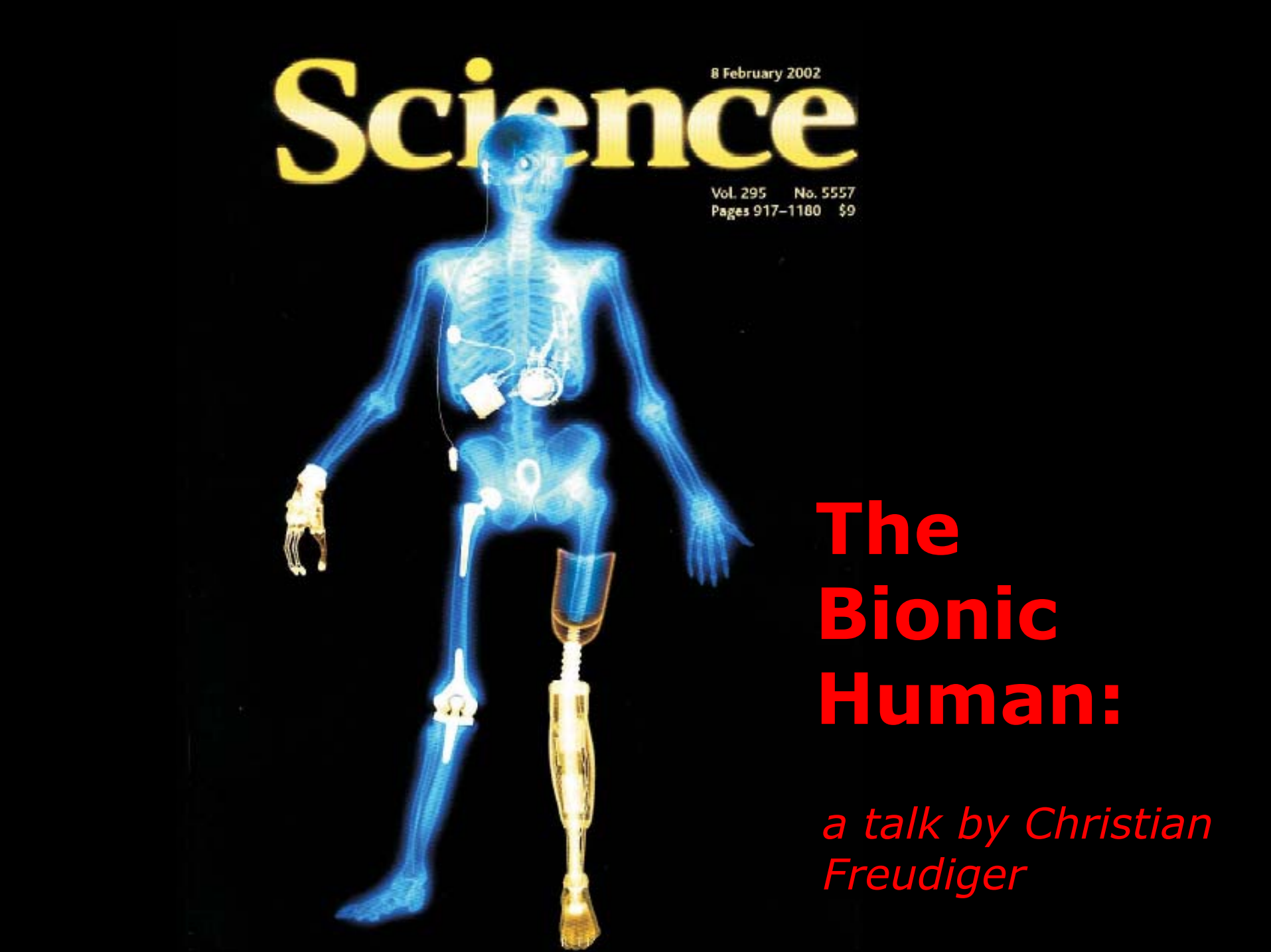
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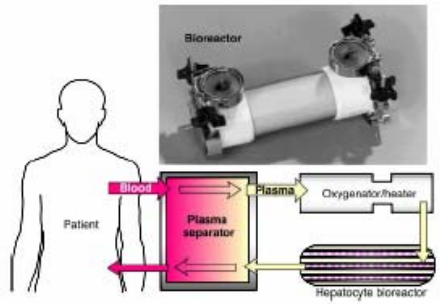
The Bionic Human:
a talk by Christian Freudiger

# The Bionic Human

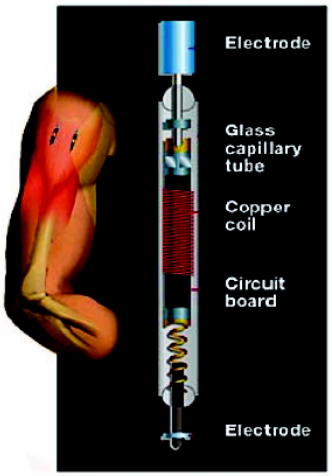
## Overview

**Implants and hybrid technologies find many fields of applications:**

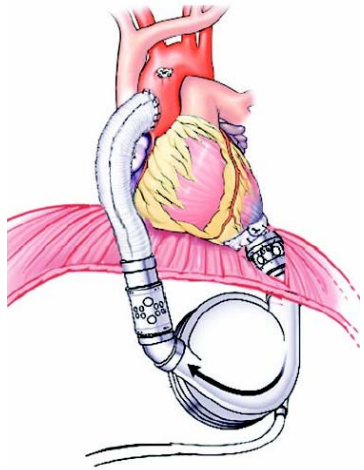
Artificial organs (e.g. liver)



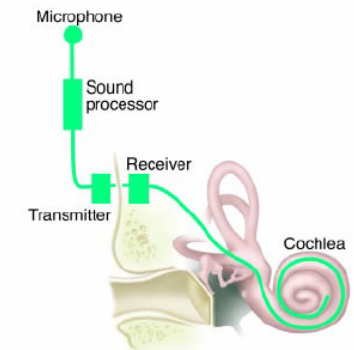

Artificial muscles, bones and joints

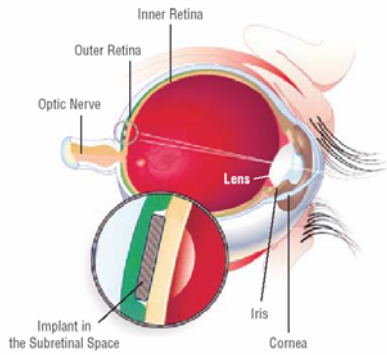



Circulatory support (e.g. pacemakers)



Restoring senses (e.g. artificial retina)



# The Bionic Human

## 1. What's the problem

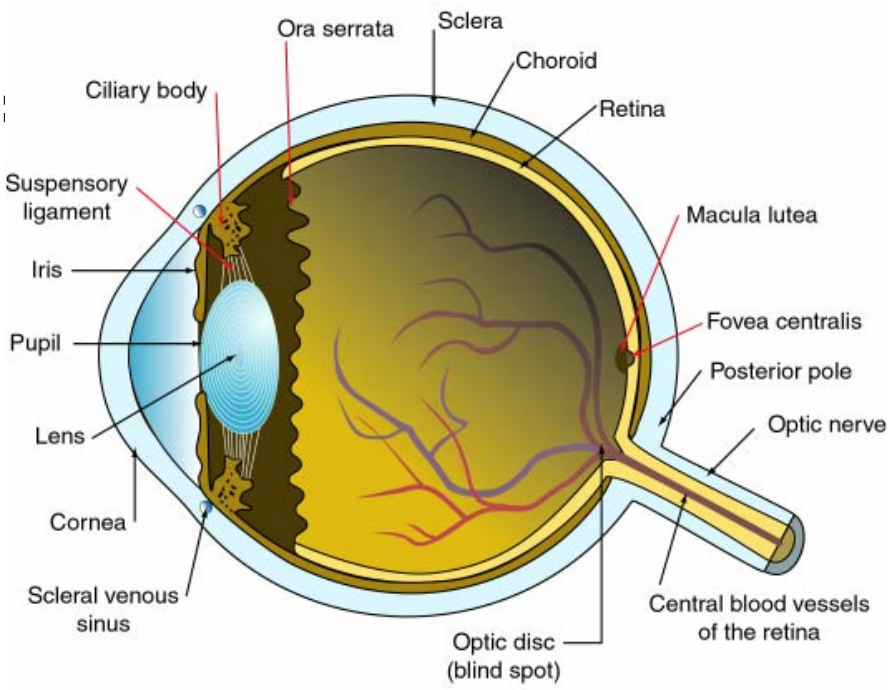
**Features of the visual system:**

- Resolution: 75 µm at distance of 25 cm (=angular difference of 1')
- refresh rate: approx. 40 Hz
- color contrast: approx. 100Mio different colors
- intensities: 60 Photons (=100W bulb in 600 km distance)

**Functioning of the visual system:**

<u>1. Optical part:</u>

- reproduce sharp picture on the retina
- adjust light intensity



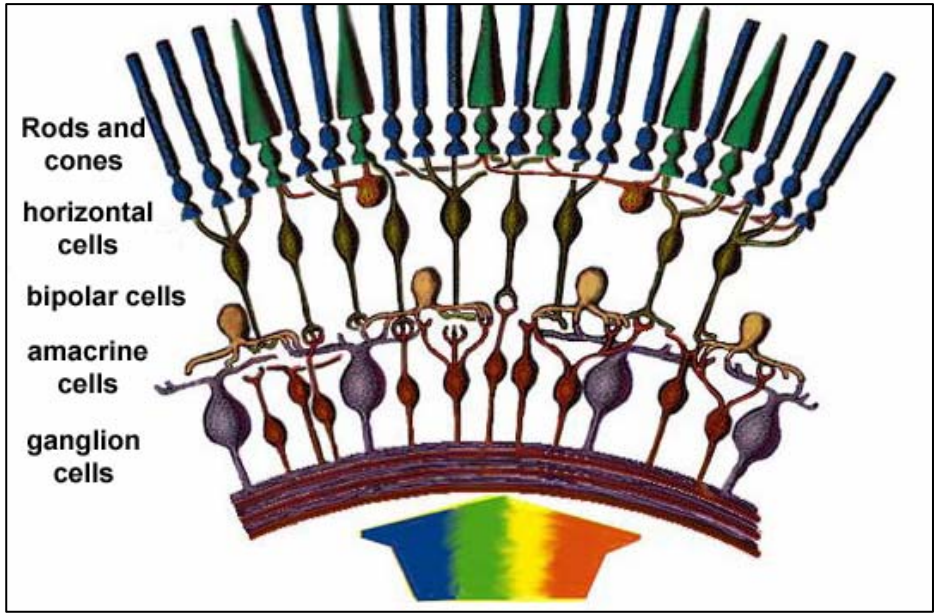
# The Bionic Human

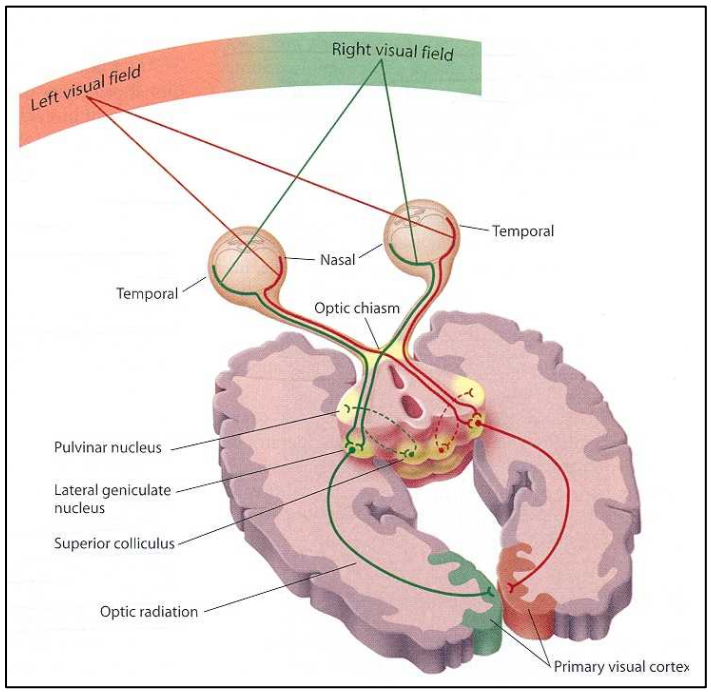
## 1. What's the problem

2. Detection (retina):

- photoreaction with rhodopsin (1 photon)
- amplification cascade (x $10^6$)

  ➔ action potential




3. Information processing (visual cortex)

- information form 130 Mio. photo-receptors
- reduction to 1.2 Mio specialized ganglion neurons
- enrichment with data from memory

# The Bionic Human

## 1. What's the problem

**Typical illnesses that could be healed:**

- **Retinitis Pigmentosa:**
  - continuous degeneration of the retina
  - inherited blindness
  - most common form of blindness:
    1.5 million people affected worldwide
    (= 1 of 3500 births)

- **Age-related macular degeneration:**
  - continuous degeneration of rods in the macula (visual disk)
  - typical disease of older people
  - more and more people are affected
    70.000 new patients in the U.S. a year

**But:** neurons mainly stay alive

# The Bionic Human

## 1. What's the problem

**Different approaches to stimulate nerves of the visual system:**

**Cortical prosthesis**:

direct stimulation of the visual cortex in the brain with electrodes:

- surface electrodes
- intracortical electrodes

First experiments in 1947 (wires through the skull)

**Retinal prosthesis:**

implant into the eye that replaces the retina (at least in parts)

**Subretinal prosthesis:**

replacement of photo-receptors by "solar cells"

**Epiretinal prosthesis:**

stimulation of ganglion cells with signal form external detector

**Optic nerve prosthesis:**

stimulation of the optical nerve (1.2 Mio ganglion cells within 2mm-diameter cylinder)

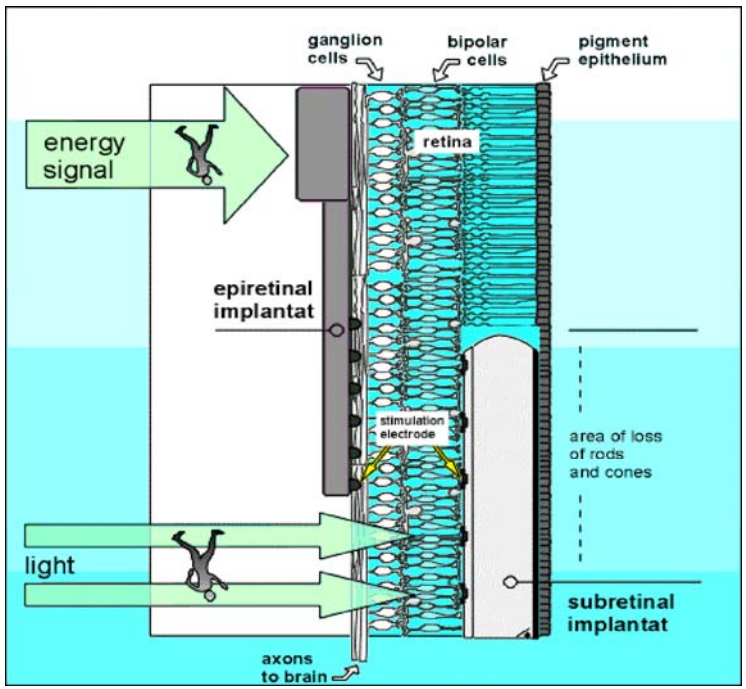
Method was mainly pursued in the 70s

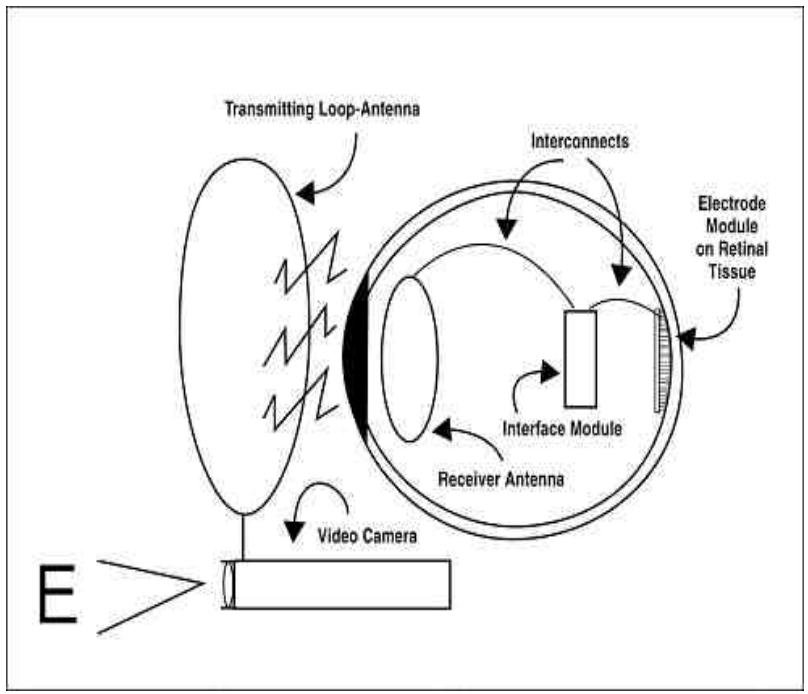
# The Bionic Human

## 1. What's the problem

### Types of retinal prosthesis

| Subretinal prosthesis: | Epiretinal prosthesis |
|---|---|
| Replacement of photoreceptors in the retina by photosensitive devices | Stimulation of ganglion cells with signal form external detector (camera) |



# The Bionic Human

## 1. What's the problem

System-Engineering:
Design of implant and fabrication

Materials layout and encapsulation:
- resistance
- protection of tissue

Understanding the nervous system:
- proper stimulation parameters
- suitable electrode design

**How can physicists and engineers help?**

Power supply and information transfer:
- inductive coupling
- converting near infrared light

Sensor design:
- photodiodes
- solar cells



**Outline of the talk:**

1. *What's the problem*

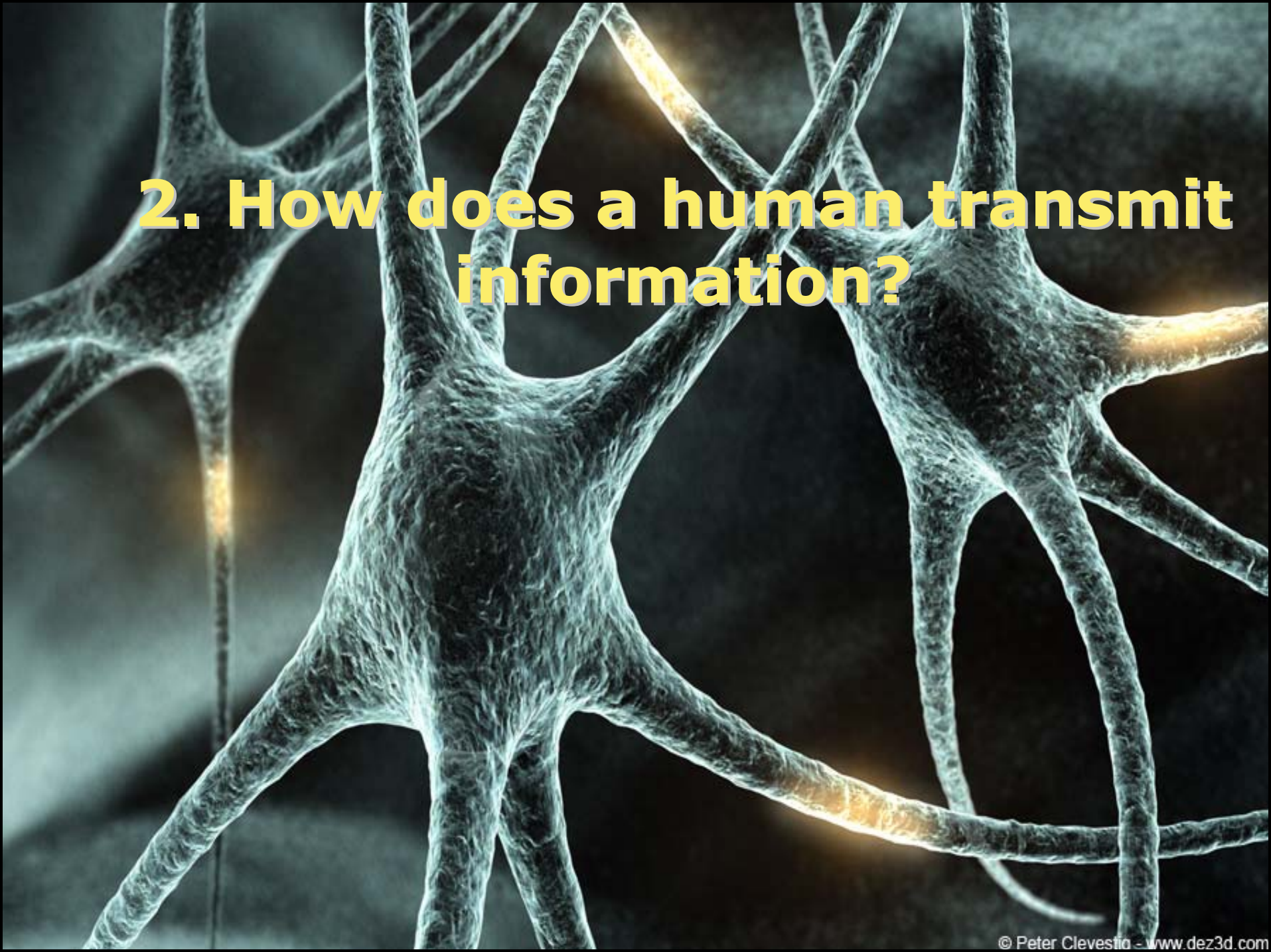
2. Functionality of neurons and consequences for stimulation
   - information transmission in neurons
   - electrical stimulation of neuronal activity
   - proper parameters and electrode design for effective stimulation

3. Sensor design: functionality of a solar cell and a photo-conductor

4. Wireless power supply and information transmission

5. Suitable materials and encapsulation

6. State of the art systems:
   - epiretinal prototypes
   - subretinal prototypes → especialla MPDA


2. How does a human transmit information?
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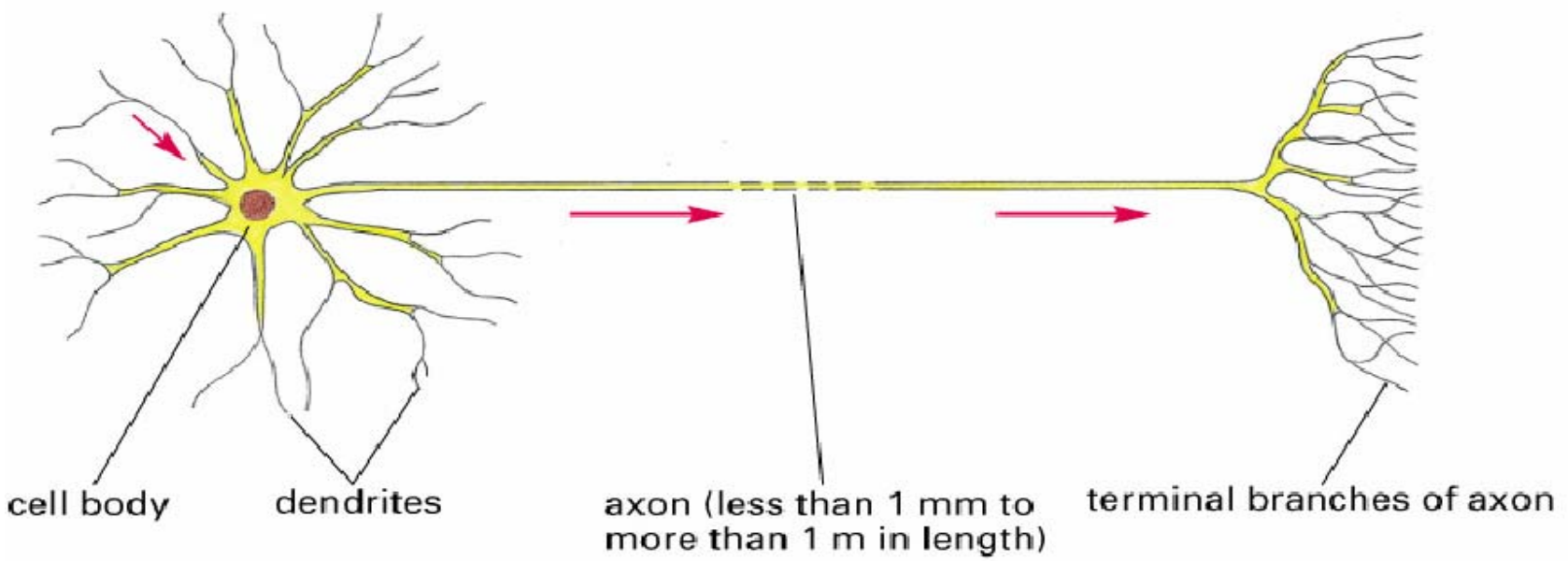
# 2.1 How does the hand know, what the leg is doing?

**The neuron (= nerve cell):**




**Difference between a "telephone cable" and a neuron:**

- neurons are purely isolated
- bathed in a conductive bath

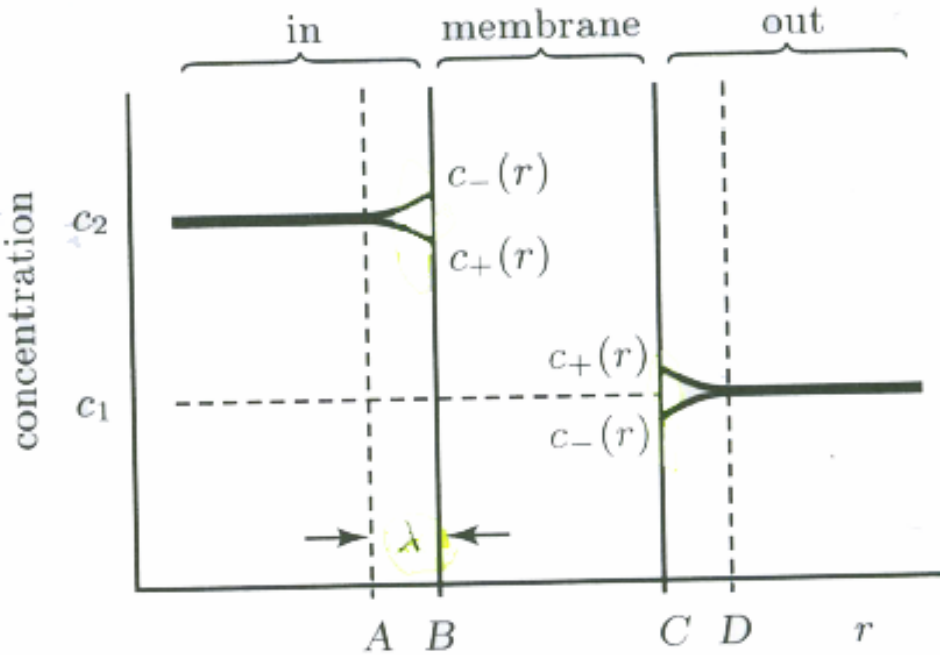
⇒ How can a leaky cable carry a sharp signal over a long distance?



**The Nernst Potential:**

Example system for **stationary case** (no net flux):

- 2 chambers filled with neutral ion solution: $c_1^+ = c_1^-$, $c_2^+ = c_2^-$, $c_2 > c_1$
- membrane is only permeable for positive Ions




➔ Positive ions cross the membrane (increase entropy)

➔ electrical field across the membrane

➔ equilibrium

Quantitative description via Boltzmann distribution:

$$\frac{c_2}{c_1} = e^{-\frac{Z \cdot e \cdot \Delta V}{k_B \cdot T}} \quad \Rightarrow \quad V_{Nernst} = -\frac{k_B \cdot T}{Z \cdot e} \cdot \ln\left(\frac{c_2}{c_1}\right)$$

**(Nernst Potential)**



## Generalization to more mobile species: The Donnan Potential

Applicable to neuron cell:

- Proteins, DNA, … (inside): negatively charge and immobilized
- Ions (mainly: $K^+$, $Na^+$, $Cl^-$) diffuse through membrane

**Results:**

$V_{mem} \approx$ -60mV and $\frac{c^{inside}_{Na^+}}{c^{outside}_{Na^+}} = \frac{c^{inside}_{K^+}}{c^{outside}_{K^+}} = \frac{c^{outside}_{Cl^-}}{c^{inside}_{Cl^-}}$

**But:** Experimentally measured ion-concentration

| Ion | Valence $z$ | Interior $c_{2,i}$ (mM) | Relation | Exterior $c_{1,i}$ (mM) | Nernst potential $\mathcal{V}_i^{\text{Nernst}}$ (mV) |
|---|---|---|---|---|---|
| $K^+$ | +1 | 400 | > | 20 | −75 |
| $Na^+$ | +1 | **50** | < | **440** | +55 |
| $Cl^-$ | −1 | 52 | < | 560 | −60 |



**So what's wrong?**

**If you are able to apply equilibrium statistical mechanics to a biological system,**

**Your system will be dead!**

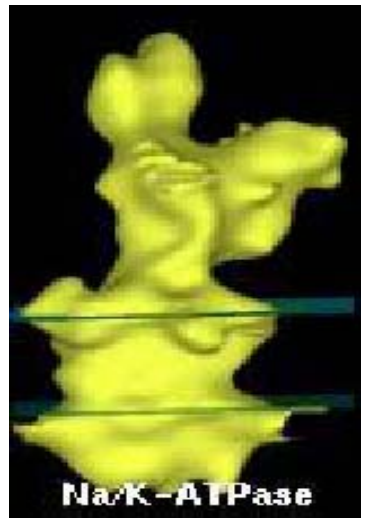
(Pincus Conjecture)

Cells at rest burn food

➔ combat the drive towards equilibrium.

In the case of neurons:
Membrane protein $Na^+$-$K^+$-ATPases pumps:

- $Na^+$ to the outside (3 ions per cycle)
- $K^+$ to the inside (2 ions per cycle)
- under consumption of ATP





**Non-Equilibrium model of membrane-potential:**

Ohm's hypothesis: $j_i = -g_i \cdot \left(\Delta V - V_i^{Nernst}\right) + j_i^{pump}$ (with i=$Na^+$,$K^+$,…)

with: - ΔV is the membrane potential (charged capacitor)

- **generalization of Nernst Potential** (non-equilibrium): "translation" of entropic forces into an electrical potential

$$V^{Nernst} := -\frac{k_B \cdot T}{Z \cdot e} \cdot \ln\left(\frac{c^{in}}{c^{out}}\right)$$

- $j_i$ and $j_i^{Pump}$ are current densities

**Assumption: steady state:** $j_i=0$ (more general $\sum_i j_i = 0$)

➔ $$\underbrace{j_K^{pump} = g_K \cdot \left(\Delta V - V_K^{Nernst}\right)}_{j_K=0} = \underbrace{-\frac{2}{3} \cdot j_{Na}^{pump} = -\frac{2}{3} \cdot g_{Na} \cdot \left(\Delta V - V_{Na}^{Nernst}\right)}_{j_{Na}=0}$$

with $j_K^{pump} = -\frac{2}{3} \cdot j_{Na}^{pump}$ due to the characteristics of the Na-K-ATPase



➔ **simplified Goldmann-Equation:**

$$\Delta V = \frac{2 \cdot g_{Na} \cdot V_{Na}^{Nernst} + 3 \cdot g_K \cdot V_K^{Nernst}}{2 \cdot g_{Na} + 3 \cdot g_K}$$

**Interpretation:**

- cell at rest (depolarization): $g_K >> g_{Na}$

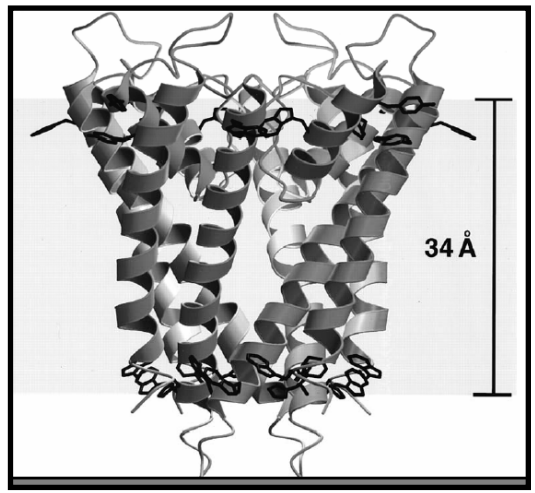
  ➔ membrane potential is dominated by Nernst Potential: $V_K^{Nernst} \approx -75mV$

- excited cell (action potential): $g_{Na} >> g_K$

  ➔ membrane potential is dominated by Nernst Potential: $V_{Na}^{Nernst} \approx +55mV$

➔ **Voltage-gated ion channels**

- pores in the membrane
- open when the membrane potential exceeds a threshold
- high, ion-specific conductance (when open)





**How is an action potential (=nerve impulse) created?**

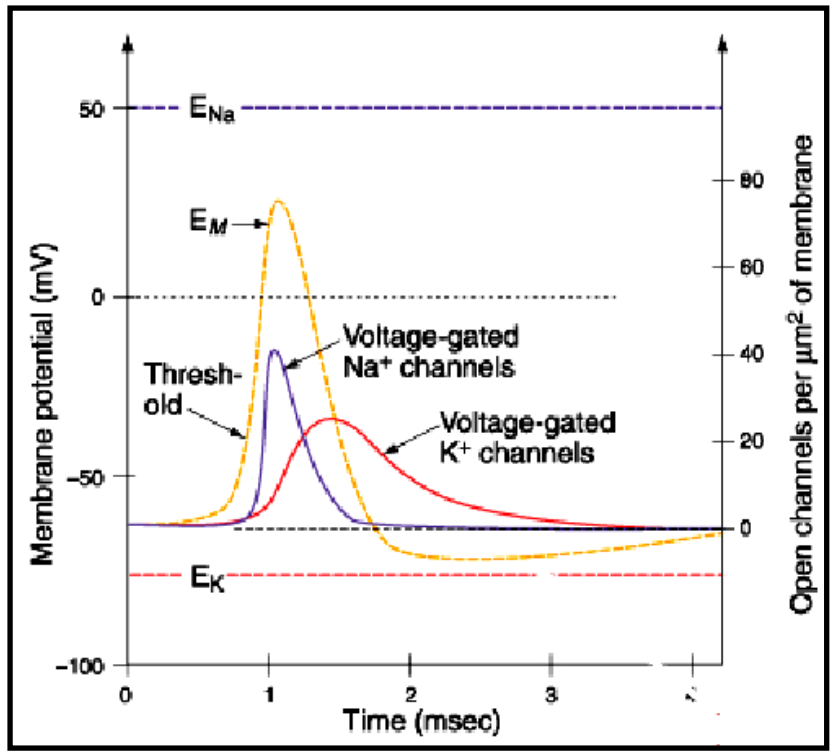
**Cell at rest:** $Na^+$- and $K^+$-ion-channels closed

➔ membrane at rest potential (≈-65mV)

**Excitation above threshold:**

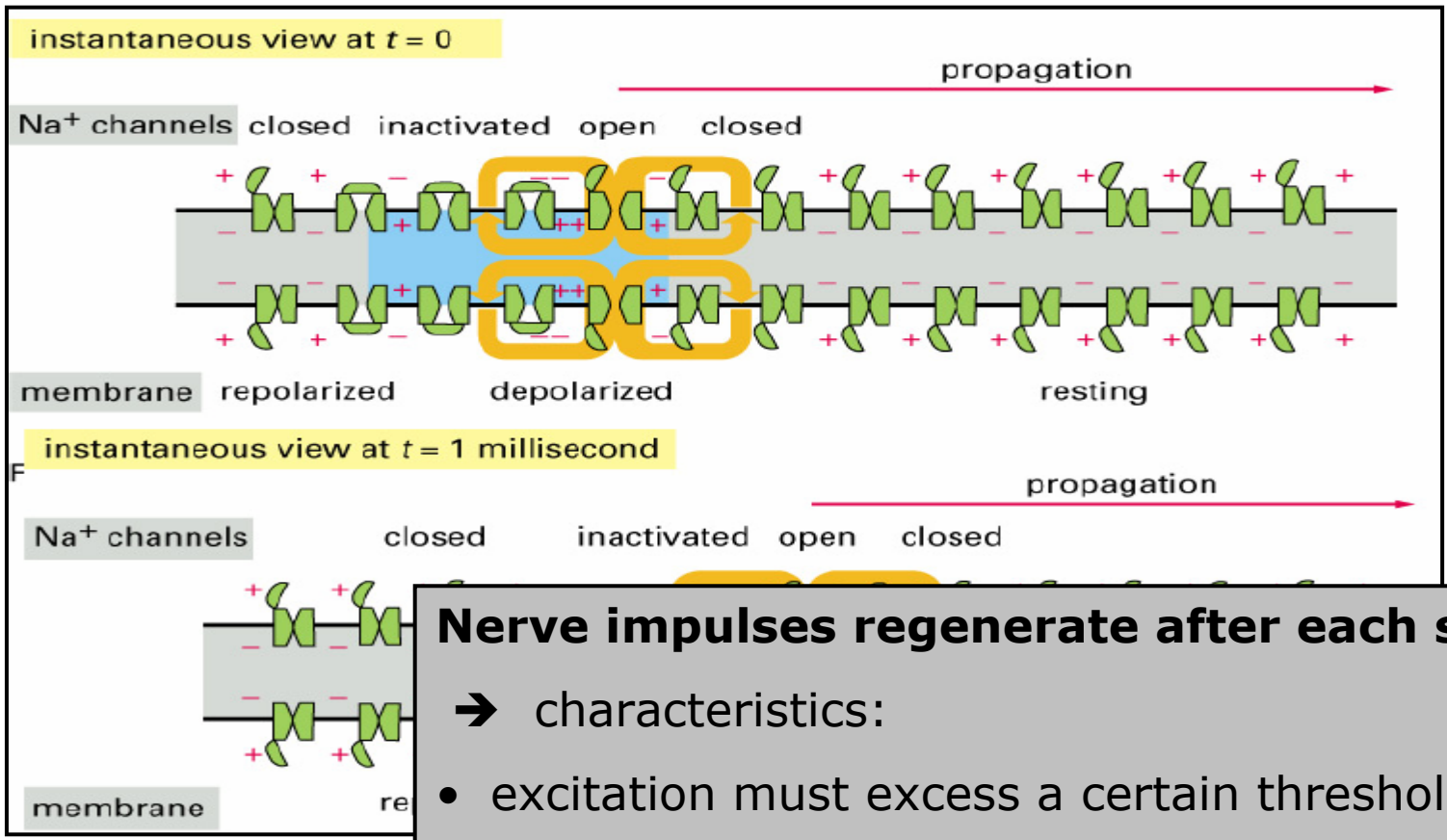
1. $Na^+$-channels open
   ➔ m.p. increases
2. $K^+$-channels open delayed
   Na-channels close with further delay
   ➔ m. p. has maximum (≈+20mV)
   ➔ cell hyperpolarizes (≈-70mV)
3. $K^+$-channels close
   ➔ membrane at rest potential

**= action potential (AP)**





## Propagation of neuronal signals




**Nerve impulses regenerate after each step**

➔ characteristics:

- excitation must excess a certain threshold
- neurons show "all-or-nothing" response

➔ no graded signals



# Summary:

**Biological Question:**

How can a leaky cable carry a sharp signal over a long distance

**Physical answer:**

Nonlinearity in a cell membrane's conductance (=***ion channels***) turns the membrane into an excitable medium, which can transmit waves by continuously regenerating (=***action potentials***) them.

➔ **Characteristics of information transmission:**

- excitation must excess a certain threshold
- neurons show "all-or-nothing" response

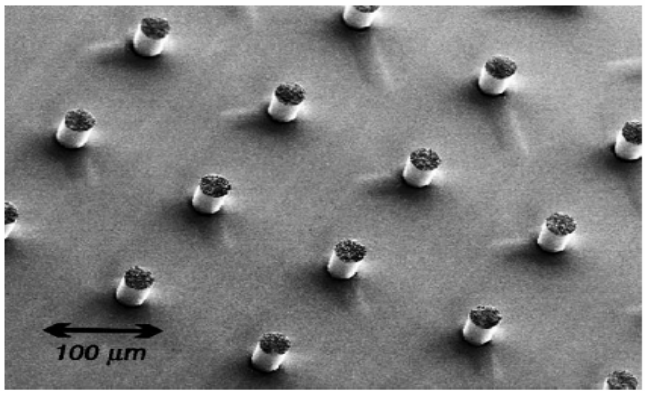
  ➔ no graded signals



## 2.2 How to stimulate an action potential with a battery?

**Answer**: Just increase the membrane potential above the threshold with an electrode!

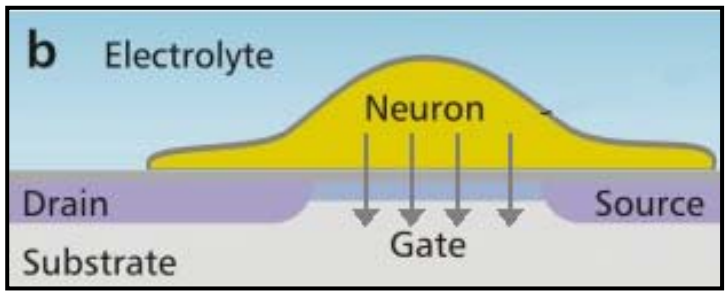
**Methods pursued:**

| amperiometric electrode | capacitive electrode |
|---|---|
| mainly platinum electrodes | mainly semiconductor covered with oxide layer |
|   |   |



**The interface:**

- simplest guess: neuron and substrate form ***compact dielectric***

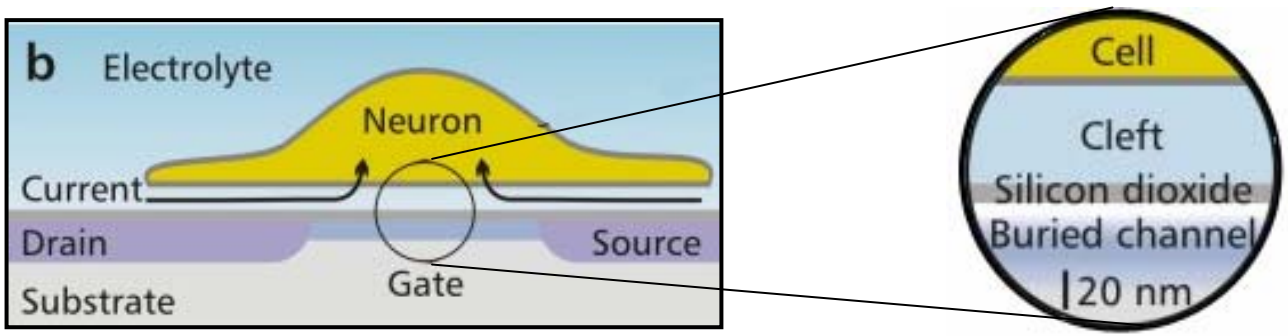



higher charge density in the substrate

➔ electric field across the oxide-layer and cell-membrane

= ***charging a capacitor***

- real case: ***conductive cleft*** between neuron and substrate



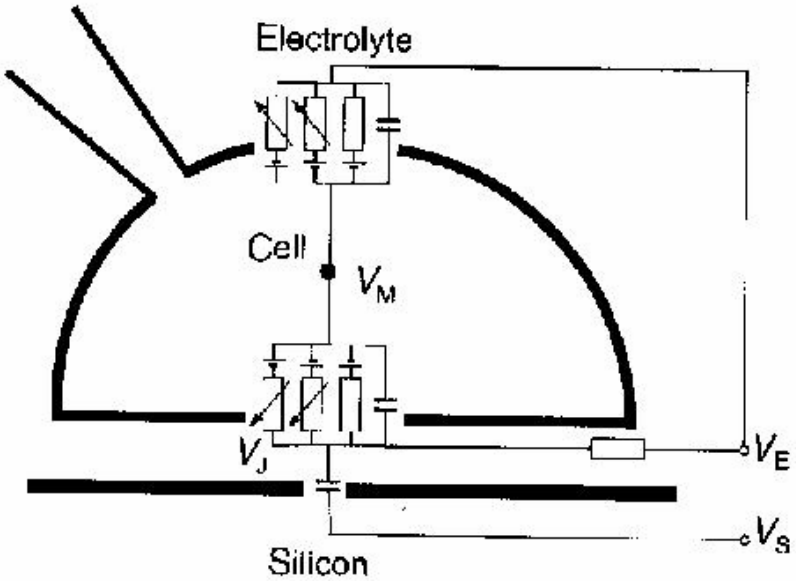

higher charge-density in substrate

➔ current through the conductive cleft (R ≈ MΩ) ➔ voltage drop

**= Transductive Extracellular Potential**



**Mathematical description:** **The planar core-coat-model**




Identification of structural elements with parts of electrical circuit, e.g.:

- conductive cleft = resistor
- oxide-layer = capacitor
- membrane = complicated circuit

➔ **Equivalent circuit**

**Underlying physical principal:** **Kirchhoff's Law**

At any point in an electrical circuit the sum of currents flowing towards that point is equal to the sum of currents flowing away from that point.

e.g.:

$$\sum_i g_{JM}^i \left(V_M - V_J - V_0^i\right) + c_M \left(\frac{dV_M}{dt} - \frac{dV_J}{dt}\right) = g_J \cdot (V_J - V_E) + c_S \left(\frac{dV_J}{dt} - \frac{dV_S}{dt}\right)$$



**Results:**

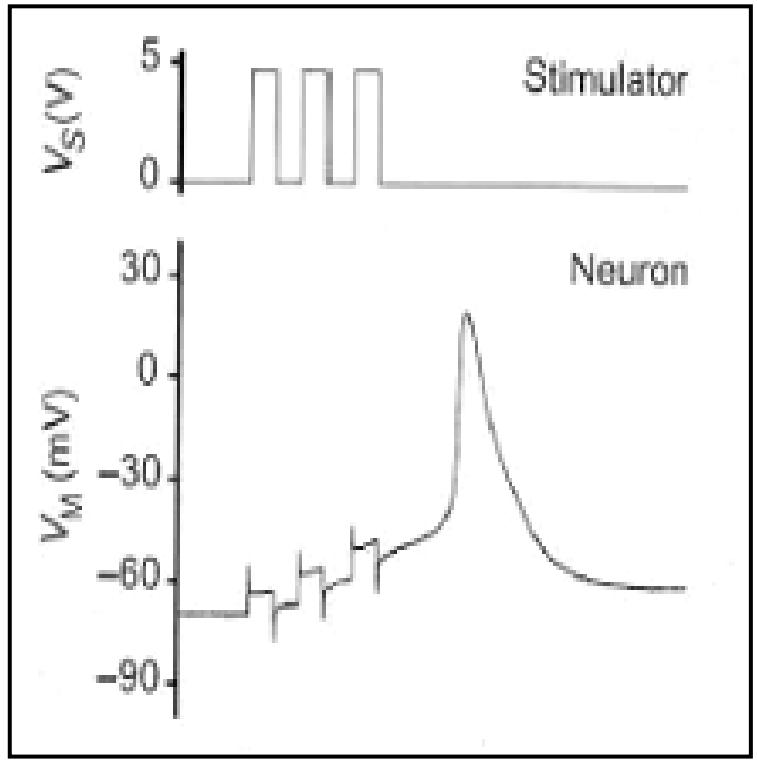
- it is possible to stimulate an action potential electrically
- but: high voltages are needed (≈1-5V)

$$V_M = V_M^0 + V_{st} \cdot \left[ a \cdot \exp\left( -\frac{t}{\tau} \right) + \beta \right]$$

rest potential

charging the membrane

ohmic current into the neuron




- periodic pulses are most effective

- distance neuron-substrate (cleft thickness) is crucial parameter

  ➔ surface modification to decrease distance (=nanotechnology)

  e.g. Poly-L-Lysin coating



## 2.3 Stimulation parameters – a thin line between life and death


in-vivo thresholds:
- current: 50-200 µA
- charge density: 0.2-70 µC/cm$^2$

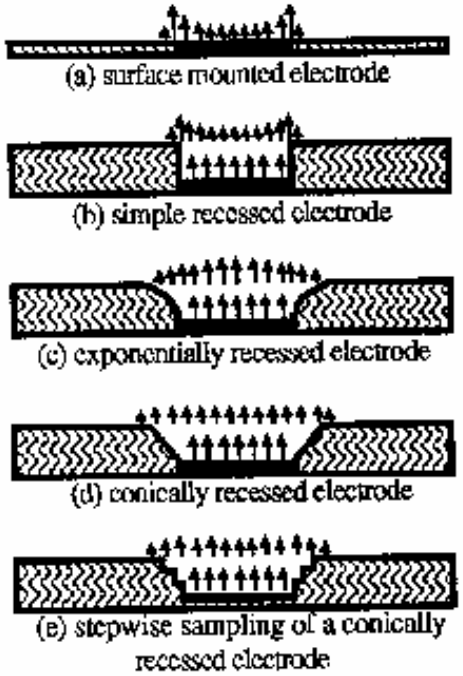
safe parameters (chronic implantation):
- current: 10-100 µA
- charge density: 100 µC/cm$^2$

**But: cochlear implants have helped deafs for years**

Other important parameters:
- pulse length
- rate of stimulation
- polarity (anodic/cathodic/bipolar current) → wave-form



## Electrode design:



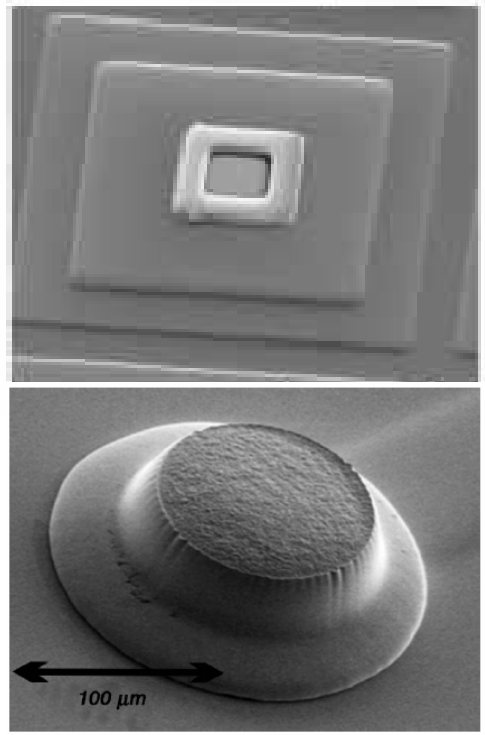

- high current densities

→ destruction of tissue by irreversible electro-chemical reaction

- delocalized stimulation

→ low contrast of the perceived picture

➔ homogeneous, but localized currents

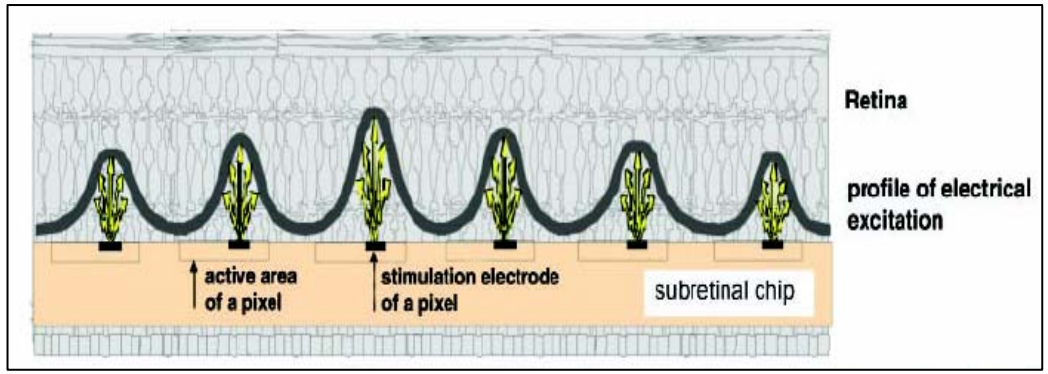


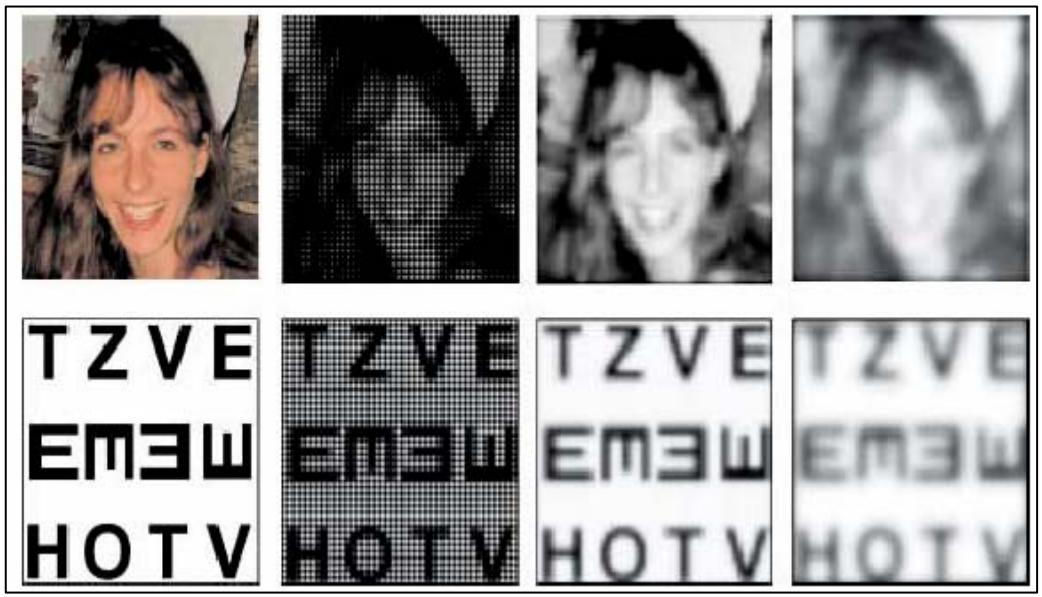


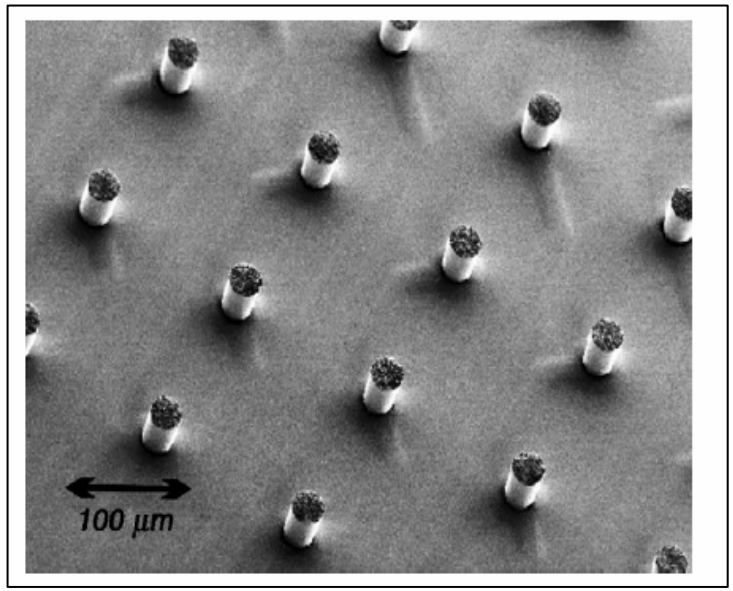
**Predicted perception:**

Not only a single neuron is stimulated:

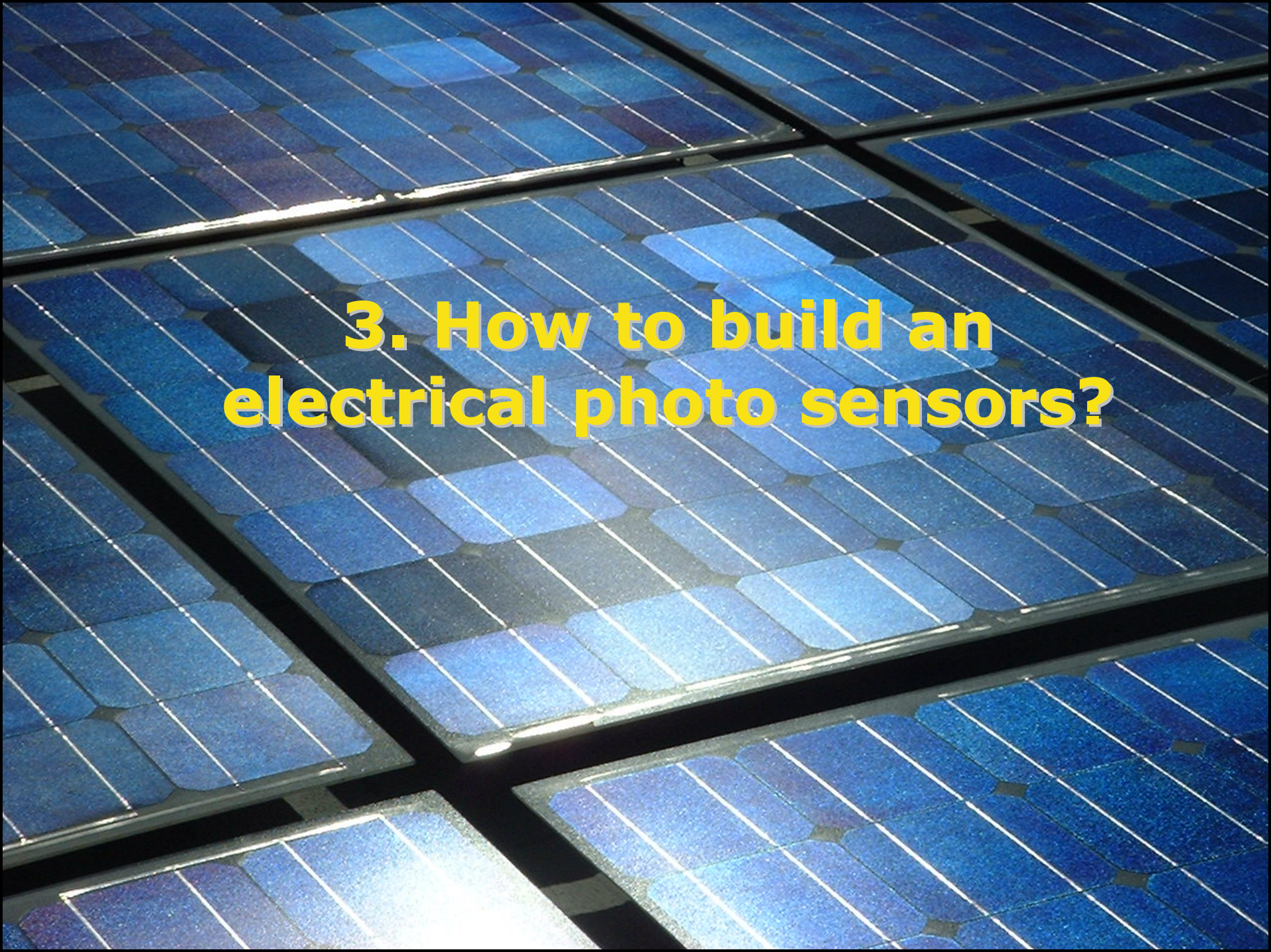
- no color-vision
- low contrast vs. pixeled




➔ **Proper array layout:** Distance of electrodes ≈ 70-200 µm


3. How to build an
electrical photo sensors?

# The Bionic Human

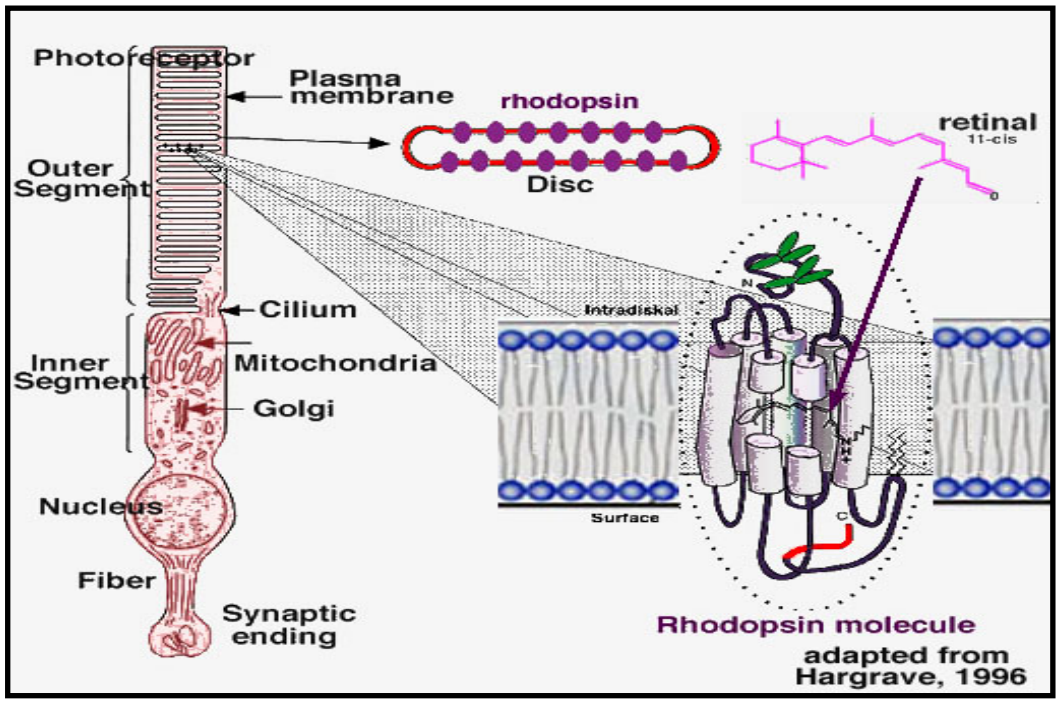
## 3. Electrical photo sensors

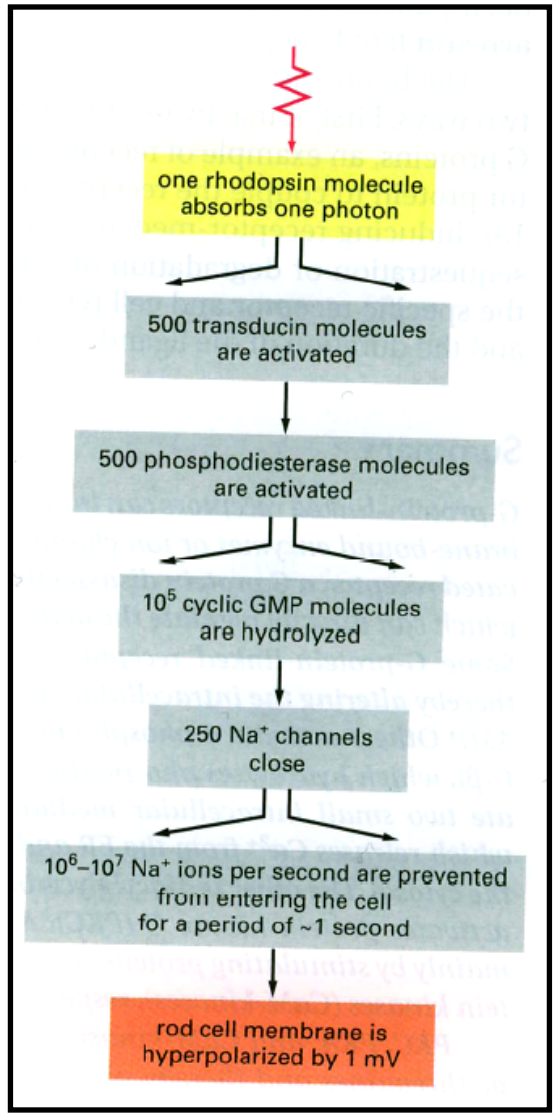
### How does the eye sense light?

Rods and Cones contain rhodopsin as photo-sensitive molecule:

Photon ➔ conformational change in chromophore

➔ activation of transduction cascade



# The Bionic Human

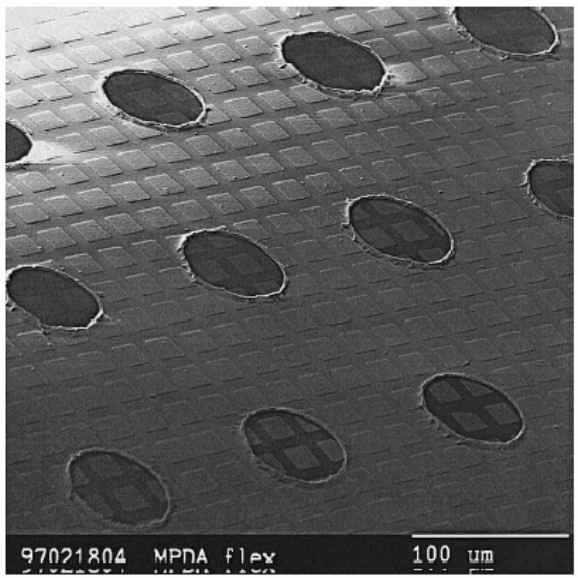
## 3. Electrical photo sensors

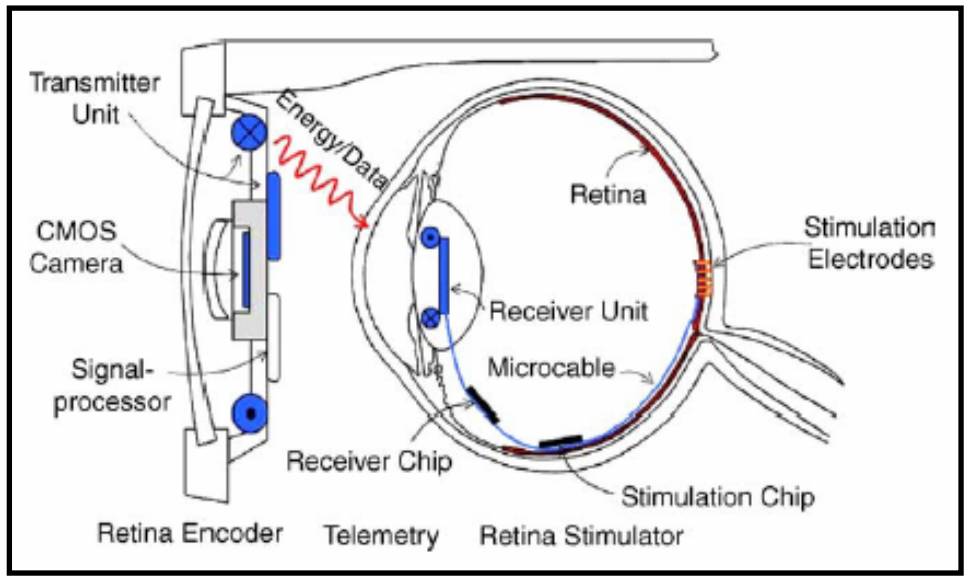
**Underlying physical principal:**

Photon ⟶ electric pulse

**Technical realization:**

- solar cell / photodiode → subretinal implant (receptor substitution)
- CCD / CMOS-Camera → epiretinal implant (extern camera)

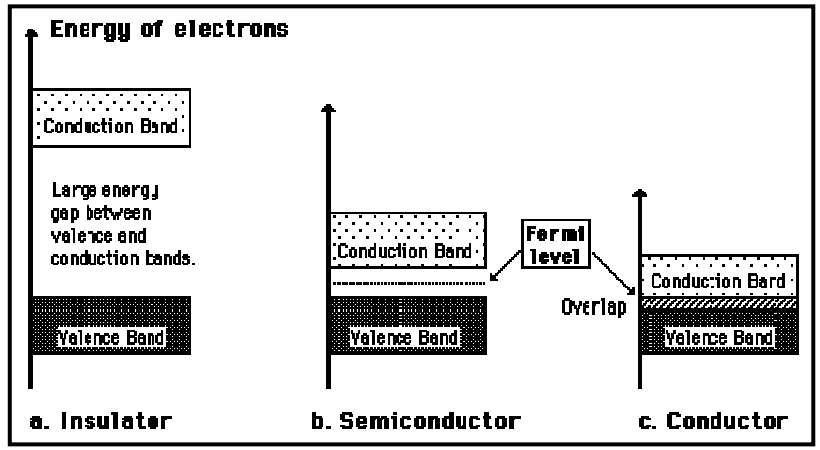


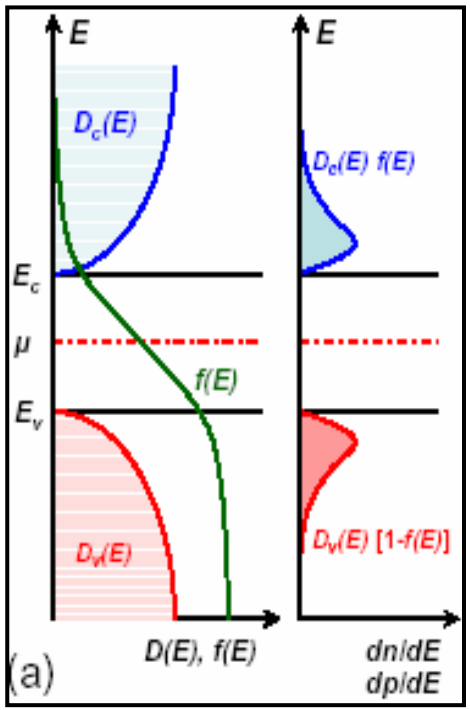





## Devices based on semiconductors

➔ **How do semiconductors work?**
(a semi-quantitative description)




### Intrinsic semiconductors:

Thermal excitation produces electron-hole-pairs, i.e. an electron from the valence band is lifted into the conduction band and leaver a hole

charge-carrier densities: $n_c = \frac{1}{V} \cdot \int_{E_c}^{\infty} D_c(E) \cdot f(E,T) dE$

$$p_v = \frac{1}{V} \cdot \int_{-\infty}^{E_v} D_v(E) \cdot [1 - f(E,T)] dE$$

with $n_c = p_v \quad \Rightarrow \quad \boxed{\mu = E_v + \frac{1}{2} \cdot E_g}$ (chem. potential)



**Doped semiconductor:**

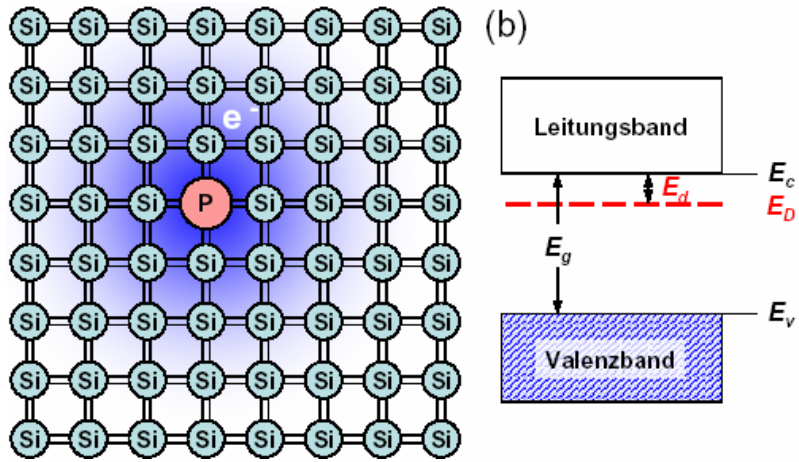
intentional introduction of impurities into a pure semiconductor

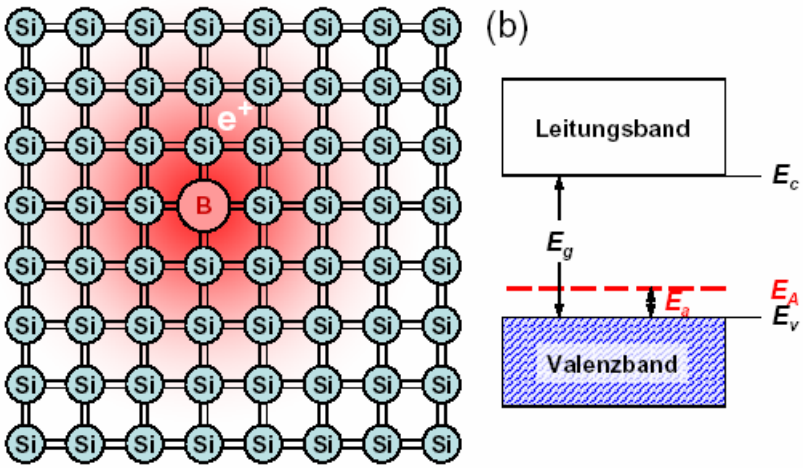
➔ movement of Fermi-level

**n-type:**

introduction of foreign atom with more valence electrons (e.g. P in Si)

➔ more electrons in conduction band




**p-type:**

introduction of foreign atom with less valence electrons (e.g. B in Si)

➔ more holes in valence band



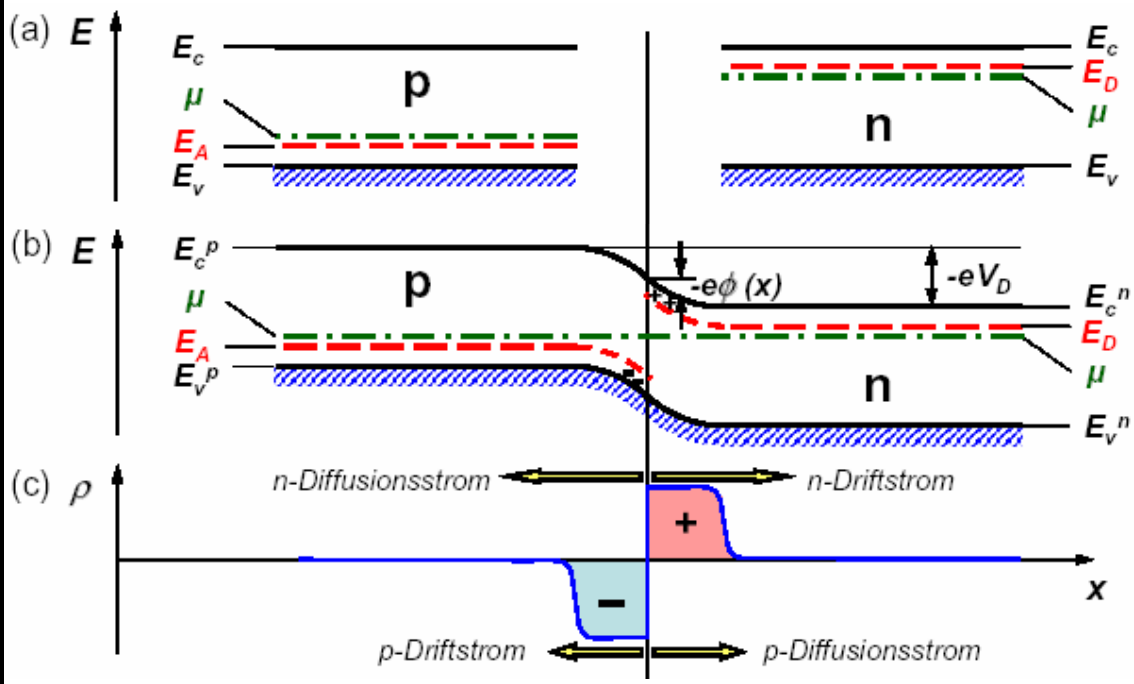
## Inhomogeneous semiconductors: p-n-Interface

One semiconductor is treated with different impurities

e.g. left: p-type right: n-type

$$N_A(x) = \begin{cases} N_A & \text{für } x < 0 \\ 0 & \text{für } x > 0 \end{cases}$$

$$N_D(x) = \begin{cases} 0 & \text{für } x < 0 \\ N_D & \text{für } x > 0 \end{cases}$$




Separate:

different Fermi-levels

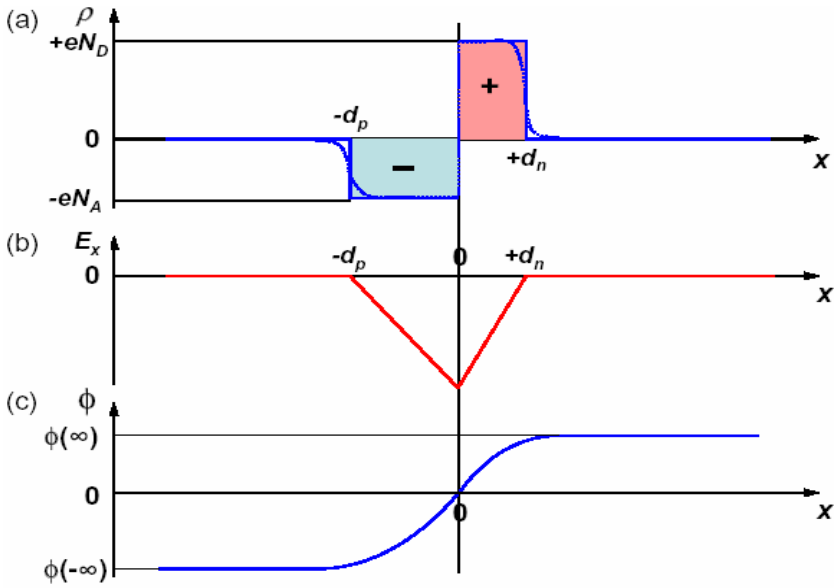
Contact + thermal equilibrium

→ same chemical potential

→ binding of bands due to depletion layer



**Shottky model:** Depletion layer is homogeneous and sharply bounded



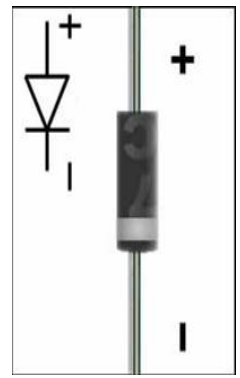

simplified charge distribution

➔ linear increase in electric field density

➔ sigmoidal increase in potential

**Functionality as diode**

- Forward bias: charge carriers move in the "proper" direction of the internal electric field
  ➔ diode conducts
- Reverse bias: charge carriers move in the "wrong" direction
  ➔ diode blocks
  (small reverse current)

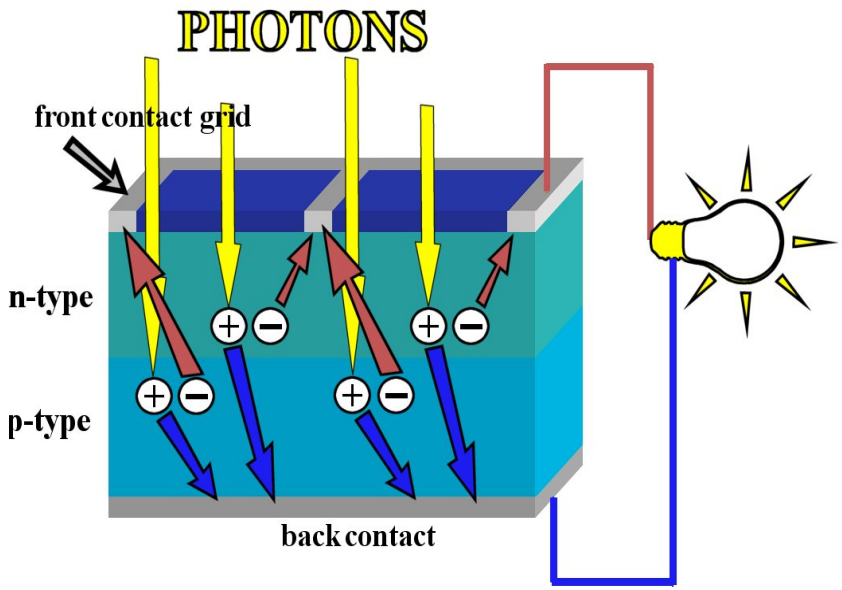


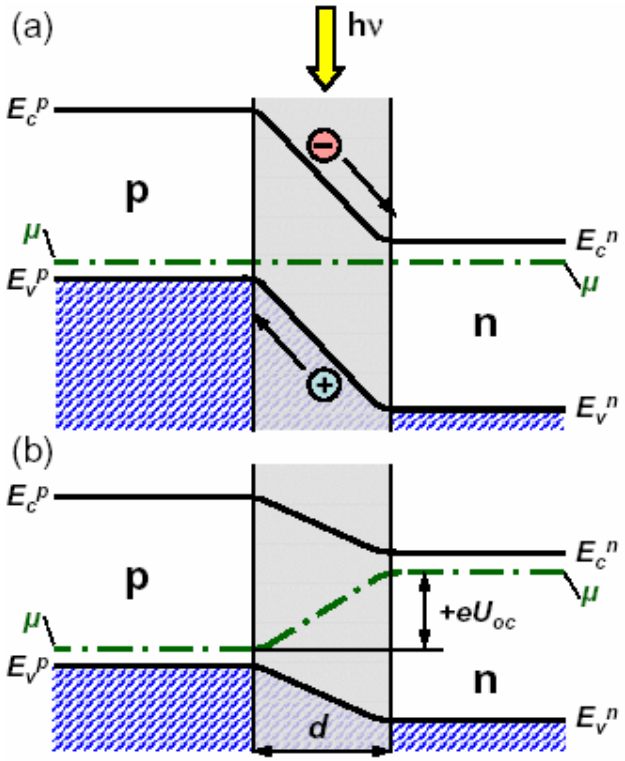


**Solar cell =** n/p-diode exposed to light

Photons create electron-hole-pairs in the depletion layer

➔ charge separation in the internal electric field




Continuous light-exposure

➔ non-equilibrium:

drift-current > diffusive current

➔ Fermi-Level is shifted

➔ potential difference $U_{oc}$ between n- and p-type layer



**Photodiode**

= resistor with resistance that depends on the incoming light intensity

**Realization:**

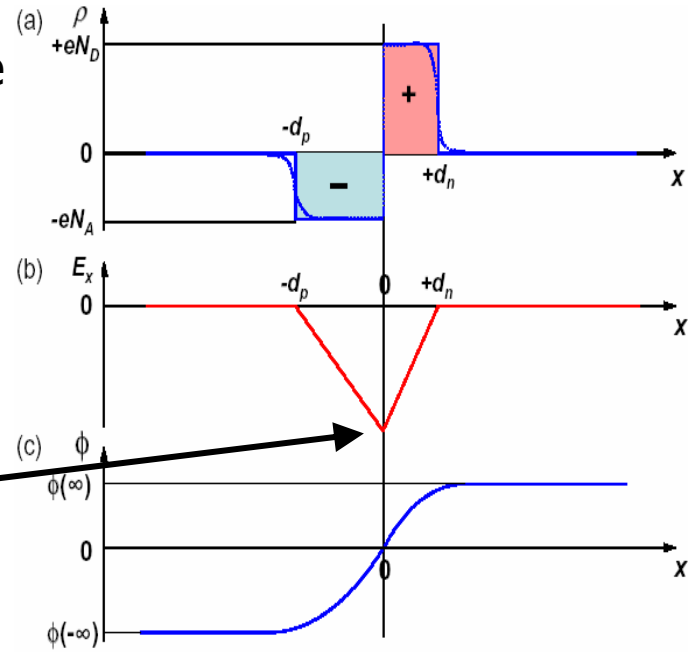
Solar cell run in reverse bias mode

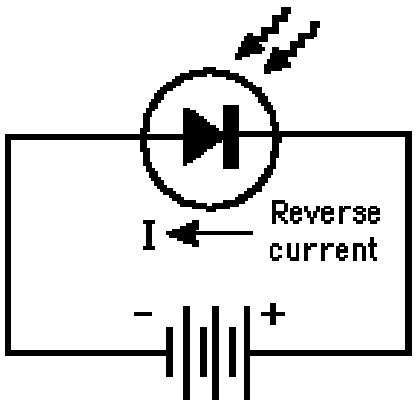
**Functionality:**

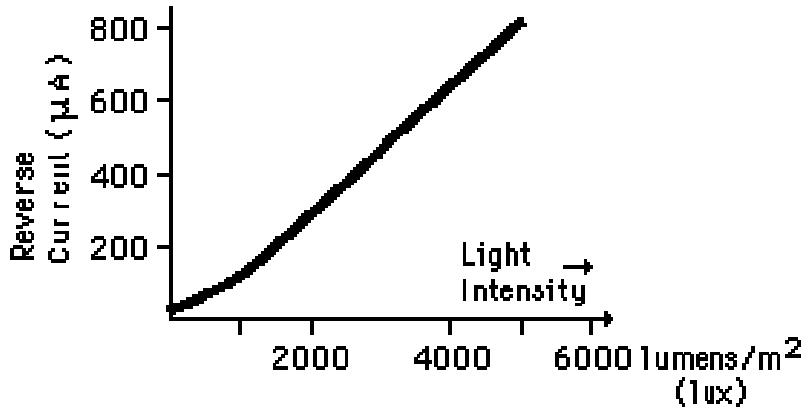
dark: diode blocked (R → ∞)

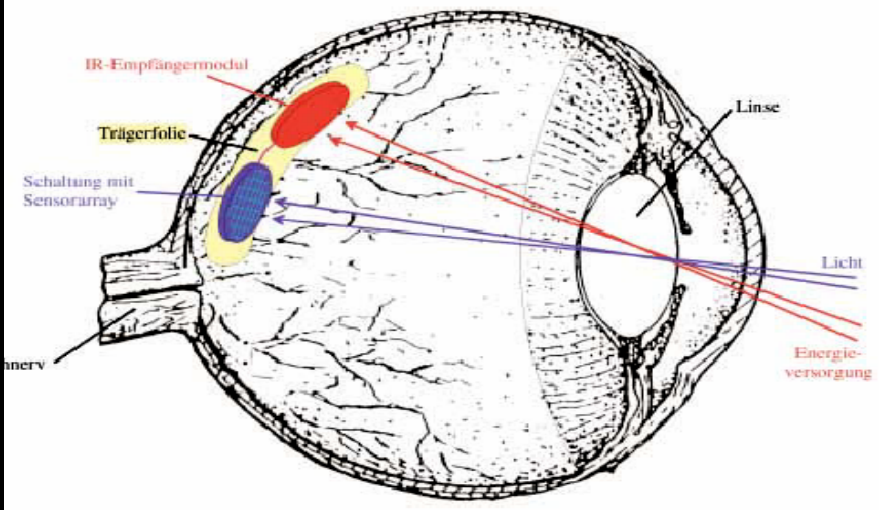
bright: internal electrical field decreased

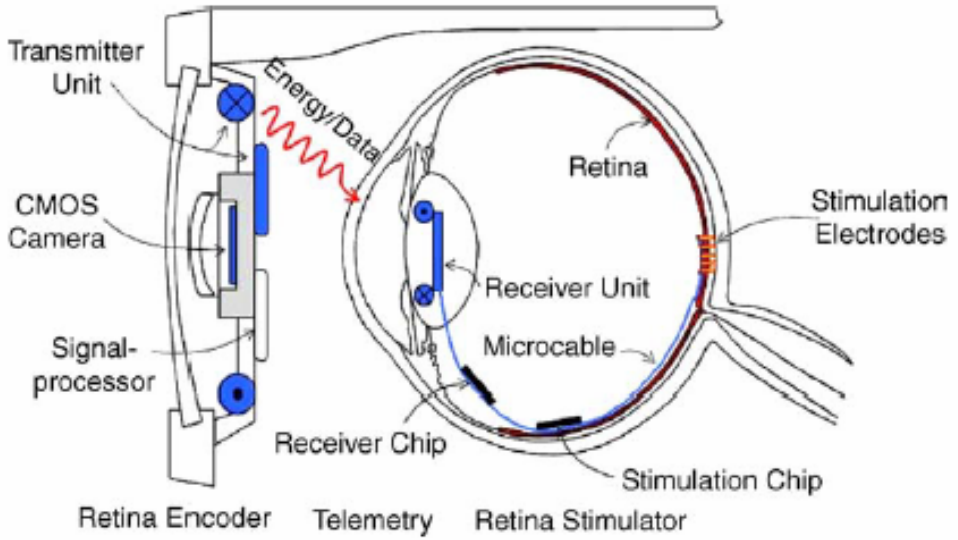
→ reverse current increases



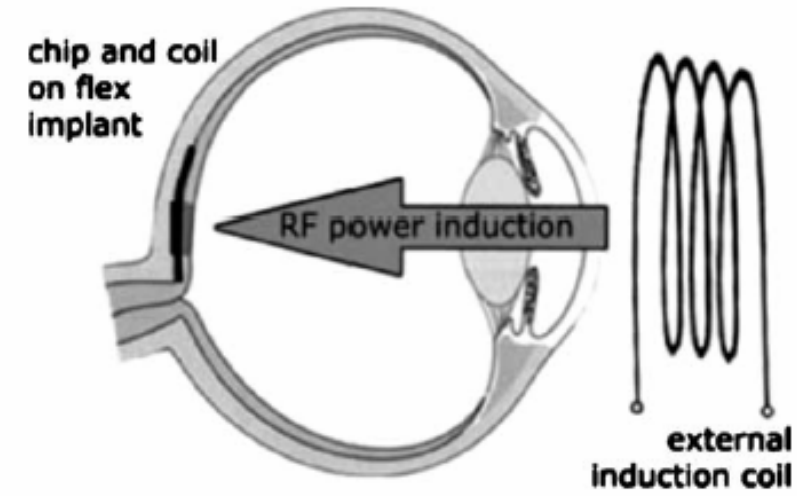



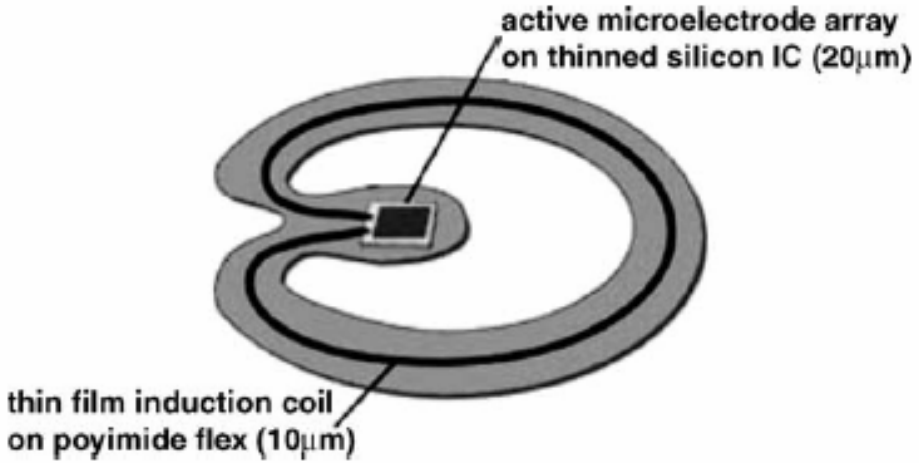






# 4. How to supply the implant with power?





**Power needed:**

- Epiretinal implants (computation +3500 electrodes): ≈ 50mW
- Subretinal implants (stimulation): ≈ 200mW/cm$^2$

**Power density in visible light** (on retina):

- artificial light: ≈ 1mW/cm$^2$
- sunlight (at noon): ≈ 10mW/cm2

**Tolerated light intensity of human eye:** << 200mW/cm$^2$

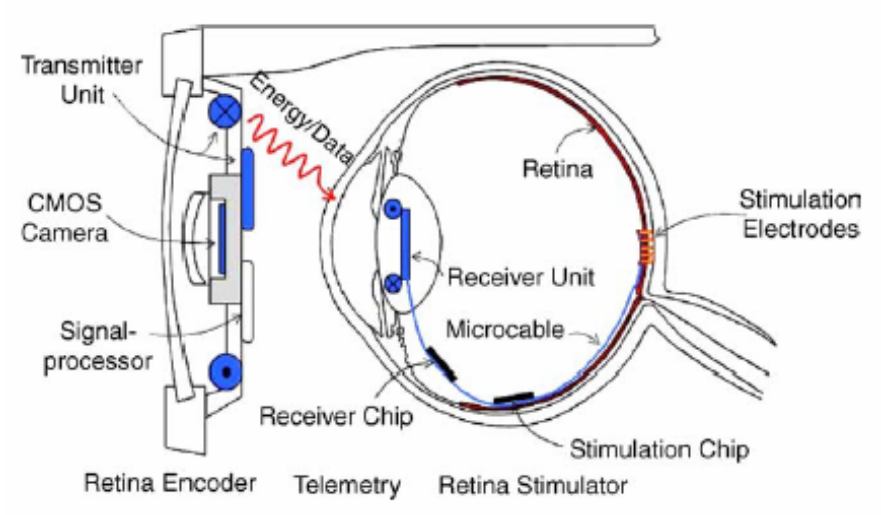
➔ **Need for wireless power supply!**

# The Bionic Human

## 4. Power supply and information transmission

**Solutions:**

**i) Inductive coupling** (for epiretinal implants)




technical properties:

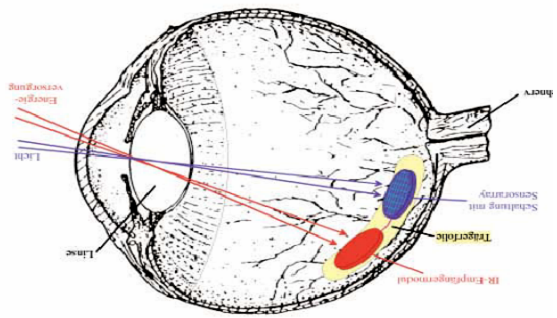
- primary coil: 5cm diameter
  secondary coil: 1.5mm diameter
- frequency: 1 MHz
- alignment: coplanar (glasses)

➔ **efficiency of 2%**

**ii) Near-infrared solar-cell** (for subretinal implants)

technical properties:

- tolerated NIR power density: ≥ 200mW/cm²
- absorption of eye (900nm): ≈ 5-10%
- Light generation: LED



# 5. Which materials will survive decades of implantation?

# The Bionic Human

## 5. Suitable materials and encapsulation

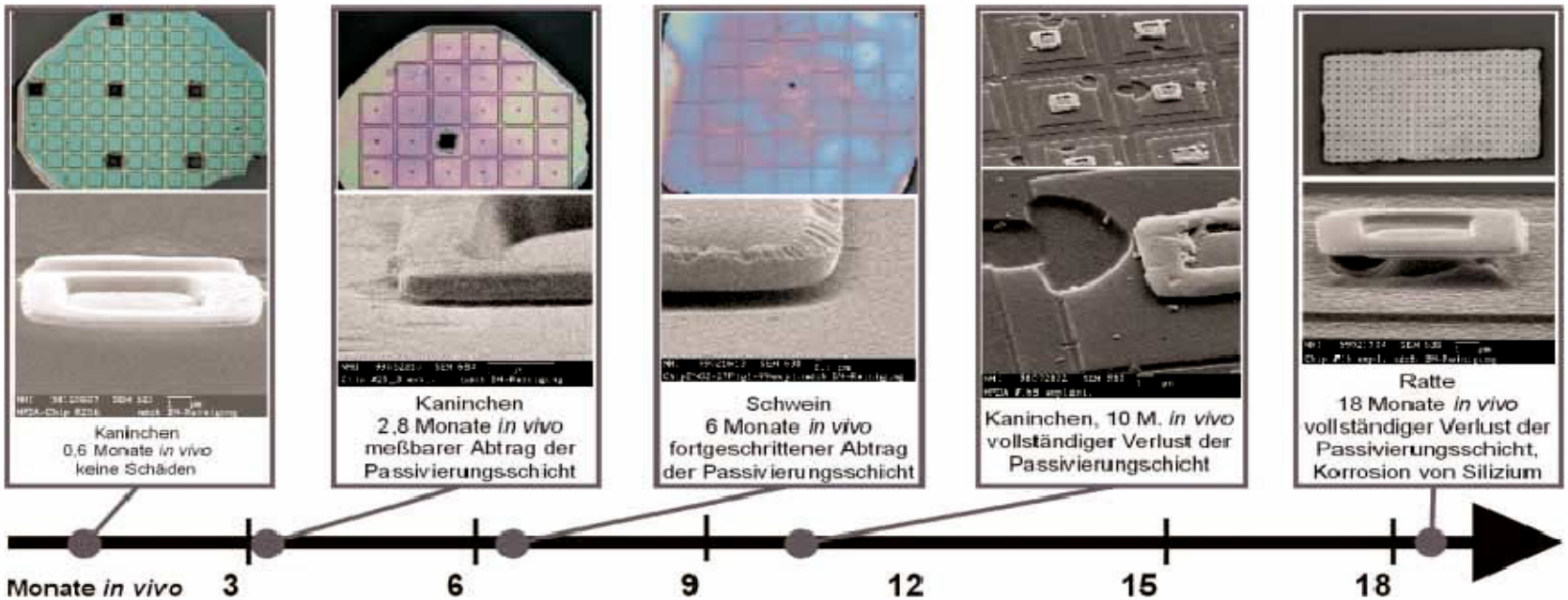
**Major problems:**

- **Biocompatibility:**
  - limits for electrical current- and charge-densities
  - avoid infections and inflammation
  - heat drainage
  - surface-functionalization

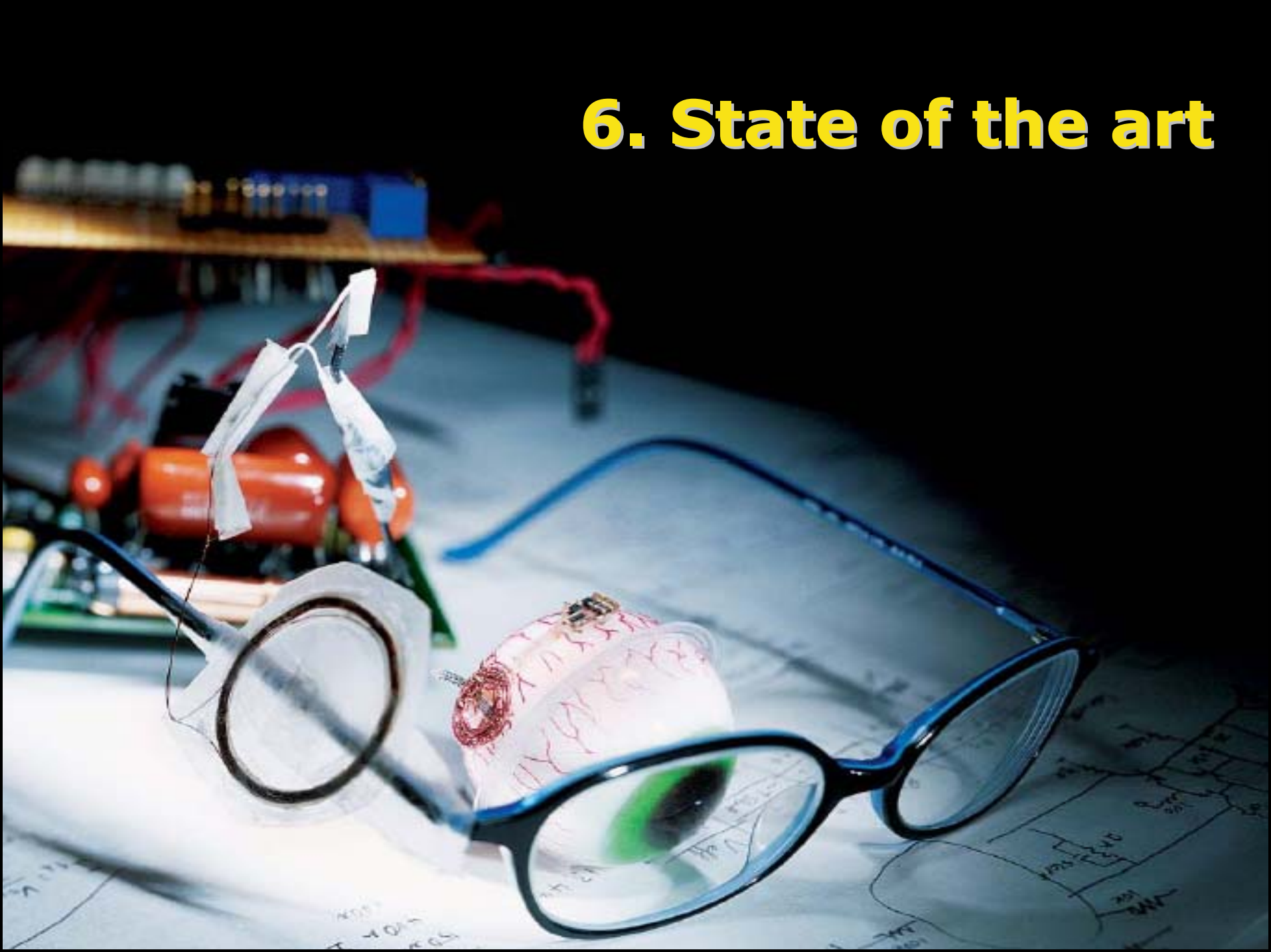
cochlea implants show long-time acceptance

- **Circuit protection**
  - proper electrode materials: e.g. Pt and alloys with Ir
  - encapsulation: e.g. silicon-to-glass solder bonding → 10-MPascal-seal

"mild" climate in the eye



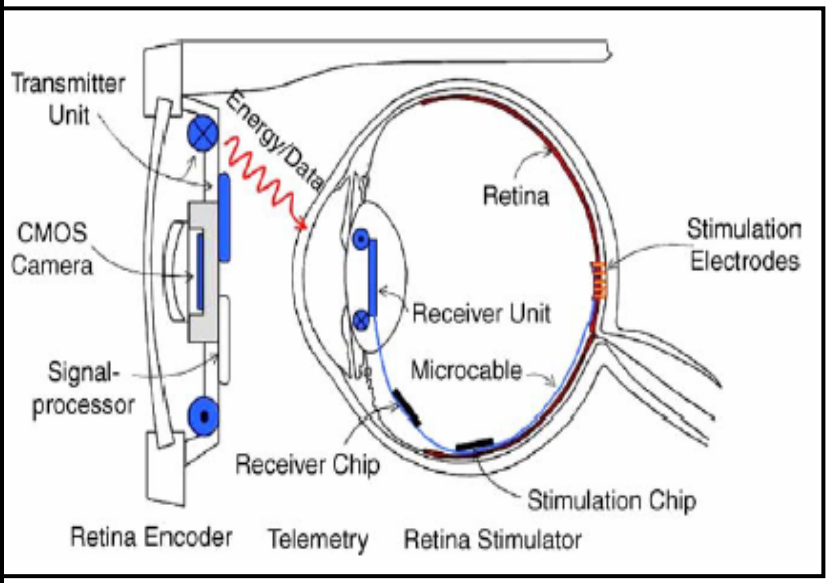
# 6. State of the art



# The Bionic Human

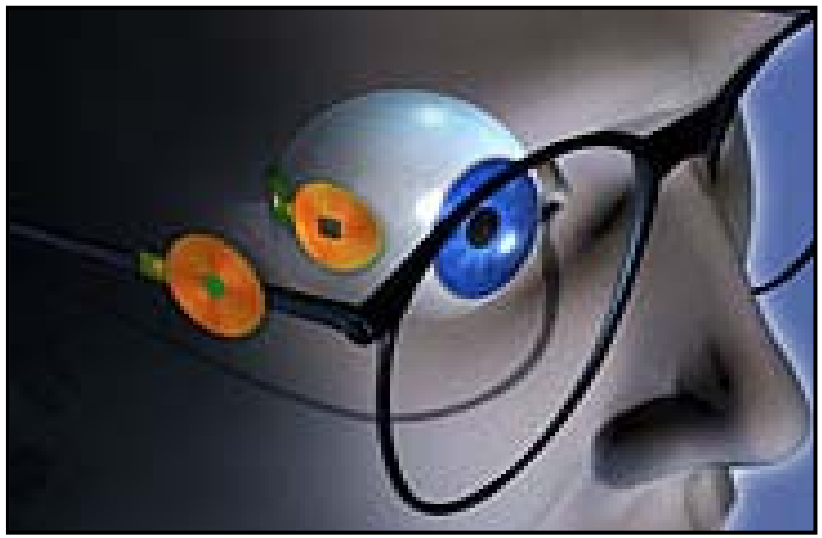
## 6. State of the art systems

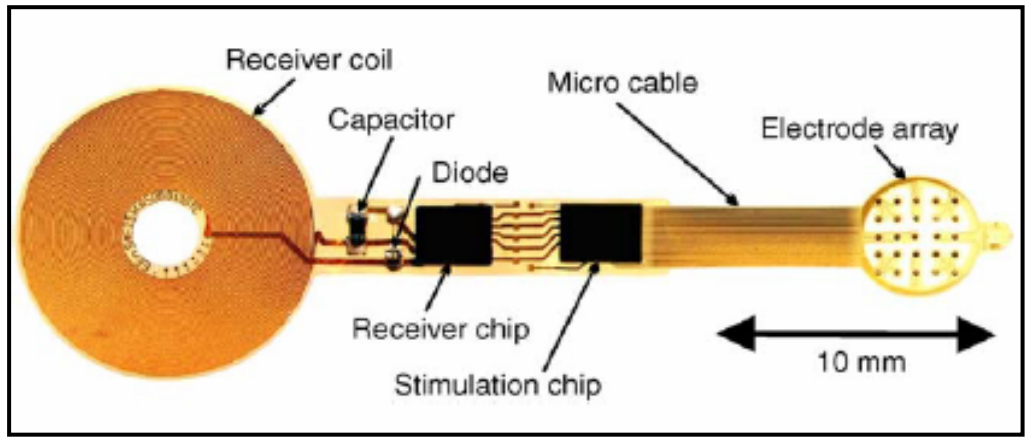
### Epiretinal implants:




- **Prof. Görtz et al. (Bonn):**
  - successful test (cortically evoked potentials) in cats and minipigs
  - implantation in human patients planed (adaptive patterns generator) after further material test and pattern studies

- **Prof. Rizzo et al. (Harvard):**
  - in-vitro: threshold and stimul. patterns
  - in-vivo: study with 6 patients:
    → perception of small light patterns





# The Bionic Human

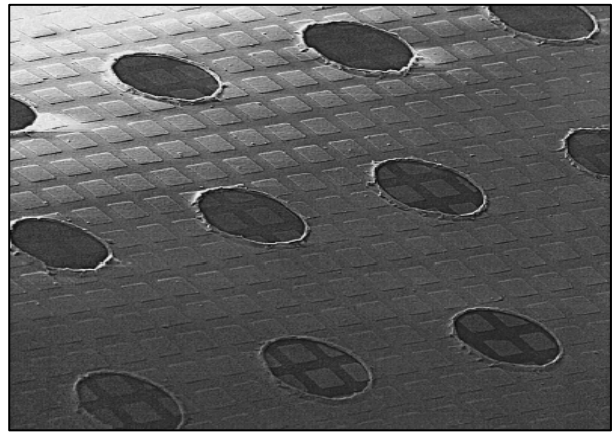
## 6. State of the art systems

### Subretinal Systems:

- **Prof. Zrenner et al. (Tübingen):**

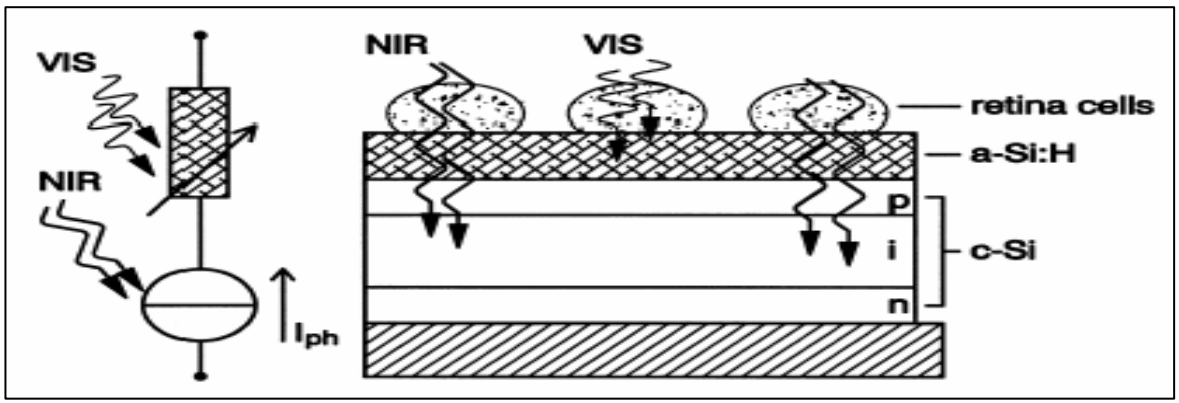
  **Thin film micro photodiode array (MPDA)**
  - NIR-cell (doped c-Si): provide voltage 2-3V
  - VIS-photodiode (a-Si:H)

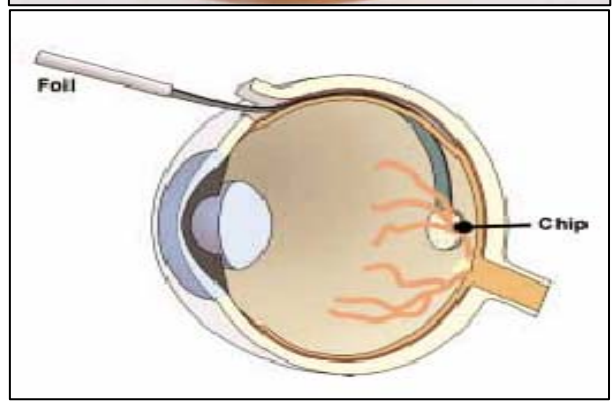
  ➔ preparations of first study (8 patients)



- **Prof. Chow et al. (Chicago):**

  first study with 6 patients over 18 months
  - full functionality of electronics after 18mths
  - no rejections, infections,…
  - visual function improvements:
    perception of shades of objects but no letters

# The Bionic Human

## Sources:

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http://www.eye-chip.com (Zrenner et al. / Tübingen)

http://www.pat.rwth-aachen.de (Görtz et al. / Bonn)

http://www.bostonretinalimplant.org/ (Rizzo et al. / Harvard)

http://www.optobionics.com/ (Chow et al. / Chicago)

### Publications:


**M.B. Schubert et al. , *Sensors and Actuators (1999):***
*Optimizing photodiode arrays for the use as retinal implants*

**M. Görtz et al., *Sensors and Actuators (2005):***
*Production processes for a flexible retina implant*

**J. Rizzo et al., J. Wyatt et al., *American Scientific (2004):***
*Artificial Retina*

**A.Y. Chow et al., *Arch Ophthalmol (2004)***
*The Artificial Silicon Retina Microchip for the Treatment of Vision Loss From Retinitis Pigm.*

**M.S. Humayun et al., J.D. Weinland et al., *Survey of Ophthalmology (2002)***
*Retinal Prosthesis for the Blind*

**Script of Prof. Gross (TU Munich):** *Solid State Physic*