Biomedical Microsystems

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Biomedical Microsystems

Lecture 11

Biocompatibility

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The prerequisite for long-term functionality of biomedical microsystems

Outline

- Biocompatibility of materials
  - material classes
  - desired reactions
  - testing of biocompatibility

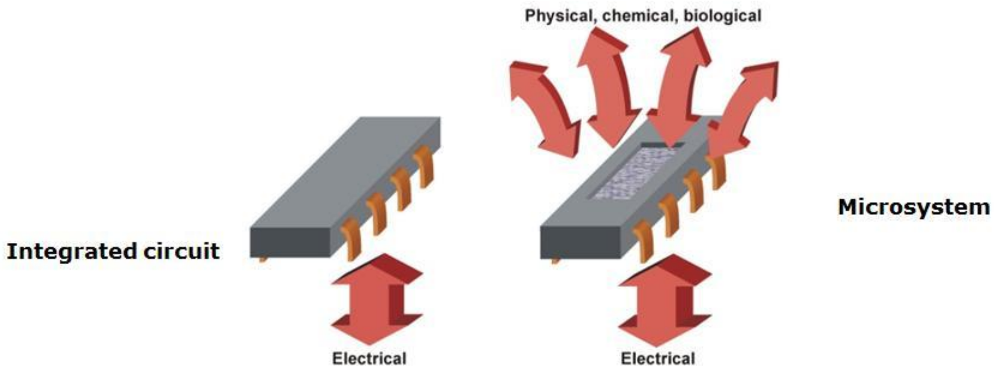
- The material-tissue interface
  - some applications of biomaterials
  - some fundamentals of the interaction mechanisms
  - some statements

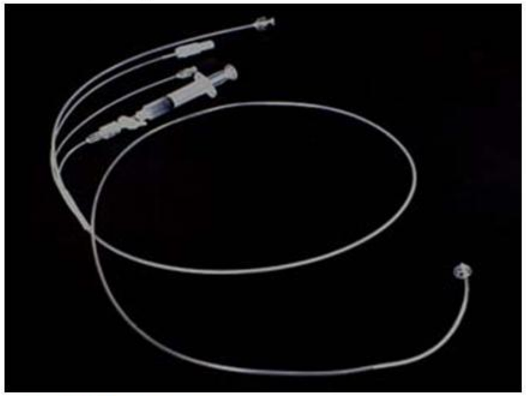
- A short guide to material selection

Biocompatibility of Materials

Medical Devices vs. Microsystems

- Microsystem technology evolved from semiconductor device technology
  - completely different requirements in terms of packaging





Medical device

  - some important requirements: hermeticity, ease of handling, portability, sterilisability

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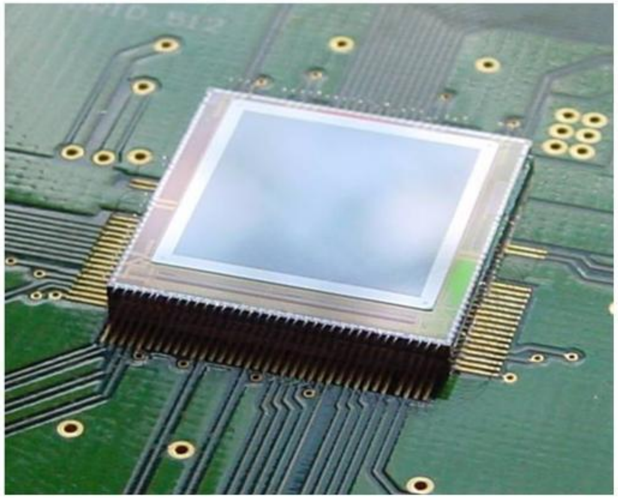
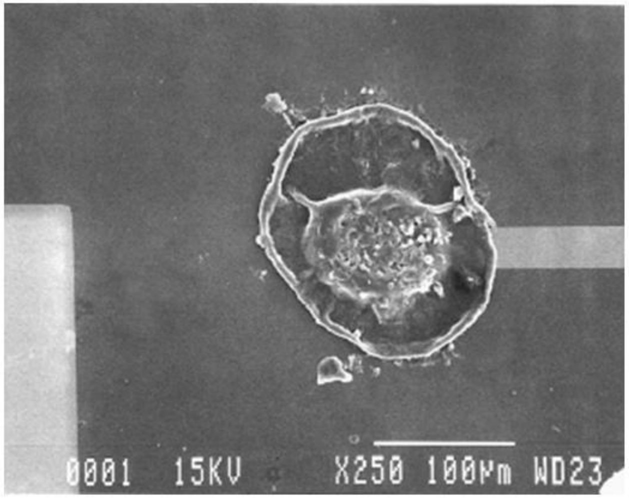
The Nature of Medical Devices

- The reality of medical devices is quite different from the electronic paradigm from which micro and nanosystems evolved





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FBGC blocking a microwell
(after Voskerician et al.,CWRU, *Biomaterials*, 2003)

The Quest for Minimally Invasive Solutions

- … but what does 'invasive' really mean?
- Invasiveness can take many forms
  - perceived mainly as the need for surgery ("the more one cuts, the more invasive it gets")
  - use of anaesthesia, radiation (e.g. x-rays) are also important forms of invasiveness
  - in certain environments (e.g. intensive care unit) – where the patient will already have an intravenous catheter and perhaps an arterial line already in – the concept of invasiveness is much changed
  - benefits may well outweigh risks

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Compatibility, Stability and Fouling

Compatibility, Stability and Fouling

- ***Biocompatibility***: quality of a material regarding the response of an organism to its presence. Example: piercing jewelry, latex gloves.
  - not a 'digital' concept
  - the living organism will *always* encounter a foreign object
  - best to talk about 'biotolerability'
- ***Biostability***: quality of a material regarding its response to in vivo exposure. Example: myringotomy tube.
- ***Biofouling***: response of an organism to the introduction of a foreign material in which it is coated, blocked or encapsulated with biological material. Example: heart implants.

Characteristics of the Natural Environment

- Hostile environment: changes in materials due to corrosion and diffusion

- Natural structures are dynamic and dispensable

- Lines of defense in a living system:
  - first: skin, fluids (saliva, mucus)
  - second: lymphatic system
  - third: antibodies

  → "eat it or wall it out" !

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The Material-Tissue-Interface

(more in detail)

Host Reactions to Biomaterials

- Depend on
  - implantation site
  - surgical intervention
- Effect of the implant on the host
  - local
  - systemic and remote
- Effect of the host on the implant
  - physical-mechanical effects
  - biological effects

Reaction to Device Insertion

- The protein matrix at the injury site has a random distribution of proteins (including cell-adhesion proteins)

- Such proteins undergo conformational changes and eventually get denatured: a robust layer is created

- As a consequence there is adhesion of multiple types of cells (neutrophils, macrophages, platelets, etc): encapsulation

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Attack to the Implant

- Leaching: constant removal of material from the implant by biological fluids
- Oxidation: organic molecules can be strong oxidizing agents

In general, the body tries to isolate the foreign material → "frustrated phagocytosis"

The inflammatory process tends to cease when the aggression is no longer present. With an implant, this process becomes chronic (now called a foreign body reaction), with an attempt to encapsulate the material.

The Race for the Surface

- Bacteria, matrix molecules, tissue cells
- Tissue integration vs. bacterial adhesion
  - competitive, mutually exclusive
  - bacteria cause infection
  - encourage settling and integration of healthy tissue cells

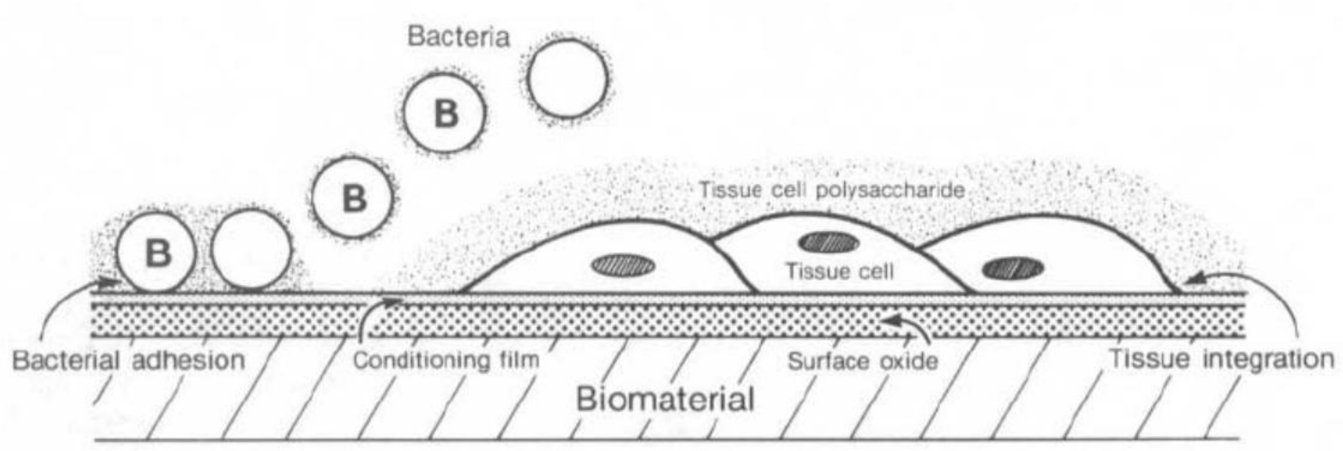

FIG. 1. At the instant of insertion, a biomaterial represents a ready surface for colonization. The outer atomic layers of biomaterial surfaces interact instantly with the juxtaposed biologic environment. Macromolecules, bacteria, and tissue cells compete for surface domains at the reactive interface. (Reprinted with permission from *Science* **237**: 1588–1595, 1987.)

Ratner et al. 1996

Summary of Important Issues

- A given material which works very well in one part of the body may not work at all elsewhere.
- A material that works well for one individual may not work for someone else.
- In time, changes in material properties may affect the performance of the implant.
- Cytotoxicity: a host of materials is known for their toxic effects to cells and tissues (e.g. Ni, Cu, V).
- Biofouling may cause the implant to stop working altogether.

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Biocompatibility Testing

Biocompatibility Testing

- ISO 10993 "Biological Evaluation of Medical Devices“
- Framework of tests
- Categories
  - duration
  - nature of body contact

Table 1 — Initial evaluation tests for consideration

Medical device categorization by			Biological effect							
Nature of body contact (see 4.1): Category	Contact	Contact duration (see 4.2) A — Limited (≤ 24 h) B — prolonged (> 24 h to 30 days) C — permanent (> 30 days)	Cytotoxicity	Sensitization	Irritation or Intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Surface device	Skin	A	x	x	x					
		B	x	x	x					
		C	x	x	x					
	Mucosal membrane	A	x	x	x					
		B	x	x	x					
		C	x	x	x		x	x		
	Breached or compromised surface	A	x	x	x					
		B	x	x	x					
		C	x	x	x		x	x		
External communicating device	Blood path, indirect	A	x	x	x	x				x
		B	x	x	x	x				x
		C	x	x		x	x	x		x
	Tissue/bone/dentin	A	x	x	x					
		B	x	x				x	x	
		C	x	x				x	x	
	Circulating blood	A	x	x	x	x				x
		B	x	x	x	x		x		x
		C	x	x	x	x	x	x		x
Implant device	Tissue/bone	A	x	x	x					
		B	x	x				x	x	
		C	x	x				x	x	
	Blood	A	x	x	x	x			x	x
		B	x	x	x	x		x	x	x
		C	x	x	x	x	x	x	x	x

NOTE This table is a framework for the development of an assessment programme and is not a checklist (see clause 6).

Proposed Tests to Evaluate the Hazard of a Medical Device / an Implant

- Toxicity
  - cytotoxicity
  - systemic toxicity
- Haemocompatibility
- Pyrogenicity
- Genotoxicity (teratogenicity)
- Cancerogenicity
- Sensitisation

'Official' Biocompatibility Tests (I)

Prior to clinical studies, medical implants have to undergo a series of standardized biocompatibility tests. These are defined – somewhat loosely – in ISO 10993. In total, ISO 10993 consists of 20 parts (so far).

ISO 10993, part 1 presents the introduction and the "philosophy" of the standard

Some key specifications in ISO-10993 are:

- **ISO 10993-5: Cytotoxicity tests.** Cell lines are grown near confluence and exposed to the implant:
  - Directly, but having the implant placed in the cell culture
  - Indirectly, by testing extracts
  - Preferred cell lines: fibroblasts (e.g. L929, 3C3), kidney epithelial cells (e.g. PtK2) → check what contact you might have.

'Official' Biocompatibility Tests (II)

- ***ISO 10993-6: Local effects after implantation.*** Implantation in mice, guinea pigs or rabbits, followed by hystopathological analysis.

- ***ISO 10993-10: Sensitisation and irritation.*** Guinea pig as animal model. Two main methods for sensitisation tests:
  - Buehler: expose shaved skin to the implant.
  - Magnuson-Kligman: an extract is first injected than applied topically.
  - Irritation tests are carried out by injecting extracts subcutaneously in albino rabbits.

- ***ISO 10993-11: Systemic toxicity.*** Injection of implant extract in mice, most commonly done intravenously or intraperitoneally, followed by observation of animals. If absorbable materials are present, it is often preferred to an implantation performed instead.

- These tests should be understood as preliminary steps for material verification purposes only. Passing them is a necessary but not sufficient condition in proceeding towards device certification.

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A Short Guide to Material Selection

The Complete List of Perfectly Biocompatible Bulk Materials

What can we do?

- Modify the surface to prevent the early stages of the process
  - -texturization
  - -surface functionalization
- Promote a smooth transition between the implant and the biological medium
  - -"structural biocompatibility" → mechanical mismatch
  - -grafting of polymers and proteins
- Dispense drugs
  - -drug elution
- Protect the implant from attacks

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NeuroProbes imec

Common Material Classes

- Metals
  - stable, hard
  - load bearing
  - hermetic
  - e.g.: stainless steel, titanium
- Ceramics
  - hermetic
  - (stable),hard
  - load bearing
  - e.g.: Alumina (Al_2O_3)
- Glass
  - stable, hermetic OR degradable
- Polymers → see following slides

Materials for Medical Devices

- Should have FDA approval for the USA
- Certificate for "restriced" / "unrestricted" use
- Otherwise: detailed biocompatibility studies for each application

Table 1-1. Class of Materials Used in the Body

Materials	Advantages	Disadvantages	Examples
Polymers (nylon, silicone rubber, polyester, polytetrafuoroethylene, etc)	Resilient Easy to fabricate	Not strong Deforms with time May degrade	Sutures, blood vessels other soft tissues, sutures, hip socket, ear, nose
Metals (Ti and its alloys, Co–Cr alloys, Au, Ag stainless steels, etc.)	Strong, tough ductile	May corrode Dense Difficult to make	Joint replacements, dental root implants, pacer and suture wires, bone plates and screws
Ceramics (alumina zirconia, calcium phosphates including hydroxyapatite, carbon)	Very bio-compatible	Brittle Not resilient Weak in tension	Dental and orthopedic implants
Composites (carbon–carbon, wire- or fiber- reinforced bone cement)	Strong, tailor-made	Difficult to make	Bone cement, Dental resin

Park & Lakes, 2007

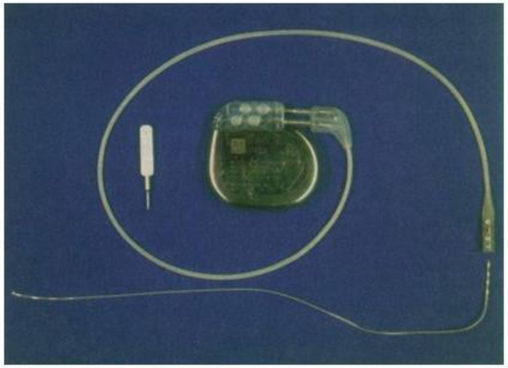
Biomedical Microsystems

Lecture 8

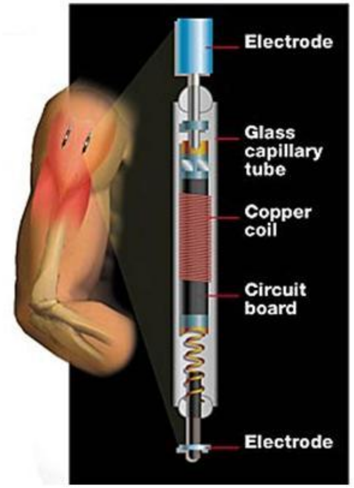
Packaging and Housing Concepts

Active Implants in Conventional Technology

- Stiff housing
  - titanium
  - ceramics
  - glass

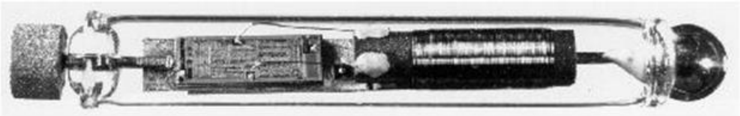


neuromodulation implant
(MEDTRONIC INTERSTIM)



implantable grasp neuroprothesis
(Freehand, Neurocontrol)

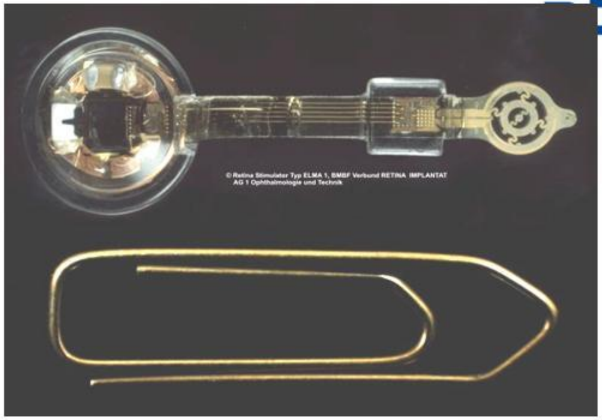
Cochlea Implant
(Clarion)



injectable stimulator (BION,
Advanced Bionics)

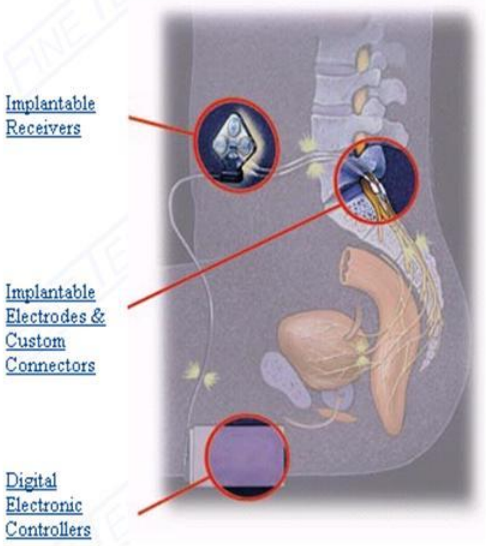
Implants with Flexible Housing

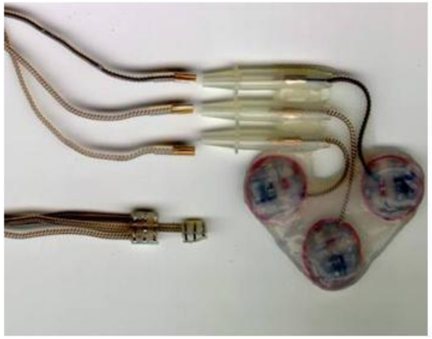
- Flexible encapsulation
  - parylene C
  - polyimide
  - silicone rubber
- IC housing
  - hermetic (metal)
  - silicon or nanocrystalline carbon
  - DLC (diamond like carbon)



Retina Implant (EPI-RET consortium, Germany)

intraocular pressure sensor (IWE I, RWTH-Aachen)





Spinal root stimulator (SARSI, Fintech-Brindley-Stimulator) (Finetech Medical, UK)

Different Sizes - Common Technologies ?

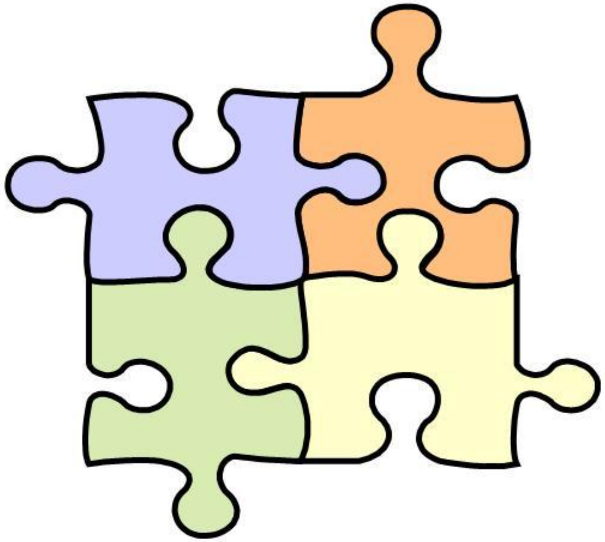
- Design Principles
- Hermeticity
- Feedthroughs

Desired Properties of Materials for Housing, Packaging and Encapsulation

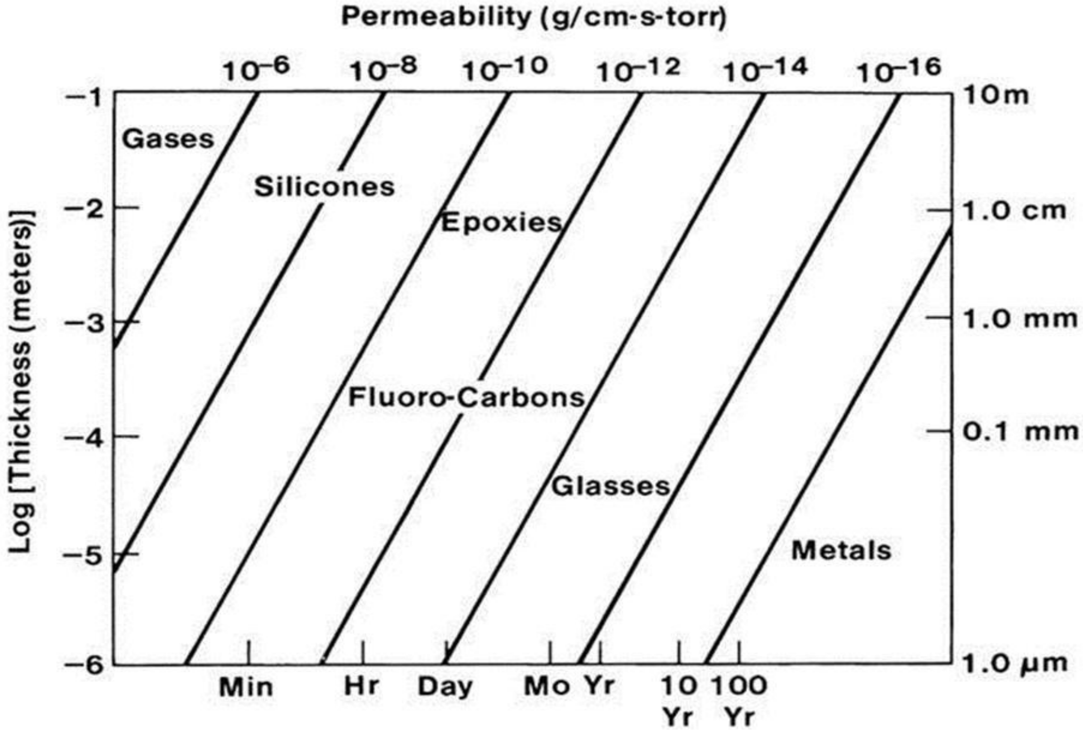
- Mechanically robust
- Electrical insulator
- Barrier against gasses, water and ions (hermeticity)
- Permeable for electromagnetic waves (inductive coupling)
- Possibility to integrate electrical feedthroughs

Components in Active Implants

- Functional components and groups
  - sensor / actuator
  - cable
  - plugs
  - implant housing with electronics
  - extracorporal application device
- Material selection and design according to
  - anatomy
  - mechanical load
  - energy demand
- Modularity does not include definitions about data exchange



Permeability of Materials



from *Microelectronics Packaging Handbook* part II pg.888

time for package interior to reach 50% of exterior humidity

Hermeticity: definition of leakage rate over time (< 10^{-9} mbar l/s)

Literature

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Take Home Message

- Biocompatibility is a set of many properties not a digital criterion

- The material-tissue interface should be carefully chosen and designed to protect both, material and the host

- Proper selection of bulk material and surface depends on the application and the implantation site

- There are no universally valid statements