced to maintain the activity and viability of these samples such as proteins, cells and tissues .
- The biocompatibility of sensor surface materials affects the biological sample's viability and activity.
- Two types of surface materials: passivated (钝化) materials or metal and metal oxide materials.
- Functional proteins such as enzyme, antigen and antibody play an important role as receptors in biomedical sensor systems.
- Various physical and chemical methods are utilized to immobilize these proteins onto sensor substrate surfaces.
- Various approaches are used to modify the characteristics in electrostatics, physical adsorption, and surface chemical group immobilization of the biomedical sensor surfaces.
- Besides, these samples are very sensitive to temperature and pH value changes

2.5 Microfabrication of Biomedical Sensors

2.5.1 Lithography

- Photolithography: When the wafer is exposed to the ultraviolet radiation, the absorber pattern on the photo mask is opaque to ultraviolet light and the pattern is transferred to the photoresist based on its polarity.
- Electron beam lithography: The major advantages of electron beam lithography are the ability to register accurately over small areas of a wafer, lower defect densities, and a large depth of focus because of continuous focusing over topography.

2.5.2 Film Formation



2.5.3 Etching

- Etching is a process to remove material from the unprotected area for forming functional structure on a wafer.
- Wet etching
  - reactive species diffuse from liquid bulk to the surface of the film.
  - reaction happens at the surface to form solvable species.
  - reaction products are diffused away from the surface of the film to liquid bulk.

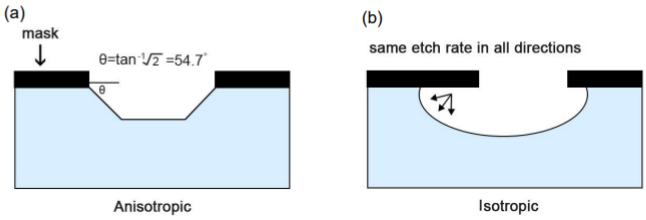
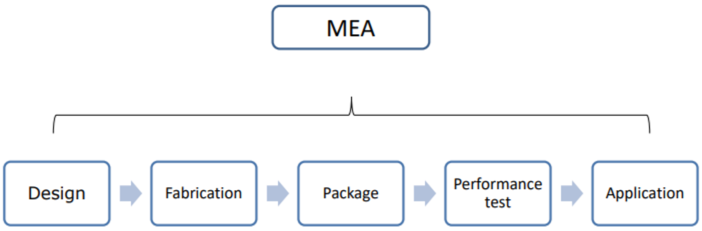
- 

Fig. 2.15. (a) An anisotropic etch on a silicon wafer creates a cavity in the cross-section. The sides of cavity are <111> planes with an angle of 54.7° . (b) In isotropic etch, it has same etch rate in different directions.

- Dry etching
  - chemical reactions with reactive gases or plasma.
  - physical bombardment of atoms.
  - the combination of both physical removal and chemical reactions.
  - Plasma etching
  - Reactive ion etching (RIE)

2.5.4 Design of the Biomedical Sensor



MEA

- A wafer of glass is cleaned and then the Cr (30 nm) and Au (300 nm) are sequently sputtered or evaporated onto it.
- The photoresist is then spin coated on the metallic layer and protects the pattern of electrodes and traces by standard photolithographic.
- A composited metallic layer (Cr/Au) is chemically etched away.
- The alternative $SiO_2/Si_3N_4/SiO_2$ as a passivation layer is deposited onto the surface of the chip by PECVD. • The photoresist is spin coated on the chip again and exposes the sensory sites by photolithography with a second mask.
- We take the TiN as the surface treatment option.

- scribed into individual ones
- fixed onto a PCB board
- bonded with pads of PCB board by gold wire
- A chamber is fixed onto a chip to form a room for the cell culture