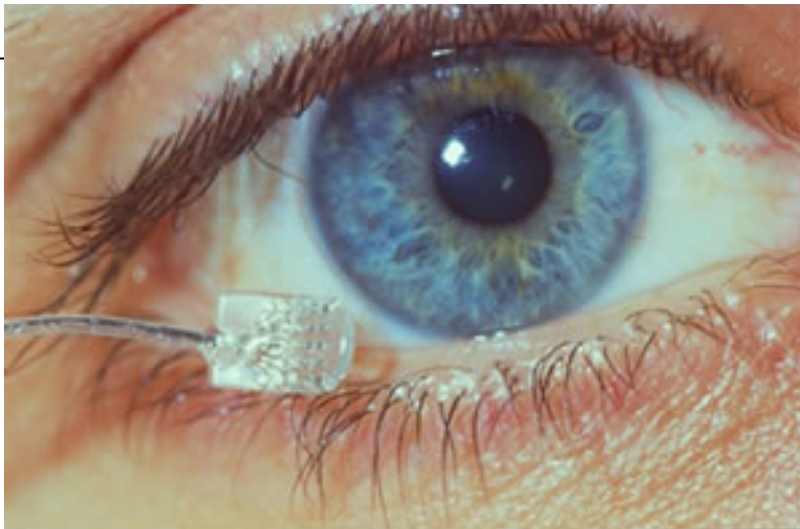


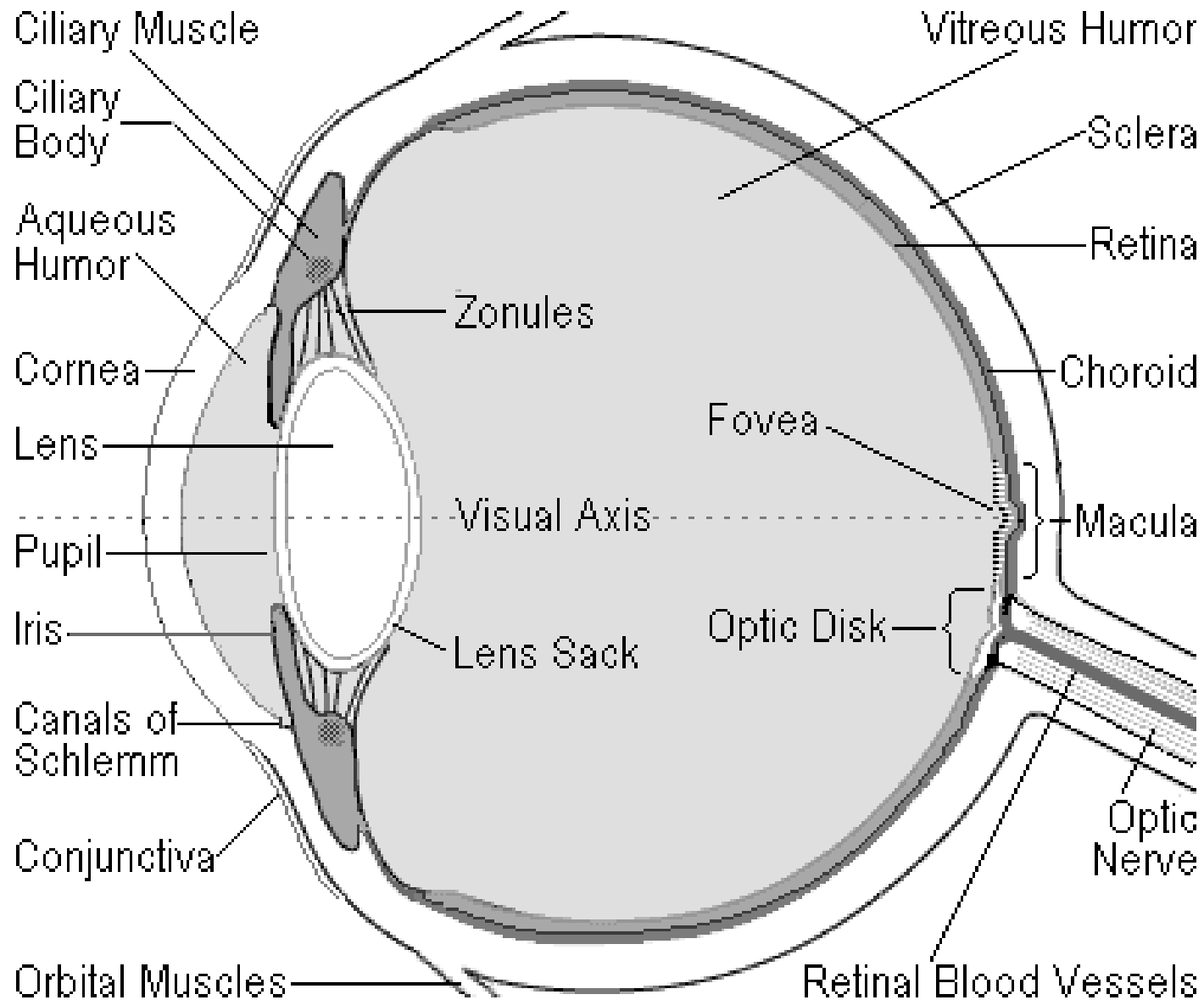
## ***Retinal Prosthesis for the Blind***



*The artificial retina consists of an electrode-studded silicon chip (shown) that is tacked to the retina inside the eye.*



# Eye



# Contents

## I. General consideration

### A. Efficacy of a visual prosthesis

1. Psychophysical Experiments
2. Neuronal Electrical Excitation
3. Electrodes
4. Power supply

### B. Safety of Electrical stimulation

1. Damage Caused by Electrical Current
2. Infection and Inflammation
3. Heat Damage
4. Hermetic Sealing of the Electronics



**More than 1 million Americans are legally blind and approximately 10% have no light perception from all causes.**

For age-related macular degeneration (AMD)

- Photodynamic
- Conventional laser therapy

For retinal diseases

- Gene therapy
- Drug therapy

Other experimental treatments

- Gene therapy for retinal degeneration
- Retinal transplantation for different retinal diseases
- **Visual prosthesis**



# Guidance on the use of photodynamic therapy for age-related macular degeneration

## 3 The technology

- 3.1 The aim of photodynamic therapy (PDT) is to destroy CNV lesions without damaging the overlying retina, thereby slowing or halting the progression of vision loss. The treatment involves the infusion of a light-sensitive agent, followed by light activation of the drug. At present only verteporfin (Visudyne), a benzoporphyrin derivative, is available for this indication, but other agents are in development.
- 3.2 Verteporfin is given by intravenous infusion over 10 minutes, at a dose of 6 mg/m<sup>2</sup> of body surface area. Fifteen minutes after the start of the infusion, a low-powered laser calibrated to a specific wavelength is applied over a circular area slightly larger than the lesion. The laser is not powerful enough to cause any damage on its own, but the light is



# **1. If an electrical stimulation of a small area of neuronal tissue in the visual pathways will create light perception?**

yes, we can stimulate a small area of neuronal tissue and get a light perception (Foerster, a German neurosurgeon, noted that electrical stimulation of the visual cortex caused his subject to see a spot of light (phosphene). The spatial psychophysical location of the phosphene depended on the location of electrical stimulation spot over the cortex. Others followed with similar results at different locations of the visual pathways, including the visual cortex, the optic nerve, and the retina (Table 1))



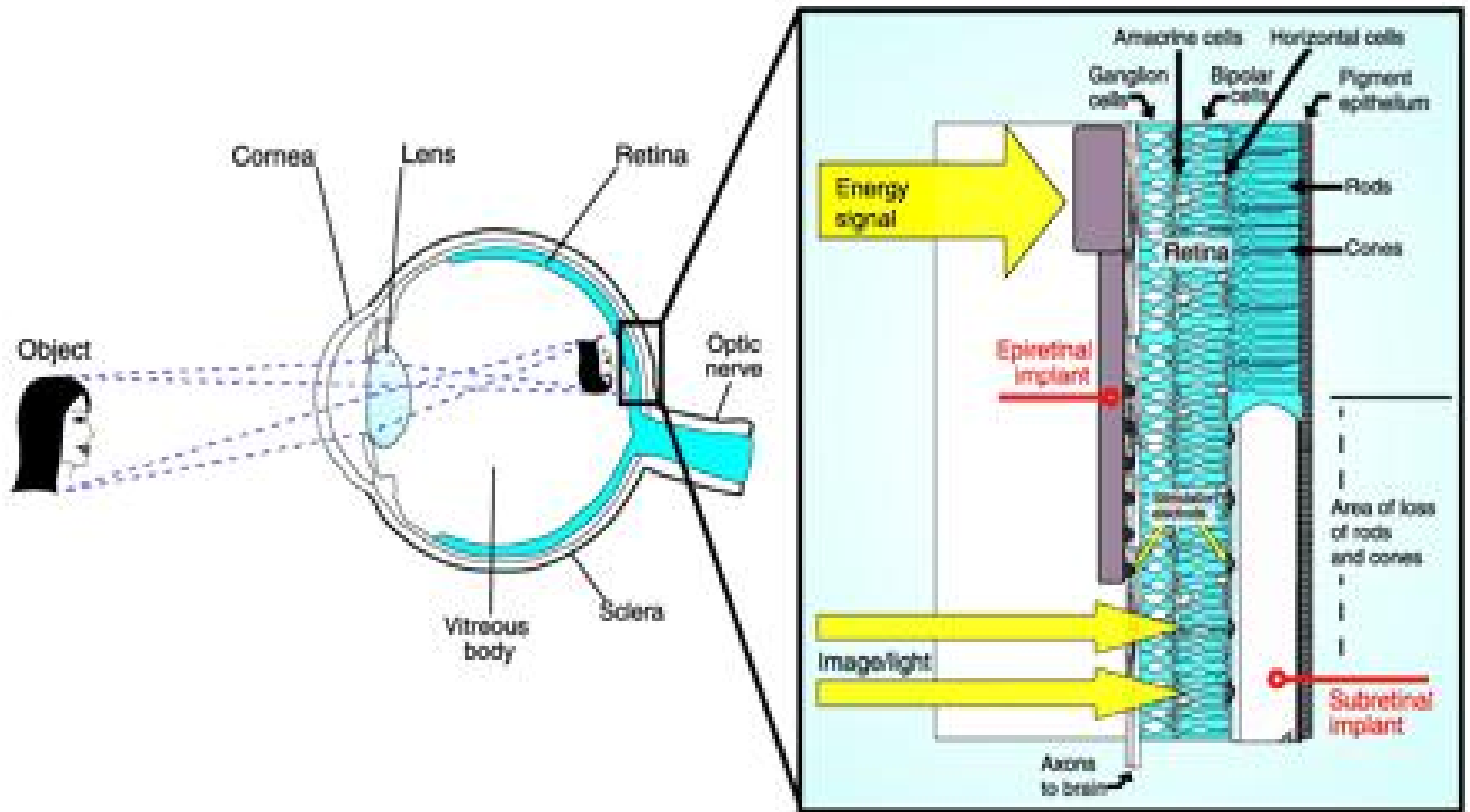
TABLE 1

*Experimental Results of Visual Stimulators That Were Implanted in Human Subjects at Different Locations of the Visual System*

Reference	Type of Stimulation	Spatial Orientation	Patients	Reading Letters	Localization of an External Light Source	Time of Implant	Number of Electrodes
70,71	Epiretinal	+	Blind from RP and AMD	+		Acute	1–25
157	Epiretinal	+	Laser ablated retinas			Acute	1
153	Optic nerve	+	Blind from RP			Chronic	4
98	Subretinal	Not published	Blind from RP	Not published	Not published	Chronic	3,500

RP = retinitis pigmentosa; AMD = age-related macular degeneration.







2. That is comparable to that created by light stimulation of retinal photoreceptors?

no, it is not comparable to light stimulation. The phosphene is seen usually as a white, round, or oval point of light, and it has different sizes.



Q. whole visual image can be created by stimulation of many small areas of neuronal tissue (pixels)?

Q. how many pixels are required for such an image?

Q. what are the electrical stimulus parameters (amplitude, duration, shape etc.) needed for each pixel to make it safe and effective.



2. Neuronal Electrical Excitation
3. Electrodes
4. Power supply

## General consensus

- small number of electrodes cannot be expected to provide unaided understanding of visual information.

## Several psychophysical experiments to define the minimum acceptable resolution for useful vision

- Reading ordinary print: 600 points of stimulation
- Large-print reading: 80–120 points
- Simple obstacles: 200 points may allow recognition
- certain tasks: 625 electrodes could produce a phosphene image with a visual acuity of approximately 20/30 (These studies were conducted with a portable phosphene simulator small head-mounted video camera. An opaque perforated film masked the monitor. The visual angle was 1.7' or less,)



2. Neuronal Electrical Excitation
3. Electrodes
4. Power supply

These studies **impractical** to translate to a design of a retinal prosthesis

- the electrodes would be spread over the entire macular region

Thus, to simulate pixelized prosthetic vision and to produce an array of dots

- a low vision enhancement system (LVES) has been modified to filter images on a head-mounted display.
- for facial recognition and reading large-print text(25x25 grid in a 10' field, 4 or more gray levels)



2. Neuronal Electrical Excitation
3. Electrodes
4. Power supply

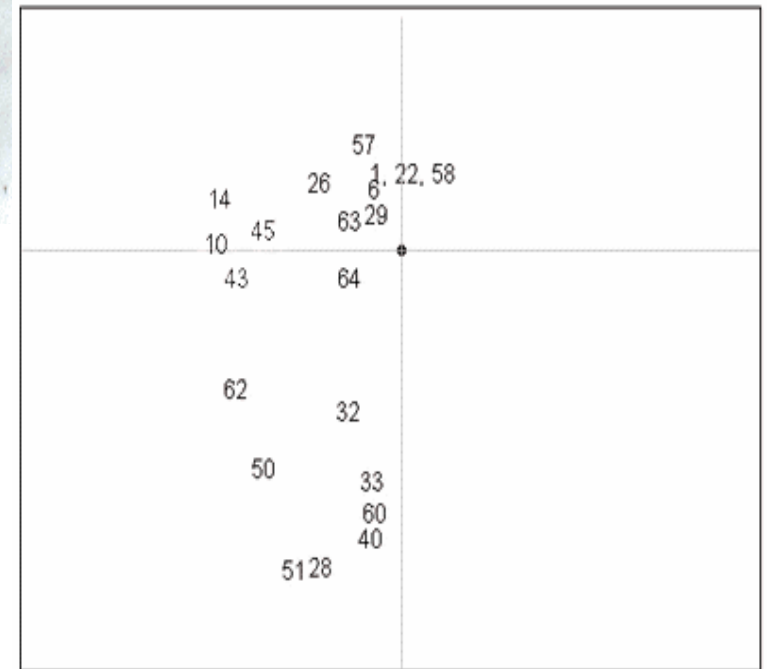
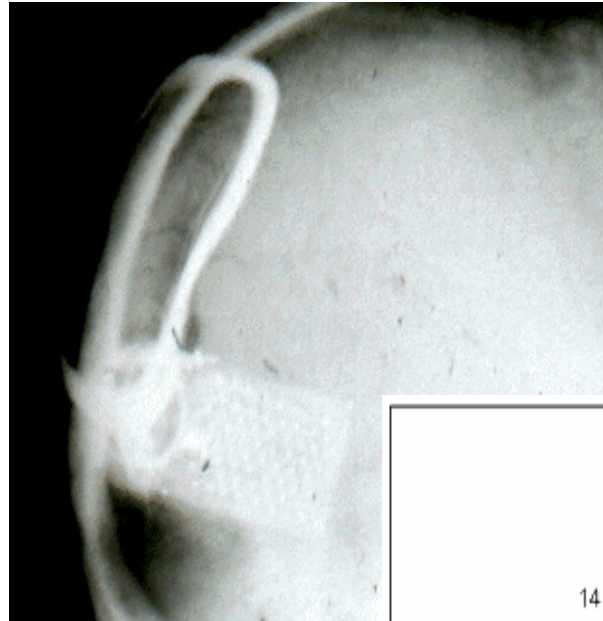
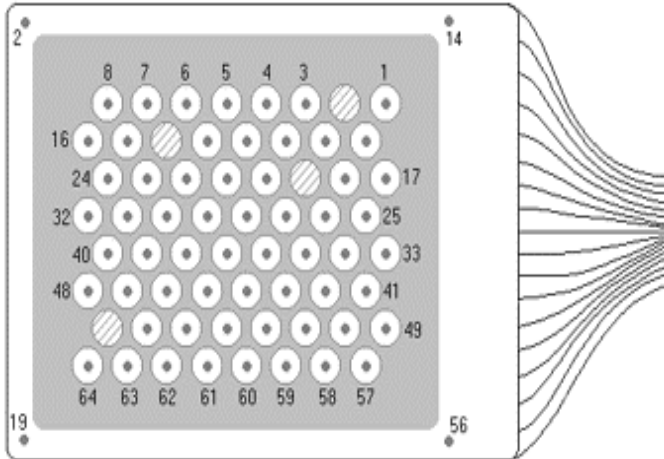
A blind volunteer with a 20-year-old electrode implant (8x8 electrodes) on the visual cortex surface can

- navigate
- perform
- simple tasks
- count fingers
- identify large print letters

(These abilities were acquired after a long period of training)



## 2. Neuronal Electrical Excitation



2. Neuronal Electrical Excitation
3. Electrodes
4. Power supply

Experiments with the cochlear implant demonstrated that electrical stimulation with only 4~8 input channels allows deaf patients to hear and even talk over the phone.

Perhaps a similar phenomenon (redundancy in visual information) and the **plasticity** of the visual system will permit fewer retinal or cortical stimulating electrodes (compared to the estimated number of 600 electrodes), to give blind patients some useful vision



2. Neuronal Electrical Excitation
3. Electrodes
4. Power supply

To predict the correct number of channels needed for functional vision.

- visual prosthesis phosphenes may be of variable size
- may show varying persistence
- may interact with each other
- there might be multiple phosphenes induced by the same electrode

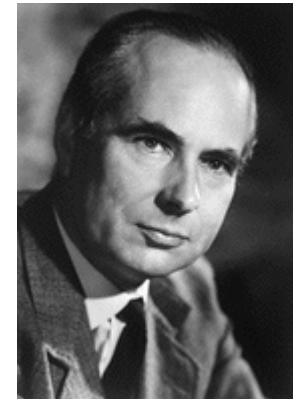
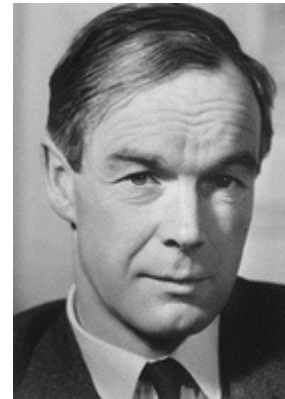
(Most of these problems were encountered during cortical electrical stimulation)





## 1. Psychophysical Experiments

Hodgkin and Huxley used the **voltage clamp technique** in the squid axon to give the first complete description of the **ionic mechanisms** underlying the **action potential of neurons** sequence of events.



## 1. Psychophysical Experiments

- A **depolarization** of the membrane causes **Na<sup>+</sup> channels to open** rapidly resulting in an **inward Na<sup>+</sup> current** (because of a higher concentration of this ion outside the cell membrane)
- This current, by discharging the membrane capacitance, causes **further depolarization**
- Thereby **opening more Na<sup>+</sup> channels**
- Resulting in increased **inward current**
- This regenerative process causes the **action potential**
- The depolarization state of the action potential then **limits the duration of the action potential** in two ways: 1) it gradually inactivates the Na<sup>+</sup> channels 2) it opens the voltage gated K<sup>+</sup> channels with some delay
- Consequently, the **inward Na<sup>+</sup> current** is followed by an **outward K<sup>+</sup> current** that tends to **repolarize the membrane current** (because of higher concentration of this ion inside the cell membrane)



# 1. Psychophysical Experiments

## Other conclusions

- 1) the **basic mechanism of action potential generation** is the same in all neurons
- 2) the nervous system expresses a **large variety of voltage-gated ion channels** (i.e., Ca<sup>+</sup> channels)
- 3) gating of voltage-sensitive channels can be influenced by **intracellular ion concentrations** (i.e., Ca<sup>+</sup> ions)
- 4) excitability properties **vary** among neurons mainly because of the **variety of ion channels properties**
- 5) excitability properties **vary** within **regions** of the neuron (i.e., axon vs. dendrites)

The Hodgkin–Huxley model (equation) has been derived by **fitting analytic curves** to **empirical data** from the **squid axon**.



# 1. Psychophysical Experiments

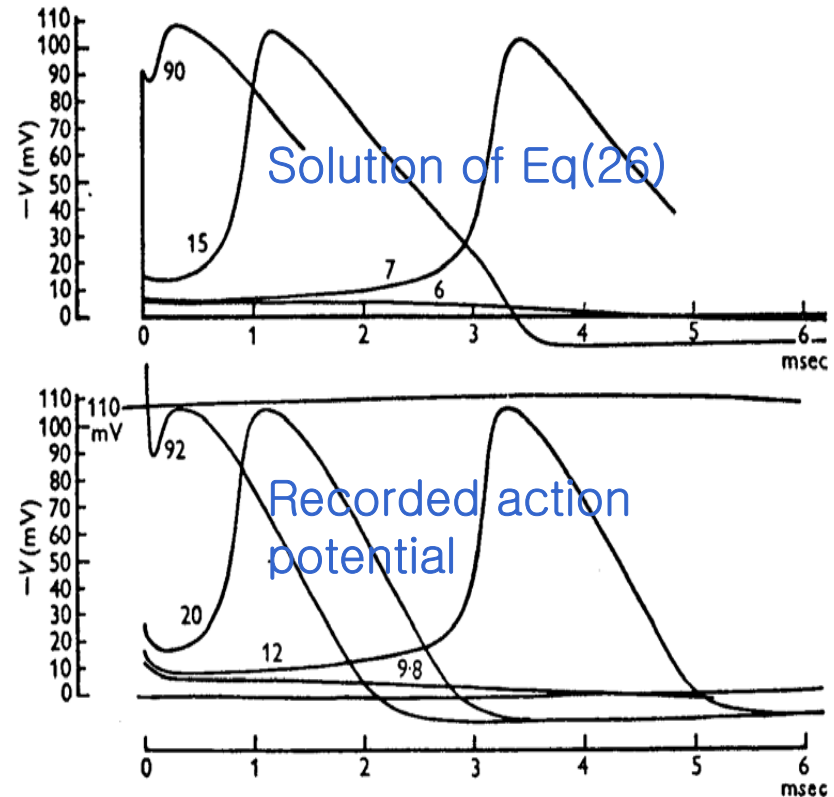
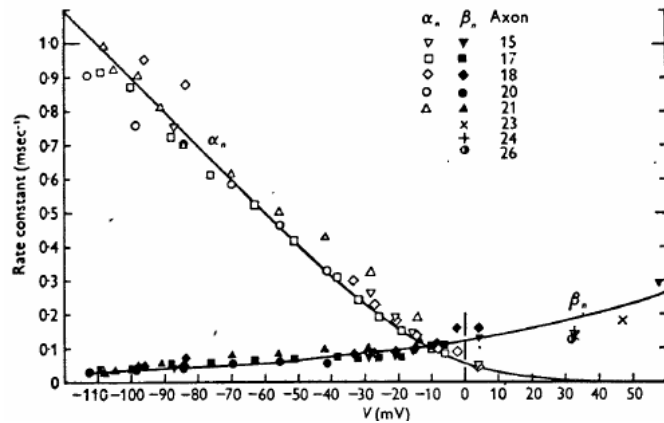
$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l), \quad (26)$$

where

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m,$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h,$$



- A. L. Hodgkin and A. F. Huxley "A quantitative description of membrane current and its application to conduction and excitation in nerve", J. Physiol.(1952) 117, 500~544



## 1. Psychophysical Experiments

A number of factors can influence the **efficacy of electrical stimulation**

**First**, the threshold depends on the **electrical properties and anatomy of the target neural elements**, and what **portion of the cell**

**Second**, the threshold is obviously affected by the **distance** from the electrodes to the target cell.

**Third**, the threshold during bipolar stimulation is also affected by the **pulse duration**

**Fourth**, threshold can vary significantly due to **the impedance of tissues** and errors can be associated with the assumption that tissue **electrical properties** are the same in every stimulated compartment (homogenous and isotropic tissue properties), especially with bipolar electrical stimulation



## 1. Psychophysical Experiments

Fifth  
threshold current/charge

the  
stimulus pulse duration

Sixth  
stimuli

repetition rate of

Seventh      polarity

Eighth  
waveform



# 1. Psychophysical Experiments

the different threshold values found for electrical stimulation of several points along the visual pathways

TABLE 2  
*Threshold Electrical Stimulation Parameters That Were Used by Different Groups During In Vivo Experiments*

Reference	
Epiretinal stimulation parameters 117 71	Rabbits, extradural recording, current threshold <u>105–720 <math>\mu\text{A}</math></u> , PD <u>100 <math>\mu\text{sec}</math></u> , electrode diameter <u>40 <math>\mu\text{m}</math></u> , charge density threshold <u>0.8–5.7 <math>\text{mC}/\text{cm}^2</math></u> . Determination of threshold was done by <u>repeating the stimulation and recording at different anatomical positions</u> .
157	<b>RP and AMD patients, current threshold <u>500 <math>\mu\text{A}</math></u>, PD <u>2 ms</u>, charge density threshold <u>0.16–70 <math>\text{mC}/\text{cm}^2</math>, (1 <math>\mu\text{C}/\text{phase}</math>)<sup>70</sup></u>. Determination of threshold by counting the electrical stimuli with varying frequencies of stimulation.</b>
Subretinal stimulation parameters 30	<b>Laser treated human retinas, current threshold <u>100–600 <math>\mu\text{A}</math></u>, charge threshold <u>0.1–0.6 <math>\mu\text{C}</math></u>, charge density threshold <u>0.8–4.8 <math>\text{mC}/\text{cm}^2</math></u>. Determination of threshold by counting the electrical stimuli with varying frequencies of stimulation.</b>
Optic nerve stimulation parameters 153	Normal rabbits cortical recordings), electrode surface area <u>0.36 <math>\text{cm}^2</math></u> , charge density threshold <u>2.8–100 <math>\text{nC}/\text{cm}^2</math></u> . Determination of threshold was done by <u>reversing the input leads</u> ?
	<b>RP patient, current threshold <u>30 <math>\mu\text{A}</math></u>, PD <u>400 <math>\mu\text{sec}</math></u>, electrode area <u>0.2 <math>\text{mm}^2</math></u>, repetition rate <u>160 Hz</u> charge density threshold <u>24 <math>\mu\text{C}/\text{cm}^2/\text{pulse}</math></u>. Determination of threshold by <u>two-staircase limit method</u>. ?</b>

RP = retinitis pigmentosa; AMD = age-related macular degeneration; PD = pulse duration.  
 Human Experiments Are Bolded



# 1. Psychophysical Experiments

TABLE 3

*Threshold Electrical Stimulation Parameters That Were Used by Different Groups During In Vitro Experiments*

Reference	
Epiretinal stimulation parameters	
69	Charge density thresholds (using Pt electrodes): <u>2.98 <math>\mu\text{C}/\text{cm}^2</math></u> (bullfrog), <u>8.92 <math>\mu\text{C}/\text{cm}^2</math></u> (normal rabbit), <u>11.9 <math>\mu\text{C}/\text{cm}^2</math></u> (chemically RD rabbit). Determination of threshold was not mentioned.
59	Rabbit isolated retina, electrode diameter <u>10 <math>\mu\text{m}</math></u> , PD <u>400 <math>\mu\text{sec}</math></u> , threshold current <u>0.06–1.8 <math>\mu\text{A}</math></u> , threshold charge density <u>30–917 <math>\mu\text{C}/\text{cm}^2</math></u> . Determination of threshold was done by <u>counting only response waveforms with ten or more sample points</u> and by <u>using synaptic transmission blockage</u> .
Subretinal stimulation parameters	
141	Chick isolated retina, current threshold <u>35 <math>\mu\text{A}</math></u> , PD <u>0.4 ms</u> , electrode surface area <u>0.01 <math>\text{mm}^2</math></u> , charge threshold <u>14 nC/phase</u> , charge density threshold <u>178 <math>\mu\text{C}/\text{cm}^2</math></u> . Determination of threshold was not mentioned. Determination of threshold was done by <u>control with light stimulation</u> and by using <u>synaptic transmission blockage</u> .
140	Retinal degenerate rates (RCS) isolated retina, charge density threshold <u>500 <math>\mu\text{C}/\text{cm}^2</math></u> . Determination of threshold was not mentioned.

RP = retinitis pigmentosa; AMD = age-related macular degeneration; PD = pulse duration.





1. Psychophysical Experiments
2. Neuronal Electrical Excitation

**The electrodes' charge transfer efficiency affect Power requirement and the electrode density**

**platinum, iridium, rhodium, gold, and palladium were tested for the fabrication of electrode arrays**



1. Psychophysical Experiments
2. Neuronal Electrical Excitation

### **Platinum + iridium**

**(most widely used for neural stimulating)**

- **resistance to corrosion**
- **charge carrying capacity**

**(unavoidable dissolution)**

- **protein is included in the solution**
- **continuous stimulation**



1. Psychophysical Experiments
2. Neuronal Electrical Excitation

### **Iridium oxide (IrOx)**

- **exceptionally resistant to corrosion**
- **withstand more than 2 billion 10 mA current pulses without degradation**



1. Psychophysical Experiments
2. Neuronal Electrical Excitation

### **titanium nitride (TiN)**

- **charge injection limits** is higher than both platinum and IrOx
- **better mechanical properties** than IrOx
- **used for fabricating electrode arrays** in **animal research**



1. Psychophysical Experiments
2. Neuronal Electrical Excitation

	<b>platinum</b>	<b>IrOx</b>
<b>safe charge density limit</b>	<b>100 <math>\mu\text{C}/\text{cm}^2</math></b>	<b>1mC/cm<sup>2</sup></b>
<b>Acceptable dimensions</b>	<b>0.01 cm<sup>2</sup></b>	<b>0.001 cm<sup>2</sup></b>
<b>minimum disc radii</b>	<b>0.56 mm</b>	<b>0.18mm</b>



1. Psychophysical Experiments
2. Neuronal Electrical Excitation



### capacitor electrodes

- without any **faradaic reactions**
- A thin surface layer of dielectric material **insulates** and prevents **electrochemical reactions**
- practical material is **anodized tantalum** (small amount of DC leakage)
- **lower** safe injectable charge density and charge storage ability than Pt, IrOx, or TiN electrodes



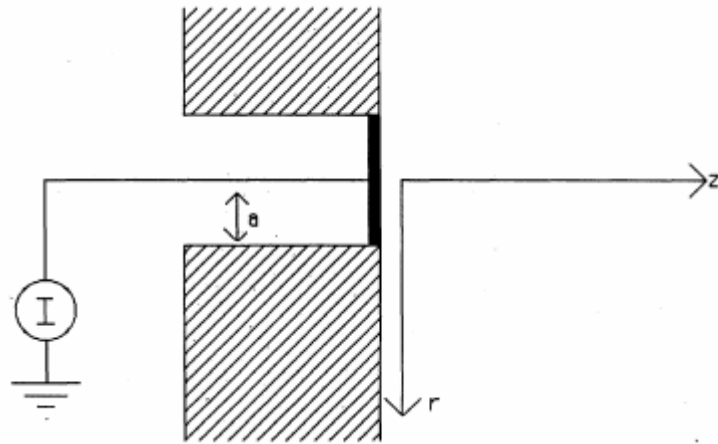
1. Psychophysical Experiments
2. Neuronal Electrical Excitation

### **uniform current distribution.**

- neural prosthesis electrodes are likely to have **non-uniform** current distributions
- highest densities or “hot spots” being near the **edges** of the disk
- If the disks are **recessed** even to a small depth, the current density is more **evenly distributed**



1. Psychophysical Experiments
2. Neuronal Electrical Excitation



$$\nabla^2 G(r, z; r', 0) = 0 \quad r < a, -b \leq z \leq 0 \quad (2-1)$$

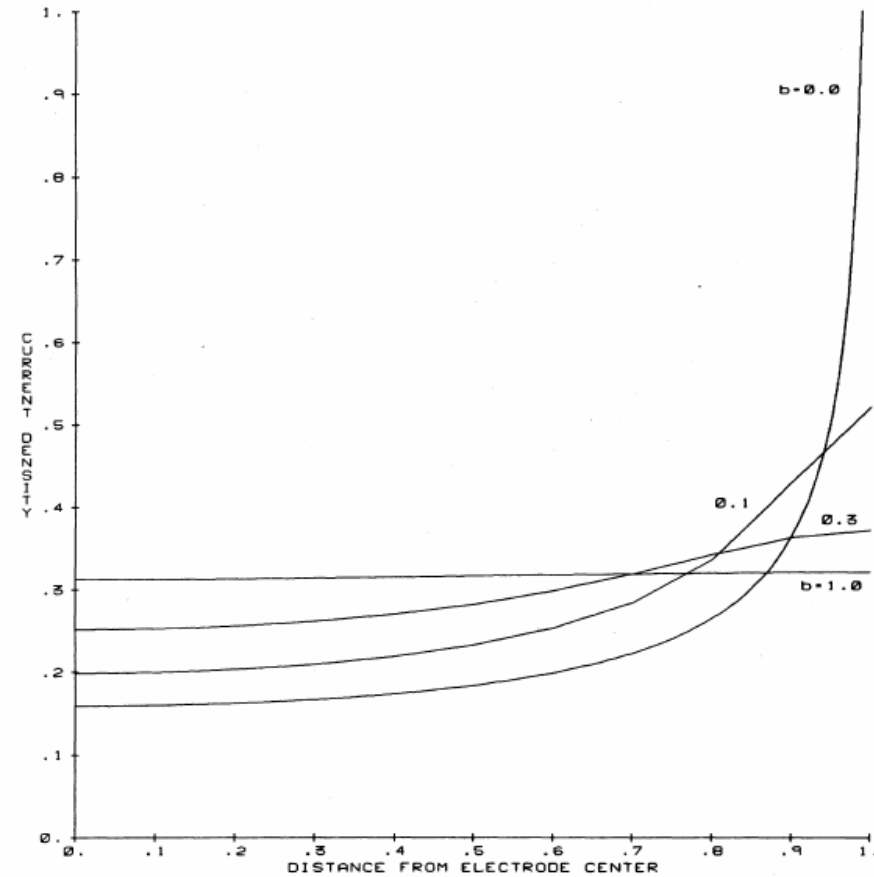
with boundary conditions

$$G = 0 \quad \text{at } z = -b \quad (2-2)$$

$$\frac{-1}{\rho} \frac{\partial G}{\partial z} \Big|_{z=0} = \frac{I}{2\pi r} \delta(r - r') \quad (2-3)$$

and

$$\frac{\partial G}{\partial r} \Big|_{r=a} = 0 \quad (2-4)$$





1. Psychophysical Experiments
2. Neuronal Electrical Excitation

**The global shape of the array, the shape of each electrode, the way to insert and attach it, and so forth, depends on the anatomical location of stimulation.**

**If either IrOx or TiN can be smaller electrodes, then**

- **more channels**
- **higher image quality**
- **reduced power consumption.**



1. Psychophysical Experiments
2. Neuronal Electrical Excitation
3. Electrodes

## Battery

### inductive link (wirelessly)

- consideration

: diameter

: number of turns of the primary and secondary coils

: position of the two coils

: frequency of the radio wave (typically over 1 MHz)

: size (aesthetic reasons and anatomical constraints)

: coplanar (Power transfer is maximized)

- power transfer rates are approximately 2%

**5mW** power supply may be adequate to drive both the inductive link and the stimulator chip (for 100 electrodes)

up to **50 mW** can be transmitted using a 9-cm diameter primary coil and a 1.5-mm secondary coil

->Enough



1. Psychophysical Experiments
2. Neuronal Electrical Excitation
3. Electrodes

### **infrared laser**

- using transparent optical pathway
- excite implanted photodiodes to produce electric current (this link would be more efficient than the inductive link)
- safety concerns
  - : eye movements
  - : deleterious effects of laser light on the retina



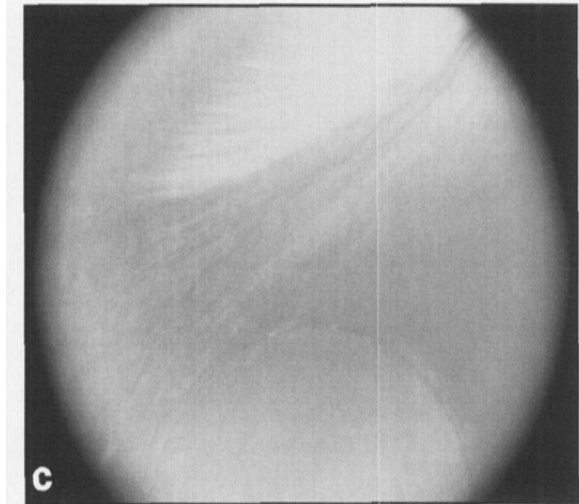
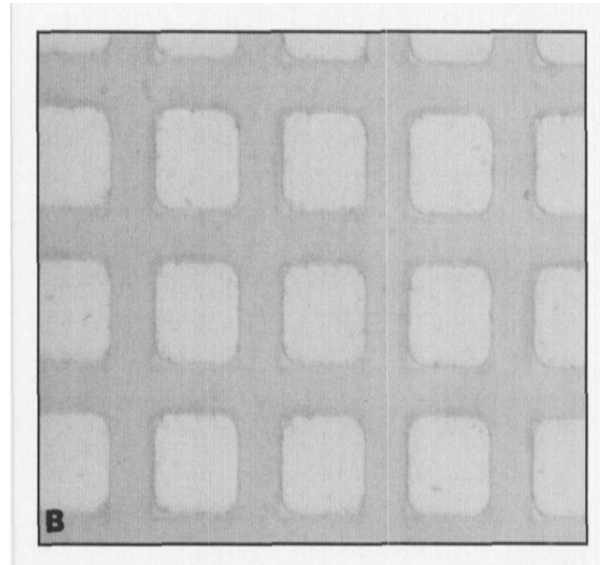
1. Psychophysical Experiments
2. Neuronal Electrical Excitation
3. Electrodes

### **Visible light or Near Infrared (NIR) light**

- using transparent optical pathway
- using **micro photodiode array (MPDA)**
- convert the **light energy** from images into **electrical impulses** to stimulate the retina
- this link would be more efficient than the inductive link
- safety concerns
- : **eye movements**
- : [visible] need 2000W/m<sup>2</sup> to perform -> **eye hazard!**  
(fluorescent light 10 W/m<sup>2</sup>, sunlight 100 W/m<sup>2</sup>)
- : [NIR] **deleterious effects** of laser light on the retina



1. Psychophysical Experiments
2. Neuronal Electrical Excitation
3. Electrodes



**Figure 1.** The appearance of the semiconductor microphotodiode array (SMA) implant. (A) A low-magnification photograph of the implant, relative to the size of a penny. (B) A higher-power photograph showing the appearance and distribution of the individual  $20 \times 20\text{-}\mu\text{m}$  microphotodiode subunits, separated by  $10 \mu\text{m}$  of channel block. (C) A fundus photograph of a rabbit retina approximately 10 months after surgical implantation.



2. Infection and Inflammation
3. Heat Damage
4. Hermetic Sealing of the

Electronics

**DC current could lead over time to irreversible electrolyte reactions.**

**safety: biphasic > mono**

**A biphasic waveform**

- has **no** DC component

**A monophasic waveform**

- it delivers DC

- creates irreversible **faradaic** processes



2. Infection and Inflammation
3. Heat Damage
4. Hermetic Sealing of the Electronics

### **Faradaic reactions**

- electron **transfer** across the electrode-tissue interface
- **oxidation** or **reduction** of chemicals



2. Infection and Inflammation
3. Heat Damage
4. Hermetic Sealing of the Electronics

### **Chemical reversibility**

**(requirement)**

- **opposite polarity** -> chemically **reverse all processes**
- **H<sub>2</sub> and O<sub>2</sub> evolution will be prevented**

**(examined by)**

- **cyclic voltammetry analysis**
- **gas bubbles observation**
- **UV spectroscopy**
- **atomic absorption**





# Cyclic voltammetry

From Wikipedia, the free encyclopedia

**Cyclic voltammetry** is a type of **potentiodynamic electrochemical** measurement. To obtain a cyclic voltammogram, the voltage is varied in a solution and the change in current is measured with respect to the change in voltage. It is a specific type of **voltammetry** used for studying the **redox** properties of chemicals and **interfacial structures**.

## Contents [hide]

- 1 Explanation
  - 1.1 Cyclic voltammetry
    - 1.1.1 Electrodes
  - 1.2 Potentiodynamic techniques
- 2 See also

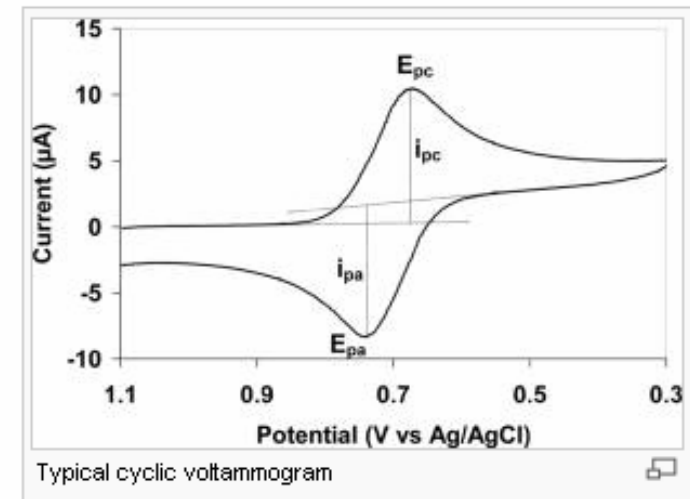
## Explanation

[edit]

In a cyclic voltammetry experiment, as in other controlled potential experiments, a potential is applied to the system, and the faradaic current response is measured (a faradaic current is the current due to a redox reaction). The current response over a range of potentials (a potential window) is measured, starting at an initial value and varying the potential in a linear manner up to a pre-defined limiting value. At this potential (often referred to as a switching potential), the direction of the potential scan is reversed, and the same potential window is scanned in the opposite direction (hence the term cyclic). This means that, for example, species formed by oxidation on the first (forward) scan can be reduced on the second (reverse) scan. This technique is commonly used, since it provides a fast and simple method for initial characterization of a redox-active system. In addition to providing an estimate of the redox potential, it can also provide information about the rate of electron transfer between the electrode and the analyte, and the stability of the analyte in the electrolyzed oxidation states (e.g., do they undergo any chemical reactions)

For the majority of experiments the electroactive species is in the form of a solution. The **three-electrode method** is the most widely used because the electrical potential of reference does not change easily during the measurement.

The method uses a **reference electrode**, **working electrode**, and **counter electrode** (also called the secondary or auxiliary electrode). **Electrolyte** is usually added to the test solution to ensure sufficient **conductivity**. The combination of the **solvent**, electrolyte and specific working electrode material determines the range of the **potential**.



## 1. Damage Caused by Electrical Current

the eye have been described as immunological **privileged sites**

### Inflammation factors

- **Biodegradation**
- **toxic substances** released from the implant
- **infected implants**
- **surgical or nursing staff**

to avoid bacterial colonization

- coating **polymers** with **proteins** or **antibiotics**
- strict **sterilization**



1. Damage Caused by Electrical Current
2. Infection and Inflammation
3. Hermetic Sealing of the Electronics
4. Hermetic Sealing of the Electronics

Different **components** of the visual prostheses can produce excessive **heat** and cause **damage** to any neuronal tissue

Disrupt a rat during a behavioral task

- whole-body exposure: **4 W/kg** (the animal stops performing a task and spread saliva on the tail)

The safe limit (safety factor: **10–50**)

- whole-body exposure for the general public: **0.08 W/Kg**
- occupational exposures: **0.4 W/Kg**



1. Damage Caused by Electrical Current
2. Infection and Inflammation
3. Hermetic Sealing of the Electronics
4. Hermetic Sealing of the Electronics

**retina's ability to dissipate and tolerate heat**

- no more than **50 mW** of power over a **1.4 mm<sup>2</sup>** area can be applied directly for more than **one** second.

(using the **same heater**, a power of **500 mW** in the mid vitreous for 2 hours did not cause any histological damage.)

**Any electronic component that produces relatively large amount of heat should be put as far away as possible from the retina**



1. Damage Caused by Electrical Current
2. Infection and Inflammation
3. Heat Damage

**connections** are the most vulnerable leakage points of the system

**titanium can**

- The pacemaker industry has developed
- effective encapsulation

**glass and ceramic** packages

- proven hermetic



1. Damage Caused by Electrical Current
2. Infection and Inflammation
3. Heat Damage

**glass to silicon (electrostatic bonding)**

- generates a **high electric field** at the glass-silicon interface
- causes a **permanent and irreversible** fusion bond between silicon and glass

**aluminum/silicon-to-glass solder bonding**

- **10 mega** pascals bonding strength
- a **good** hermetic sealing.



1. Damage Caused by Electrical Current
2. Infection and Inflammation
3. Heat Damage

Many types of welding or sealants tend to **leak** over time, are **not biocompatible** and are **expensive**

techniques for coating the electronics are a fundamental step to the **future feasibility** of any visual prosthesis.

