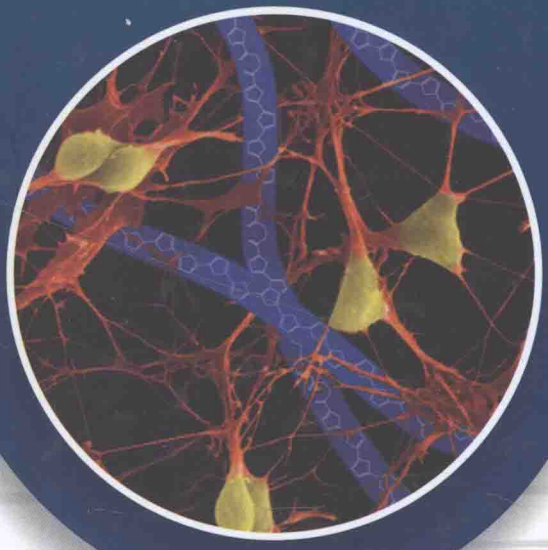
Recent Progresses in BIOELECTRONICS

生物电子学最新进展

顾忠泽　主编



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北京

内 容 简 介

美国国家标准与技术研究所(NIST)将生物电子学定义为生物学与电子学的融合领域。这主要包括两部分内容：一是生物系统中电子学现象，包括研究生物分子的电子学特性、信息的传输和储存；二是利用电子学的手段解决生物学问题，包括利用传感器获取和分析生物信息等。近几十年以来，生物电子学有了飞速的发展，其内涵和外延也不断变化。2015 年是东南大学生物电子学国家重点实验室成立 30 周年。本书汇集了该实验室成立以来的主要研究进展，由实验室的现任研究人员和曾经在实验室工作过的人员编写，其内容涵盖材料与界面、生物传感与芯片、生物信息学和生物医学影像等四个方面，主题包括生物分子相互作用、自组装、单细胞分析、生物芯片、生物信息学、神经接口、多模态成像技术等，这些也是生物电子学的重要内容。

本书适合生物医学工程、电子工程、分析化学、材料工程和生物工程，以及其他生物医学相关专业的本科生、研究生及研究人员阅读和参考。

图书在版编目（CIP）数据

生物电子学最新进展=Recent Progresses in Bioelectronics/顾忠泽主编. —北京：科学出版社，2016

ISBN 978-7-03-047280-9

Ⅰ. 生… Ⅱ. 顾… Ⅲ. 生物电子学–英文 Ⅳ. Q-331

中国版本图书馆 CIP 数据核字（2016）第 025434 号

责任编辑：张淑晓 张翠霞 / 责任校对：贾伟娟
责任印制：肖 兴 / 封面设计：耕者工作室

科学出版社出版
北京东黄城根北街 16 号
邮政编码：100717
http：//www.sciencep.com

中国科学院印刷厂印刷
科学出版社发行 各地新华书店经销
*
2016 年 3 月第 一 版 开本：720 × 1000 1/16
2016 年 3 月第一次印刷 印张：21 1/2 插页：16
字数：410 000

定价：128.00 元

（如有印装质量问题，我社负责调换）

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Preface

Bioelectronics was first published in 1912 and focused on measurement of electrical signals generated by the body, which is the basis of the electrocardiogram. In the 1960s two new trends appeared in bioelectronics. One was implantable electronic devices and systems, such as the pacemaker. The other was the study of electron transfer in electrochemical reactions. In 1970s-1980s, Erwin Neher and Bert Sakmann invented patch clamp and investigated the potential of cell membrane. In 1990s, bioelectronics went to single molecule level and molecular electronics appeared. In February 2009, the National Institute of Standards and Technology (NIST) of the U.S. Department of Commerce published *A Framework for Bioelectronics*: *Discovery and Innovation* and defined bioelectronics as "the discipline resulting from the convergence of biology and electronics". The convergence contains two aspects: one is to study the electronics phenomena in biological systems, including the electronic characters of biomolecules, the transmission and storage of information; the other is to solve biological problems with tools of electronics, such as acquisition and analysis of bioinformation, and the related biomedical detection techniques, sensors, instruments and therapeutic methods.

Today, the concept of bioelectronics is broaden and cross-disciplinary, especially when it is boosted by nanotechnology. In general, the content of bioelectronics covers acquisition system and detection system of bioinformation, modelling and simulation of biosystem, nanobiology, biochips and micro total analysis system (μTAS), and biomedical instrumentation. In the next five years, the rising of flexible bioelectronics and bioelectronics medicine as frontiers of bioelectronics will be anticipated. It allows wearable and implantable sensors, actuators and drug delivery systems, which will monitor the health of human, and intervene or treat diseases in real-time. Bioelectronics allows people to understand life more precisely and deeply, and engineering life more effectively and creatively. It has very close relationships with material science, electronics, nanotechnology, biology and medicine and thereby it is of great significance to the industry, medicine and security.

State Key Laboratory of Bioelectronics (SKLB), Southeast University of China, was founded in 1985 by Dr. Yu Wei, one of China's noted experts in electronics. The laboratory was conferred on the name of Chien-Shiung Wu Laboratory by the

world-famous physicist Dr. Chien-Shiung Wu in 1992 and was approved as an open laboratory of molecular and biomolecular electronics by the Ministry of Education (MOE) of China in the same year. In 1997, the laboratory was renamed the Key Laboratory of Molecular and Biomolecular Electronics of the MOE. In 2005, the laboratory was promoted to the State Key Laboratory of Bioelectronics by the Ministry of Science and Technology of China, which represents the highest level of research in bioelectronics in China. The objective of the laboratory construction is to conduct frontier research in the light of the development of bioelectronics; to come up with innovative research methods and technologies by applying the rapid developments in information science with emphasis on the study of life process, related pathologensis and its medical application on the level of nanometers and molecules. Now, there are four main research directions—biomaterials and interfaces, biosensors and chips, genomics and bioinformatics, and biomedical imaging. The research activities in the laboratory focus on the fabrication of biomaterials and biodevices, acquisition and sensing of bioinformation, and application of bioinformation systems. The research fields cover the preparation of nano (molecular) materials, assembly and characterization of molecular ordered structures, application of bio/nano materials, nano (molecular) devices, implantable bioelectronic devices, detection of single molecule and single cell, biosensor, micro-array chip, microfluid biochip, bioinformatics, application of biomimic information processing system, modeling and using of brain information system, etc.

Over 30 years of fast development, lots of achievements are accomplished by SKLB. The faculties have published hundreds of articles in significant international academic journals like *Nature*, *Cell*, and *Nature Materials*, obtained dozens of provincial and ministerial awards, and held over 100 patents. The laboratory has organized many academic conferences and initiated fruitful cooperation with famous laboratories in United States, Japan, Germany, United Kingdom, France, Switzerland, etc. With all the endeavors of faculties, SKLB gains their leadership in gene sequencing, biochips and nano-medicine all over the country and pioneers in the frontier of bioelectronics in the world.

In order to fulfill the need of the national and local economic development, SKLB also has established five laboratories, i.e., Wuxi Biochip Key Laboratory, Suzhou Biomedical Materials and Technology Key Laboratory, Suzhou Environment and Biosafety Key Laboratory, and Nanjing Innovation Center of Strategic Biomedical Industry in collaboration with local governments, which contributed a lot to the innovation and development of cities in Jiangsu Province. In this year, SKLB also

established Institute of Biomaterials and Device in alliance with six other province key laboratories in the field of biomedical engineering in Southeast University. This institute is affiliated with Jiangsu Industry Technology Research Institute, whose aim is to reform the construction of industry in Jiangsu Province and bridge the gap between fundamental research, application development and industrialization. By these affiliated laboratories and institutes, SKLB aims to transfer the original innovative research to the productivity, explores new models of innovation and addresses the innovation driven development.

2015 is the 30th anniversary of SKLB and the fast growing bioelectronics is also attracting more and more attention from people especially when "internet+health" is widely acknowledged and the fusion of "bio" and "electronics" is more and more deep. To celebrate this, this book was proposed and the recent progress of the aforementioned four directions was reviewed, which ranges from interfaces and materials to imaging and algorithms and covers all levels of bioelectronics. By this book, the readers could not only learn the research development of bioelectronics in China, but also the cutting edge technologies in the related fields of bioelectronics.

Zhongze Gu

December 30, 2015

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Chapter 1 The Photoelectric Detection at the Single Cell Level

Can Li, Ning Gu

1.1 Introduction

Cells are the basic structural and functional units of living organisms. Highly efficient and sensitive detection of the components in cell will explain some important physiological processes such as metabolism, signal transduction and so on.

In the past years, increasing interest has evolved for single-cell analytical methods, which could give exciting new insights into genomics, proteomics, transcriptomics and systems biology. Therefore, single-cell analysis has become a "hot topic", various high sensitivity, high selectivity, high temporal resolution and high throughput techniques have been developed for single-cell analysis.

In the recent years, single-cell analysis has gone deep into subcellular (local of cytoplast, cellular membrane, vesicular) and single molecule level[1, 2], while the detection methods determine accuracy and degree of analysis. As it is known to all, optical and electrical methods are more direct and fundamental in single-cell detection. By optical or electrical detection, we can directly get the signal of single cell such as impedance, voltage, which may be more accurate and fast as there is no need for conversion. Here we review the single main optical and electrical methods for single-cell detection and analysis. There are many excellent research results. While it is not realistic to cover all of them, here we just list parts of them.

1.2 Dielectrophoresis

Positioning single cells is of utmost importance in areas of biomedical research as diverse as *in vitro* fertilization, cell-cell interaction, cell adhesion, embryology, microbiology, stem cell research, and single-cell transfection. Dielectrophoretic tweezers, a sharp glass tip with electrodes on either side, are capable of trapping single cells with electric fields. Mounted on a micromanipulator, dielectrophoresis tweezers can position a single cell in three dimensions, holding the cell against fluid

flow of hundreds of microns per second with more than 10 pN of force[3]. Figure 1.1 (a) is an illustration of how dielectrophoretic tweezers work. Two electrodes a few microns apart provide a non-uniform electric field which polarizes a nearby cell. If the cell is more polarizable than the solution, it will be attracted to the field maximum at the tip of the electrodes. The movement of the cell due to the force on the induced dipole is called dielectrophoresic (DEP). In more detail, the DEP force on a spherical particle is given by

$$F_{\mathrm{DEP}} = 2\pi\varepsilon_{\mathrm{f}} r^3 Re[\mathrm{CM}(\omega)]\nabla E_{\mathrm{rms}}^2 \tag{1.1}$$

where r is the radius of the particle; E_{rms} is the root mean squared electric field; ε_{f} is the fluid permittivity; ω is the frequency of the electric field; and CM (ω) is the Clausius-Mossotti factor which depends on the permittivity and conductivity of the cell and the fluid. For a given cell, a positive CM (ω) can be achieved by adjusting the frequency of the electric field and the conductivity of the fluid, which will trap the cell at the electric field maximum at the tip of the DEP tweezers. The tweezers are also capable of being used when the CM factor is negative, in which case, cells will be pushed away from the tip. Using MHz AC voltages for DEP minimizes the induced potential across the trapped cell membrane and the electro-osmotic flow of the charged double layer[3].

T. P. Hunt and R. M. Westervelt[4] fabricated dielectrophoretic tweezers [Figure 1.1 (b)] by a standard method for fabricating micropipettes first, and then depositing electrodes. The sharpened glass rod was placed in a high-vacuum thermal evaporator. 7 nm Ti and 20 nm Au were evaporated on one side of the rod. Figure 1.1 (c) is an electron micrograph of the tweezer tip. With the dielectrophoretic tweezers, they show that cells are trapped without harm while they divide in the trap.

DEP with geometry of 2D microelectrode has limitations on the movement and placement of a particle at a desired position. The methods using 2D microelectrodes have shown results mainly on trapping of multiple particles. In general, the size of 2D microelectrode is larger than the objects such as a single bead or cell, which causes the difficulty in manipulation for a single particle. Kiha Lee et al.[5] proposed a localized and 3D movable electric field configuration, and analyzed for the functional requirements of dielectrophoretic tweezers. To achieve a steeply focused field, they developed an electrochemical machining method for a sharp probe electrode with the range of 200-300 nm in its radius of curvature (ROC), and used the developed dielectrophoretic tweezers to manipulate cells and beads.

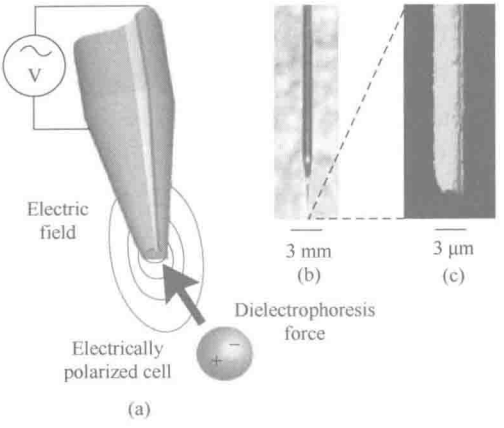

Figure 1.1 Dielectrophoretic tweezers for cell manipulation. (a) Schematic of dielectrophoretic tweezers in operation. A voltage across two electrodes on either side of a sharp glass tip creates an electric field which polarizes a cell and pulls the cell into the field maximum at the end of the tip; (b) Photograph of dielectrophoretic tweezers; (c) SEM image of the tweezer tip. Electrodes appear light while the insulating gap between electrodes is dark

Rupert S Thomas et al.[6] present a novel design of micron-sized particle trap that uses negative dielectrophoresis (nDEP) to trap cells in high conductivity physiological media. The design is scalable and suitable for trapping large numbers of single cells. Each trap has one electrical connection and the design can be extended to produce a large array. The trap consists of a metal ring electrode and a surrounding ground plane, which creates a closed electric field cage in the center. The operation of the device was demonstrated by trapping single latex spheres and HeLa cells against a moving fluid. The dielectrophoretic holding force was determined experimentally by measuring the displacement of a trapped particle in a moving fluid. Then they compared this with theory by numerically solving the electric field for the electrodes and calculating the trapping force, demonstrating good agreement. Analysis of the 80 mm diameter trap showed that a 15.6 mm diameter latex particle could be held with a force of 23 pN at an applied voltage of 5 V peak-peak.

Growth monitoring is the method of choice in many assays measuring the presence or properties of pathogens, e.g., in diagnostics and food quality. Established methods, relying on culturing large numbers of bacteria, are rather time-consuming, while in healthcare time often is crucial. Several new approaches have been published, mostly aiming at assaying growth or other properties of a small number of bacteria.