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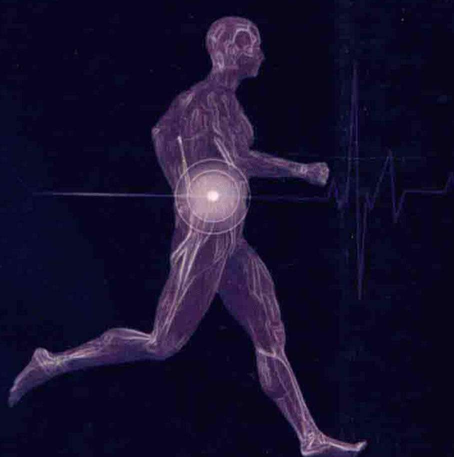
王 平 刘清君 吴春生 Chung-Chiun Liu 编著

Biomedical Sensors and Measurement

生物医学传感与检测

（第二版）



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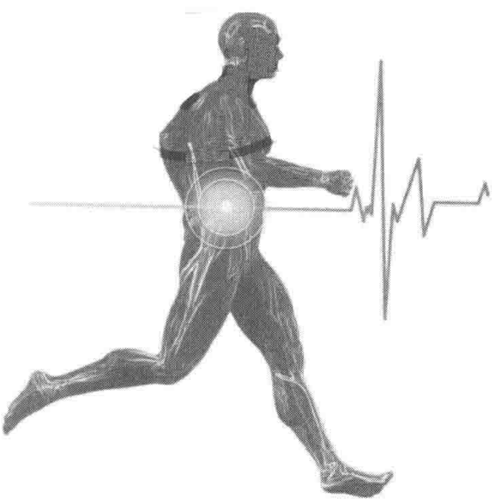

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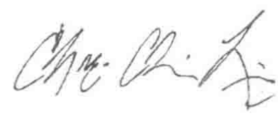
Foreword

This book introduces the basic fundamentals of biomedical sensors and the measurement technology as well as the recent advancements in this field in recent years. There are five chapters in this book which can be subdivided into two major parts. The first part places emphasis on the fundamentals and the development of modern biomedical sensors and measurement technology including their basic features and special requirement in application. This part also provides essential information on the basic sensitive reaction mechanisms, characteristics and processing approaches of the biomedical sensors. The second part introduces the typical sensors including the physical, chemical and biological sensors as well as the discussion of their measurement techniques. The practical applications of each of these sensors are also described in detail. There are two unique features in this book: (1) The combination of the discussion on the biomedical sensor technologies and their required measurement techniques which include the fundamentals and the practical applications of the biomedical sensors; (2) The rationale and the needs of the integration of discrete sensing elements into a meaningful and practical sensor array which can become an intelligent sensing system. The authors have given a very persuasive and sound approach in this important scientific and practical endeavor. It also should be acknowledged that the authors have systematically provided a clear roadmap for the development of various sensors by first introducing macro-size sensors for the detection of physical properties and then leading to the advancement of micro-size chemical and biological sensing systems.

The advancement of the micro-size for chemical, biological and biomedical sensors or sensor micro-systems requires multi-disciplinary skills and expertise. This includes the understanding and expertise in microfabrication and micromachining processing, electronic and ionic conductive materials, sensor operational principles, electronic transduction interface technologies and many others. In this book, the authors have logically and systematically discussed and analyzed the interwoven relationship of these techniques and their applications to the development of scientifically and commercially sound practical chemical, biological and biomedical sensors.

The authors have been engaging, for many years, in the research and teaching of sensor technology, particularly in the field of biomedical sensors. They have been involved in this research effort more than a decade and, their appreciation of the multi-disciplinary nature of the sensor research and the unique requirements for the advancement of the biomedical sensors and their measurement techniques can be well recognized throughout this book. As mentioned, this book is derived from the research work on biomedical sensors and measurement, in recent years, at Zhejiang University, Hangzhou, China. While it also contained many references to the teaching materials from Case Western Reserve University, Clevland, USA. Thus, this book will serve as an excellent reference source for researchers in biomedical sensor and measurement. It is intended for scientists, engineers, and manufacturers involved in the development, design, and application of biomedical sensors and measurement. The reference list given in each chapter is very thorough and relevant. This book will also be a very good book for the senior undergraduate and graduate students who wish to pursue a professional career in this field.

Biomedical sensors and the measurement are scientifically and commercially important in numerous applications at this juncture, and this book will be most welcome for researchers and students who wish to understand this field further and to make a meaningful contribution to this important endeavor.



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August, 2015

Preface

In the 21st century, technological innovation has had such a rapid development that science and technology permeates all aspects of our lives, especially in the biomedical field which attracts a large number of professional scientists and engineers. Biomedical engineering is a combination of two developing areas: biomedicine and information technology. It promotes the biomedical sensor design and development, as well as applications in clinical diagnosis and treatment technology. Biomedical engineering covers many research areas: bio-mechanics, bio-materials, physiological modeling and sensing technology, detection technology, signal and image processing. One important research field is biomedical sensor and measurement technology, which obtains original information from primitive organisms (especially human body), one of the most crucial procedures.

In the 1960s, scientists and engineers paid more attention to sensors for they met many of the practical requirements. The development of chemical and biological sensors creates selective sensors, which makes the direct detection of a variety of ions and molecules possible. Micro-sensors and micro-electrodes quickly replaced traditional large-size sensors and were applied to biological and medical fields.

At present, the quick body digital thermometer, blood pressure monitors, and wearable home-used blood glucose meter have been widely used. CT (computed tomography scanning) and ultrasound technology are recognized as common advanced diagnostic tools. However, many have omitted that sophisticated sensors play an important role in these instruments. Sensors have brought about revolutionary changes in the field of biomedical diagnostics and application of medical instrumentation, and it will have a positive effect on human life quality in the 21st century. It has the following applications:

- Digital medical image tools like CT, fMRI and ultrasound, etc.;
- For the traditional image tools such as X-ray machines, it improves and gets more information and reduces the amount of radiation;
- Portable clinical multi-parameter monitoring equipment;
- Portable and wearable home-use monitoring and diagnostic equipment;
- Implantable, self-calibration equipment which will be widely used in the future;
- Intelligent systems of sensors that can replace our sense system, such as sight, hearing, touch, smell and taste, etc.;
- Rapid diagnosis tools based on immunization and DNA-chip technology.

Although biomedical sensors are being applied more and more, in many cases, the theory is not entirely clear. It's controversial in the expression of stimulus signal theory, signal extraction and measurement. The development of new biomedical sensors indicates a great fundamental research work, which is the key part at present.

Biomedical sensors convert biomedical signals into easy-to-measure electrical or optical signals. It is the interface between organisms and electronic systems. Meanwhile, effective detection technology, including low-noise and anti-jamming circuits and data processing techniques are essential during the conversion from biomedical to electronic signals, as well as for further processing. This book adds the measurement technology with sensing technology according to the actual teaching requirement, so that students and other researchers may systematically learn and comprehend the relevant knowledge in this field.

This book can be used as a reference book for researchers and senior undergraduates and graduate students. This book combines measurement technology with sensor technology and strengthens the links between them. In addition, the authors have added an introduction of regular physical sensors and chemical sensors, reorganized and reviewed the latest international development trends of chemical sensors, biological sensors and their intelligent systems, such as electronic nose, electronic tongue, microfluidic chips and micro-nano biosensors, and their applications.

Biomedical sensors and measurement techniques require synthesizing the interdiscipline of physics, electronics, materials, chemistry, biology, and medicine, etc. The authors are trying to meet this requirement through a detailed description of working principles, sensing technology, detection circuit, and identification system theory of sensors or devices. We believe that this book will be of great value for those academics, engineers, graduates and senior undergraduates in the biomedical and relevant fields.

The book is composed of five chapters. Chapter 1 introduces the development of biomedical sensors and measurement technology; Chapter 2 describes fundamental knowledge of modern sensors and measurement technologies; Chapter 3 describes the physical sensors and measurement technology; Chapter 4 describes chemical sensors and measurement techniques; and Chapter 5 describes the biosensors and measurement technology. Some content in this book belongs to the international research frontier. Biomedical sensors and measurement technology promotes the reorganization of biomedical information transmission, processing and perception, as well as the development of biomedical engineering and the interdisciplinary field.

The book is the result of many years of study, research and development of the faculties, PhD candidates and many others affiliated to the Biosensor National Special Laboratory of Zhejiang University. We would like to give particular thanks to Jun Wang, Wei Cai, Qi Dong, Gong Cheng, Di Wang, Jun Zhou, Cong Zhao, Lin Wang, Liang Hu, Kai Yu, Wen Zhang, Huixin Zhao, Liping Du, Ning Hu, Yishan Wang, Yingchang Zou, Liujing Zhuang, Ning Xu, Qian Zhang, and Xuanlang Zhang. We sincerely thank them all for their contributions.

And we are deeply grateful to the financial supporting for us overall systematization, teaching, and research work on biomedical topics through over the past ten years: by National Natural Science Foundation and National Distinguished Young Scholars Fund of China (Grant Nos. 31470956, 31571004, 60725102, 30700167, 61320106002, 81071226, 31000448), Zhejiang Provincial Natural Science Foundation of China (Grant Nos. 2006CB021, 2010C14006, Y2080673), National Basic Research Program of China (973 Program, Grant No. 2015CB352101) and National Marine Public Welfare Project China (Grant No. 201305010), State Key Laboratory of Transducer Technology of China (Grant Nos. SKT1101, SKT1301), etc.

As biomedical sensors and measurement involved in wide interdisciplinary areas, and in consideration of the limit of authors' knowledge and experiences, errors of judgment are, of course, inevitable, therefore, comments and suggestions will, be very appreciated.

Ping Wang
Zhejiang University, Hangzhou, China
June, 2015

Contents

Chapter 1

Introduction

1.1 Definition and Classification of Biomedical Sensors

Sensors are devices that can be used to transform non-electrical signals into electrical signals. The biomedical sensors are very important kinds of sensors. First we will introduce some basic knowledge about biomedical sensors including the definition and classification.

1.1.1 Basic Concept of Sensors

Sensors or transducers are devices which can respond to measured quantities and transform the quantities into signals which can be detected. A sensor is usually composed of a sensitive component which directly responds to a measured quantity, a conversion component and related electronic circuits. Sensors often provide information about the physical, chemical or biological state of a system.

Measurement is defined as operations that aim to obtain the measured value of the quantity. Sensor measurement technology uses sensors to transform other measured quantities into physical quantities which are easier for communication and processing; then we can go on with display, recording and analysis. Along with the development of modern electronic technology, micro-electronic technology and communication technology, electrical signals are most convenient for processing, transportation, display, and recording; which make electrical signals represent some of the various types of useful signals. Therefore, sensors are also narrowly defined as devices that can transform non-electrical signals into electrical signals.

Biomedical sensors are special electronic devices which can transfer the various non-electrical quantities in biomedical fields into easily detected electrical quantities. They expand the sensing function of the human sense organ. For this reason, they are the key parts of various diagnostic medical analysis instruments and equipment and health care analysis. Biomedical sensing technology is the key to collect human physiological and pathological information and is an important disciplinary branch of biomedical engineering.

1.1.2 Classification of Biomedical Sensors

Biomedical sensors can be classified into the following categories according to their working principles, including physical sensors, chemical sensors, and biological sensors.

Physical sensors: It refers to the sensor made according to physical nature and effect. This kind of sensor is mostly represented by sensors such as metal resistance strain sensors, semiconductor piezoresistive sensors, piezoelectric sensors, and hotoelectric sensors.

Chemical sensors: It refers to the sensor made according to chemical nature and effect. This kind of sensors usually uses ion-selective sensitive film to transform non-electrical quantities such as a chemical component, content, density, into related electrical quantities, such as various ion sensitive electrodes, ion sensitive tubes, and humidity sensors.

Biological sensors or biosensors: It refers to the sensors using biological active material as a molecule recognition system. This kind of sensors usually uses enzyme to catalyze some biochemical reactions or detect the types and contents of large organic molecules through some specific combination. It is a kind of new developed sensors in the second half of the century, and examples include enzyme sensors, microorganism sensors, immunity sensors, tissue sensors, DNA sensors, etc.

Classified by detection type, there are displacement sensors, flow sensors, temperature sensors, speed sensors, pressure sensors, etc. As for pressure sensors, there are metal strain foil pressure sensors, semiconductor pressure sensors, capacity pressure sensors and other sensors that can detect pressure. As for temperature sensors, it includes thermal resistance sensors, thermocouple sensors, PN junction temperature sensors and other sensors that can detect temperature.

There is another method that classifies sensors according to the human sense organ that the sensor can replace, such as vision sensors, including various optical sensors and other sensors that can replace the visual function; hearing sensors, including sound pick-up sensors, piezoelectric sensors, capacity sensors and other sensors that can replace the hearing function; olfaction sensors, including various gas sensors and other sensors that can replace the smelling function (Harsányi, 2000). This kind of classification is good for the development of simulation sensors.

In many situations, these classification methods mentioned above are used together. For example, the strain gauge pressure sensor, conductance cardiac sounds sensor, thermoelectric glucose sensor and so on. The classification has met problems as a result of the diverse development of sensing technology. Therefore the classification methods have their advantages and disadvantages. Any standard classification method hasn't existed so far.

1.2 Biomedical Measurement Technology

Biomedical signals are commonly weak, highly with strong random noise and interference, allowing dynamic changes, and exhibiting significant individual differences. Therefore, biomedical measurement technologies are more complex and rigid than common industrial detection technologies.

Biomedical measurement is a guiding technology in the acquisition and processing of biomedical information and is directly related to the research of biomedical sensing technology, biomedical measurement methods, electronics and measuring systems. Therefore, the innovative research and development in biomedical measurement has a direct effect 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. For example, Electrocardiograph (ECG), Electroencephalogram (EEG), and Electromyogram (EMG) are electrical physiological signals; while blood pressure, body temperature, breath, blood flow and pulse are non-electrical physiological signals; blood and urine are chemical or biological signals; enzymes, proteins, antibodies and antigens are biological signals. Similarly, the biomedical measurement systems demand particular reliability and security.

Nowadays the measurement of physical signals has been popularized and many measurements of chemical signals have practical applications. The measurement of biological signals is mostly at the laboratory research stage. With a greater combination of microelectronics, optoelectronics, quantum chemistry and molecular biology with traditional sensing technology, the measurement methods and systems for detecting complex organisms will enjoy a brighter future. Biomedical measurement technology will also develop into mini-type, multiple-parameter and practical applications. The advancements of electronics, IC technology, computer technology and advanced signal processing and intelligent algorithms will promote the application of biomedical measurement.

1.2.1 Bioelectrical Signal Detection

The detection of physiological quantities in the circulatory system and nervous system develops relatively early and rapidly, and its importance always leads to a large amount of research reports in this field. Take ECG as an example. Many researchers are still working on automatic extraction and discriminating arrhythmia information from ECG under strong interference. In addition, the detection of the P wave and the ST segment in ECG, the research on obtaining an ECG of a fetus from a mother's body surface and on high frequency ECG and on body surface, the real-time detection and the late potential detection have been improved to different extents. ECG detection is mainly applied in diagnosing heart diseases and preventing sudden cardiac death. Moreover, it could also aid in surgical investigational procedures (Tigaran et al., 2009). Although these research achievements are not mature enough to be put into clinical use, they improve the function of ECG diagnosis and monitoring devices.

1.2.2 Biomagnetic Signal Detection

The biomagnetic field comes from the human body with biological electrical activities, such as Magnetocardiogram (MCG), Magnetoencephalogram (MEG), and Magnetomyogram (MMG). In addition, it also includes the magnetic field caused by the magnetic medium in the tissue when affected by an external magnetic field. An invasive strong magnetic mass can also cause an internal biomagnetic field. At present we can detect these magnetic fields in the laboratory. However, commonly a biological magnetic field is very weak. For example, the intensity of MCG is about 10^{-10} T and the intensity of MEG is about 10^{-12} T. Therefore SQUID (superconducting quantum interference device) in the liquid nitrogen container is used to detect the biological magnetic field and the measurement system should be placed in a special shielding environment.

In contrast to the detection of bioelectricity, the detection of a biomagnetic field has many features. Take the measurement of MCG as an example. The detection system does not directly come in contact with the organism, which means that the detection uses a detecting coil rather than an electrode to pick up the biological signals. Therefore it receives no effect from the surface of the objects and does not cause an electrode artifact, which is electrically safe. Besides, the detecting signals come from a certain spot or place rather than the difference between two points. Therefore, a location measurement can take place. The magnetoconductivity in tissue is well-distributed which means that biomagnetic signals will not distort when spread in the body. As a result, research on biomagnetic detecting methods has become one of the pioneering and hot topics and has good application prospects. With the development of room temperature superconductor technology, biomagnetic detection will reach the clinical application stage.

1.2.3 Other Physiological and Biochemical Parameter Detection

It has become a common practice to use sensors non-invasively to detect non-invasive blood pressure, blood flow, breath, pulse, body temperature and cardiac sounds, which leads to wide applications in clinical examinations and other monitoring techniques. The trend is to develop new non-invasive or slightly invasive detecting methods and users one sensor each time to detect multiple physiological parameters. For example, we use the photoelectric method to detect the pulse as well as other information such as the heart rate, blood pressure, oxygen saturation; use electromagnetic coupling or optical coupling to detect intracranial pressure, and pressure in the mouth. Non-contact and long-distance detection also lead current development trends.

Biochemical parameter detection usually uses blood and body fluid as samples to conduct the measurement. Therefore, most of the methods are invasive and cannot measure the changes of the parameters over a long-time and in real-time. At present, non-invasive and slightly invasive biochemical parameter detecting methods have received great attention. For example, researchers have detected phenacetin in the saliva and compared it with the results of blood plasma tests; researchers extract lixivium by exerting a small amount of negative pressure on the skin and then using ion field effect transistor sensors to detect blood sugar; dielectric spectroscopy (DS) has been applied to monitor changes in the glucose level by combining electromagnetic and optical sensors (Talary et al., 2007).

1.3 Characteristics of Biomedical Sensors and Measurement

Biomedical sensors and measurement have specificities when they are used for human signal detection such as interdisciplinarity, knowledge-intensity, biocompatibility, which is non-invasive, safe and reliable. The measurement of biomedical sensors has become an important research area in recent years. In this chapter, the features and special requirements of biomedical sensors and measurement are introduced. In addition, the most different aspect in designing biomedical sensors from other sensors, the biocompatibility, is also discussed.

1.3.1 Features of Biomedical Sensors and Measurement

Interdisciplinary Research: Biomedical sensor technology, as an active discipline, combines electronic science with biomedicine. Biomedical sensor technology meets the requirement of early diagnosis, quick diagnosis, bedside monitoring, monitoring *in vivo* and more advanced health care, and provides indispensable support for gene probes, molecular recognition, monitoring of neurotransmitters and neuromodulators, and more advanced scientific study. The developing disciplines such as microelectronics technology, biological technology, molecular biology and photonics technology lay the foundation for biomedical sensors technology. With such a background, biomedical sensor technology has made significant and rapid progress.

Basic research and technological innovation: In the 1970s, sensors were involved in the technological and scientific fields and focused on new product development. The basic research paid more attention to the advanced and high-level product exploration process. The primary target was a description of the molecular recognition mechanism, which was the basis of improving SNR, the mastery of the interface process, and the key to shortened response time. To put results into products, all kinds of processing technology including precision machining, semiconductor technology, chemical etching and biotechnology should be applied to technological innovation.

Sensitive materials and film formation technology: The core components of a sensor-sensitive membrane consist of sensitive materials combined with the matrix material. As to popular film formation technology, semiconductor thin-film, thick-film and molecular beam extension are used in physical sensors, physical adsorption and embedded technology, chemical cross-linking and molecular assembly for chemical sensors, and multi-enzyme system membranes, monoclonal antibody films, conductor films and LB film for biochemistry sensitive membranes.

Knowledge-intensive: Many disciplines are involved in sensor design, production and utilization. Take a chemical sensor for example. A knowledge of quantum chemistry is necessary for sensitive materials design; the same as that super-molecular chemistry, host-slave chemistry and biotechnology for materials synthesis; interface chemistry, physical interface and molecular assembly technology for film formation technology; microelectronic technology, photonics technology and precision machining for transfer devices.

High reliability: For a biosensor to be in direct contact with the human body, it must have high reliability. Sensors should be controlled strictly by the FDA in America and put on the market only if proved to be safe for the human body in the long term and to provide reliable monitoring data. Sensors detecting body fluids should have the corrosion resistant and be easy to clean; embedded or implanted sensors should withstand rejection by the human body.

Fine technology: Fine technology is necessary for high-precise sensors. A matrix sensor, in the operation of integration technology, needs special implantable technology to reject leaking or deformation when soaked for a long time; coupling of a sensitive membrane and fiber cross Section requires fine technology; although a glass microelectrode can be stretched by certain machines. Precision machining is the combination of machining and chemical technology. The sensor is not only a product but also a fine artwork.

1.3.2 Special Requirements of Biomedical Sensors and Measurement

For biomedical measurement, it has specificity when it is used for human signal detection: it is a non-invasive, safe and reliable measurement. It has become an important research project in recent years. Non-invasive detection, which causes no wound or a slight wound, is easily received by people. It helps to keep the physiological status of objects and long-time or real-time monitoring take place. Therefore it is convenient for clinical examination, monitoring and recovering evaluation. Non-invasive detection has become an important part of biomedical measurement technology.

Biomedical measurement research fields involve some special measurement method, e.g., low-noise and anti-interference technology, picking up signals and analyzing and processing technology and measurement systems and analog-digital circuits and computer hardware and software even BCI (brain-computer interface) technology, etc. It also depends on the development of life sciences (such as cytophysiology, neurophysiology, biochemistry, etc.). The diversity of research objects in biomedical detecting technology make the research projects dispersive in this field. However, any promotion of detection methods in physiological quantities and biochemical quantities will greatly compel the advancement of the whole life science as well as the invention of new diagnosis and treatment devices.

The most different aspect in designing biomedical sensors from other sensors is the consideration of biocompatibility. Because this type of sensors directly makes contact with tissue or blood, the sensor design should include hemocompatibility and histocompatibility.

The first and the most important issue in manufacturing sensors is the material selection. The metallic materials are used in sensors should be inert metals such as stainless steels, titanium alloys. The polymers should be degradable materials, such as PMMA (polymethyl methacrylate), silicones. All the materials used for sensor structure should be strictly selected to avoid serious host response and should function normally after being inserted into the animal body. The rigidness and flexibility of materials should also meet the requirement since the implanted sensors need to adjust to anatomical structures of the measured objects.

Secondly, a series of experiments on animals and clinical trials should be carried out before clinical applications. Besides choosing inert and least harmful materials at present, we still have to do full sequence tests for biocompatibility because the implanted sensors are under a different physiological environment.

Finally, we apply biological methods to evaluate the host responses. The *in vivo* biocompatibility can be evaluated by analyzing the cell population present, measuring the mediator and metabolite cells excreted, and analyzing the morphologic characteristics of the tissue and the capsule thickness around the implant.

Besides, some biological samples such as enzymes, proteins, cells and tissues have to be analyzed externally. An appropriate immobilization on the sensor surface is required for maintaining biological viability and activity. Hence, the biocompatibility for *in vitro* biomedical sensors should also be taken into account in sensor design.

1.4 Development of Biomedical Sensors and Measurement

Biomedical sensors and measurements have been developing rapidly over the past 30 years, and the development is represented in various aspects. The development of the medical sensors has basically changed the traditional mode, forming the development trend of smart, micro, multi-parameter, remote-control and non-invasive, and achieved some technical breakthroughs. Other new types of