生物材料學 BIOMATERIALS

Introduction to Biological Environment

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Purpose of the Class

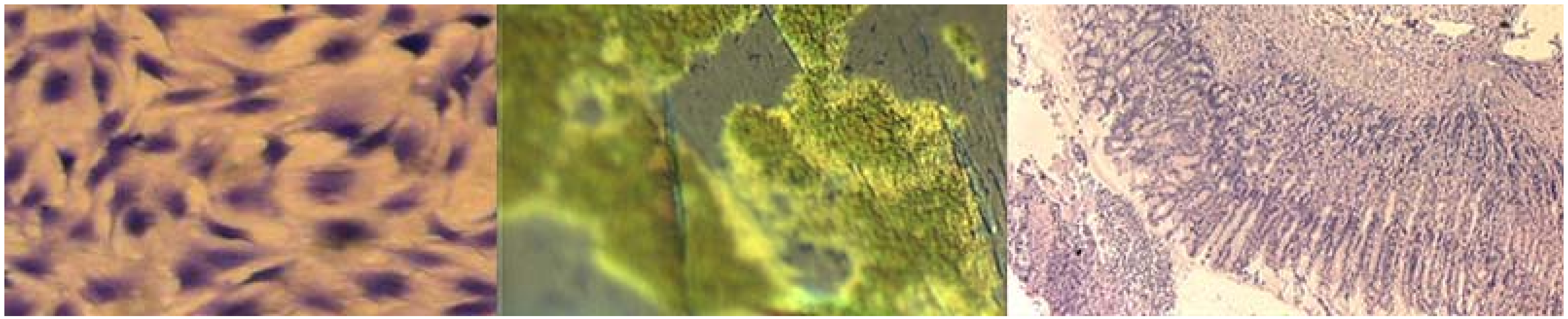
To develop in the students a familiarity with the uses of materials in medicine and with the rational basis for these applications.

General Consideration

1. General Consideration

- Biological performance

  - *interaction* between materials and their operational setting (biological environment)



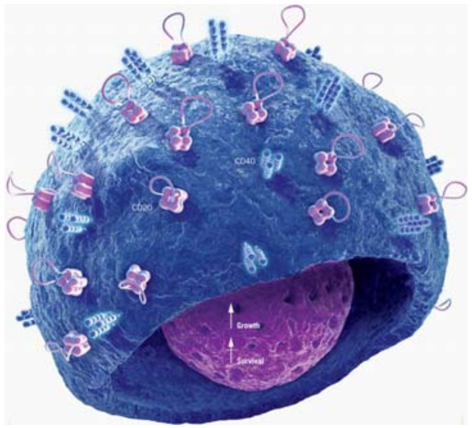
1. General Consideration

- Two *quantitative* aspects that set biological performance apart and create the need for an independent study of material and host responses:

1. High demand

Biological environment (especially internal to living systems) is a ***very aggressive one***

→ ***high chemical activity*** + ***highly variable spectrum of combined mechanical stresses***



1. General Consideration

2. Invariant conditions

Biological environment displays an extraordinary quality of **constancy** in both physical conditions and composition

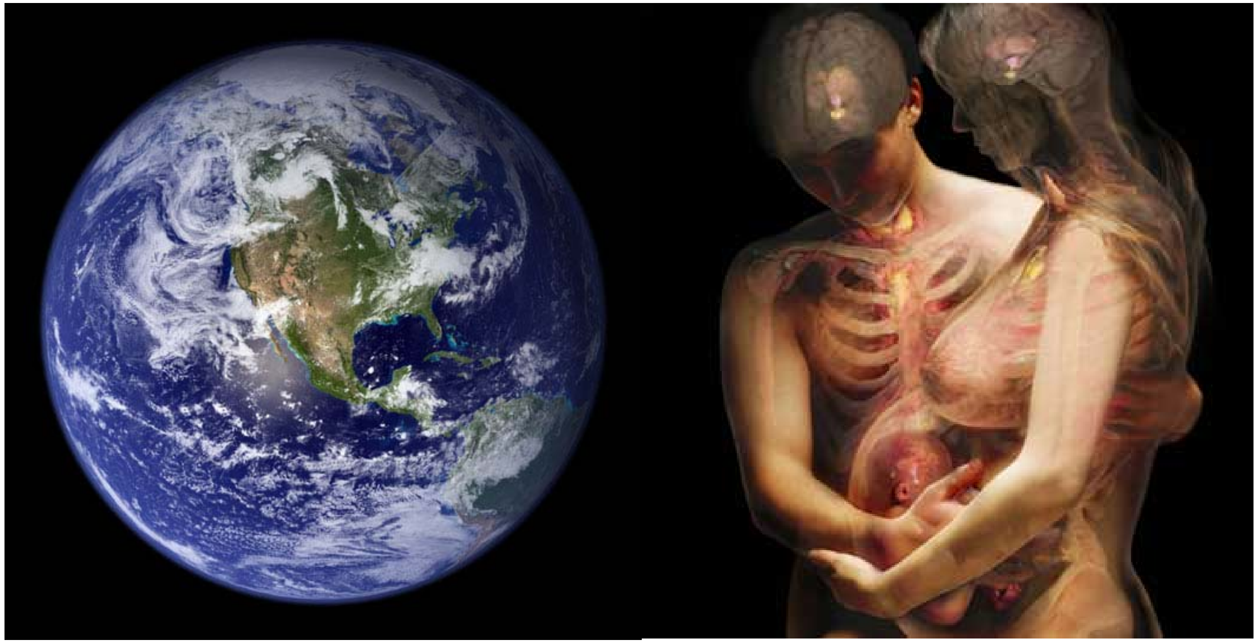
Complex control systems exist to maintain that constancy

→ ∴ deviations from established conditions (∵ presence of materials) may be expected to incite restoring responses

Comparison of External and Internal Conditions

2. Comparison of External and Internal Conditions

- External Conditions
- Internal Environment



2. Comparison of External and Internal Conditions

- **External Conditions (≈ physical world)**
  - Most materials → ***inorganic*** and partially or fully ***oxidized***
  - While physical processes are interrelated, there is an **absence** of active environmental **control** systems
  - **Time** constants for change are **long**
    → determined by processes of chemical reaction and diffusion & driven by source that supply energy primarily through radiation, conduction, and convection
  - A **wide variety** of atomic species are present
  - There is a great variety in structure and chemical content
    ↔ There is **little** evidence of compositional or structural **optimization**

2. Comparison of External and Internal Conditions

Internal Environment

- Arising from a system in which materials (molecules and tissues) → largely ***organic*** and partially or fully ***reduced***
- Most changes are mediated by active, energy-requiring ***control systems***
- Usually multiple parallel systems with **different time constants** and **extensive intersystem interactions** control a single transformation or process

Internal Environment

- Time constants < < for most inorganic reactions

  (∵ mediation by specialized organic catalysts (enzymes) + derivation of energy from chemical sources through coupled reactions)

- While there is a great variety of chemical content and structure

  → a few elements (primarily C, O, H, N) provide the vast majority of this **complexity**

- Elements (that are present) are generally utilized + structures display a ***parsimonious efficiency***

  → an overall impression of ***design optimization***

Internal Environment

- Biological systems are impressed by their ***complexity*** and their ***economy of action***

→ exclude all materials other than **healthy**, **autologous** (belonging to the same organism) tissue

Problems in Definition of the Biological Environment

3. Problems in Definition of the Biological Environment

- It is difficult to define the ***actual*** environment in which a material or device is called upon to ***function***

  → lack of detailed knowledge of *in vivo* conditions and local variations that can occur in the face of ***homeostasis*** (overall maintenance of conditions), necessary for life

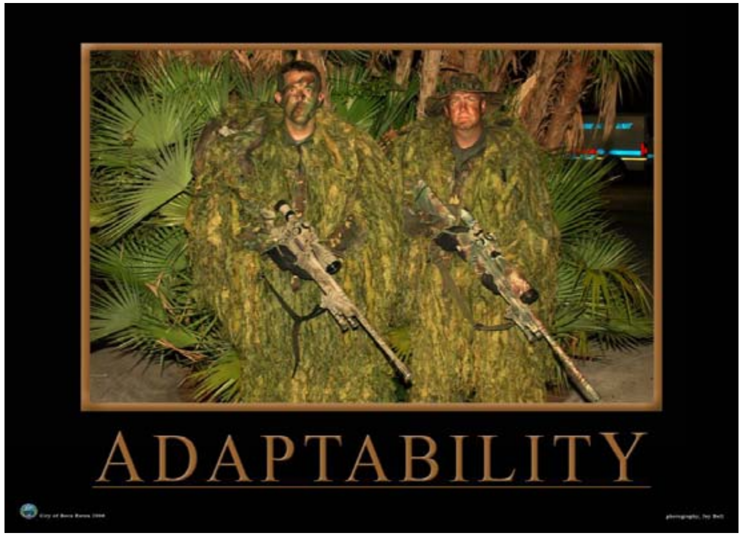
- Also, there is ambiguity in defining the region that is coupled with an ***implant***

  → Implants in isolated locations can interact with the rest of the system through diffusion of ions and fluids, circulation of blood, and drainage of the lymphatics

3. Problems in Definition of the Biological Environment

- **Maintenance of homeostasis**
  - In addition to careful control of temperature, pH, pO_2, equivalent electrical potential, hydrostatic and osmotic pressure, and tissue/fluid composition

$\Rightarrow$ *adaptability* should be warranted



3. Problems in Definition of the Biological Environment

- The control systems most are those that control for the ***usual*** situation and ***small*** deviation

  → Challenges (*e.g.,* outside intrusion) can overwhelm the restorative capabilities of control (*e.g.,* coagulation, inflammation, and immune response)

  → Only challenges that occur ***within*** the design spectrum of the system can elicit satisfactory response (except by chance)

- Materials must be tested ***in vitro*** **before** implantation, even in ***animals***

  → replicate the operating environment (in large or small part) which the material may encounter after implantation

3. Problems in Definition of the Biological Environment

- It is useful to distinguish between four classes of exposure environments:

1. ***Physiological*:**

Chemical (inorganic) and thermal conditions controlled

2. ***Biophysiological*:**

Physiological conditions + appropriate cell products (serum proteins, enzyme, etc.)

***3.Biological*:**

Biophysiological conditions + appropriate viable, active cells

4. ***Pericellular* (circumcellular):**

A special case of *biological* -- the conditions in the immediate vicinity of appropriate viable, active cells

3. Problems in Definition of the Biological Environment

- ***In vitro* testing** – usually carried out under ***physiological*** or ***biophysiological*** conditions only
- **'Biological environment':**

  \- combination of conditions which an implanted material will encounter acutely and chronically in *actual* service

  * **Total combination of requirements** (intrinsic and extrinsic **environmental effects** + **overall p't requirements** during the proposed period of implantation) which the material must meet to be successful in its application

  ⇒ ***implant life history***

Elements of the Biological Environment

4. Elements of the Biological Environment

A standard or reference configuration has the macroscopic parameters as follows:

Weight: 70 kg		**Height (medium frame): 1.80 m**	
Surface area: 1.88 m²		**Volume: 0.065 m3**	
Composition		**Density**	
Water: 60% (42 liters)		**Fat**	**0.9 g/cm³**
Solid: 40% (28 kg)		**Whole body**	**1.07 g/cm³**
Distributive of tissue types			
(as percentages of body weight)			
Muscle	**43**		
Bone	**30**		
Internal organs			
Heart	**0.4**		
Liver	**2**		
Kidneys (2)	**0.5**		
Spleen	**0.2**		
Lungs	**1.6**		
Brain	**2.3**		
Viscera	**5.6**		
Skin	**7**		
Blood	**7.2 (5 liters)**		
Basal metaboli rate 37/kcal*m²/hr			

4. Elements of the Biological Environment

- Wide variations from these parameters exist

  - Age (mid-thirties male here)

  - Level of activity

  - Disease state

  - National origin

  - Genetic factors

    → will also affect absolute values

- The values given here represent an average expectation and do not account for variations within physiological limits (⇒ termed ‘biological variation’)

4. Elements of the Biological Environment

The physicochemical and mechanical conditions that are encountered in the body can be defined as follows:

	Value	Location
pH	1.0	Gastric contents
	4.5-6.0	Urine
	6.8	Intracelluar
	7.0	Interstitial
	7.15-7.35	Blood
pO_2 (mm Hg)	2-40	Interstitial
	12	Intramedullary
	40	Venous
	100	Arterial
	160	Atmospheric
pCO_2 (mm Hg)	40	Alveolar
	2	Atmospheric
Temperature (℃)	37	Normal core
	20-42.5	Deviations in disease
	28	Normal skin
	0-45	Skin at extremities

4. Elements of the Biological Environment

The physicochemical and mechanical conditions that are encountered in the body can be defined as follows:

Mechanical	Stress (MPa)	Tissues
	0-0.4	Cancellous bone
	0-4	Cortical bone
	4	Muscle (peak stress)
	40	Tendon (peak stress)
	80	Ligament (peak stress)
	Stress cycles (per year)	**Activity**
	3×10^5	Peristalsis
	3×10^6	Swallowing
	$0.5\text{-}4 \times 10^7$	Heart contraction
	$0.1\text{-}1 \times 10^6$	Finger joint motion
	2×10^6	Walking

4. Elements of the Biological Environment

When we consider the effects of release of material from the implant into the body, it is necessary to know the starting or nominal inorganic chemical composition of the body. The following table presents nominal or reference human values:

			Total body burden	Concentration (average)
Basic elements	**Oxygen**		**43,000 g**	**61.4 %**
	Carbon		**16,000 g**	**22.9 %**
	Hydrogen		**7,000 g**	**10.0 %**
	Nitrogen		**1,800 g**	**2.6 %**
		Total	**67,800 g**	**96.9 %**
Physiologic elements	**Calcium**		**1,000 g**	**1.43 %**
	Phosphorus		**780 g**	**1.11 %**
	Potassium		**140 g**	**0.20 %**
	Sulfur		**140 g**	**0.20 %**
	Sodium		**100 g**	**0.14 %**
	Chlorine		**95 g**	**0.14 %**
		Total	**2,255 g**	**3.22 %**

4. Elements of the Biological Environment

When we consider the effects of release of material from the implant into the body, it is necessary to know the starting or nominal inorganic chemical composition of the body. The following table presents nominal or reference human values:

		Total body burden	Concentration (average)
Trace elements	**Magnesium**	**19 g**	**271 ppm**
	Iron	**4.2 g**	**61.4 ppm**
	Zinc	**2.3 g**	**33 ppm**
	Iodine	**130 mg**	**19 ppm**
	Copper	**72 mg**	**1.0 ppm**
	Aluminum	**61 mg**	**0.9 ppm**
	Vanadium	**18 mg**	**260 ppb**
	Selenium	**<13 mg**	**<190 ppb**
	Manganese	**12mg**	**170 ppb**
	Nickel	**10 mg**	**140 ppb**
	Molybdenum	**<9.5 mg**	**<136 ppb**
	Titanium	**9 mg**	**130 ppb**
	Chromium	**<6.6 mg**	**<94 ppb**
	Cobalt	**<1.5 mg**	**<21 ppb**
	Total	**<25.84 g**	**<0.04 %**

4. Elements of the Biological Environment

Blood is a delicate and pervasive tissue → It is essential to understand its makeup and normal values (especially for applications involving blood contact on a chronic basis) as follows:

Blood			
Packed cell volume	**38.5%**		
Serum volume	**61.5%**		
Serum composition (mean values)			
Cations	**mEg/l**	**Anions**	**mEg/l**
Sodium	**142**	**Chlorine**	**101**
Potassium	**4**	**Bicarbonate**	**27**
Calcium	**5**	**Phosphate**	**2**
Magnesium	**2**	**Sulfate**	**1**
Total	**153**	**Organic acids**	**6**
		Proteins	**16**
		Total	**153**

4. Elements of the Biological Environment

Blood is a delicate and pervasive tissue → It is essential to understand its makeup and normal values (especially for applications involving blood contact on a chronic basis) as follows:

Other elements		
Iron		**0.75-1.75 mg/l (=ppm)**
Nickel		**1.0-5.0 μg/l (=ppb)**
Titanium		**3.3μg/l**
Aluminum		**2.0μg/l**
Copper		**0.8-1.4μg/l**
Chromium		**0.3μg/l**
Manganese		**0.4-1.0μg/l**
Vanadium		**<0.2μg/l**
Cobalt		**0.15μg/l**
Serum protein		
Total		**65-80 g/l**
Distribution (%)		
Albumin	**6.15**	
Globulins	**34.5**	
α **8.2**		
β **10.3**		
γ **12.6**		
Fibrinogen	**4.0**	

4. Elements of the Biological Environment

Blood is a delicate and pervasive tissue → It is essential to understand its makeup and normal values (especially for applications involving blood contact on a chronic basis) as follows:

Cellular distribution		
Type		**Typical dimension(μm)**
Erythrocyte	**4-5.6 x 10^6/μl**	**8-9**
Platelet	**1.5-3 x 10^5/μl**	**2-4**
Leucocyte	**2.8-11.2 x 10^3/μl**	
Leucocyte distributions (%)		
Neutrophils	**59**	**10-15**
Eosinophils	**2.4**	**10-15**
Basophils	**0.6**	**10-15**
Monocyte	**6.5**	**12-20**
Lymphocytes	**31**	**7-18**

Implant Life History

5. Implant Life History

- The thermal, mechanical, and chemical parameters described in previous sections are sufficient to predict the acute or instantaneous biological environment encountered by an *implant*

  → These acute values ***differ little from p't to p't*** (What differences there are have *only small effects* on ***acute*** host material responses)

5. Implant Life History

- ***Biological differences*** do exist that affect ***chronic*** host response to materials
  → only be discernible by clinical testing of a specific p't (analysis of body fluids and tissues → inadequate for a full understanding of individual differences)
- It is unfortunate that technology for determination of the functional behavior of implants and implant/p't interactions is weak compared with that for the study of natural organs in situ

5. Implant Life History

- Beyond these obvious similarities and possible ***individual biological differences***

→ demands and expectations of ***individuals vary considerably***:

e.g. a quite different engineering problem presented for devising a total hip replacement prosthesis for a 30-year-old head of a family *v.s.* a 70-year-old nursing home resident

5. Implant Life History

- The ***full picture*** that accounts for these **functional differences** and completes the description of the **service environment**

  ⇒ ***implant life history***

- Implant life histories ***vary*** considerably from application to application and involve a good degree of ***estimation*** (*e.g.*, a wide variety in the choice and intensity of work and leisure activities)

  → can only be regarded as ***predictive guides*** in the development, evaluation, and study of implantable biomaterials

5. Implant Life History

Implant Life History
Implant: Anterior cruciate ligament replacement
Type: Permanent
Patient indications: Post-traumatic replacement, age: 35-48 (est. mean life expectancy: 40 years)
pH = 7 $\pm$ 0.3 pO_2 = < 40 mmHg pCO_2 = < 40 mmHG
25℃ $\leq$ T $\leq$ 37℃
Mechanical conditions:
Strain (range of maximum): 5-10%
Loads: (moderate activity level, including recreational jogging)

5. Implant Life History

Activity	Peak load (N)	Cycles/year	Total cycles
Stairs			
ascending	67	4.2×10^4	1.7×10^6
descending	133	3.5×10^4	1.7×10^6
Ramp walking			
ascending	107	3.7×10^3	1.5×10^5
descending	485	3.7×10^3	1.5×10^5
Sitting anf arising	173	7.6×10^4	3.0×10^6
Undifferentiated	<210	9.1×10^5	3.6×10^7
Level walking	210	2.5×10^6	1.0×10^8
Jogging	630	6.4×10^5	2.6×10^7
Jolting	700	1.8×10^3	7.3×10^5
Totals:		4.2×10^6	2.9×10^8

Pre-Implantation Handling Effects

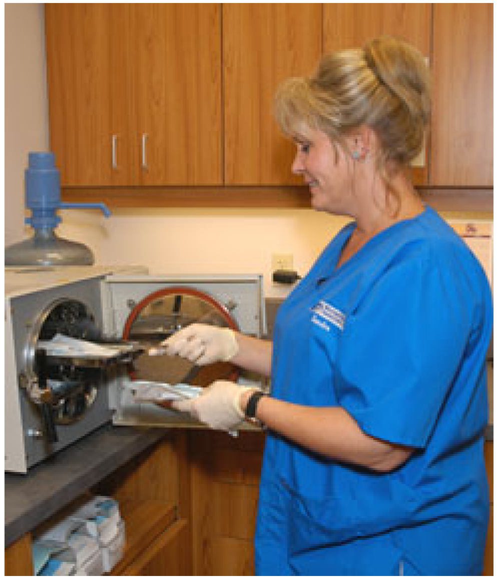
6. Pre-Implantation Handling Effects

- Biological environment is thought as one which the implant passes into after manufacture and storage

  → Overlook two intermediate processes:

  (1) The implant may become contaminated (accidentally or as a side effect of planned processing and handling) during manufacture, storage, and insertion

  (2) All implants must be sterilized before use

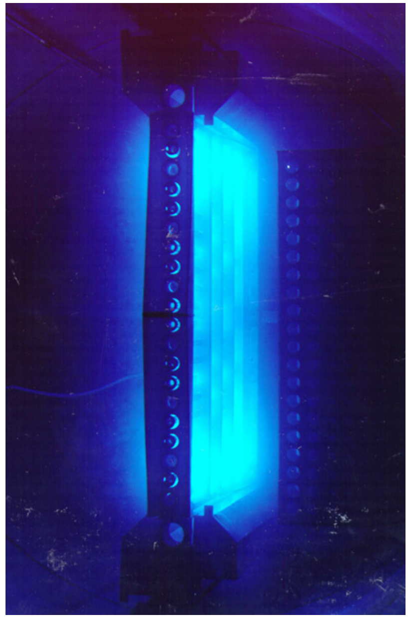


6. Pre-Implantation Handling Effects

(2) All implants must be sterilized before use

The common forms of sterilization used in implant practice are:

- Cold solution
- Dry heat
- Moist heat (steam)
- Gas
- Irradiation



6. Pre-Implantation Handling Effects

Methods and Typical Parameters of Sterilization

Method	Temperature	Time	Notes
Cold solution	RT	1-3 hr	Commercial solutions; usually include formaldehyde or gluteraldehyde
Dry heat	160-175℃ (max.)	0.5-2 hr	Time/temperature vary inversely
Moist heat	120-130℃ (max.)	2-15 min	Time/temperature vary inversely
Gas	RT-55℃	1-24 hr	Gas used is usually ethylene oxide, 400-1200 mg/liter, 48 hr degassing required
Irradiation	RT	Not applicable	^{60}Co gamma radiation, 2-4 Mrad dose

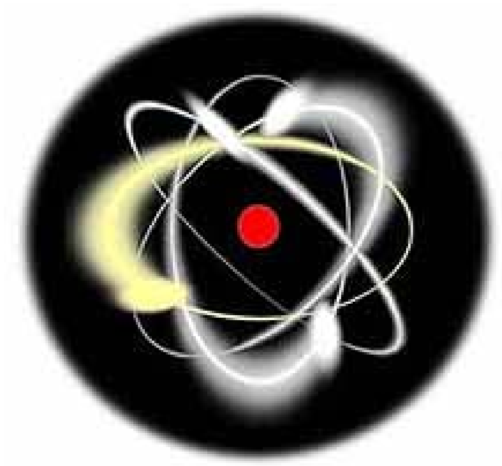
6. Pre-Implantation Handling Effects

- The particular method and parameters used must be suited to the individual implant type to provide maximum safety with minimum cost and implant degradation
- Newer methods include:
  - electron beam irradiation
  - radio-frequency plasma gas sterilization
- The process of sterilization, if overlooked, may affect our perception of both the material and the host response

6. Pre-Implantation Handling Effects

- It is possible for some sterilization processes (*e.g.,* irradiation) to change material properties

  → This might be interpreted, in error, as a material response effect if detected after implantation, or might produce changes in host response that are secondary to the changes in the materials' properties



6. Pre-Implantation Handling Effects

- It is also possible for traces of liquid or gaseous sterilants to be carried into the implant site

  → thus modifying the host response:

  The presence of an implant does not produce additional symptoms (inflammatory process) but may alter their severity and duration

- Finally, sterilization of an *unclean* implant may render it *sterile* ***but not pyrogen-free*** → thus affecting the host response

Reference

- 自行編纂

Summary

- Biomaterials
- Biocompatibility
- Biological Environment
- Swelling and Leaching
- Interfacial-Dependent Phenomena in Biomaterials
- The Structure of Solids
- Characterization of Materials