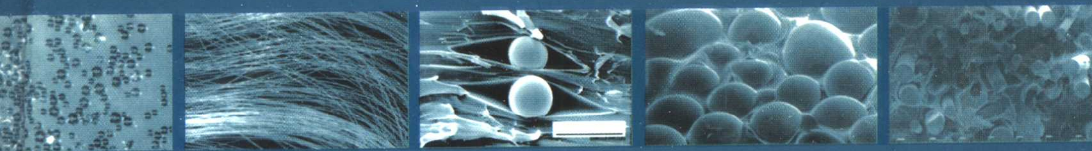
Biomaterials and Tissue Engineering



生物材料与组织工程

时东陆　主编

清华大学出版社

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内容简介

本书是"生物材料和生物技术"丛书中的第1本。本套书提供了在生物材料和生物技术领域至今最新的信息。它的重点是阐述在这些领域的基本原理和最近的发展。本书共有5章,分别是:生物活性材料、材料的生物适应性、无机玻璃的生物学应用、对于生物工艺学的生物合成材料以及细胞组织工艺学。该书可作为材料、生物等相关专业大学高年级学生及研究生的教材,也可供科研人员阅读。

图书在版编目(CIP)数据

生物材料与组织工程/时东陆主编. —北京:清华大学出版社,2004
ISBN 7-302-05881-4

Ⅰ. 生… Ⅱ. 时… Ⅲ. 生物材料 Ⅳ. Q81

中国版本图书馆CIP数据核字(2002)第071715号

出 版 者:清华大学出版社　　**地　址**:北京清华大学学研大厦
http://www.tup.com.cn　　**邮　编**:100084
社 总 机:010-62770175　　**客户服务**:010-62776969
责任编辑:张兆琪
印 装 者:三河市印务有限公司
发 行 者:新华书店总店北京发行所
开　本:153×235　**印张**:16.25　**插页**:2　**字数**:374千字
版　次:2004年3月第1版　2004年3月第1次印刷
书　号:ISBN 7-302-05881-4/Q·26
印　数:1～2000
定　价:58.00元

21 世纪科技前沿丛书
Frontiers of Science and Technology for the 21st Century

《Frontiers of Science and Technology for the 21st Century》

FOREWORD

Over the next several years, Tsinghua University Press will publish a series of books addressing progress in basic sciences and innovations in technology. We have made no attempt to pursue a comprehensive coverage of all disciplines of science and technology. Rather, topics for this series were selected with an emphasis on the currently active forefront of science and technology that will be contemporary in the next century. Most books in this series will deal with subjects of cross disciplines and newly emerging fields. Each book will be completed by individual authors or in a collaborative effort managed by an editor (s), and will be self-consistent, with contents systematically focused on review of the most recent advances and description of current progresses in the field. Sufficient introduction and references will be provided for readers with varying backgrounds. We have realize clearly the challenge of encompassing the diverse subjects of science and technology in one series. However, we hope that, through intensive collaboration between the authors and editors, high standards in editorial quality and scientific merit will be maintained for the entire series.

The international collaboration on this series has been coordinated by the Association of Chinese Scientists and Engineers-USA(ACSE). In the science community, authors voluntarily publish their results and discoveries in the full conviction that science should serve human society. The editors and authors of this series share this academic tradition, and many of them are fulfilling a spiritual commitment as well. For our editors and authors who were graduated from universities in China and further educated abroad in science and engineering, this is an opportunity to dedicate their work to the international education community and to commemorate the historical open-door movement that began in China two decades ago. When the human society enters the information age, there is no geographic boundary for science. The Editorial committee hopes that this series will promote further international collaboration in scientific research and education at the dawn of the new century.

The Editorial Committee
1999.6

《21 世纪科技前沿》

丛 书 序 言

由清华大学出版社出版的这套丛书是基础科学和应用科学领域内的专门著作。除了可作为研究生教材外，也可作为科研和工程技术人员的参考书。在丛书的题材选择中，着重考虑目前比较活跃而且具有发展前景的新兴学科。因此，这套丛书大都涉及交叉和新兴学科的内容。编写的方式大多由主编策划并组织本学科有影响的专家共同执笔完成，从而使每一本书的系统性和各章节内容的连贯性得到了充分的兼顾。丛书涵盖学科的最新学术进展，兼顾到基本理论和新技术、新方法的介绍，并引入必要的导论和充分的参考文献以适应具有不同学术背景的读者。编撰一套容纳多学科的科技丛书是一项浩繁的工作，我们希望通过主编和作者的集体努力和精诚协作，使整套丛书的学术水准能够保持在较高的水平上。

编辑《21 世纪科技前沿》丛书是由“旅美中国科学家工程师协会”发起的一项国际科技界的合作。传递信息，加强交流，促进新世纪的科技繁荣是编著者们参与此项工作的共同信念。此外，这套丛书还具有特别的纪念意义。20 年前，历史的进程使成千上万的中国学生、学者有机会走出国门，到世界各地学习和从事科学研究。今天，活跃在世界科技前沿领域的中华学子们没有忘记振兴祖国科技教育事业的责任和推动国际学术交流与合作的义务。正是基于这一共同的心愿，大家积极参与这套系列丛书的撰写、组稿和编辑工作。为此，我们愿以这套丛书来纪念中国改革开放 20 周年。

编 委 会

1999. 6

Preface

The current interest in developing novel materials has motivated an increasing need for biological and medical studies in a variety of clinical applications. Indeed, it is clear that to achieve the requisite mechanical, chemical and biomedical properties, especially for new bioactive materials, it is necessary to develop novel synthesis routes. The tremendous success of materials science in developing new biomaterials and fostering technological innovation arises from its focus on interdisciplinary research and collaboration between materials and medical sciences. Materials scientists seek to relate one natural phenomenon to the basic structures of the materials and to recognize the causes and effects of the phenomena. In this way, they have developed explanations for the changing of the properties, the reactions of the materials to the environment, the interface behaviors between the artificial materials and human tissue, the time effects on the materials, and many other natural occurrences. By the same means, medical scientists have also studied the biological and medical effects of these materials, and generated the knowledge needed to produce useful medical devices.

The concept of biomaterials is one of the most important ideas ever generated by the application of materials science to the medical field. In traditional materials research, interest focuses primarily on the synthesis, structure, and mechanical properties of materials commonly used for structural purposes in industry, for instance in mechanical parts of machinery. The evolution of the field has rapidly crossed many boundaries and interfaced with other interdisciplinary research, among which biomedical engineering, biochemistry, and the medical sciences are the most active fields, especially in the 21st century. In the development of biomaterials, researchers must not only deal with the basic problems in synthesis and characterization; new challenges are also presented by the biological behaviors of these novel materials. In particular, what kind of interface structures will form when an artificial material comes to contact with a human soft or hard tissue? Is the artificial material introducing harmful effects to a human body? Is it possible to develop more biologically compatible materials that are suitable for certain medical devices used in the human body? How are we going to quantifiably define biocompability of a material? Can a material be synthesized to be "bioactive?" Are there fundamental relationships between materials lattice structures and bioactivity? These are some of the new questions that must be answered jointly by materials scientists and medical researchers. Indeed, the unique characteristics of biomaterials research mean that it requires extensive collaboration between researchers in both fields.

A more fundamental issue concerns teaching in these disciplinary fields. Today, the teaching of biomaterials in our schools remains conventional. The current curricula still concentrate largely on structural materials. University faculty members tend to teach their courses based on the traditional concepts of materials. One reason for this is the lack of suitable biomaterials textbooks accessible to both undergraduate and graduate students. Most of the existing books adopt a traditional manner of introducing materials and/or fail to address the critical issues related to biological phenomena. While biomaterials research is actively pursued collaboratively by both materials and medical scientists, the teaching lags far behind partly due to this lack of comprehensive and systematic textbooks and monographs in the field.

Biomaterials and Tissue Engineering and its companion volume *Medical Devices and Applications* should help to fill this gap in the literature. This book is addressed to the teachers and researchers in a broad spectrum of materials, chemical, biological and medical sciences and engineering. It summarizes the wealth of experimental results in both biomaterials and tissue engineering and introduces new aspects of materials science relevant to biological and medical applications. It also demonstrates new trends in the field and presents novel methods and techniques for experiments and for the development of unique biomaterials. We are grateful to all invited authors for their excellent contributions to this book.

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June, 2003

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Min Wang

1.1 Introduction

It is widely recognized that the rapid and continuing change in emphasis in materials science away from traditional engineering materials has been largely instituted by the requirements of emerging technologies for advanced and structurally sophisticated new materials. Medical engineering, often included in the list of advanced technologies, requires the underpinning of high-tech materials. The word which is used to categorize materials for biomedical applications is "biomaterial".

A biomaterial is a synthetic material used to replace part of a living system or to function in intimate contact with living tissue (Ratner et al., 1996). The Clemson University Advisory Board for Biomaterials defined a biomaterial as "a systemically and pharmacologically inert substance designed for implantation within or incorporation with living systems". In 1986, the Consensus Conference of the European Society for Biomaterials defined a biomaterial as "a nonviable material used in a medical device, intended to interact with biological systems" (Williams, 1987a). Another definition of biomaterial is "any substance (other than drugs) or combination of substances synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body" (Hulbert et al., 1987; Helmus and Tweden, 1995). A biomaterial is different from a biological material such as bone which is produced by a biological system.

The really significant part of the Consensus Conference definition is that it has referred to the interaction with biological systems. To qualify for this descriptive definition, a material must be used in a situation in which it is to remain in contact with living systems for a sufficiently long time for some significant interaction to take place. These situations largely involve implantation in the body but can also be extracorporeal circuits (e.g., kidney machines) and devices having intentionally prolonged contact with external surfaces (e.g., contact lenses and wound dressings). To date, biomaterials are used clinically or experimentally in implantable electronic devices, drug delivery systems, hybrid artificial organs, bone substitutes, ligament and tendon replacements, extracorporeal blood separation columns, and so on.

The UK Office of Science and Technology (OST) in 1995 identified biomaterials as one of the eight priority areas within the sector of materials: i.e. a new generation of materials which encourage and enhance the restoration and repair of body tissue function (UK OST Report, 1995). "Biomaterials save lives, relieve suffering and improve the quality of life for a large number of patients every year" (IoM Report, 1995). In order to develop and use materials in medicine, one must have sufficient knowledge of different disciplines and collaborate with people of various specialties. Knowledge in the following three areas is essential:

(1) Materials science and engineering: processing – structure – property interrelationship of synthetic and biological materials, including metals, ceramics, polymers, composites, tissues, etc..

(2) Biology and physiology: cell and molecular biology, anatomy, animal and human physiology, etc..

(3) Clinical sciences: dentistry, ophthalmology, orthopedics, plastic and reconstructive surgery, cardiovascular surgery, neurosurgery, immunology, histopathology, experimental surgery, veterinary medicine and surgery, etc..

The role of biomaterials has been influenced considerably by advances in many areas of science and technology. Biomaterials can be classified in a number of ways according to different criteria (Black, 1992; Greco, 1994; Park and Lakes, 1992). The classification of biomaterials as polymers, metals, ceramics, and composites, as shown in Table 1.1, is generally adopted.

Table 1.1 Materials for use in the body

Material	Advantage	Disadvantage	Application
Polymers Nylon PTFE Polyester Silicone	Ductile, light, easy to fabricate	Not strong, prone to creep, degradable	Suture, vascular prosthesis, accetabular cup, artificial ligament
Metals Ti and its alloys Co–Cr alloys Stainless steels Au, Ag, Pt	Ductile, strong, tough	Prone to corrosion, unwanted ion release	Artificial joint, bone plate and screw, dental root implant, pacer, suture wire
Ceramics Carbon Aluminum oxide Hydroxyapatite	Biocompatible, Inert or bioactive, strong in compression, stiff	Brittle, weak in tension, sometimes fragile	Cardiovascular device, dental prosthesis, joint prosthesis, orthopedic implant
Composites Carbon-carbon Metal–PMMA HA–HDPE	Strong, stiff, tailor-made, distinctive properties	Difficult to make, high production cost	Joint implant, heart valve, bone cement

According to Hench and Ethridge, "a bioactive material is one that elicits a specific biological response at the interface of the material which results in the formation of a bond between the tissues and the material" (Hench and Ethridge, 1982). At present, bioactive materials include some calcium phosphate compounds, bioactive glasses, bioactive glass-ceramics, bioactive ceramic coatings deposited on metal substrates, composites containing bioactive ceramic phase (s), etc. A characteristic feature common to these materials is that they bond to human bone with no fibrous tissue at the interface.

1.2 Calcium Phosphate Ceramics

Calcium phosphate bioceramics have been in use in medicine and dentistry for more than 20 years. The interest in one group member, hydroxyapatite, arises from its similarity to bone apatite, the major component of the inorganic phase of bone, which plays a key role in the calcification and resorption processes of bone (Fawcett, 1986). In the mid-1970s, three groups, Jarcho et al. in the USA, de Groot et al. in Europe, and Aoki et al. in Japan, simultaneously but independently worked toward the development and commercialiation of hydroxyapatite as a biomaterial for bone repair, augmentation, and substitution.

Different phases of calcium phosphate ceramics can be used in medicine, depending on whether a bioactive or a resorbable material is desired. Table 1.2 lists calcium phosphates that are often encountered in research and clinical in use.

Table 1.2 Family of calcium phosphate compounds

Mineral Name	Chemical Name	Chemical Formula	Ca:P (Molar Ratio)
Monetite	Dicalcium phosphate (DCP)	$CaHPO_4$	1.00
Brushite	Dicalcium phosphate dihydrate (DCPD)	$CaHPO_4 \cdot 2H_2O$	1.00
	Octocalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$	1.33
Whitlockite		$Ca_{10}(HPO_4)(PO_4)_6$	1.43
	Tricalcium phosphate (TCP)	$Ca_3(PO_4)_2$	1.50
Hydroxyapatite	Hydroxyapatite (HA)	$Ca_{10}(PO_4)_6(OH)_2$	1.67
Hillinstockite	Tetracalcium phosphate (TTCP)	$Ca_4P_2O_9$	2.00

The stable phases of calcium phosphate ceramics depend considerably on the temperature and the presence of water, either during materials processing or in the in-service environment. At body temperature, only two calcium phosphates are stable when in contact with aqueous media such as body fluids. At $pH < 4.2$, the stable phase is $CaHPO_4 \cdot 2H_2O$ (brushite), while at $pH > 4.2$, the stable phase is $Ca_{10}(PO_4)_6(OH)_2$ (hydroxyapatite). At higher temperatures, other phases such as $Ca_3(PO_4)_2$ (TCP) and $Ca_4P_2O_9$ (TTCP) are present. The unhydrated high-temperature calcium phosphate phases interact with water or body fluids at 37℃ to form hydroxyapatite (HA).

1.2.1 Biological Apatites

Biological apatites constitute the mineral phase of calcified tissues such as bone, dentine, and enamel in the body and also some pathological calcifications. They are similar to synthetic HA, but they differ from HA in composition, stoichiometry, and physical and mechanical properties. Biological apatites are usually calcium-deficient as a result of various substitutions at regular HA lattice points. It is therefore not appropriate to simply refer to biological apatite as hydroxyapatite.

1.2.1.1 Composition and Structure

The general chemical formula for biological apatites is

$$(Ca, M)_{10}(PO_4, CO_3, Y)_6(OH, F, Cl)_2 \quad (1.1)$$

where M represents metallic elements such as Na, K, and Mg; and Y represents functional groups such as acid phosphate, sulfates, etc. As compared to synthetic HA with the chemical formula of $Ca_{10}(PO_4)_6(OH)_2$, substitution in biological apatites by the carbonate group for the phosphate group takes place in a coupled manner, i.e. CO_3 for PO_4 and Na for Ca. The coupled substitution is necessary to balance charges for the substitution. Differences in composition among apatites in human enamel and bone and HA are shown in Table 1.3.

Table 1.3 Composition of biological apatites and hydroxyapatite

Major Constituent	Biological Apatite		Hydroxyapatite (wt%)
	In enamel (wt%)	In bone (wt%)	
Ca	36.00	24.50	39.60
P	17.70	11.50	18.50
Na	0.50	0.70	
K	0.08	0.03	
Mg	0.44	0.55	
F	0.01	0.02	
Cl	0.30	0.10	
CO_3^{2-}	3.20	5.80	
Trace elements: Sr, Pb, Ba, Fe, Zn, Cu, etc.			
Ca:P (molar ratio)	1.62	1.65	1.67