Biomimetic MicroSystems

Bridging Engineering, Biology, and Medicine

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(A Partnership of UCSC, USC, Caltech)

Chair Professor

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Hsinchu, Taiwan

Outline

- Motivations of Biomimetic MicroSystems
  - Emerging Opportunity
  - Challenges in Design, Technology, and Education
  - Interdisciplinary Research
- Intelligent Neural Prostheses
  - Biosignal Processing
  - Wireless neural technology
  - Tools and Techniques
- Retinal Prosthesis
  - Motivation
  - Approaches and Competitors
  - Progress and Status
- Concluding Remarks

Acknowledgments

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- Faculty
  - Mark Humayun, MD, PhD
  - Gene de Juan, MD
  - Robert Greenberg, MD, PhD
  - James Weiland, PhD
  - Harvey Fishman, MD, PhD
  - Kimberly Cocherham, MD
  - NSF ERC-BMES/DOE Artificial Retina Team
- Graduate Students: more than 20 graduate students

History of Science and Technology

1864 - Maxwell's *Dynamical Theory of the Electromagnetic Field*

Wait 40 years: wireless telegraph, early radio invented

Wait 40 more years: television is dominant medium

1913 - Bohr Model of Atom

Wait 40 years: transistor invented

Wait 40 more years: electronics dominates

1953 - Watson & Crick describe structure of DNA

Wait 40 years: human genome sequenced

Wait 40 more years: biotechnology dominates

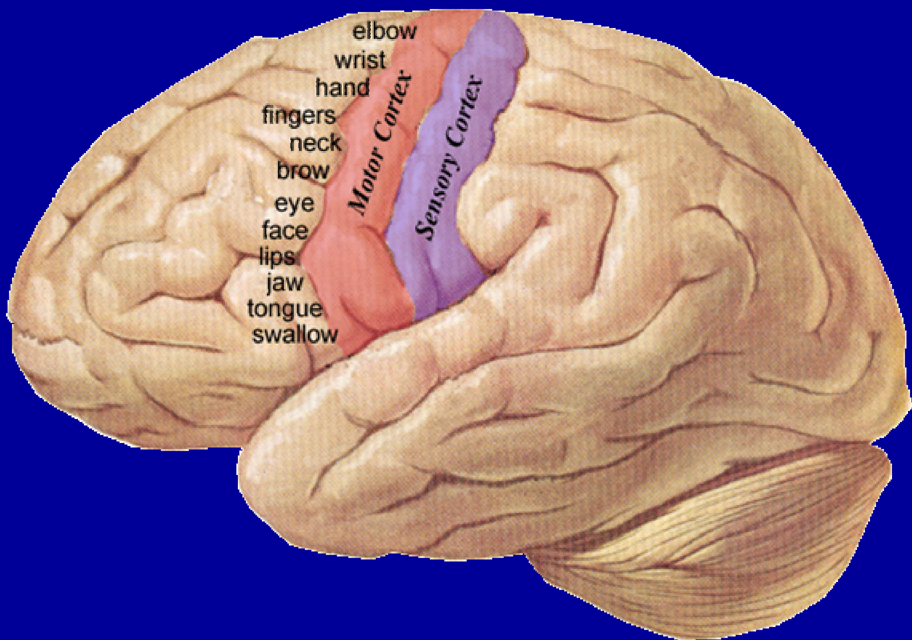
(by Professor Bruce Wheeler of UIUC)

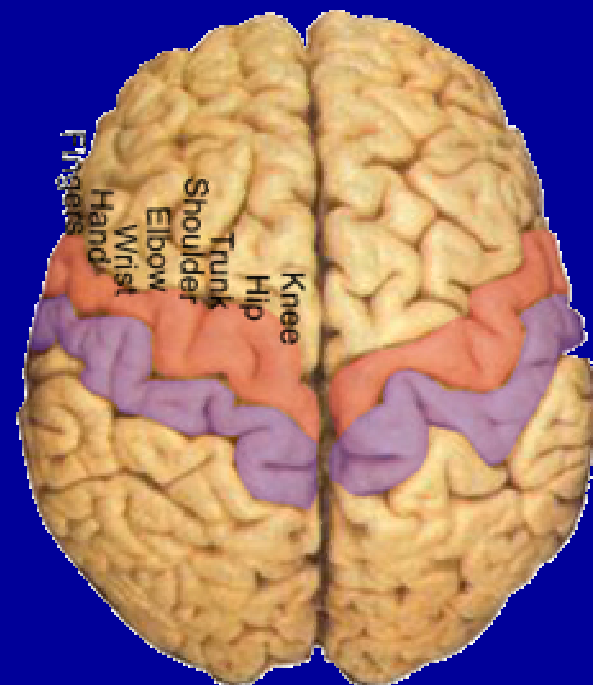
We Are All Getting Older

Year	2005				2025				2050			
Age	0-14	15-64	65+	All	0-14	15-64	65+	All	0-14	15-64	65+	All
World	1.79 billion 27.7%	4.19 billion 64.9%	0.47 billion 7.3%	6.45 billion	1.9 billion 24.1%	5.16 billion 65.3%	0.84 billion 10.6%	7.9 billion	1.94 billion 21%	5.77 billion 62.6%	1.51 billion 16.4%	9.22 billion
U.S.	60.8 million 20.6%	198.23 million 67%	36.7 million 12.4%	295.73 million	69.57 million 19.9 %	216.57 million 61.9 %	63.52 million 18.2 %	349.66 million	82.57 million 19.7 %	250.8 million 59.7 %	86.71 million 20.6 %	420.08 million
Asia	1.07 billion 27.4 %	2.59 billion 66.3%	0.25 billion 6.3%	3.91 billion	1.08 billion 22.7%	3.19 billion 67.1 %	0.48 billion 10.2 %	4.75 billion	1 billion 18.8%	3.38 billion 63.4 %	0.95 billion 17.8%	5.33 billion
Taiwan	4.51 million 19.7%	16.19 million 70.7%	2.2 million **9.6%**	22.89 million	3.83 million 15.6%	16.43 million 66.7%	4.38 million **17.8%**	24.64 million	3.18 million 13.7%	13.22 million 57%	6.81 million **29.3%**	23.2 million

Source: http://www.census.gov/ipc/www/idbagg.html

Brain - Source of the Problems





- 100 billion neurons (grey matter)
- 100 trillion inter-neural connections (white matter)
- A synaptic gap: 20-30 nm
- Power: 20-30 watts

Biomedical Engineering - Neurotechnology

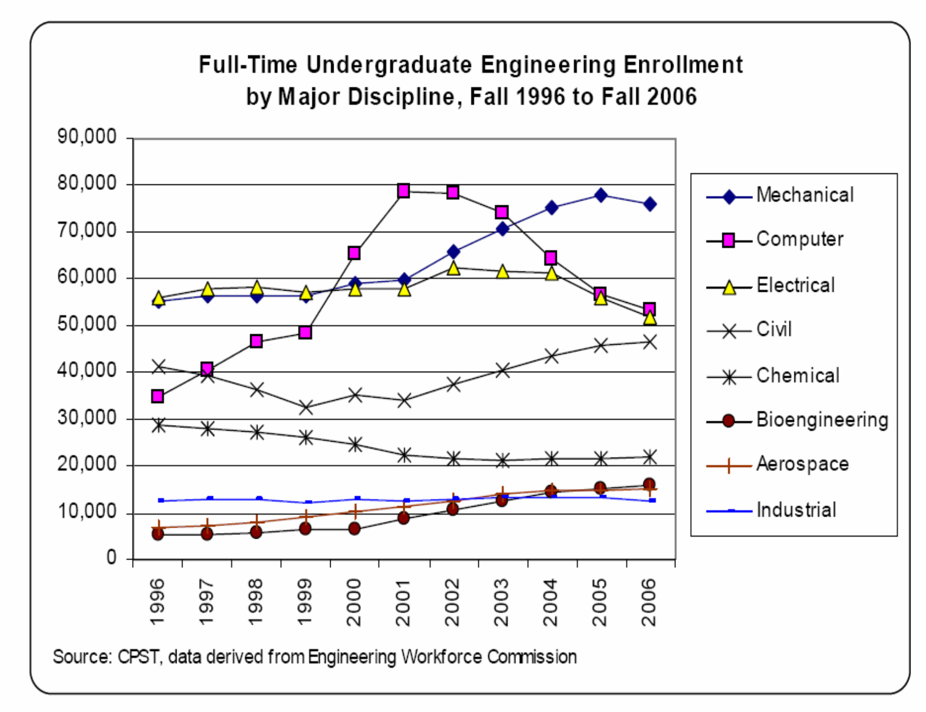
- *http://www.neuroinsights.com*
  A new NASDAQ Index (NERV) was created for neuraltechnology

- Brain-related illnesses afflict more than two billion people worldwide
- The worldwide economic burden of this problem has reached more than $2 trillion per year; more than $1 trillion in the U.S. alone
- 2006 venture capital investment in neurotechnology rose 7.5% to $1.666 billion
- Neurotech industry revenues rose 10% in 2006 to $120.5 billion; this includes neuropharmaceutical revenues of $101 billion, neurodevice revenues of $4.5 billion, neurodiagnostic revenues of $15 billion
- The Neurotech Index of publicly-traded neurotechnology companies was up 53% from its December 31, 2003 conception to March 31, 2006, outpacing the NASDAQ Biotech Index which gained 7% during the same period
- Worldwide government research, private funding and public investment trends

Biomedical Engineering – Neurotechnology

- Opportunity and Challenges in Emerging New Industry – Neurotechnology

- The overwhelming diversity of the research areas in Biomedical Engineering is rapidly fueled by
  - "Clinical Pull" that identifies more medical problems to be solved
  - "Technology Push" that invents new tools and techniques to advance the state-of-the-art

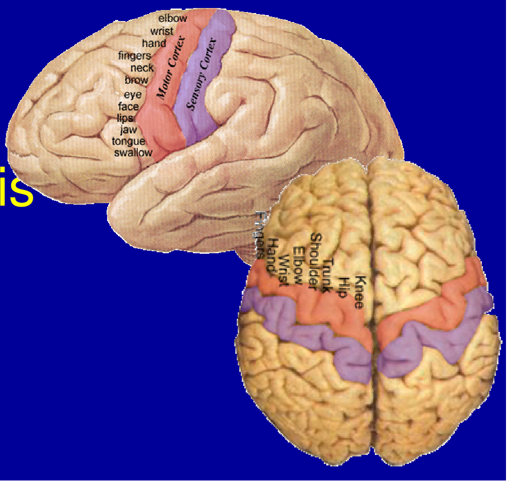


Problems Solved with Biomimetic MicroSystems

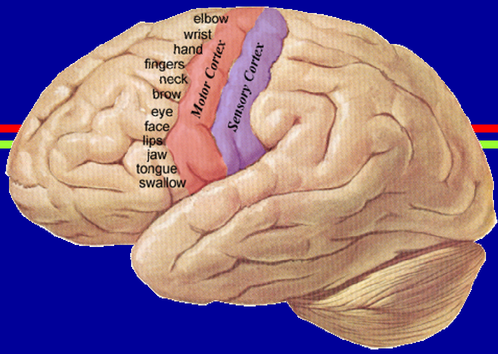
- Obesity
  - Diabetes – Implantable drug pumps
  - Heart Disease
- Anti-depression
- Pain Relief – invasive or non-invasive devices
- Intelligent Artificial Upper or Lower Limbs
- Spinal Cord Injury
- Neural Disorders
  - Alzheimer's, Epilepsy, Parkinson, Depression
  - Stroke and Dementia
  - Prostate Cancer and Impotence
- Vision
  - Blindness – retinal prosthetics
  - Presbyopia – Lens implantation for 50+
  - Denervated eye-lid (Bell Palsy)
- Deaf – Cochlear Implant
- Musculoskeletal - Orthopedic Implants for Osteoarthritis
- Defense –Technologies to Improve Warfare
- Implantable Renewable Energy
  - Metabolic fuel cell that runs on glucose
  - Powers implantable devices

➢ ***We believe the largest markets in healthcare will be solved with biomimetic devices***

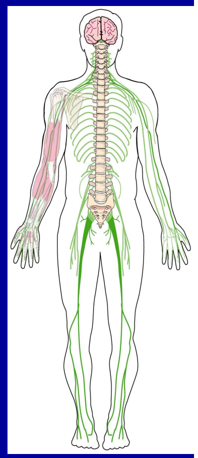
➢ ***Biomimetic Devices will significantly change lifestyles in the 21st century***



Biomimetic MicroSystems



- Treatment of neurological disorders
- Restoration and repair of biological subsystems
- Performance Enhancement (Super-man/woman)



- Must understanding the brain and body
- Toward smart prosthetics
  - Neurological disorders – blindness, paralysis, and movement disorders, etc
  - No cure method is known for most neurological disorders
  - Neuroprosthesis can provide an independence for those neurological disorders by the convergence of neuroscience, engineering, biology, and medicine
  - Neuroprosthesis restore and control function by interfacing directly to the damaged or disabled nervous system. It extracts neurological information and input information to activate or inhibit neurological pathways
- Nevertheless, significant challenges and opportunities exist in developing ever-more precise and intelligent neural interfaces that operate at the cellular level and that is capable of providing even greater precision and fidelity in restoring function

➢ This requires more powerful techniques and tools

  ➢ Need for interdisciplinary research and new curriculum

Neuro-Engineering is the Next Cardiology

- Patients with approved indications and the most promising indications in the research and clinical trial stages: (in USA only)
  - Prevalence: 76 million patients
  - Incidence is 2.5 million patients/year
  - Estimated market size for these indications is $35 billion
  - Current 2006 market size less than $400M
- Ex: Northstar Neuroscience, a developer of neuro-stimulation therapies for stroke-related motor function impairment
  - IPO in 2006 for $326M despite not completing their human clinical trial
- Cardiac Implants: $25B (9%/year growth) in 2009
  - Pacemakers $11B sales in 2006
  - Stents $6B sales in 2006
- Cochlear implants have advanced rapidly in the last 30 year
  - Over 125,000 implants worldwide with market of around $2 billion
  - 14 million potential users worldwide (cost is a barrier -> low market penetration)
- Pulmonary devices is a growing market around $3 billion by 2011. Asthma, Sleep Apnea, Chronic Obstructive Pulmonary Disease (COPD)

✓ High Value Added Industry

Some Examples of Biomimetic Devices:

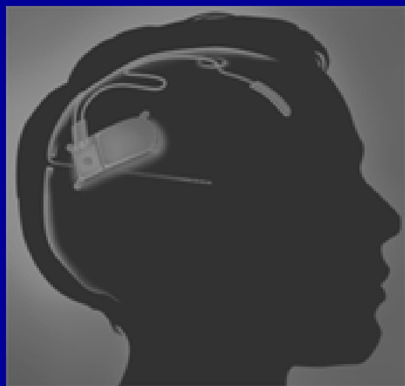
- Implantable micro-pumps for drug delivery
- Implantable bio-fuel cells and bio-batteries
- Implantable sensors
- Implantable gene pumps
- Non-invasive devices for appetite reduction
- Non-invasive glucose monitors

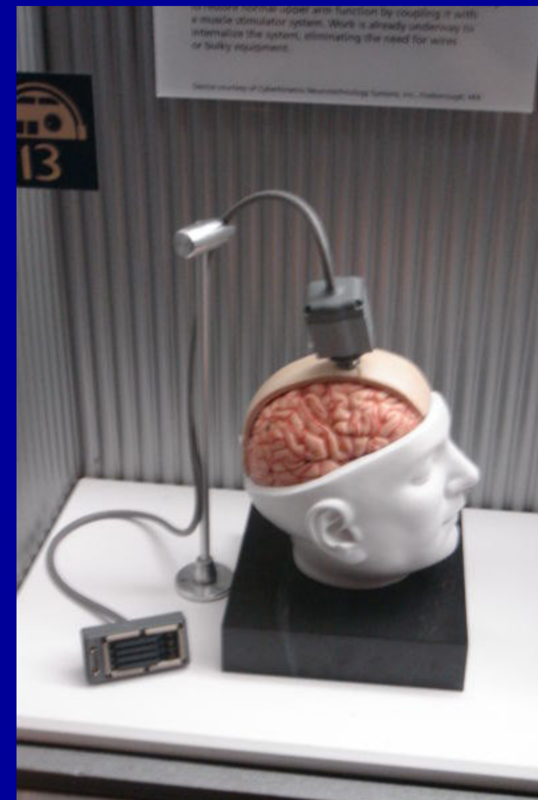
*Source: Freedonia industry study, "Implantable Medical Devices", 2005

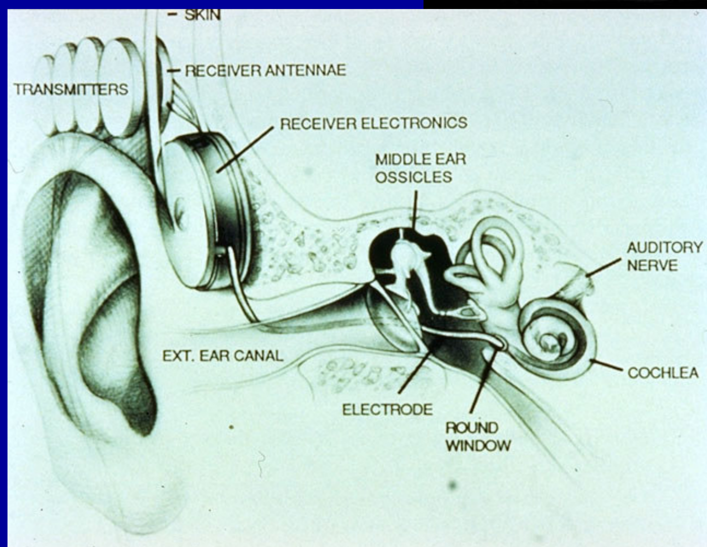

health and extending life.
Medtronic Inc

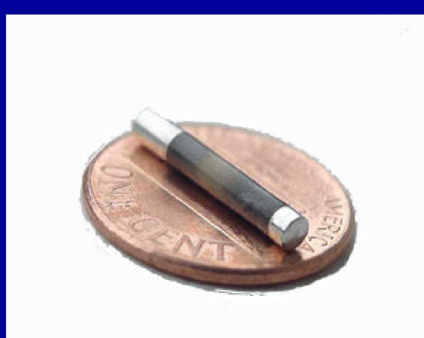
Treatment Examples of Neural Disorders

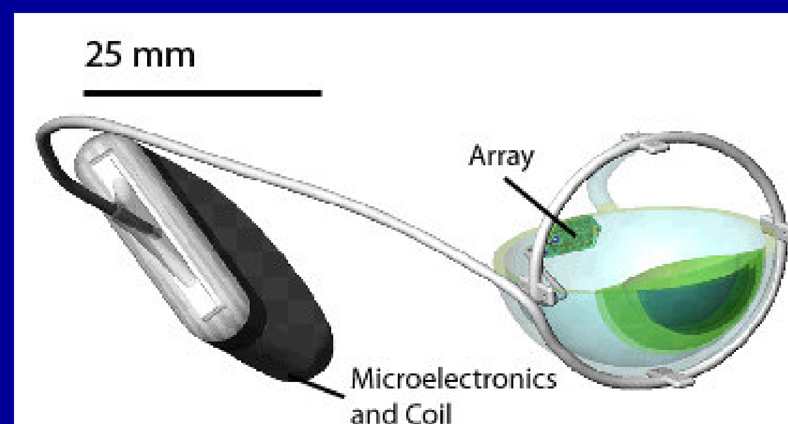
- Parkinson – Substantia Nigra pars Compacta (SNC) Region, Meditronic (clinical)
- Cochlear – Cochlear (Australia), Advanced Bionics (USA), Med-El (Austria)
- Epilepsy (Refractory) – (sub)-thalamus region
- Depression (Treatment Resistant) - Subgenual Cingulate Region, Emory Univ
- NSF Center on BMES – UCSC, USC, Caltech Partnership
  - Retinal Prosthesis
  - Neuromuscular (upper and lower limbs) Prosthesis
  - Cortex Prosthesis
- Brain Machine Interface –
  - Brown Univ. - John Donoghue
  - CalTech - Richard Andersen
  - Duke - Miguel Nicoleilis
  - Arizona State Univ - Jiping He



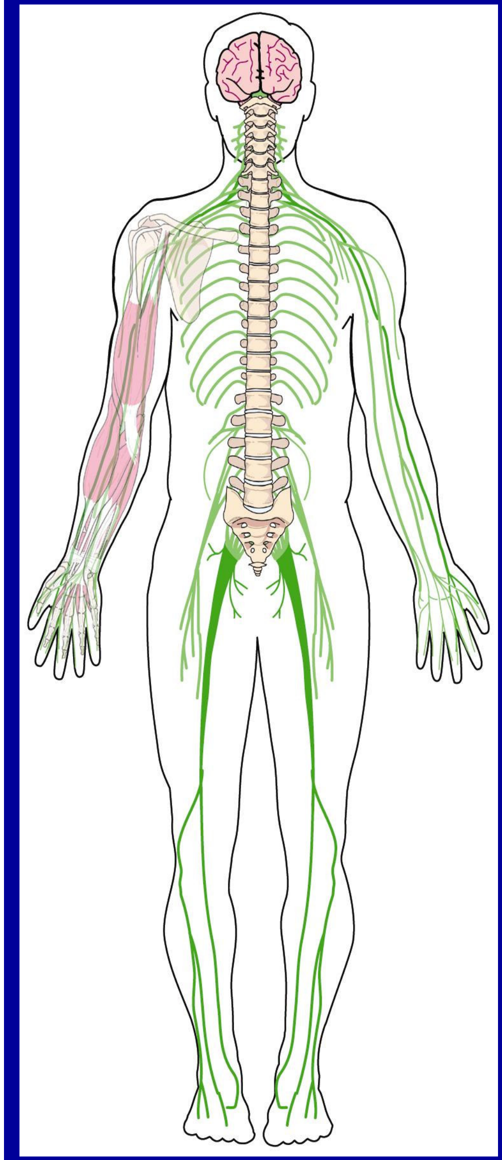



SKIN
RECEIVER ANTENNAE
TRANSMITTERS
RECEIVER ELECTRONICS
MIDDLE EAR OSSICLES
AUDITORY NERVE
EXT. EAR CANAL
COCHLEA
ELECTRODE
ROUND WINDOW

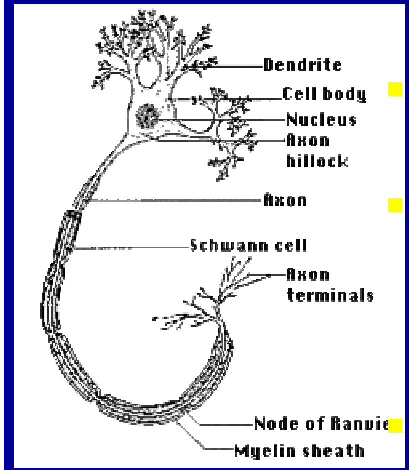



25 mm
Array
Microelectronics and Coil

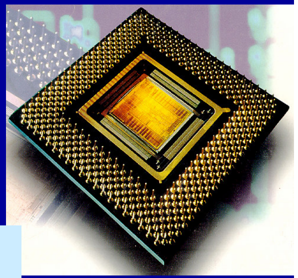
Platform – Biology Systems

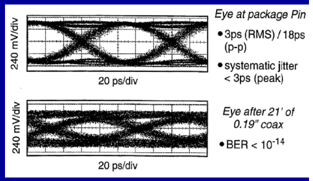


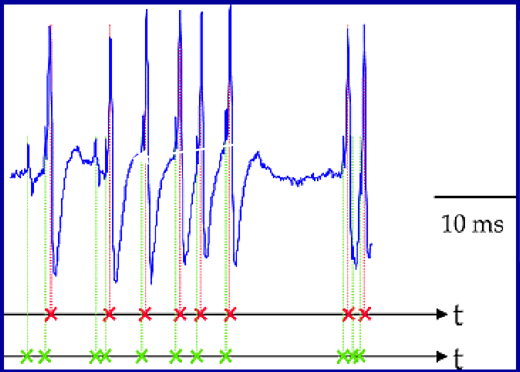
Neurons (Ions) ←TALK→ Electrons



- **Sensing:** Monitoring Physiological Conditions
- **Prosthesis:** Replacing lost functions **(hearing, sight, etc.)**
- **Actuator:** Enhancing the existing human senses **(see, hear, feel, smell, and taste)** beyond the current ability
- **Cognition**
- **New computational paradigms**



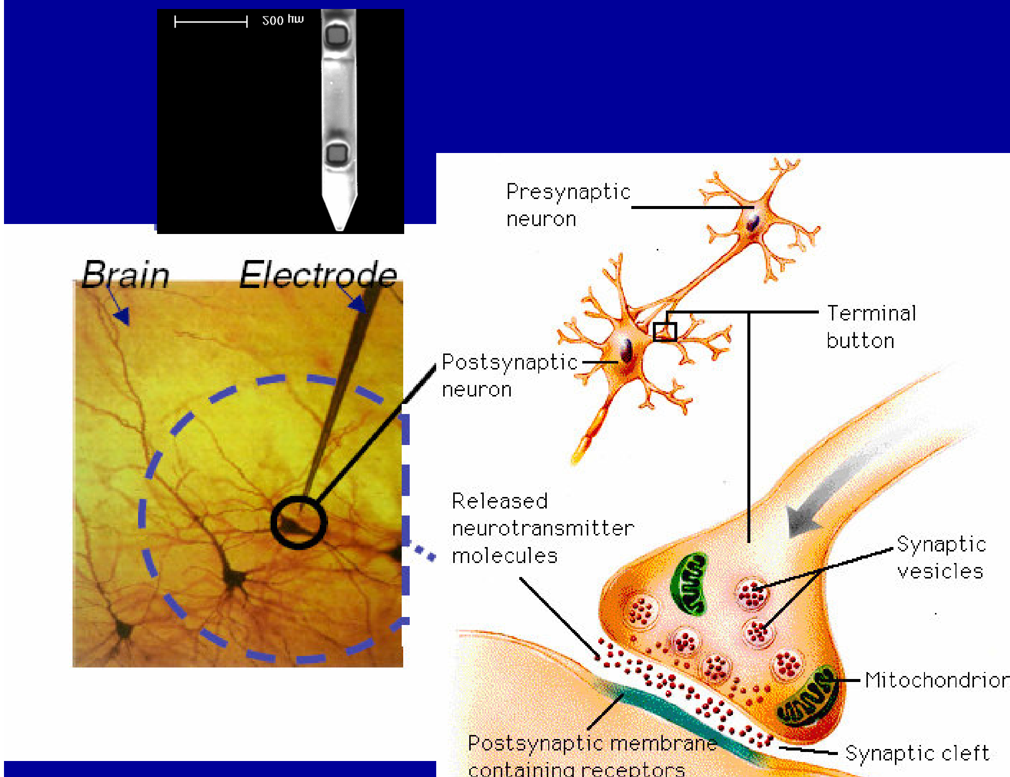




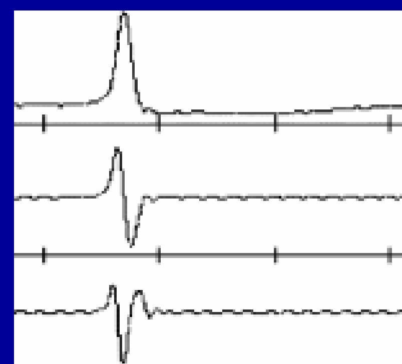
- **Neuro Signals**
  - **Large Populations**
  - **Space and Time Encoding**
  - **Non Gaussian and Non Stationary**

Neuron Stimulation and Signal Recording

- Action Potential: 100Hz-10kHz (energy dominate around 1kHz), [10uV, 500uV]
- Local Field Potential: 1Hz-100Hz, ,5mV, the composite extracellular potential field from several hundreds of neurons around the electrode tip.



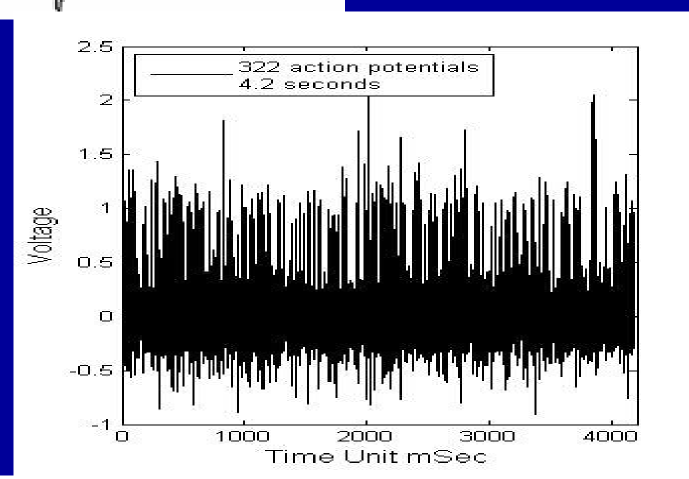
Recording:



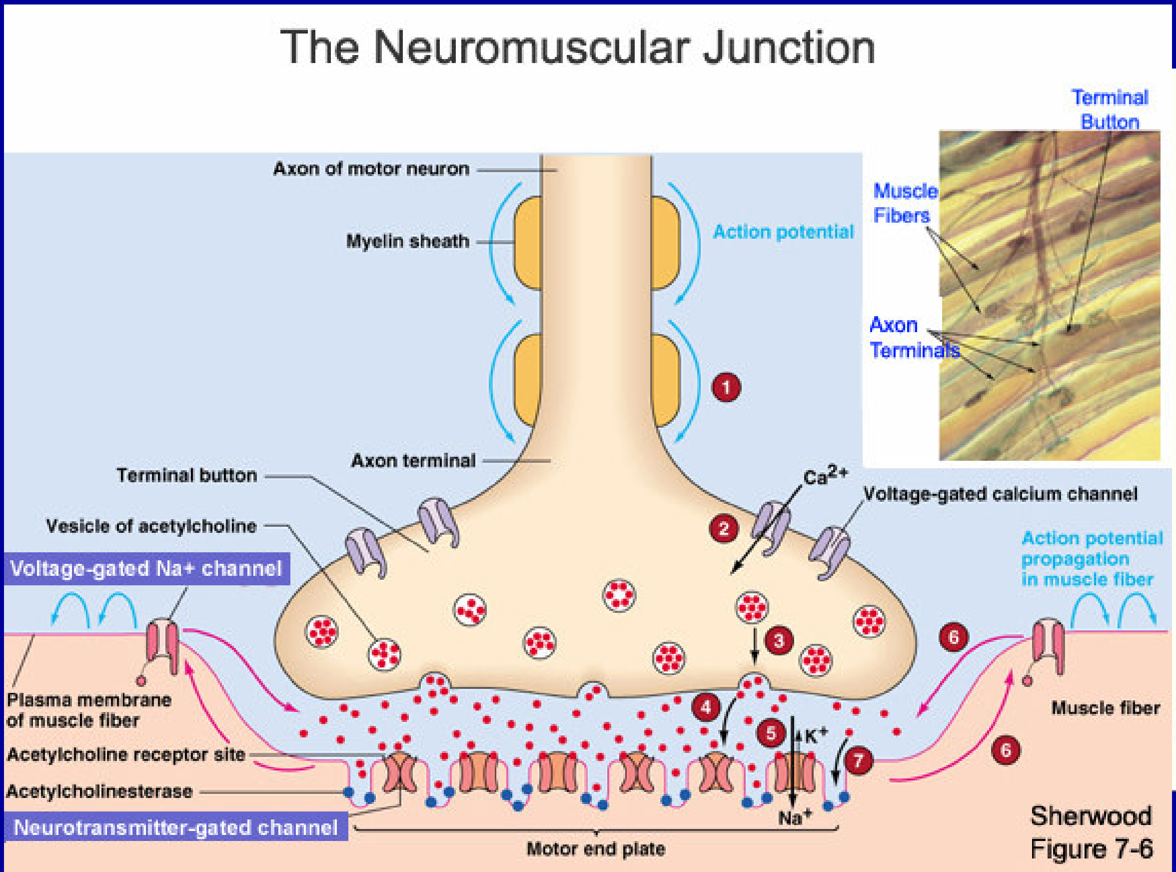
Action Potential (intracellular)

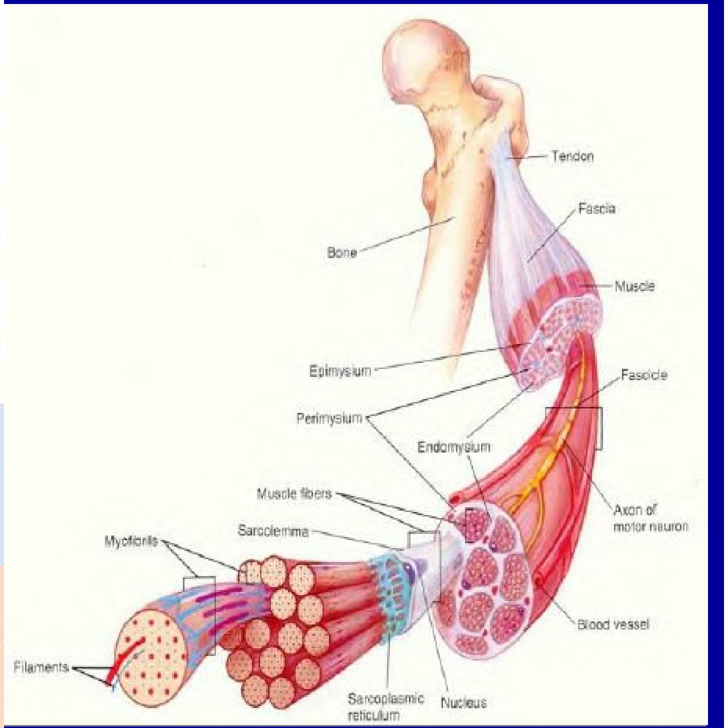
1st derivative

2nd derivative



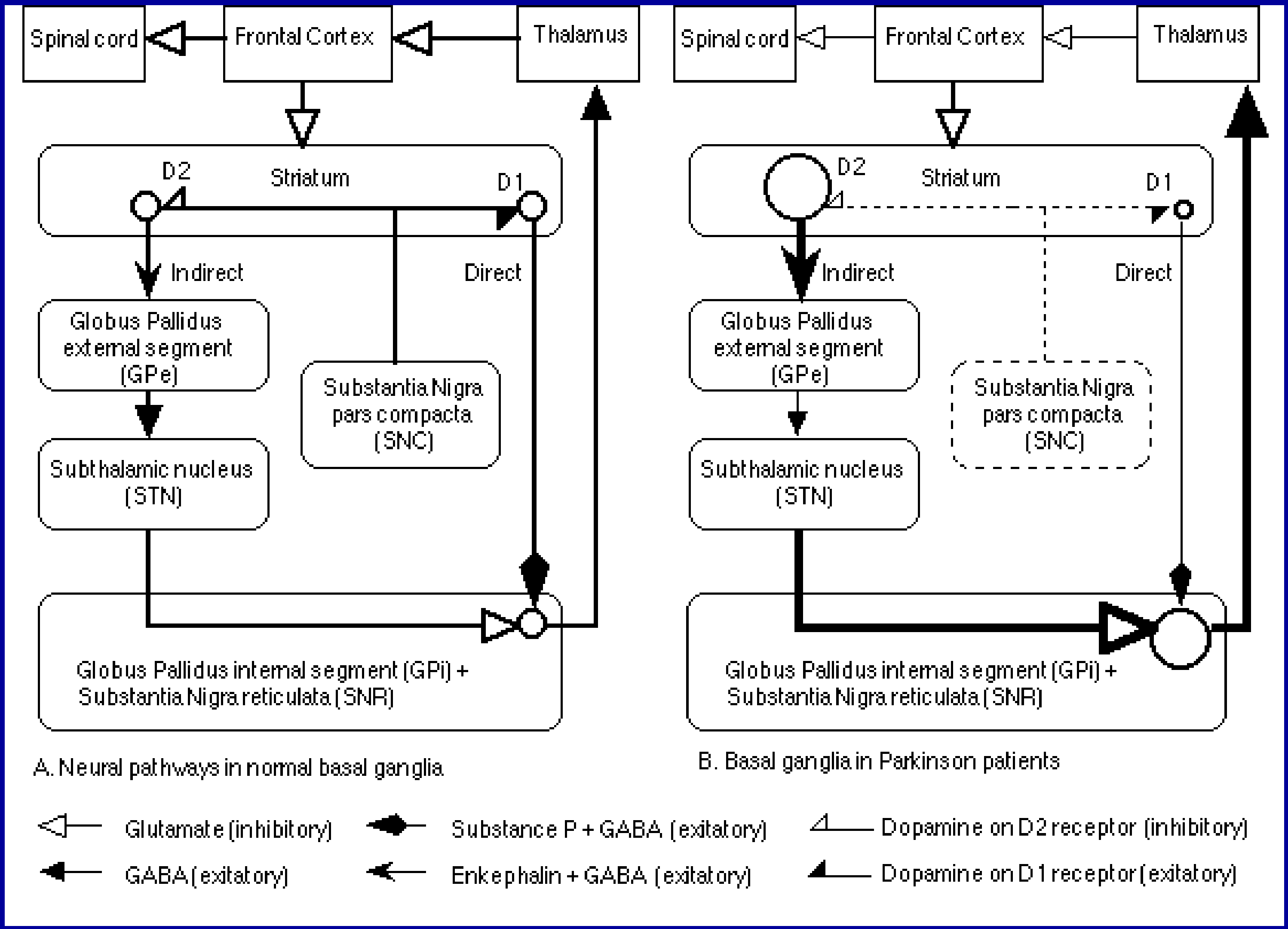
Muscle Stimulation - Contraction and Expansion





- Action potential propagates to the end plates at the buttons
- The action potential then propagates along the muscle fibers

Dopamine Model for Parkinson Disease



http://tcw2.ppsw.rug.nl/~vdbosch/pd.html

NeuroTechnology

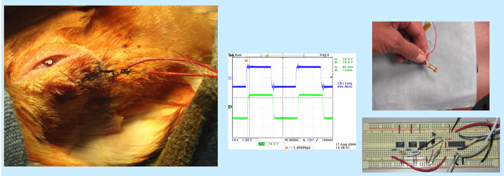
- Enabling Technology
  - Biocompatible Electrodes
  - Miniaturized 3-D Packaging
  - Hermetic Sealing Technology
  - Flexible Electronics
  - Energy Scavenging
  - Microelectronics – low power design
  - Wireless Power and Data Telemetry
  - Signal Processing
- Collaboration is the KEY
  - Life Sciences
  - Medicine/Clinical Sciences
  - Neurophyisology/Neurobiology
  - Psychology/Psychophysics
  - Micro-fluidics/MEMS
  - Materials Science
  - Computer Science
  - Electrical Engineering
  - Nanotechnology

NSF ERC Center of Biomimetic MicroElectronics Systems

at University of California, Santa Cruz

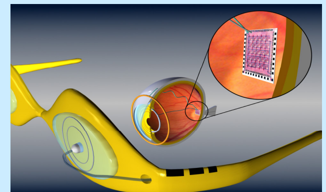
Artificial Synapse Chip for Denervated Muscles

Modeling muscle stimulation and design of electronics



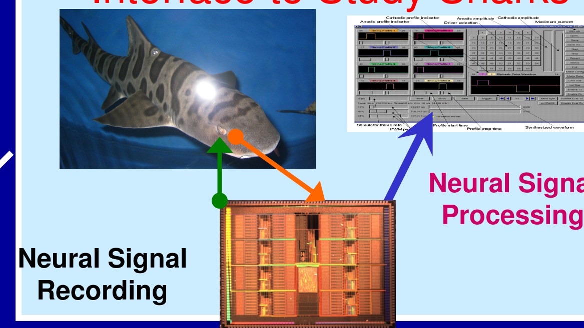
Retinal Prosthesis to Restore Vision in Blind Patients

Scientists are also working on an artificial retina to help many blind people to see…. President Clinton in his 2000 State of the Union Address

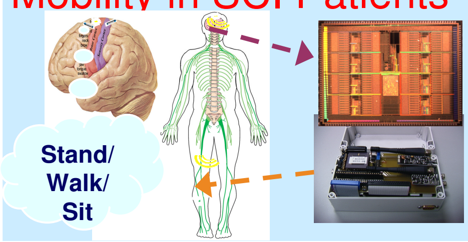


Successful implants in six patients through Stimulation of Retina

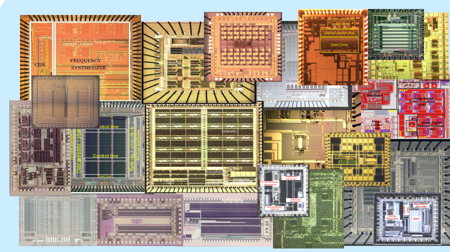
Brain-Machine Interface to Study Sharks



Prosthesis to Restore Mobility in SCI Patients



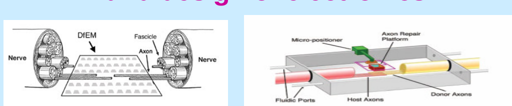
Microelectronics



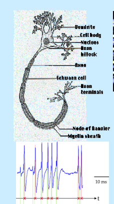
25+ years microchip design experience

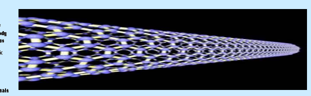
MicroSurgery for Axon Repair

Modeling dielectrophoresis, electrofusion and design of electronics

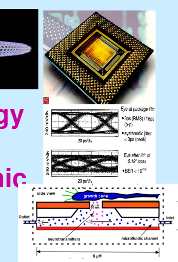


Neuron-Chip Interface to Develop Hybrid Systems





Use nanotechnology to interface living tissue and electronic chips resulting in novel applications



Prof. Wentai Liu, Campus Director of NSF Biomimetic Microelectronics Systems Engineering Research Center

Collaborators – Virtual Laboratory

Prof. Wentai Liu
Integrated BioElectronics Research (IBR)

California Institute of Technology
(Drs. Andersen and Tai)
Electrode design, Shark Physiology

University of Southern California
(Drs. Humayun and Weiland)
Ophthalmology, Retinal Surgery

UCSF and Smith-Kettelwell
(Drs. Scott and Sretavan)
Neuroscience

Santa Clara University
(Dr. Tauck)
Electrophysiology, Cell culture

NASA (AMES and JPL)
(Drs. Hines and Mojarradi)
Astrobionics, Space Wireless Communication

Huntington Medical Research Institutes (Dr. Pikov)
Spinal Cord Injury Prostheses, Bladder/Bowel Control

Arizona State Univ
(Dr. He)
Lower Limb Prosthesis

Stanford University
(Dr. Cockerham)
Plastic Surgery

Dept. of Veteran Affairs
(Dr. Lin)
Spinal Cord Medicine

Current In-Vitro/In-Vivo Experiments in my Lab

- 20 member talented and hyperactive research group conducting interdisciplinary research with $1,000,000 annual funding
- All systems are tested "beyond the bench" *in vitro* and *in vivo*
  - *Retinal implants – **human** trials already underway*
    - ✓ USC, Second Sight, USA (2007), Taiwan (2008), ***Human***
  - *Bladder and bowel control for SCI – animal trials soon*
    - ✓ Huntington Medical Research Institutes, ***Cats***
  - *Eyelid implants (closure) – animal trials underway*
    - ✓ Stanford University and VA-Palo Alto, ***Rabbits***
  - *Eyelid implants (opening) – human trials soon*
    - ✓ Smith Kettlewell Eye Research Institute, ***Rabbits***
  - *Brain Machine Interface – animal trials*
    - *CalTech, **Sharks***
  - *Muscle limb implants – animal trials soon*
    - ✓ Long Beach VA, ***Dogs***
  - *Cortical implants for cognition and motor control – animal trials soon*
    - ✓ Arizona State University, ***Rats, Monkeys***
  - *In-Vitro and Ex-Vivo validation for dynamic membrane modeling*
    - ✓ UCSC, ***Snails***

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  - Emerging Opportunity
  - Challenges in Design, Technology, and Education
  - Interdisciplinary Research
- **Intelligent Neural Prostheses**
  - **Biosignal Processing**
  - **Wireless neural technology**
  - **Tools and Techniques**
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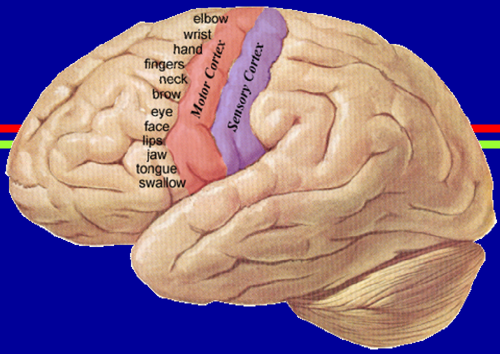
Biomimetic MicroSystems



- Treatment of neurological disorders
- Restoration and repair of biological subsystems
- Performance Enhancement (Super-man/woman)

- Must understanding the brain and body
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  - Neurological disorders – blindness, paralysis, and movement disorders, etc
  - No cure method is known for most neurological disorders
  - Neuroprosthesis can provide an independence for those neurological disorders by the convergence of neuroscience, engineering, biology, and medicine
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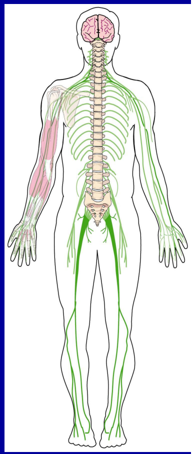
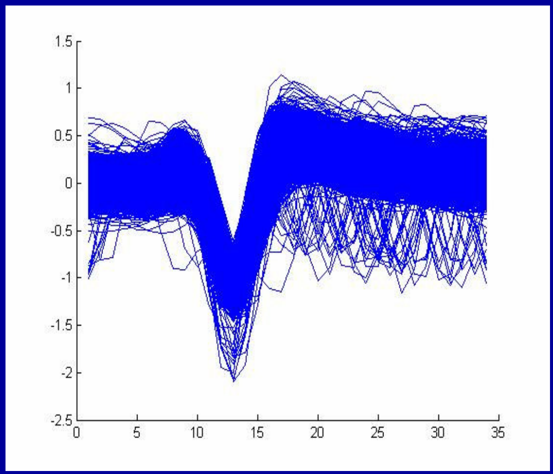
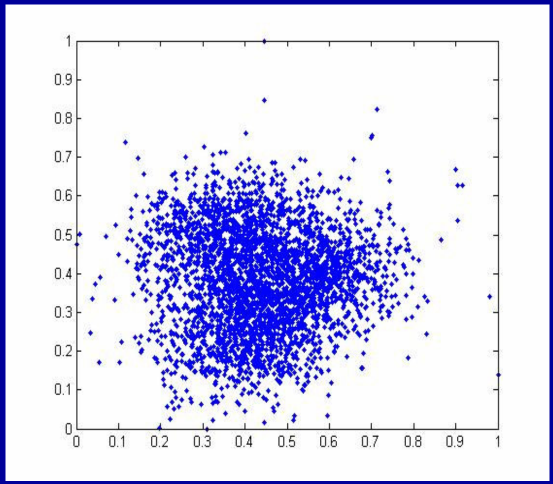


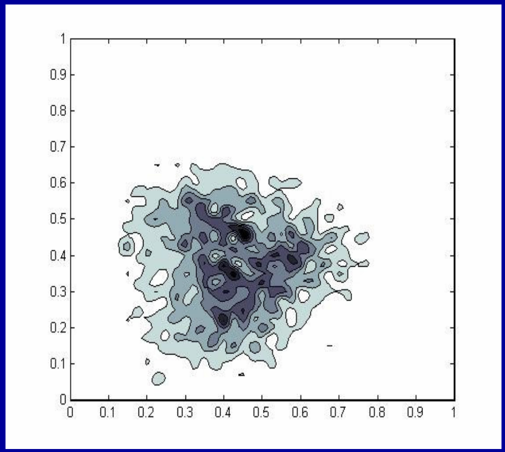
- Nevertheless, significant challenges and opportunities exist in developing ever-more precise and intelligent neural interfaces that operate at the cellular level and that is capable of providing even greater precision and fidelity in restoring function

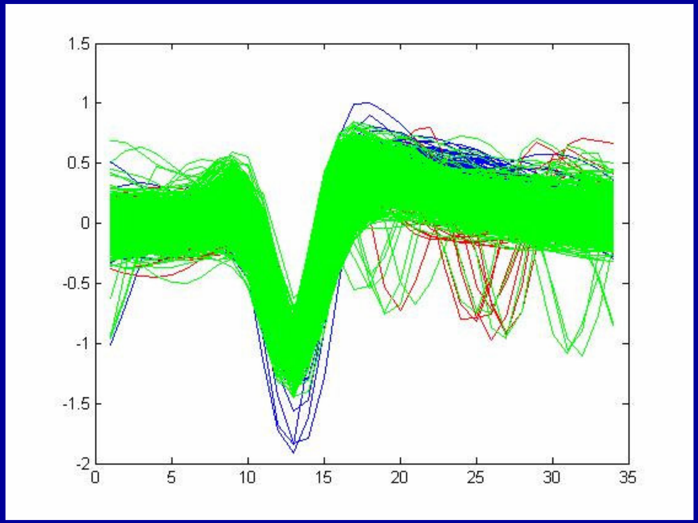
- This requires more powerful techniques and tools
  - Need for interdisciplinary research and new curriculum

Principal Components Analysis (PCA) - Conventional Spike Sorting









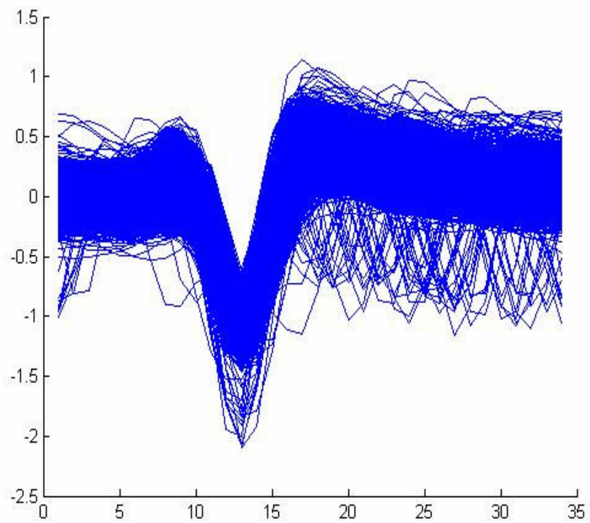
PCA Based Sorting Results

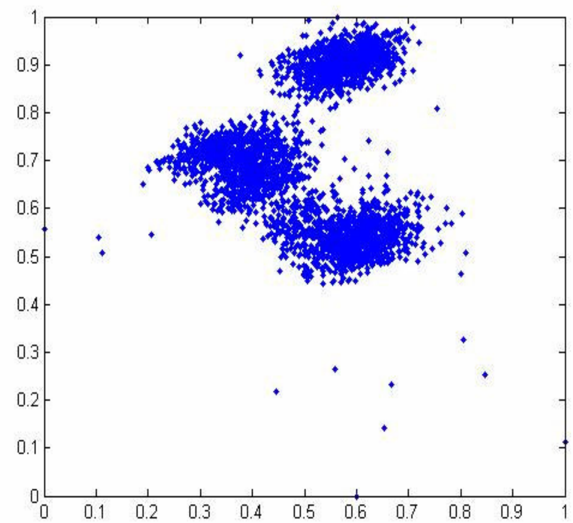
- PCA is a method to extract spike features.
- It projects the spike waveform into a lower dimensional space by maximizing the variance.

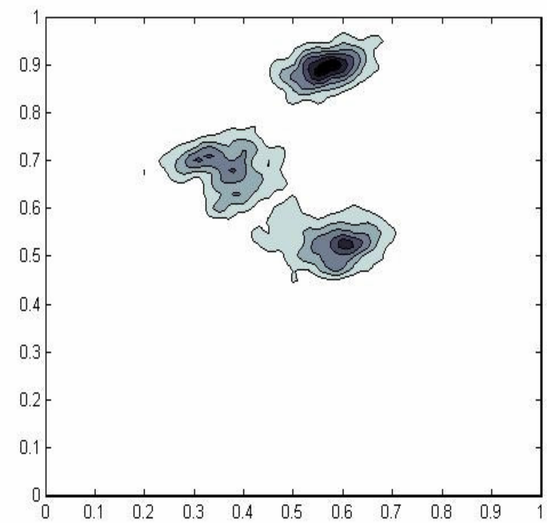
➢ Accuracy of classification is poor especially when spike waveforms are similar and very noisy

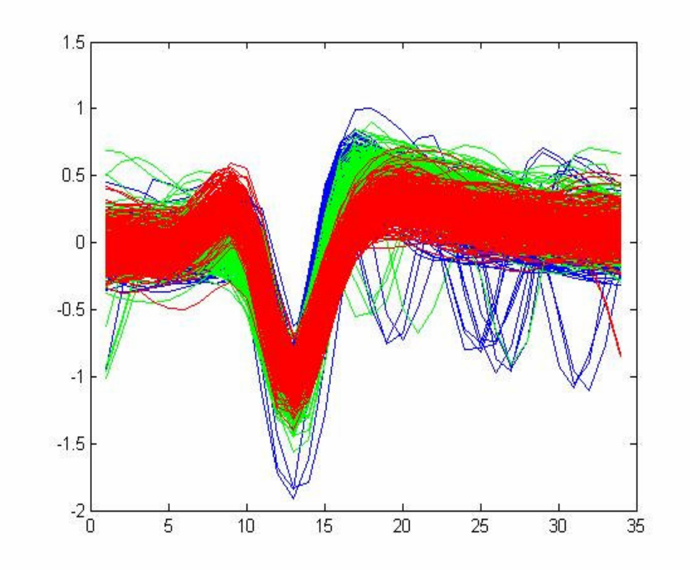
- PCA is a general purpose information processing algorithm and requires a “long” learning period.
- But, higher performance spike sorting requires dedicated neuron models – if we know the neuron better, the algorithm performs better.

NEUSORT - Our New Spike Sorting

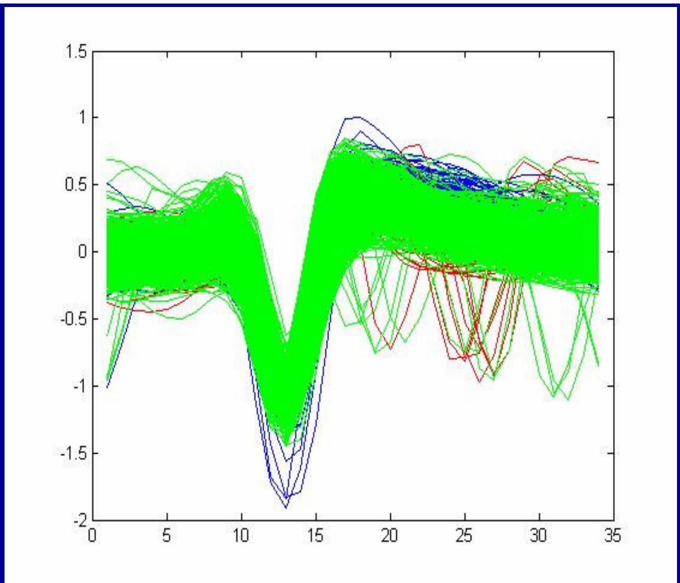








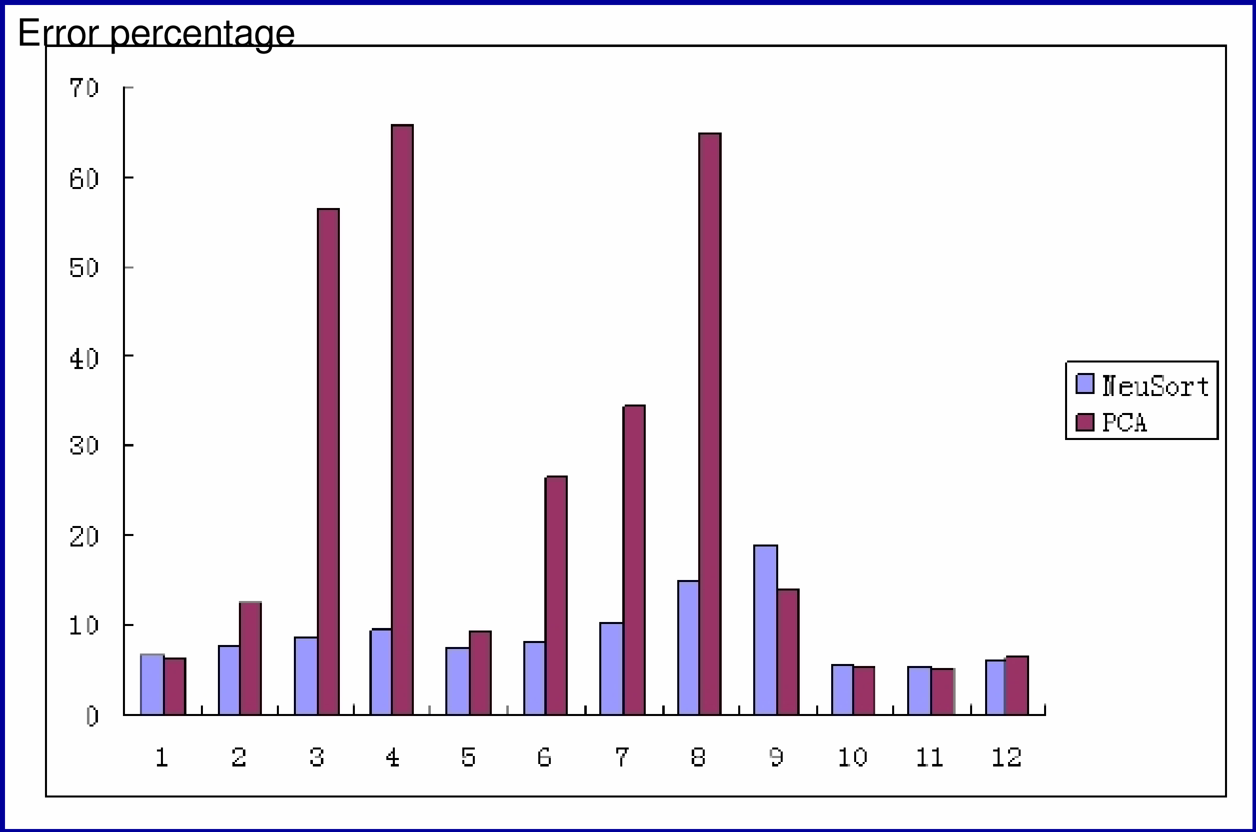
NEUSORT Based Sorting
(3 well defined clusters)



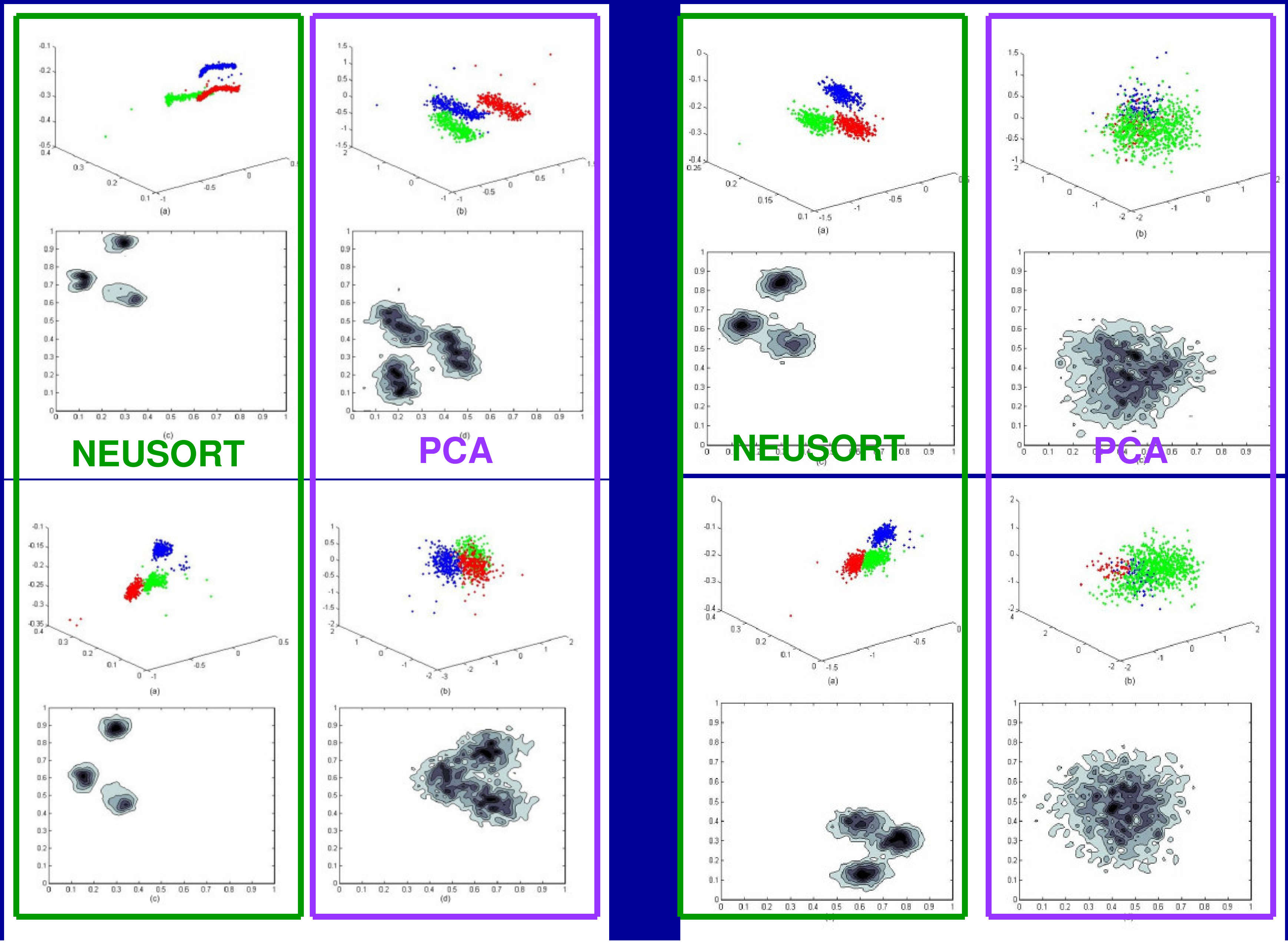
PCA Based Sorting
(only one visible cluster)

Comparison - NEUSORT *vs* PCA

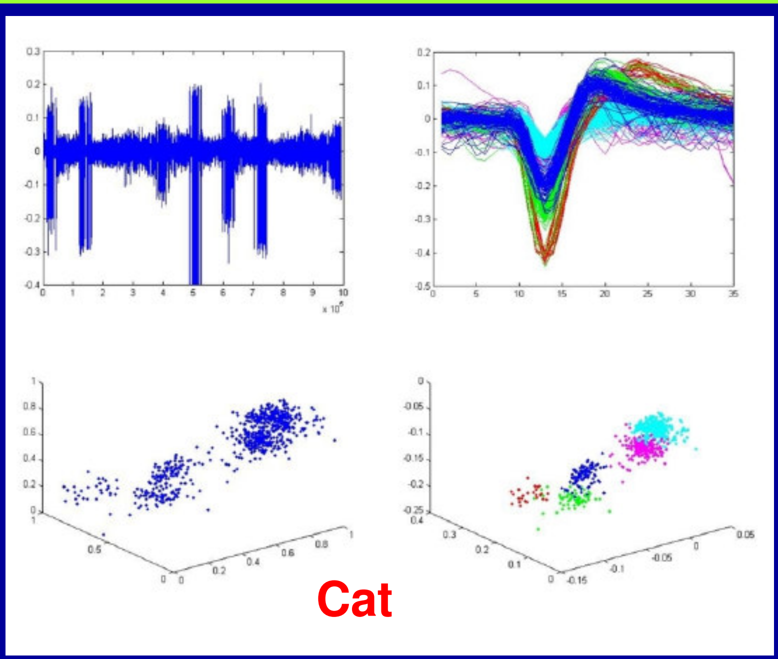
- Developed a novel spike sorting algorithm (NeuSort) which is able to identify neurons' signatures and thus achieved a better spike sorting
- On-the Fly Sorting without significant learning period

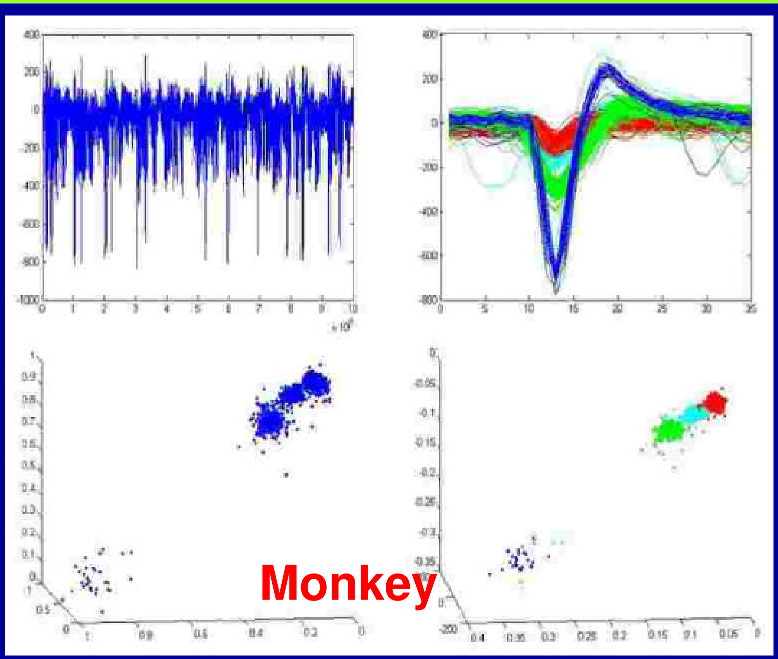


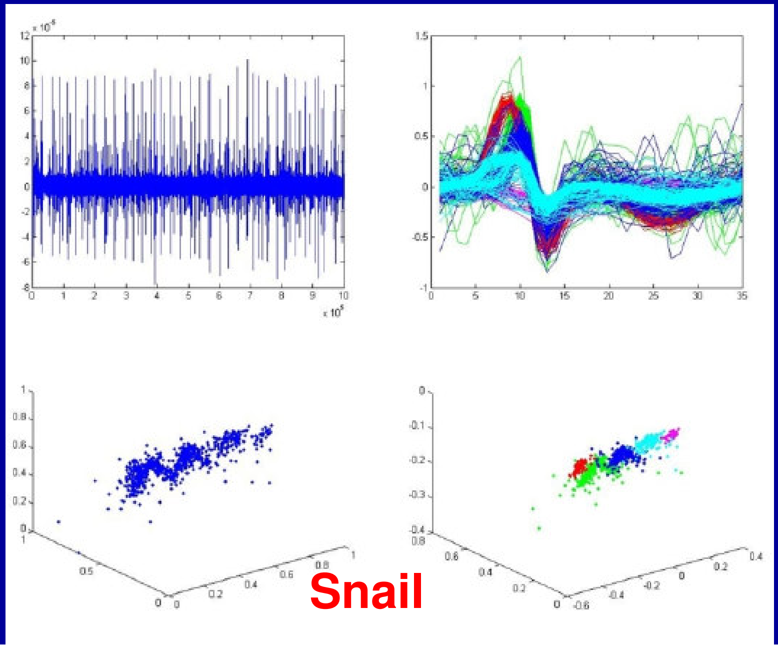
Comparison - NEUSORT *vs* PCA

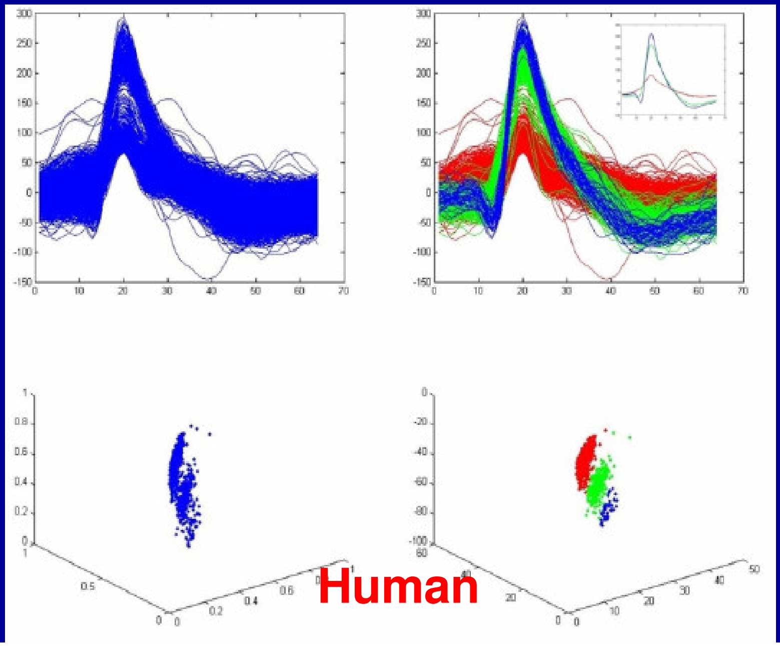


NEUSORT with Animal Neural Signals

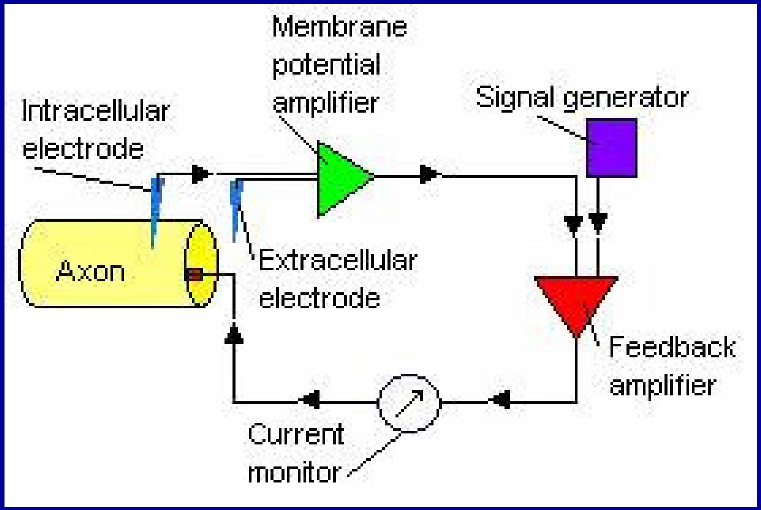


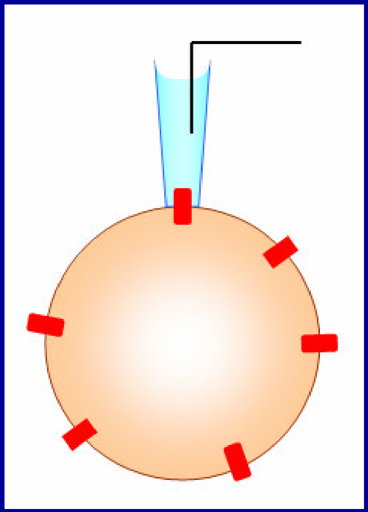


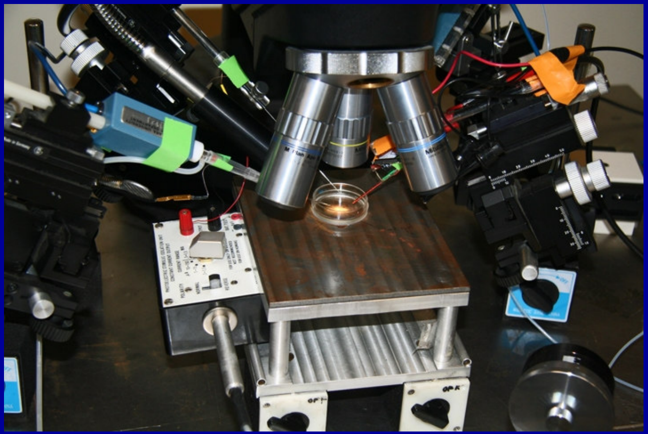




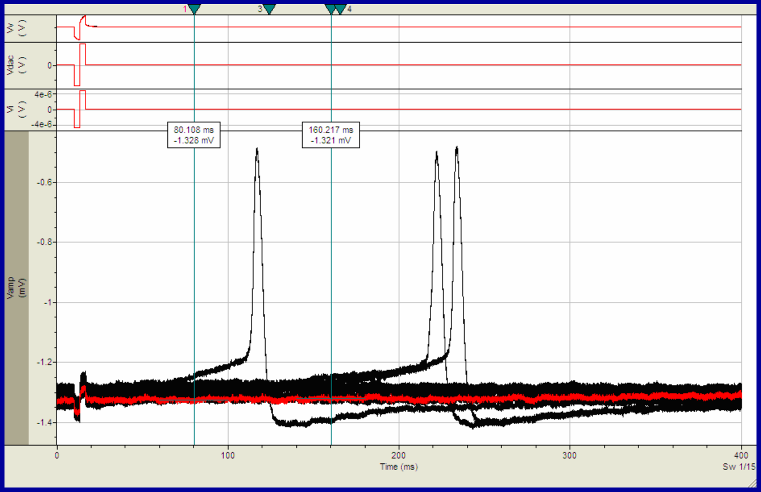
Intracellular Recordings



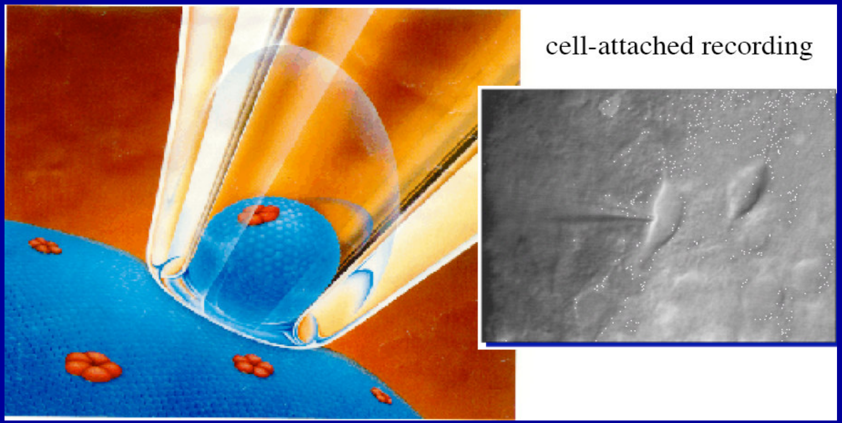




- Extracellular microelectrodes generally record superimposed neural responses from multiple neurons
- Intracellular recordings provide very localized membrane responses.
- Essential to quantify individual neuron's response to specific stimulus

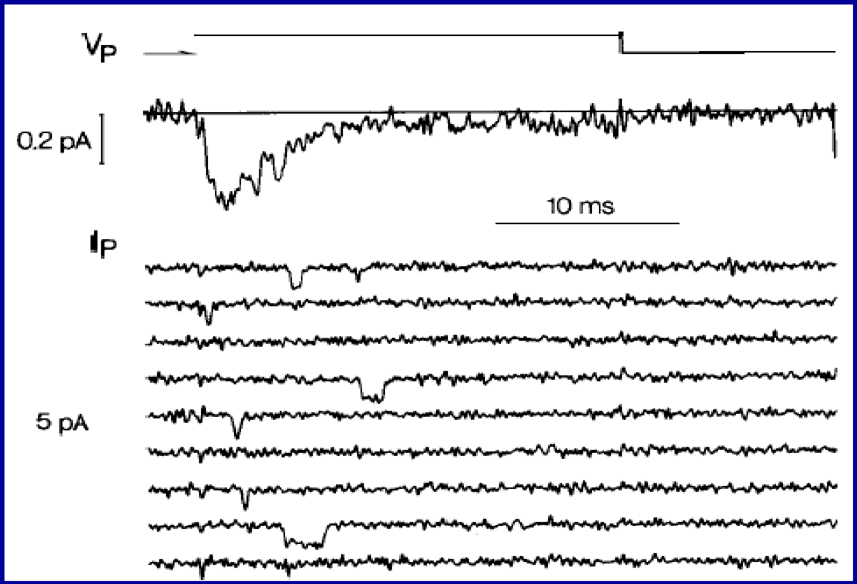


Patch Clamp Recording

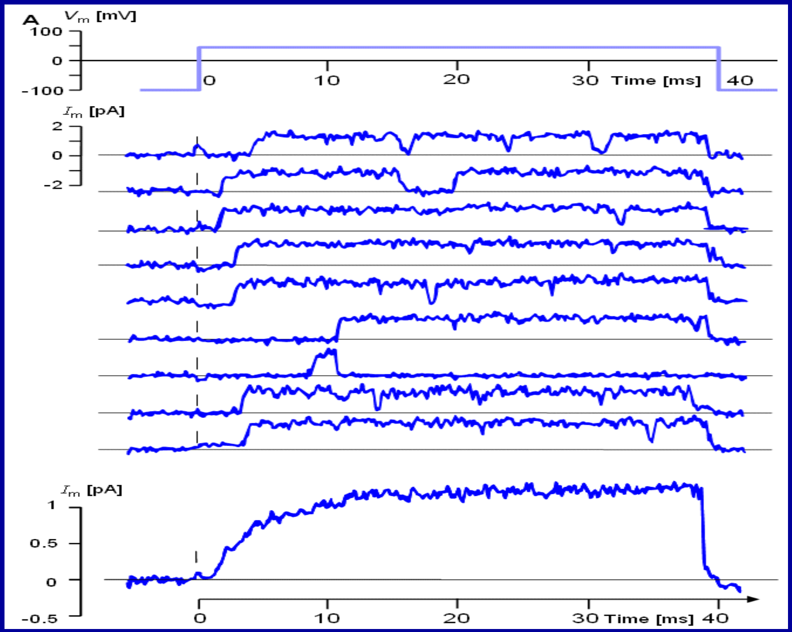


- Individual channel's response are stochastic in nature.

Na+ channel



K+ channel



E. Neher. "Ion Channels for Communication Between and within Cells," Nobel Lecture, December 9, 1991

B. Hille, "Ion channels of Excitable membranes," Sinauer Associates, Sunderland, MA, 2001.

Ion Channel Markov Model

$$\frac{dy}{dt} = -(R_{yz}(V_m,t) + R_{yq}(V_m,t))\,y + R_{zy}(V_m,t)\,z$$

$$\frac{dz}{dt} = -R_{zy}(V_m,t)\,z + R_{yz}(V_m,t)\,y + R_{qz}(V_m,t)\,q$$

$$\frac{dq}{dt} = R_{yq}(V_m,t)\,y - R_{qz}(V_m,t)\,q = -\frac{dy}{dt} - \frac{dz}{dt}$$

y: *the number of sodium channels in activation state*

z: *the number of sodidum channels in rest state*

q: *the number of sodium channels in inactivation state*

R_{yz}: *transferring rate from activation to rest*

R_{yq}: *transferring rate from activation to inactivation*

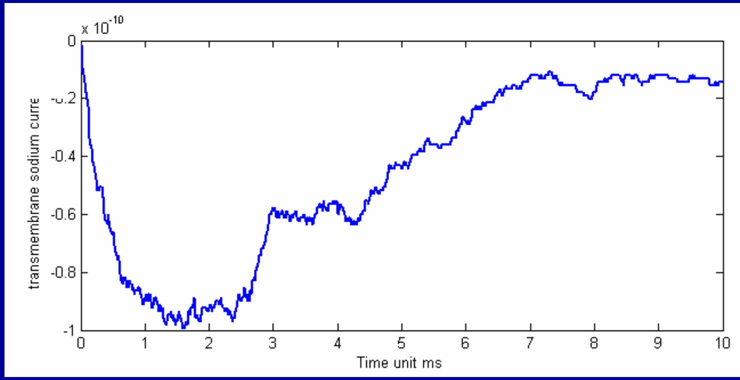
R_{zy}: *transferring rate from rest to activation*

R_{qz}: *transferring rate from inactivation to rest*

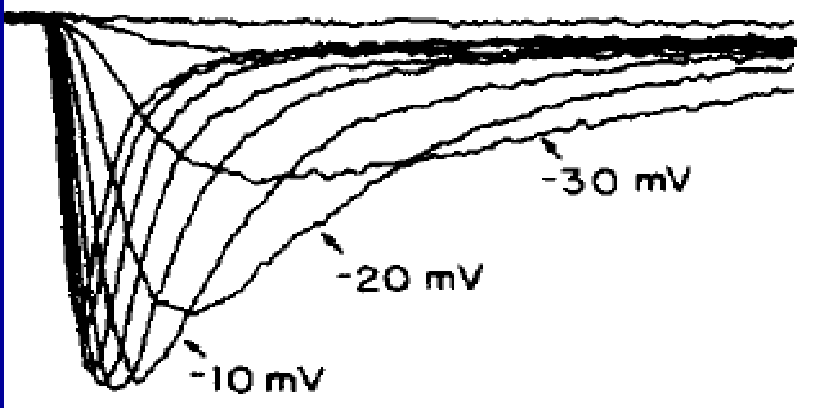
$$t_{peak} = (\ln\tau_2 - \ln\tau_1)/(\tau_1^{-1} - \tau_2^{-1});$$

$$\tau_{1,2}^{-1} = \frac{(R_{zy} + R_{yq} + R_{yz}) \mp \sqrt{\Delta}}{2},$$

$$\Delta = (R_{zy} + R_{yq} + R_{yz})^2 - 4R_{zy}R_{yq}.$$



Predicted sodium current profile based on derived expressions using Markov's model

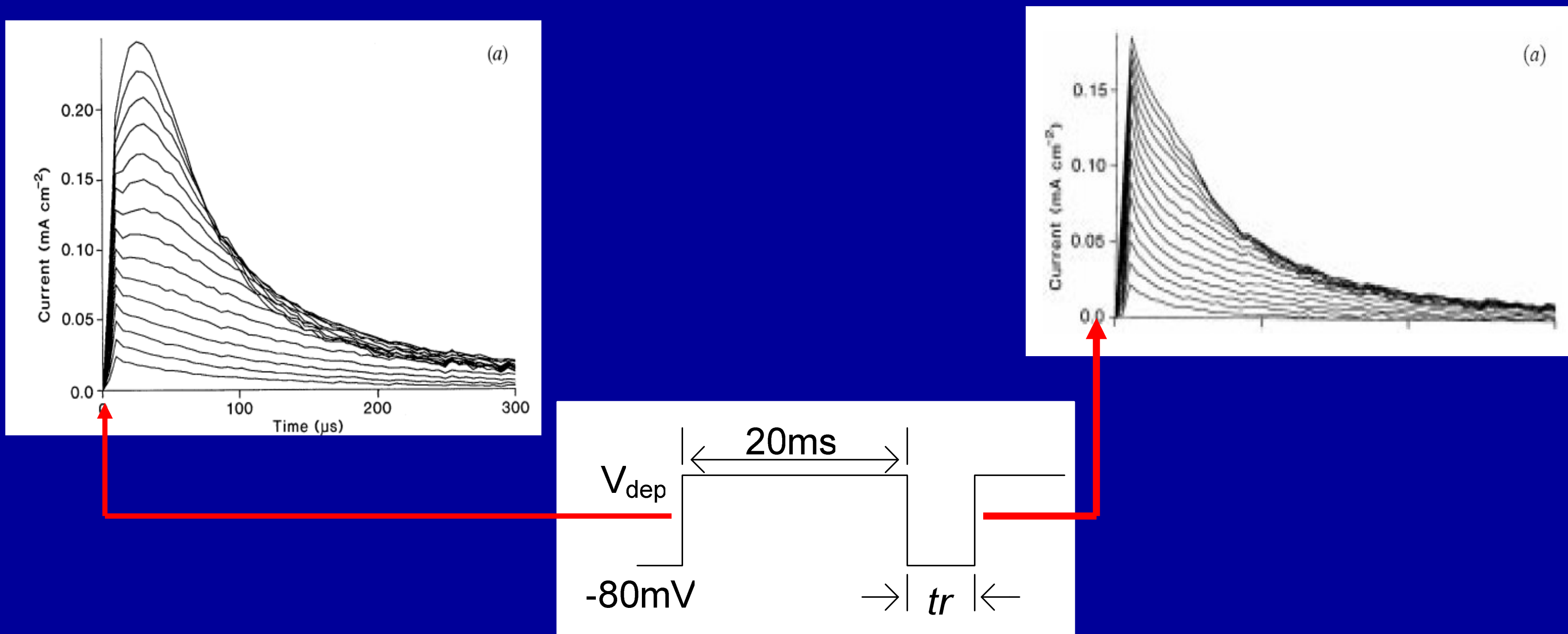


Experimental Results

Moran,O. and Conti, F. "Sodium ionic and gating currents in mammalian cells" European Biophysics Journal, 1990

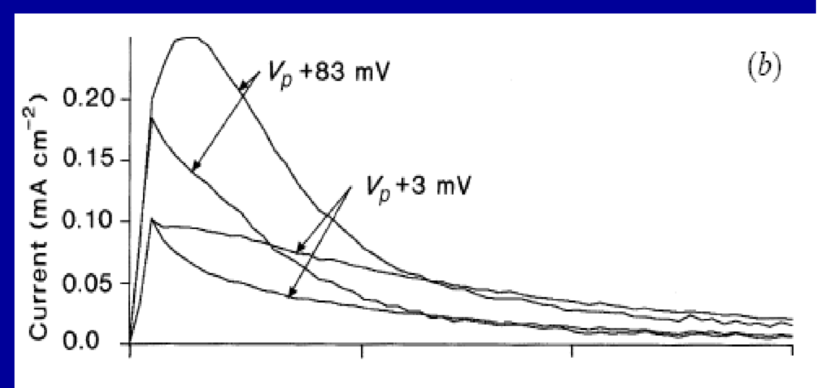
Transmembrane Gating Current

R. D. Keynes. and F. Elinder, "On the slowly rising phase of the sodium gating current in the squid giant axon," The Royal Society 1998



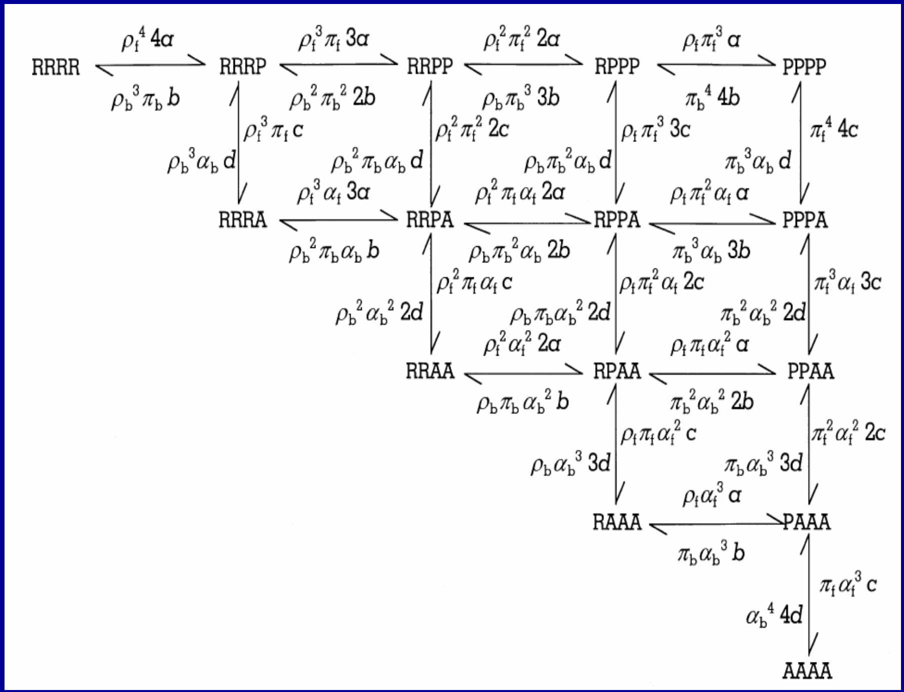
Transmembrane Current Components?

- Ionic Current
- Displacement Current
- Gating Current



Gating Current - Gating Sensor Diagram

- States diagram of the transmembrane protein currents in terms of sensor states.
- Assign the sensors with initial states, a Markov model could be used to quantify the current states of the sensors.
- Once all the sensors are in activated positions, the Na+ channel opens and ionic current appears.
- After a short period of activation, the sensors move to the inactivating state and close the channel.
- The movement of the sensors is in principle governed by thermal dynamics shown by the equations.



R. D. Keynes, and F. Elinder, "On the slowly rising phase of the sodium gating current in the squid giant axon," The Royal Society 1998

$$k_f(V) = k_{eq} e^{\frac{z\beta(V_m - V_0)F}{RT}}$$

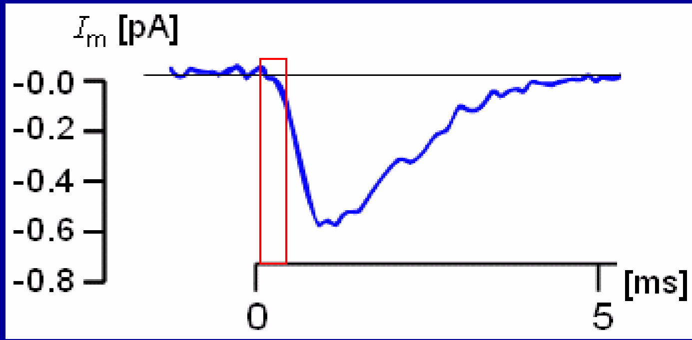
$$k_b(V) = k_{eq} e^{\frac{-z(1-\beta)(V_m - V_0)F}{RT}}$$

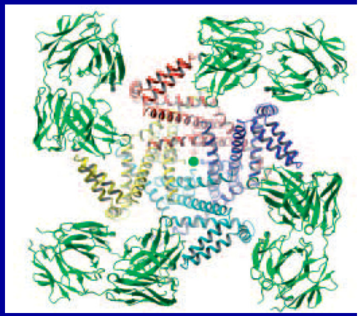
$$\beta \in (0.6, 0.8)$$

$$I_g(t) = \sum z_{ij}(k_{ij}P_i(t) - k_{ji}P_j(t))$$

Measurement of Gating Current

$$I_{gate} = I_m - I_{ion} - I_{cap}$$





- Alan Hodgkin and Andrew Huxley first predicted the existence of the transmembrane sensors and HH model was proposed accordingly. The transmembrane current is an average macro scope one. The sensors are proved to be charged proteins and responding to the transmembrane voltage changes. (Nobel Prize in Medicine, 1963)
- Bert Sakmann and Erwin Neher measured an individual ionic channel current by using patch clamp technique (Nobel Prize in Medicine, 1991)
- R. MacKinnon is able to locate the protein sensors using optical measurement (Nobel Prize in Chemistry, 2003)

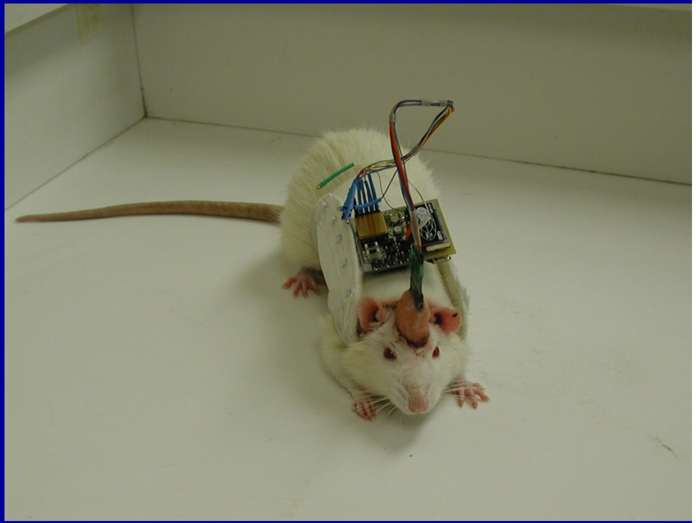
Challenges:

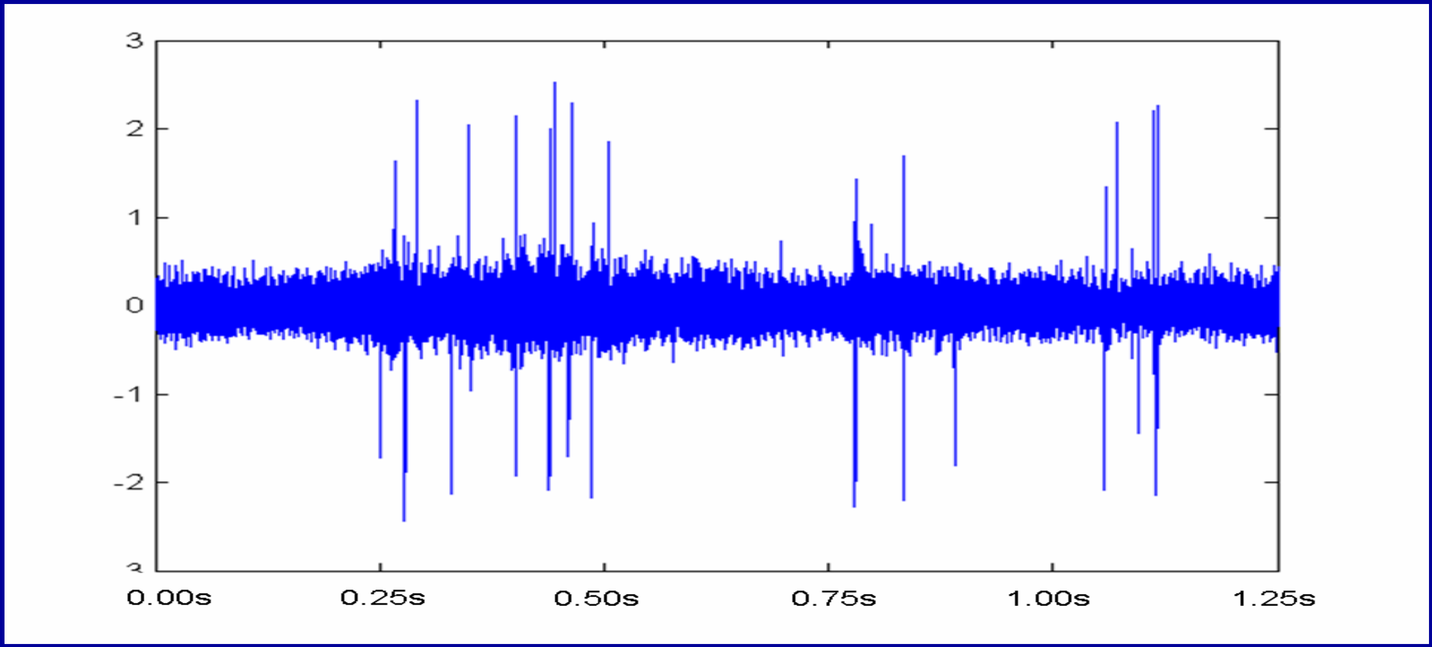
- I_{gate} is a small transient current due to protein motion. To detect a single channel protein current composed of 12e charge proteins, the recording bandwidth is >1MHz with a signal amplitude of 100fA.
- The transmembrane voltage is required to be stabilized in 10us in order to filter out the effect of the displacement current.
- The membrane/circuit interface requires a custom design.

- Cognitive Behavior and Intelligence Study in Non-Human Primates
- Spinal Cord Injury Prosthesis – Bladder Control

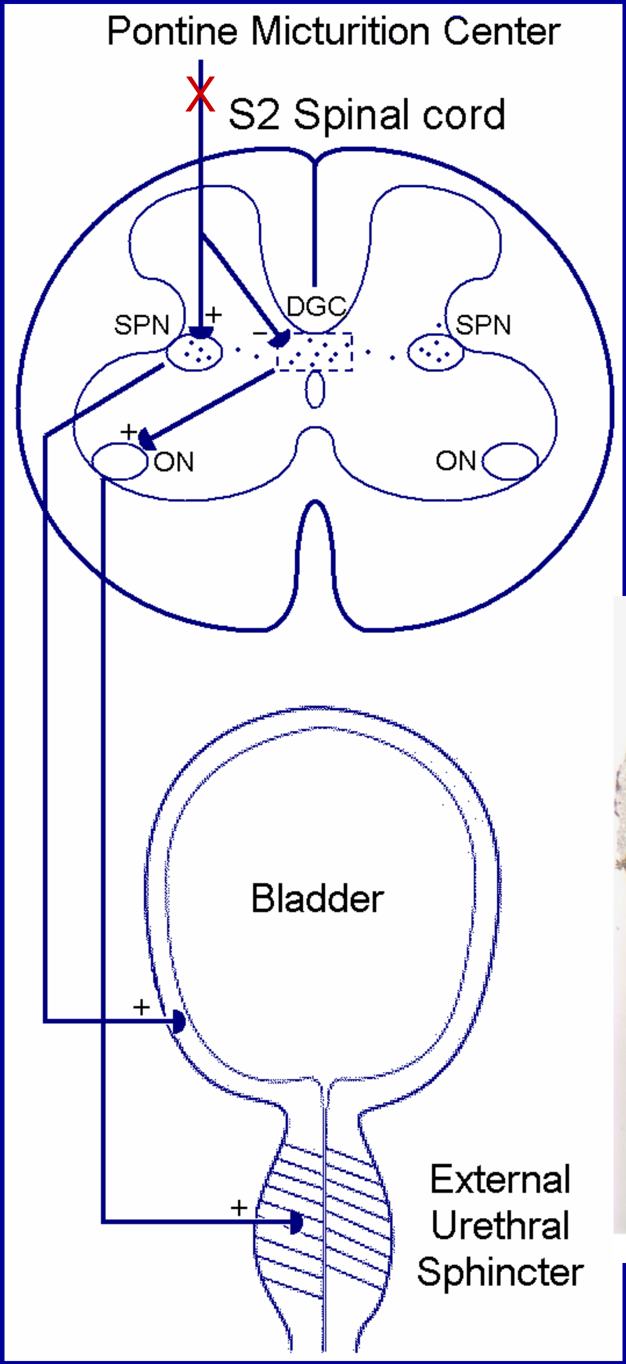
Neuro-Recording on Free Running Animals

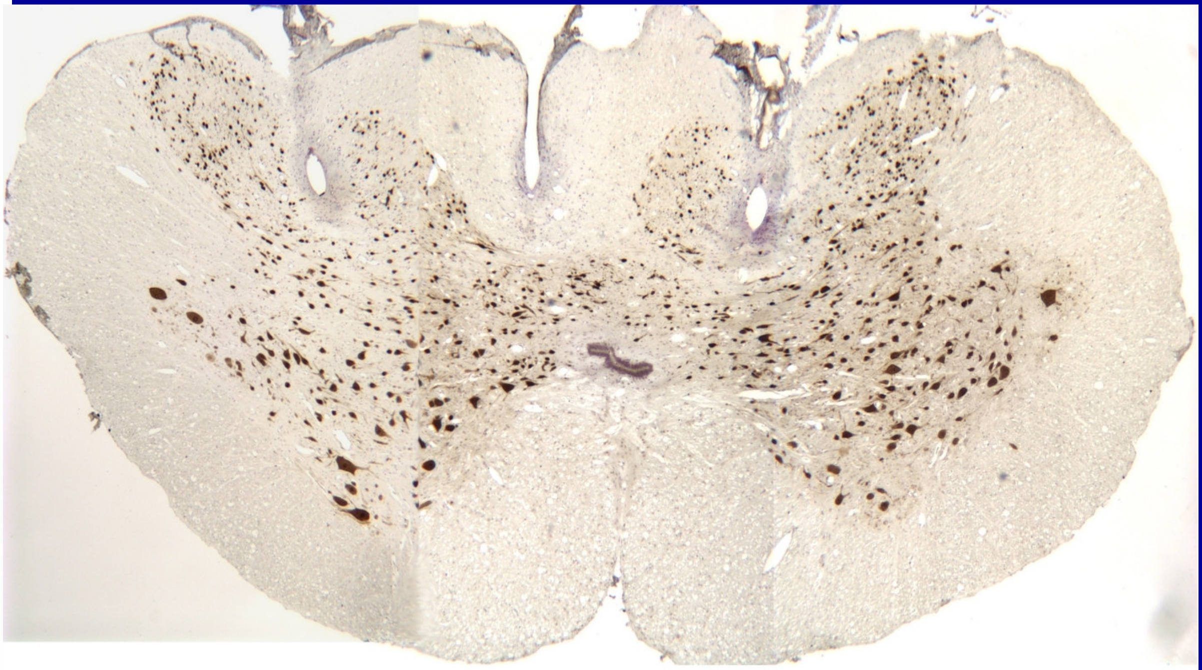
- Four Channels
- High Density Channels
- Wireless
- Low Power Miniaturized Bio-Signal Processing (BSP)
- Soon on Monkeys





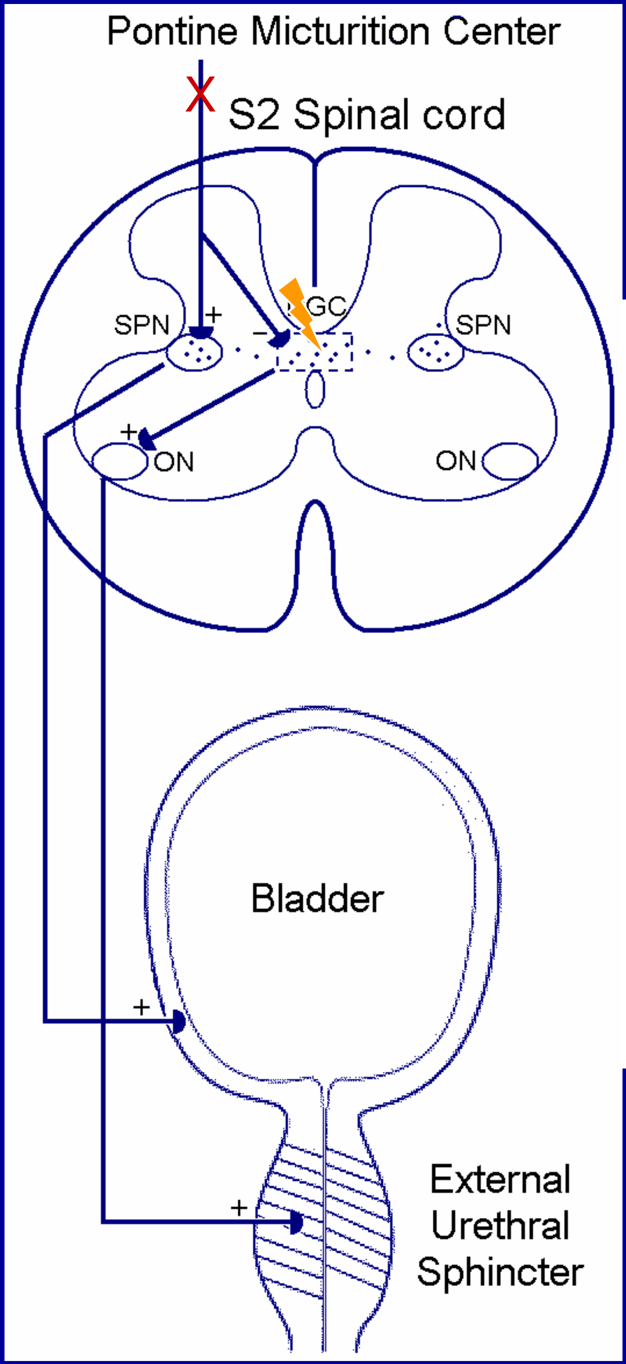
Neuroprosthetic Bladder control after spinal cord injury

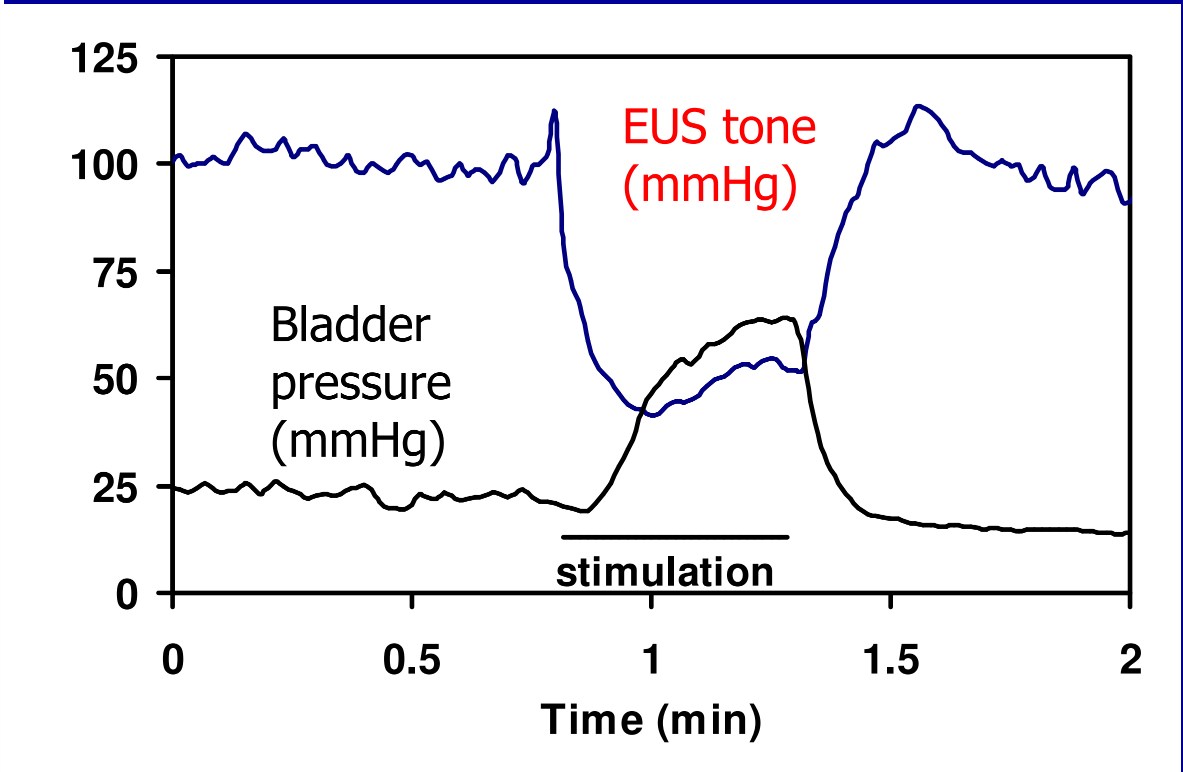




Collaboration with Huntington Medical Research Institutes

Neuroprosthetic Bladder control after spinal cord injury



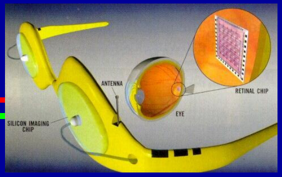


Collaboration with Huntington Medical Research Institutes

Outline

- Motivations of Biomimetic MicroSystems
  - Emerging Opportunity
  - Challenges in Design, Technology, and Education
  - Interdisciplinary Research
- Intelligent Neural Prostheses
  - Biosignal Processing
  - Wireless neural technology
  - Tools and Techniques
- **Retinal Prosthesis**
  - **Motivation**
  - **Approaches and Competitors**
  - **Progress and Status**
- Concluding Remarks

University of California



Retinal Prosthesis

- **To Bring Back Sight for the Blind with Retina Disease**
  - **Stem cell approach**
  - **Gene therapy approach**
  - **Growth factor approach**
  - **Transplantation approach**
  - **Micro/nano-electronics approach - Prosthesis**

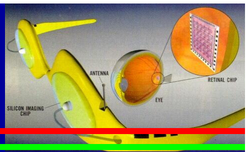
Various Methods of Retinal Prosthesis:

Electrical Stimulation (used by our project in human trials)

Chemical Stimulation (being pursued by us and more challenging)

Molecular Optical Switch (being pursued by Berkeley and Stanford)

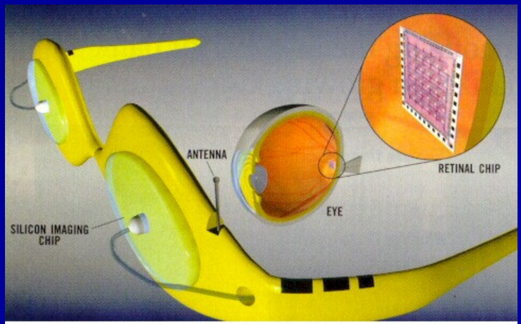
Retinal Prosthesis



President Clinton's State of Union Address –

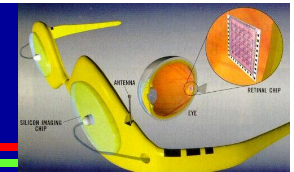
In the new century, innovations in science and technology will be the key not only to the health of the environment, but to miraculous improvements in the quality of our lives and advances in the economy. Later this year, researchers will complete the first draft of the entire human genome, the very blueprint of life. It is important for all our fellow Americans to recognize that federal tax dollars have funded much of this research, and that this and other wise investments in science are leading to a revolution in our ability to detect, treat, and prevent disease.

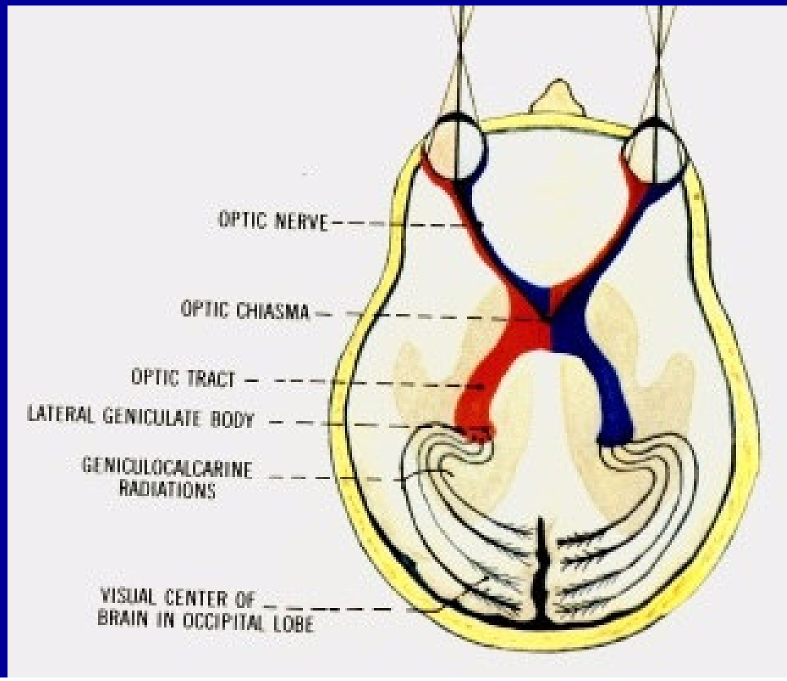
For example, researchers have identified genes that cause Parkinson's, diabetes, and certain kinds of cancer -- they are designed precision therapies that will block the harmful effect of these genes for good. Researchers already are using this new technique to target and destroy cells that cause breast cancer. Soon, we may be able to use it to prevent the onset of Alzheimer's. **Scientists are also working on an artificial retina to help many blind people to see** -- and listen to this -- microchips that would actually directly stimulate damaged spinal cords in a way that could allow people now paralyzed to stand up and walk. (Applause.)

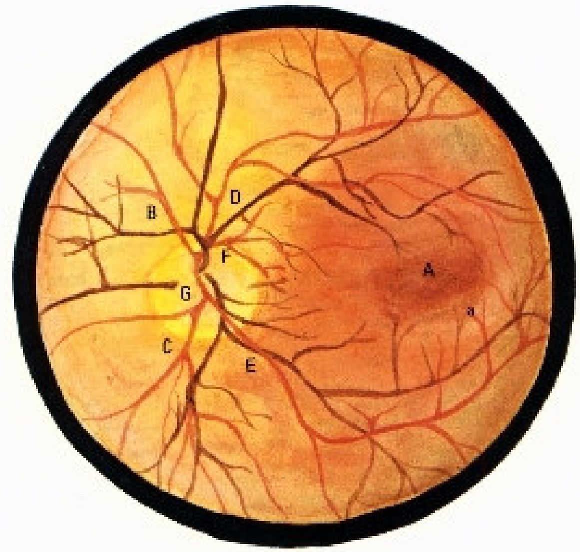


Retinal Prosthesis Project

Human Visual System

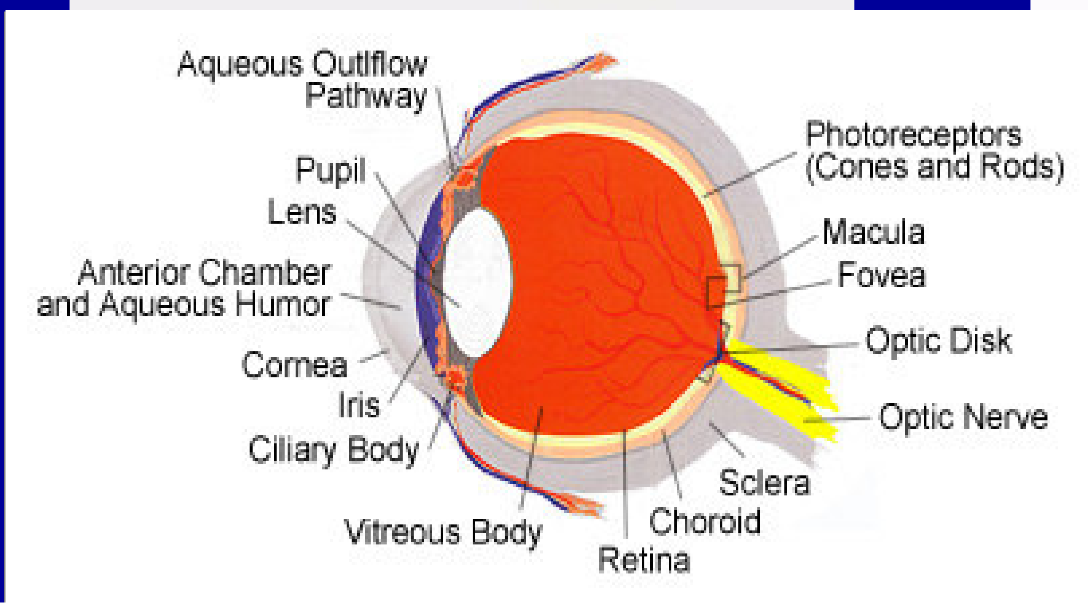




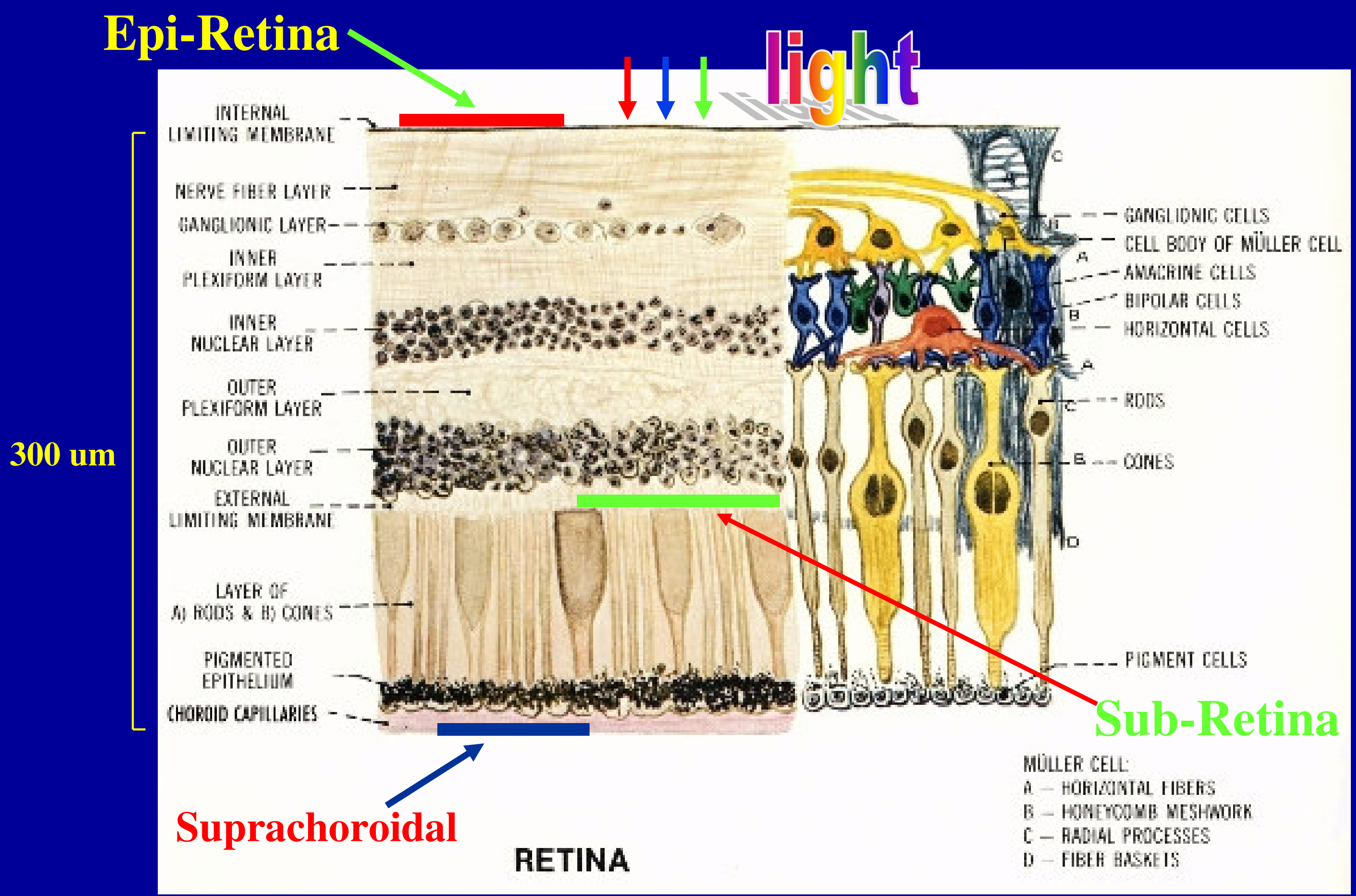


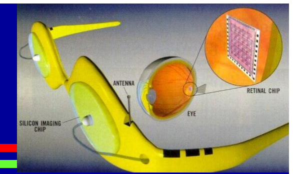
FUNDUS OF THE LEFT EYE

A. FOVEA CENTRALIS
a. MACULA LUTEA
B. SUPERIOR NASAL ARTERY
C. INFERIOR NASAL ARTERY
D. SUPERIOR TEMPORAL ARTERY
E. INFERIOR TEMPORAL ARTERY
F. CENTRAL RETINAL ARTERY
G. OPTIC NERVE



Location of Retinal Implant



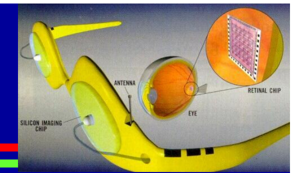


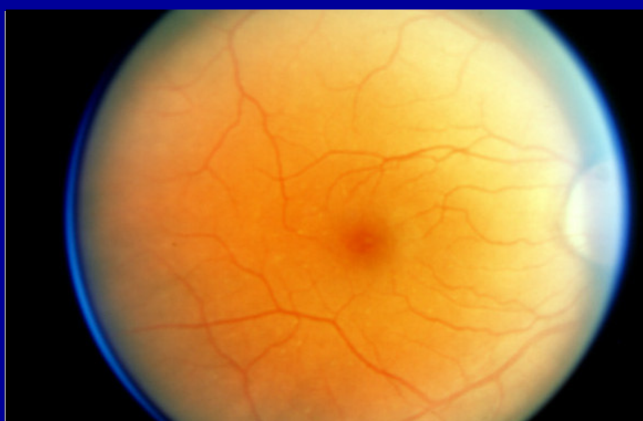
Blindness Disease

- **Blindness Caused by Diseases**
  - **Corneal Diseases**
  - **Cataracts/Glaucoma**
  - **Retina Diseases**
    - **Retinitis Pigmentosa (RP - genetic) - 1 in 4000 incidence and 100,000 in USA, 12 millions worldwide (Peripheral visions goes flat followed by gradual loss of central or reading vision)**
    - **Age-related Macular Degeneration (AMD) - 700,000 Americans yearly and 10% of them become legally blind (loss of central vision makes it difficult to impossibly perform detailed work such as reading)**
    - **Functionality loss involves only the rods and cones while cells that connect the eye to brain remain healthy (4% of rods/cones, 30% Ganglion cells, and 80% of inner layer)**
  - **Optic Nerve**
  - **Brain**

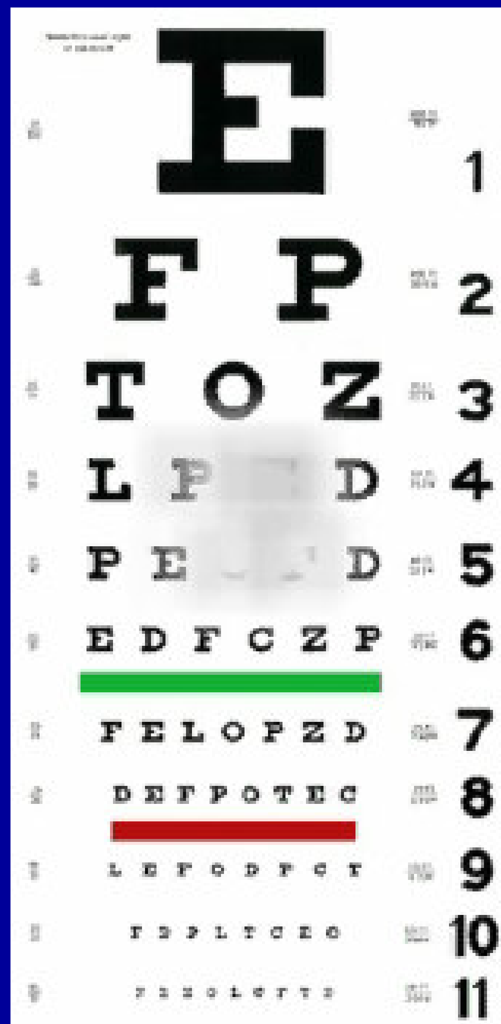
Retinitis Pigmentosa (RP)

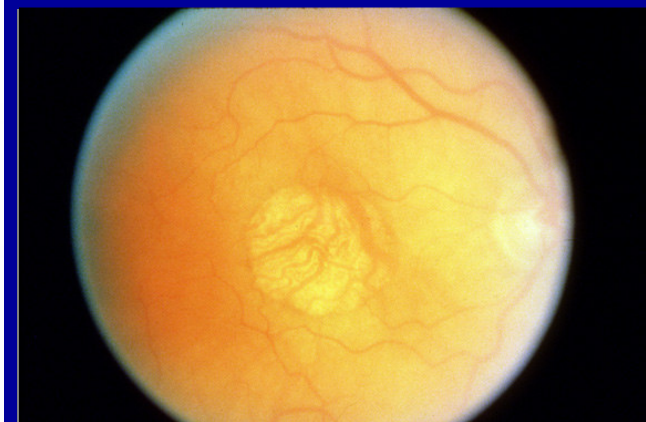
Age Related Macular Degeneration (AMD)





Healthy Macula

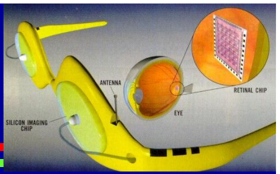




Dry AMD

Wet AMD

UC University of California



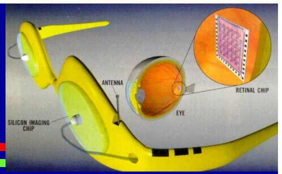
Engineering Solutions for Societal Problems

- **Emerging Field: Integration of a Dysfunctional Biological Subsystems with Microelectronics Systems**
- **The potential benefit to society**

➢ **Alleviating human suffering**

➢ **Reducing the government resources now directed to assist people with disabilities**

➢ **Example: Retinal Prosthesis, an estimated $4 billion federal dollars would be saved even if only 20,000 blind patients were be helped for 20 years**



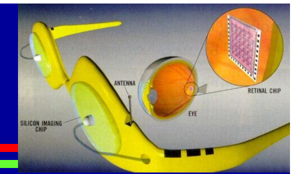
Visual Prosthesis - Competitors

- **To Bring Back the Sight for the Blind**
  - **Intraocular Prosthesis**
    - **Epi-Retinal Prosthesis**

      USC/UCSC, Harvard/MIT, Univ of Bonn (Germany), Tohoku Univ. (Japan), Seoul Univ (S. Korea), Sydney Univ. (Australia)
    - **Sub-Retinal Prosthesis**

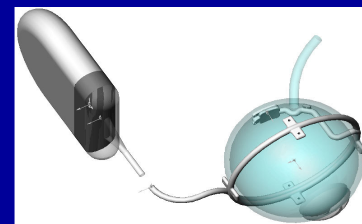
      Univ. of Tubingen (Germany), Optobionics (USA), Nat'l Chiao-Tung Univ. (Taiwan)
    - **Suprachoroidal Transretinal**

      Osaka Univ. (Japan)
  - **Prosthesis at Optic Nerve – Univ. of Louvain (Belgium)**
  - **Prosthesis at Visual Cortex – Univ. of Utah, Dobelle Inst.**



Retinal Prosthesis Clinical Trials

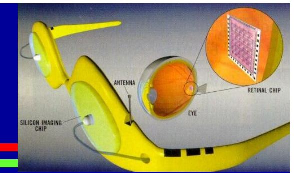
- Second Sight Medical Products
  - 5 subjects using device at home
  - 3-5 years, no device failures
  - FDA has approved IDE trial for 2nd generation device for implantation
- Intelligent Medical Implants
  - 4 subjects, no camera
  - 3 month limit on lifetime (packaging)
- Retina Implant GmbH
  - 7 subjects
  - 30-day limit on implant
  - 4/7 chips worked after implantation



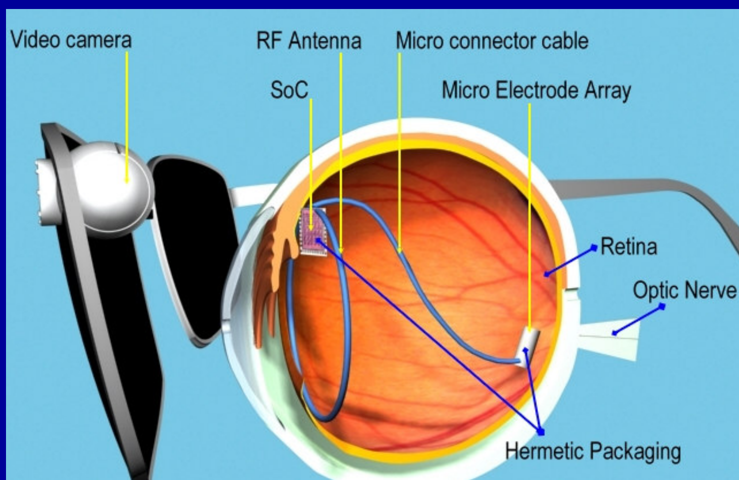
Second Sight Medical Products

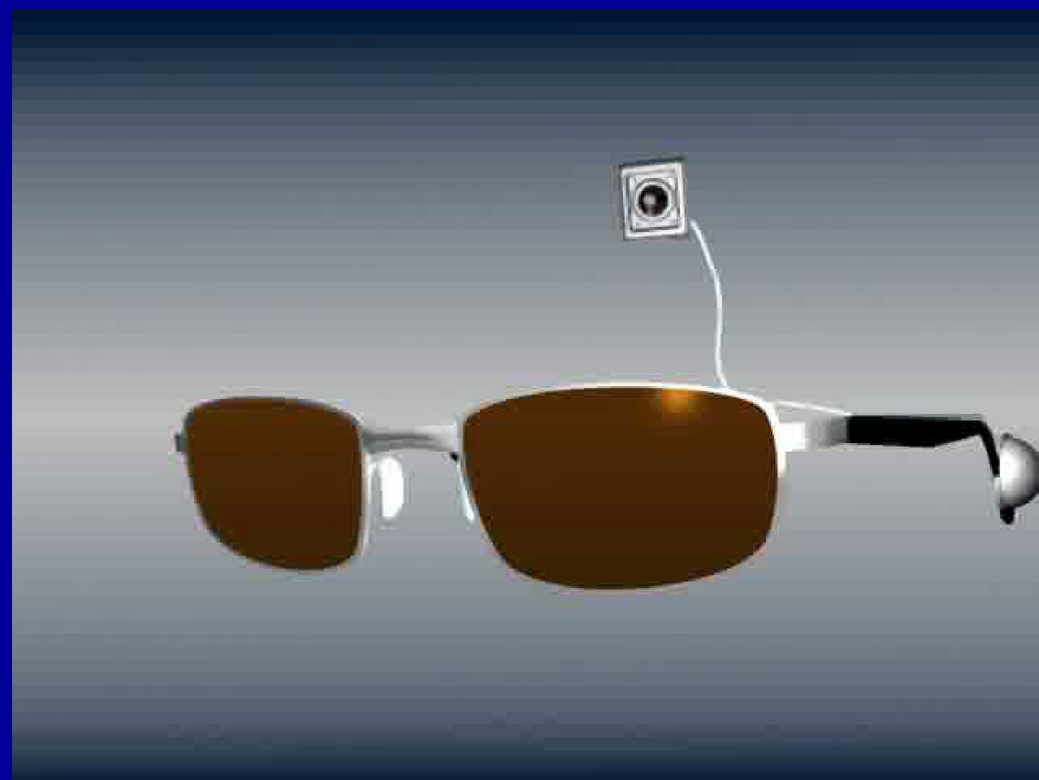
Intelligent Medical Implants

Retina Implant, GmbH



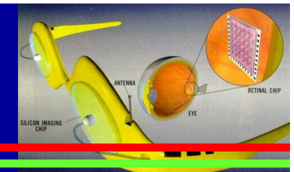
Prosthetic Device and Animation



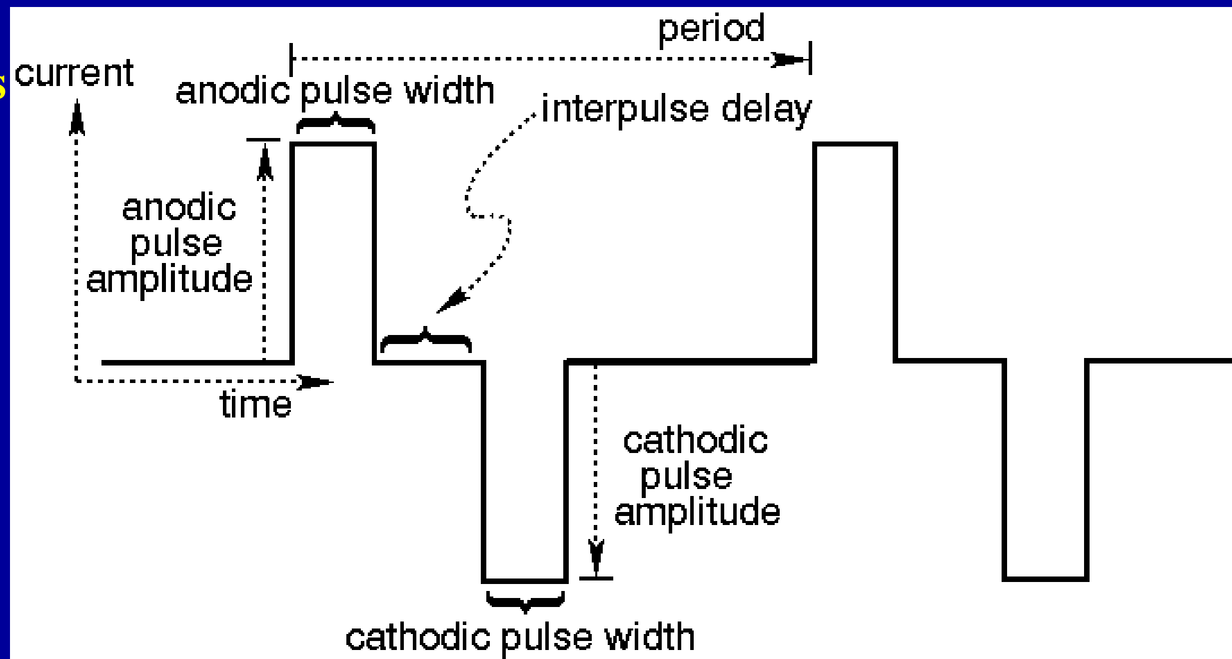


- **Wireless power and data**
- **Miniaturization/package**
- **Biocompatibility**
- **Reliability and Safety**

Stimulus Waveform Parameters



- Charge balance biphasic pulses to prevent electrochemical reactions in saline
- Current amplitude typically 10μA-200μA (depending on extent of retinal degeneration)
- Pulse widths typically 1ms duration
- Interphase delay typically 1ms duration



- Period at least 60Hz (16ms) to minimize flicker perception (300Hz easily achievable)
- Limitation to stimulation frequency is typically wireless-link data-bandwidth

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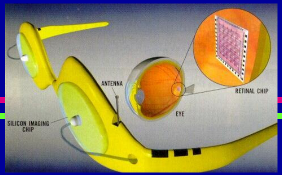
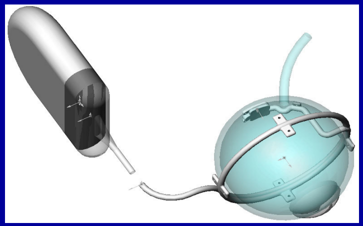


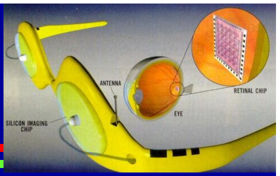
- First Generation - An implantable prototype (at low resolution 4x4) has been completed and the first clinical chronic trial was conducted on Feb 19, 2002. The 2nd one was done in August 2002. The 3rd one was done in March 2003. Three more have been done in 2004. Device has been no failure and used at home by patients.



- Second Generation (8x8) – IDE approval by FDA, started in 2007 in five clinical centers in USA, one in Mexico, one in Taiwan

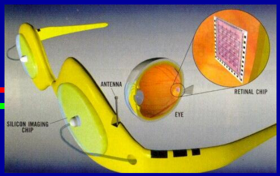
- Future Generation - Prototypes at higher resolution (16x16,32x32) are being developed

Retinal Prosthesis – 1st Generation

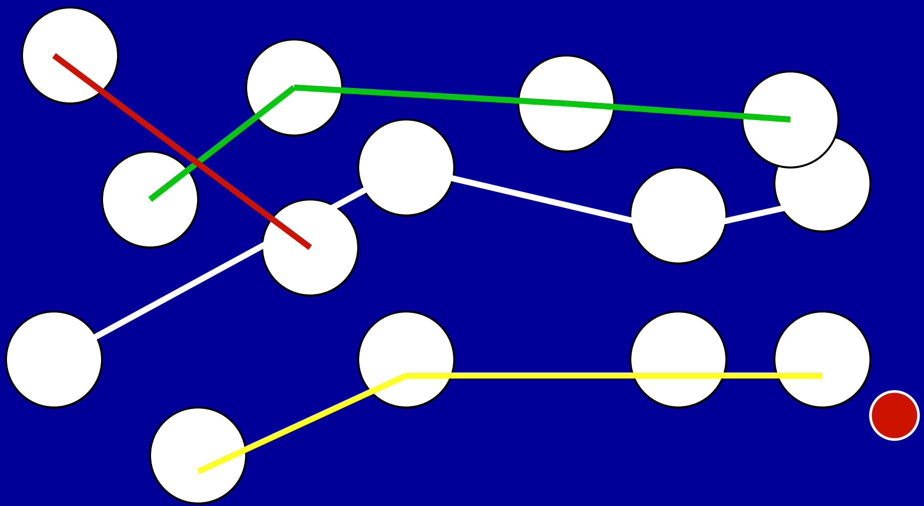


Implant Surgery
(First Chronic Implant in Feb. 2002)

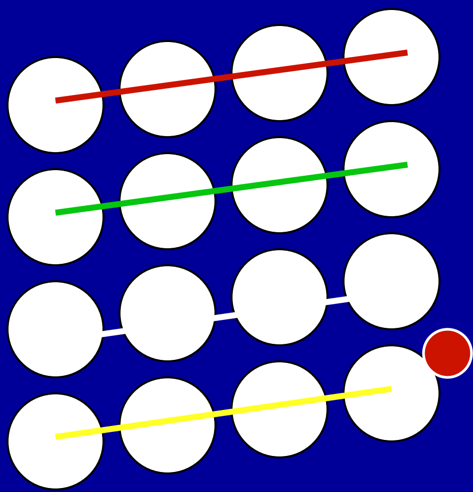
- **1st Generation (16 electrodes)**
  - **Six Permanent Implants**
  - **UCSC and USC**
  - **Collaborations since 1988**
  - **To restore eyesight for Patients with Retinitis Pigmentosa (RP) or Age-related Macular Degeneration (AMD)**
- **2nd and Future Generations**
  - **UCSC and USC**
  - **NSF/ERC, NIH/BRP, DOE/Artificial Sight**
  - **Five National Labs**
  - **Second Sight LLC**



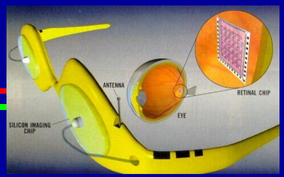
HEC01 Spatial Map - Horizontal



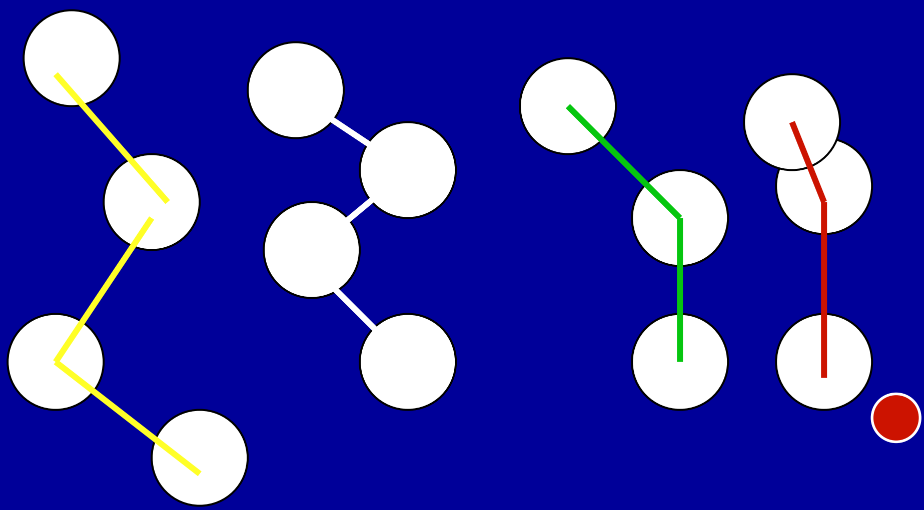
Patient Reported Locations



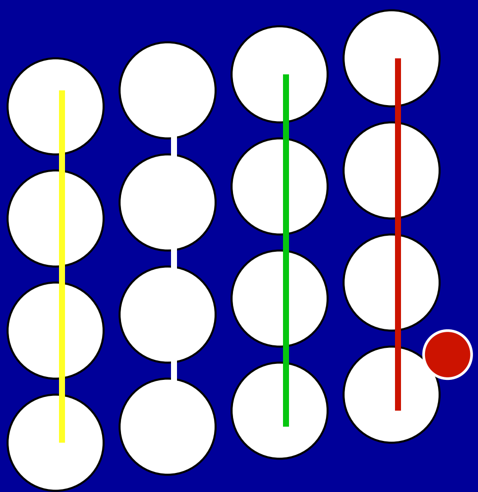
Expected Results based on Retinal Location



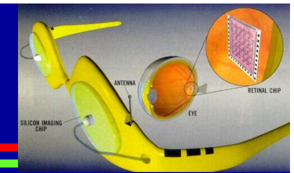
HEC01 Spatial Map - Vertical



Patient Reported Locations



Expected Results based on Retinal Location

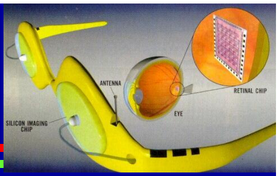


First in Sight (Reading)

(First Chronic Implant in Feb. 2002)

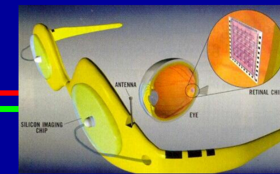
UC University of California

Retinal Prosthesis



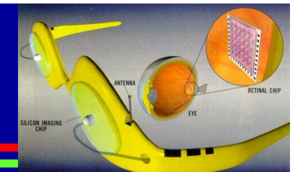
First in Sight
(Object Recognition)

Object Location



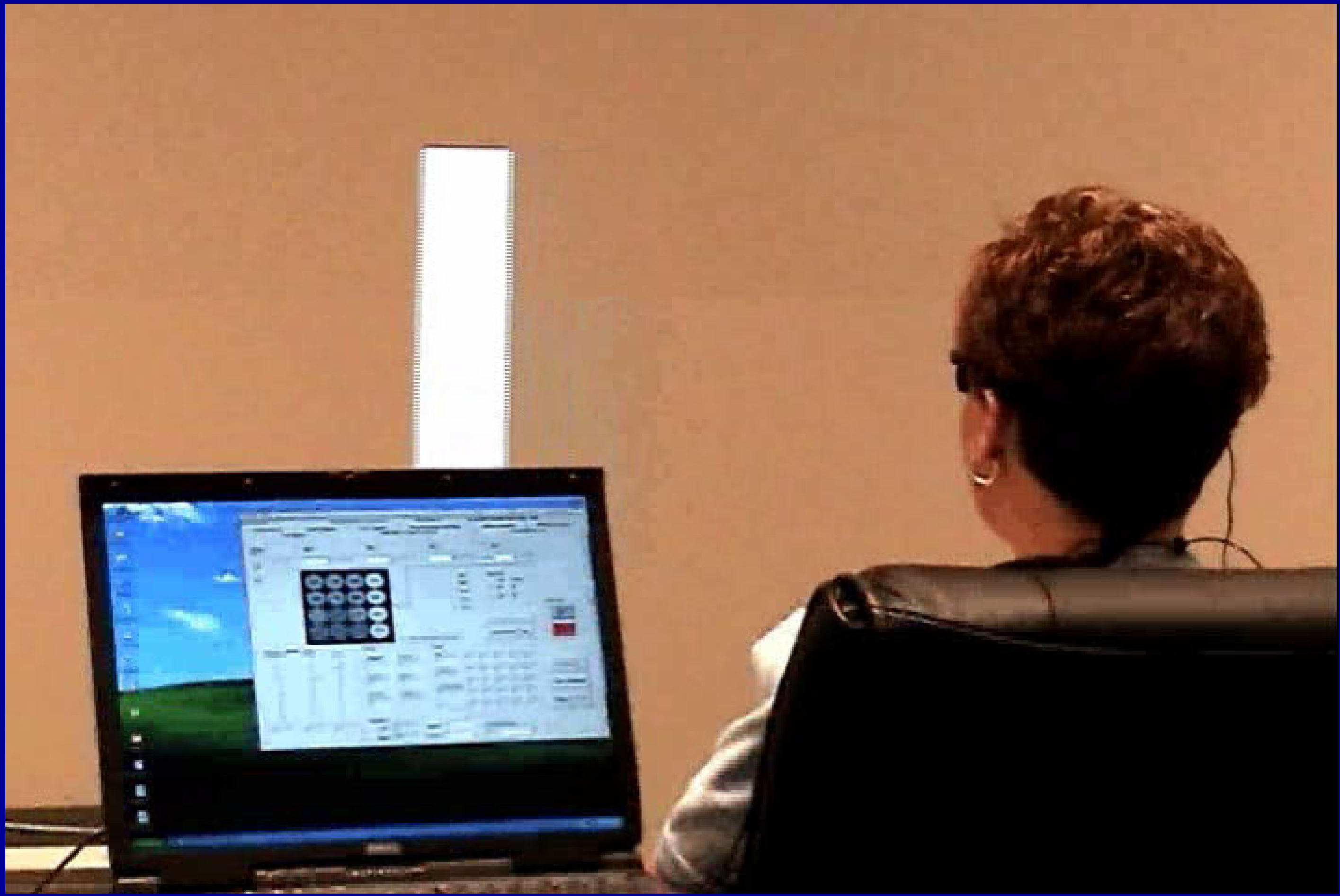
72-year old, blind test subject performing Object location task.

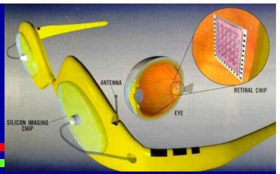
Retinal Prosthesis



First in Sight

(Motion and Direction)

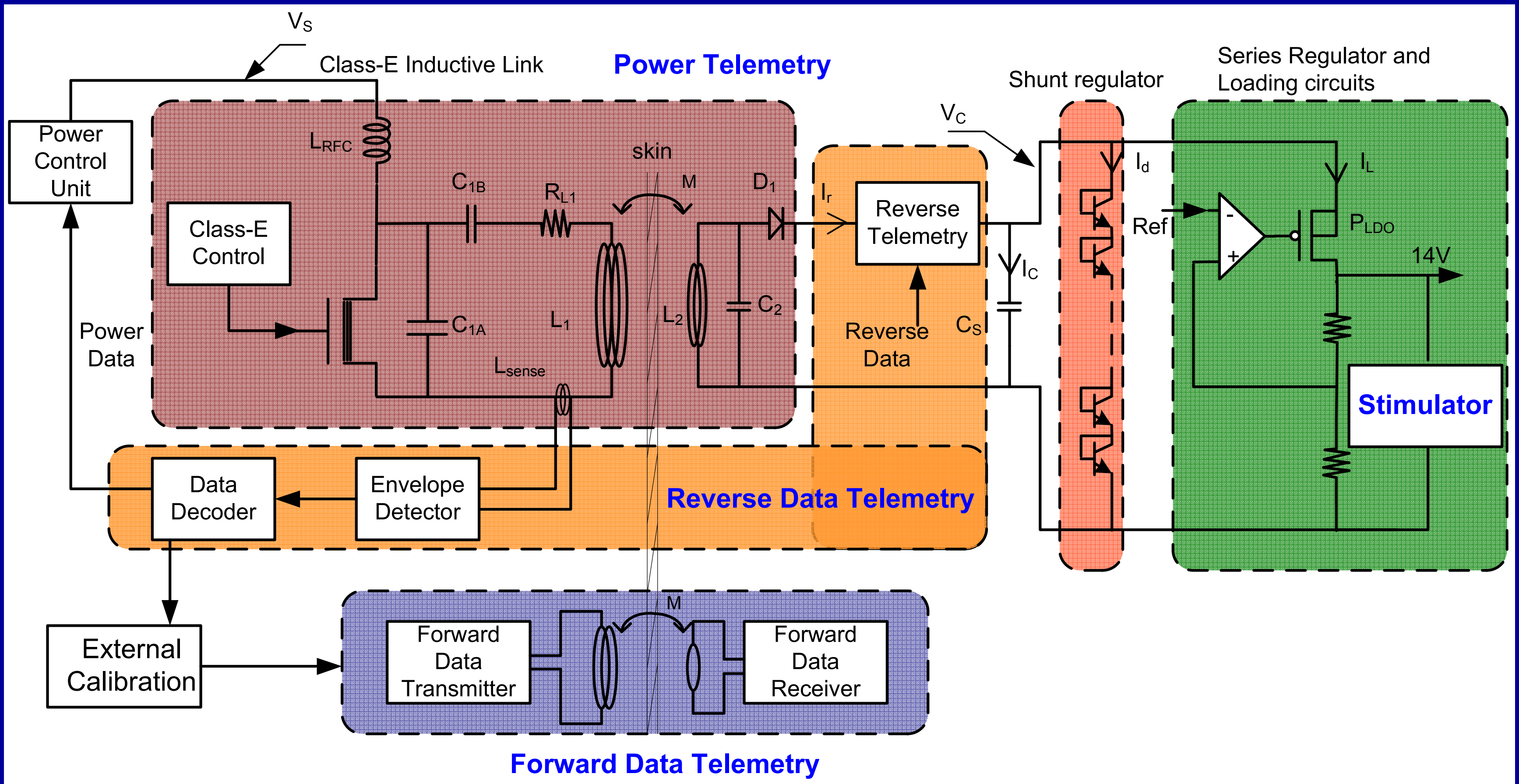




First in Sight

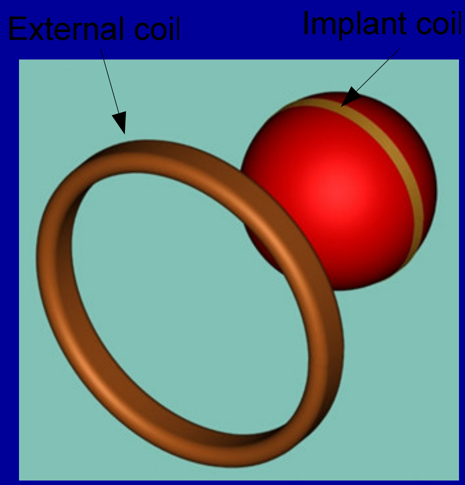
(Object Recognition)

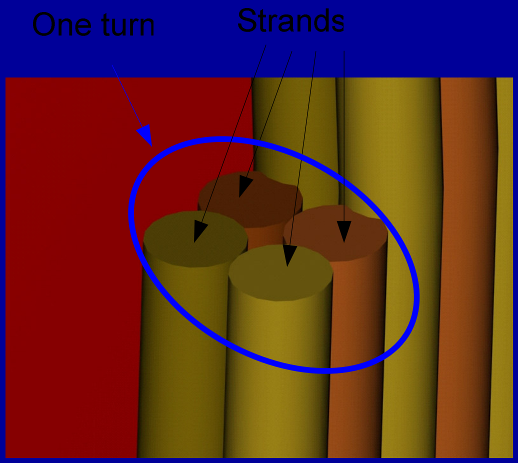
Dual Band Power and Data Telemetry

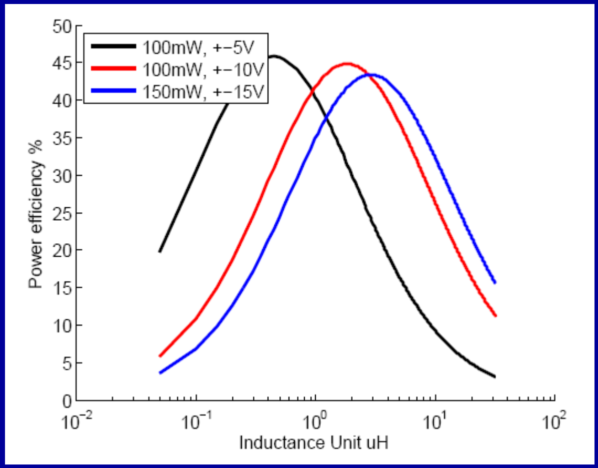


- Power carrier: 1 MHz
- Data carrier: 20 MHz
- Hybrid telemetry link achieving
  - High power transmission efficiency
  - High forward data rate

Power – Transmission Efficiency





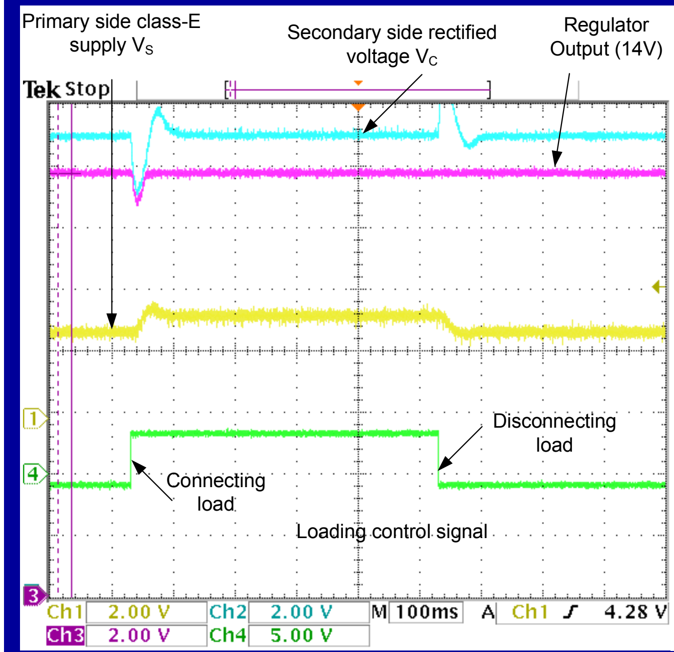


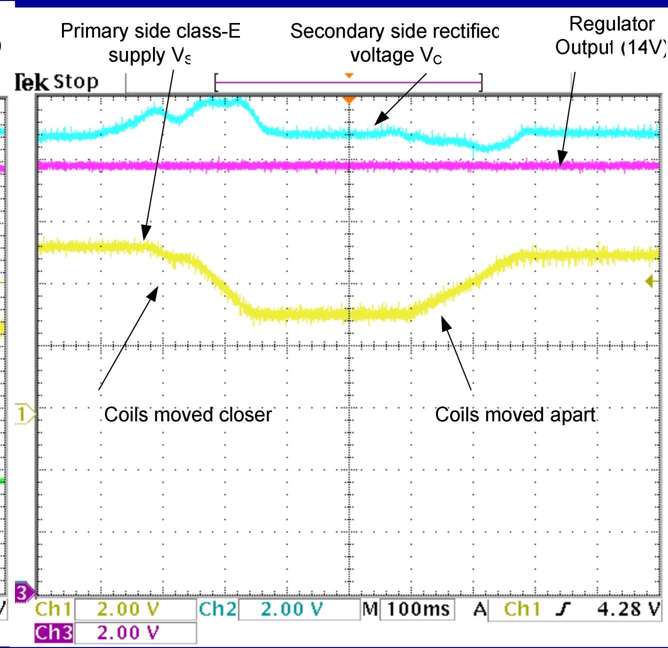
➢ Formal and Optimal Design Methodology

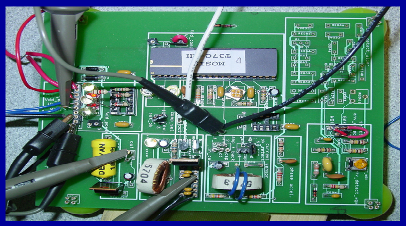
- Arbitrarily choosing coil size and parameters often leads to poor efficiency
- Coil design is a critical challenge to achieve high power efficiency
- Formal method for optimal coil design starting from implant coil size has been developed for the first time

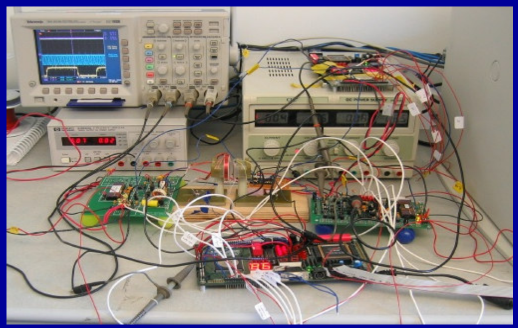
G. A. Kendir, W. Liu, G. Wang, M. Sivaprakasam, R. Bashirullah, M. S. Humayun, and J. D. Weiland, "An Optimal Design Methodology for Inductive Power Link with Class-E Amplifier," *IEEE Transactions on Circuits and Systems – I,* Volume: 52, Pages: 857 – 866, May 2005.

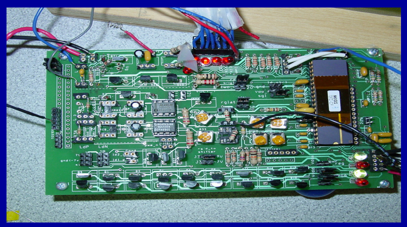
Adaptive - Coupling and Loading Variations







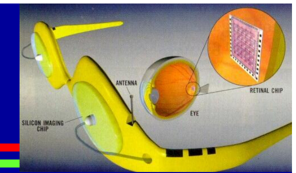


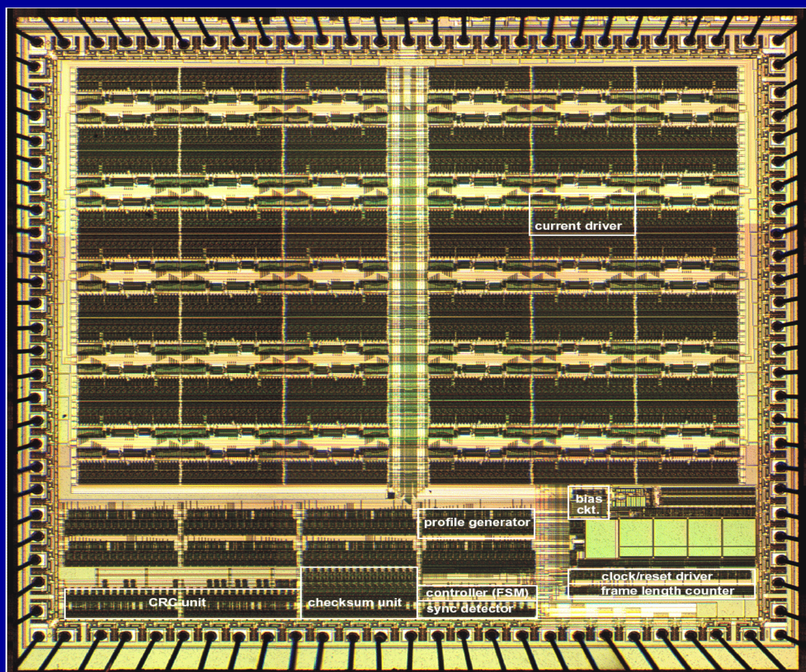


- Automatically adjusts the transmitted power to counteract coil movements and implant power variations
- Delivers the ‘just-needed’ power by closed loop adaptive control

G. Wang, W. Liu, M. Sivaprakasam, and G. A. Kendir, “Design and Analysis of an Adaptive Transcutaneous Power Telemetry for Biomedical Implants,” IEEE Transactions on Circuits and Systems – I, Volume: 52, Pages: 2109 – 2117, October 2005.

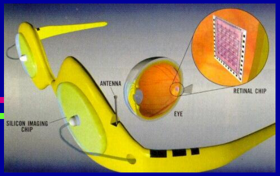
2^{nd} Generation Chip Specifications





Technology	1.2-µm CMOS
Die size	5.5 mm x 5.25 mm
Circuit area	4.7 mm x 4.6 mm
Number of current generators	60
Number of stimulation outputs	60
Data packet size	1024
Timing resolution (edge placement)	4 clock cycles (1/256 of frame time)
Supply voltage	+7 V, -7 V
Amplitude resolution	4 bits
Full-scale settings	200 µA, 400 µA, 600 µA
Anodic/cathodic matching	7.24%
Supply sensitivity	16 µA/V
Power consumption (600 µA, 1 ms pulse widths, 60 Hz)	42 mW

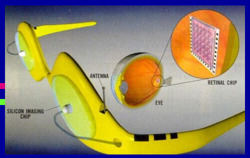
Currently being used in clinical trials



Future Prosthesis: How Many Pixels Are Enough?

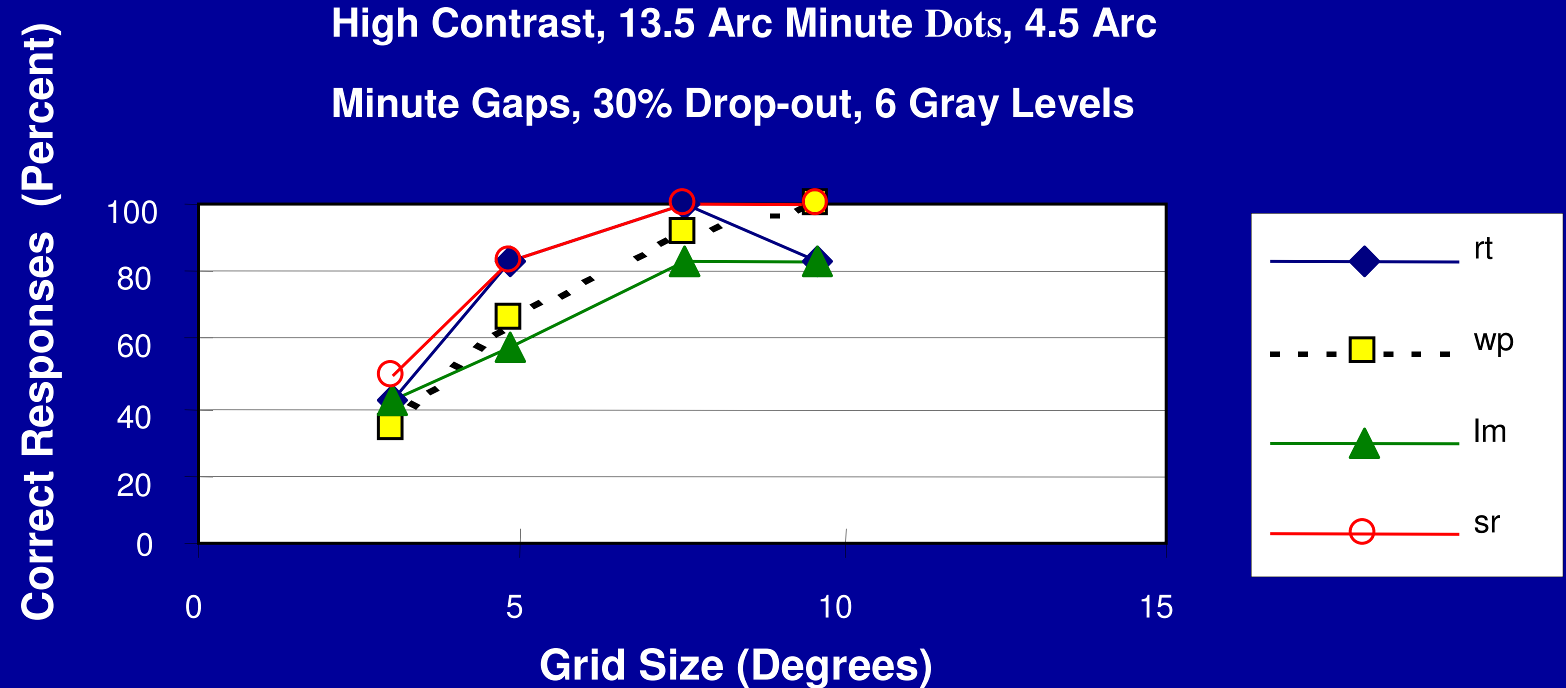
Quality of Life

- Facial Recognition
- Reading
- Unaided Mobility



Simulation of Visual Acuity

Face Recognition

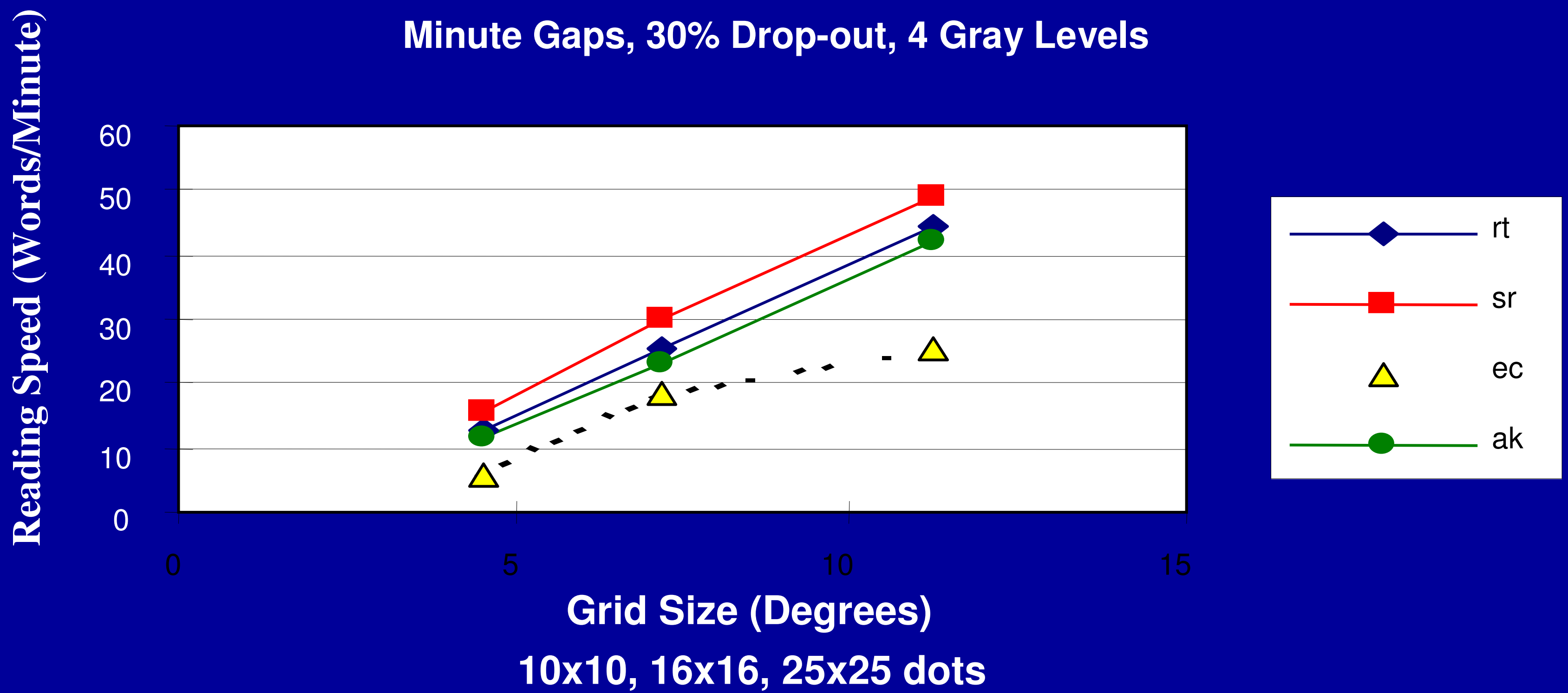


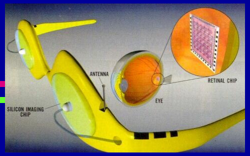
10x10, 16x16, 25x25, 30x30 dots

Simulation of Visual Acuity

Reading Task

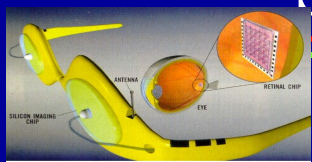
High Contrast, 22.5 Arc Minute Dots, 4.5 Arc Minute Gaps, 30% Drop-out, 4 Gray Levels





University of California

Summary of Retinal Prosthesis



Retinal Prosthesis Project

- **Promising results for intraocular prosthesis have been obtained**
- **First generation of prosthetic device (4x4 electrodes) has been in IDE trial with six patients**
  - **Demonstrate the ability of character reading, object recognition, and direction detection**
- **Second generation of prosthetic device (60 electrodes) has been designed and received FDA approval of IDE trials**
- **Trials will be done at centers in USA, Mexico and Taiwan**
- **Design of future generation of prosthetic device (>1,000 electrodes) is in progress**

➢ Clearly demonstrate the need of inter-disciplinary research

Concluding Remarks

- Understanding the brain is a serious challenge
- Interdisciplinary research, especially for the noble humanity applications, is always highly rewarding
- Grand opportunity, but high barrier right now
  - New engineering curriculum is of great need for interdisciplinary research
  - New infrastructure is needed
  - New way of research