Engineering Hope with Biomimetic Systems

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NSF Biomimetic MicroElectronics Systems Engineering Research Center
(A Partnership of UCSC, USC, Caltech)

SRC BioElectronics Round Table (BERT)

11/4/2008

Outline of Presentation

- Introduction
- Biomimetic Systems
- Enabling Technology for Biomimetic Systems
- Concluding Remarks

Acknowledgments

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  - Robert Greenberg, MD, PhD
  - James Weiland, PhD
  - Harvey Fishman, MD, PhD
  - Kimberly Cocherham, MD
  - Yu-lung Hsin, MD
  - J. C. Chiou, PhD
  - NSF ERC-BMES/DOE Artificial Retina Team
- Graduate Students: more than 20 graduate students

History Patterns 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

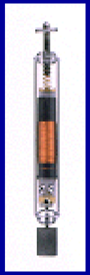
(by Professor Bruce Wheeler of UIUC)

Biotechnology

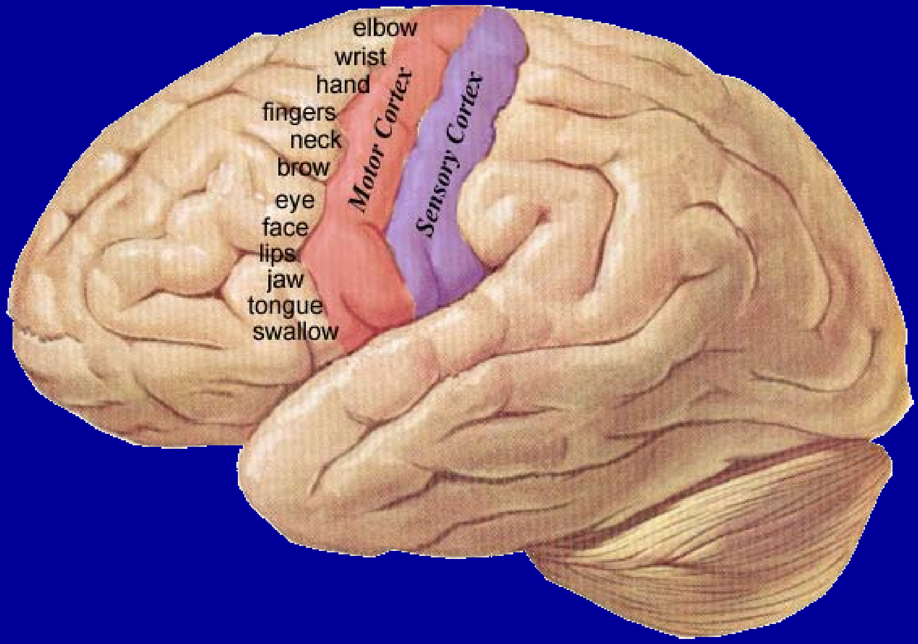
- Pharmaceutics and Bio-Pharmaceutics
  - $350B
- Biomedical Engineering
  - Biomedical devices and Instruments
  - Diagnostic tools
  - $300B at present and $1,800B at 2020 (Academia Sinica)
- Healthcare Cost – 16% of GDP in USA

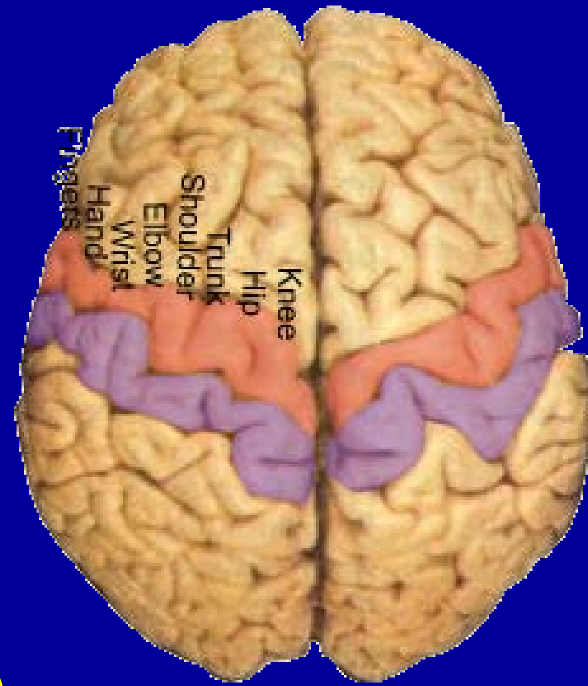
NeuroTechnology

- Opportunity and Challenges in Emerging New Industry-Neurotechnolog for neural disorders (Revenue of $120.5B in 2006, growing rate > 10%)
  - Neuro-Pharmaceutics ($101B)
  - Neuro-Engineering
    - Biomedical devices ($4.5B)
      - Prosthetics
      - Neural/muscle stimulation
      - Neuro-surgical
    - Diagnostic tools ($15B)
      - Bio-imaging
      - Bio-informatics
      - Neuroscience/cognition tools



Brain - Source of Neural Disorders





- 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

- Brain-related illnesses afflict more than two billion people worldwide, 100 million in USA

- The worldwide economic burden of this problem has reached more than $2 trillion per year; more than $1 trillion in the U.S. alone

- *http://www.neuroinsights.com*

  A new NASDAQ Index (NERV) was created for neurotechnology

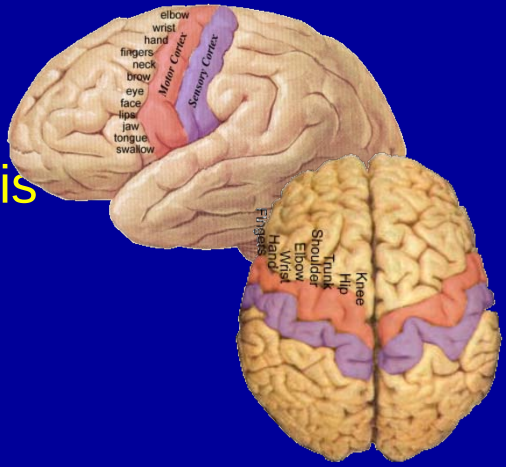
- Worldwide government research, private funding and public investment trends

Disorders Treated by Biomimetic Systems

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

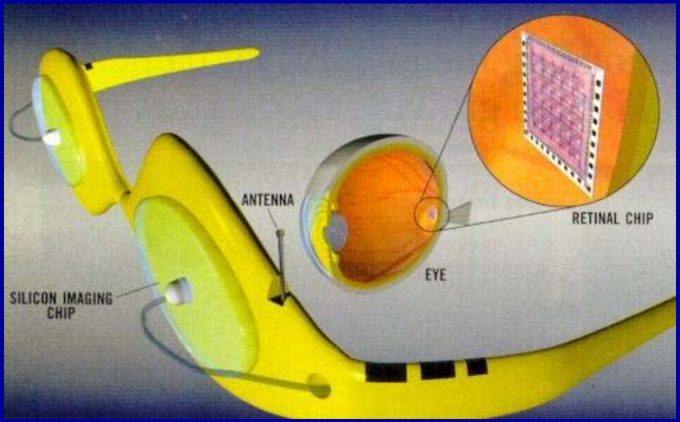
➢ ***We believe the largest markets in healthcare will be solved with biomimetic devices***

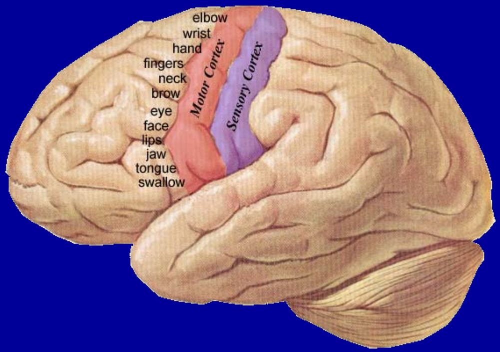
➢ ***Biomimetic Devices will significantly change lifestyles in the 21st century***

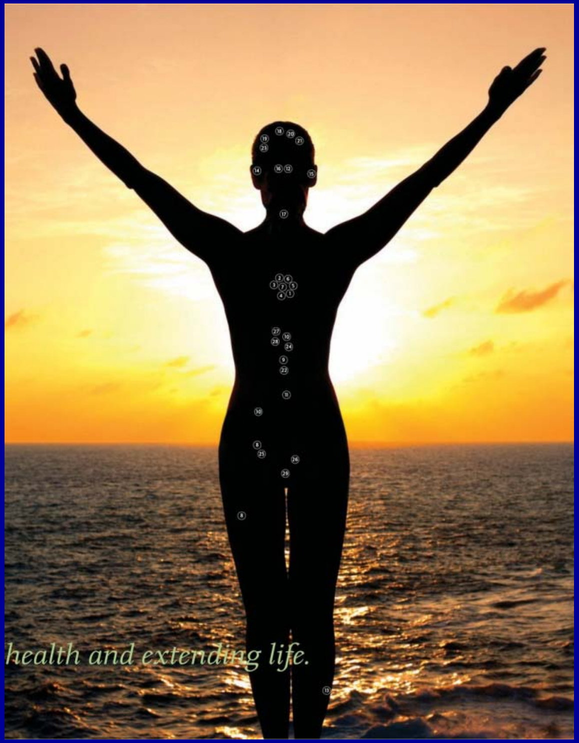


Biomimetic Systems

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



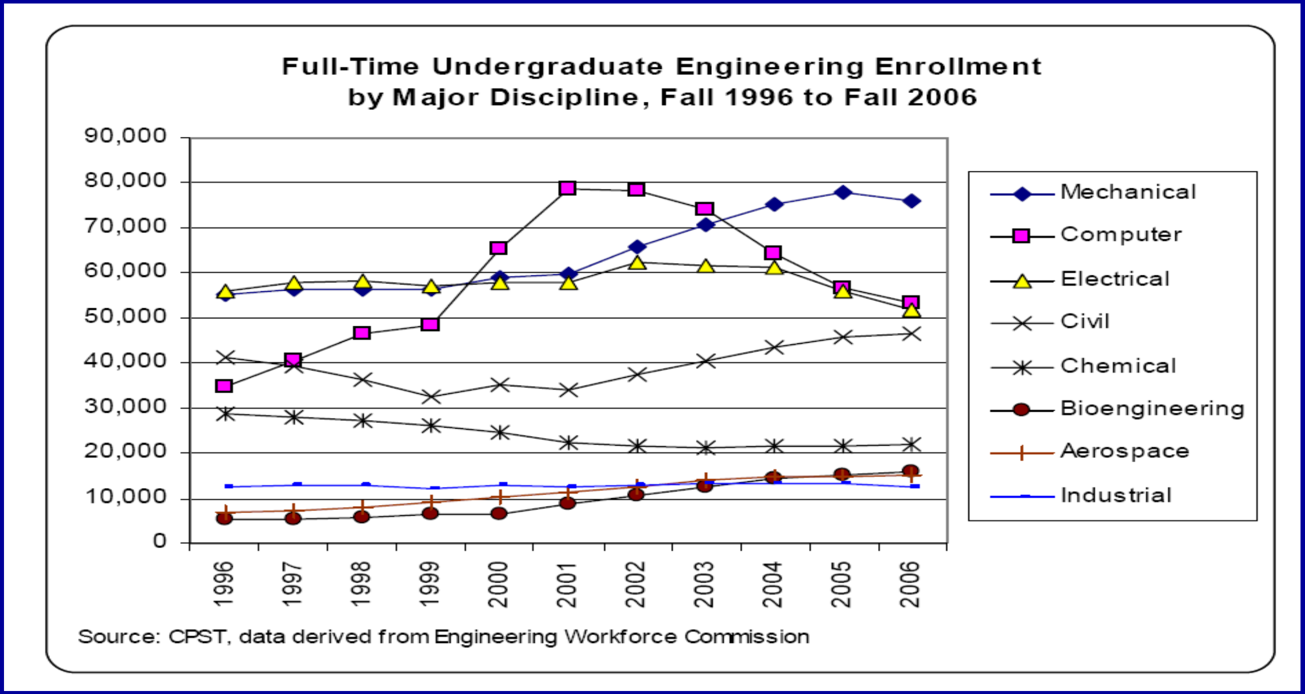


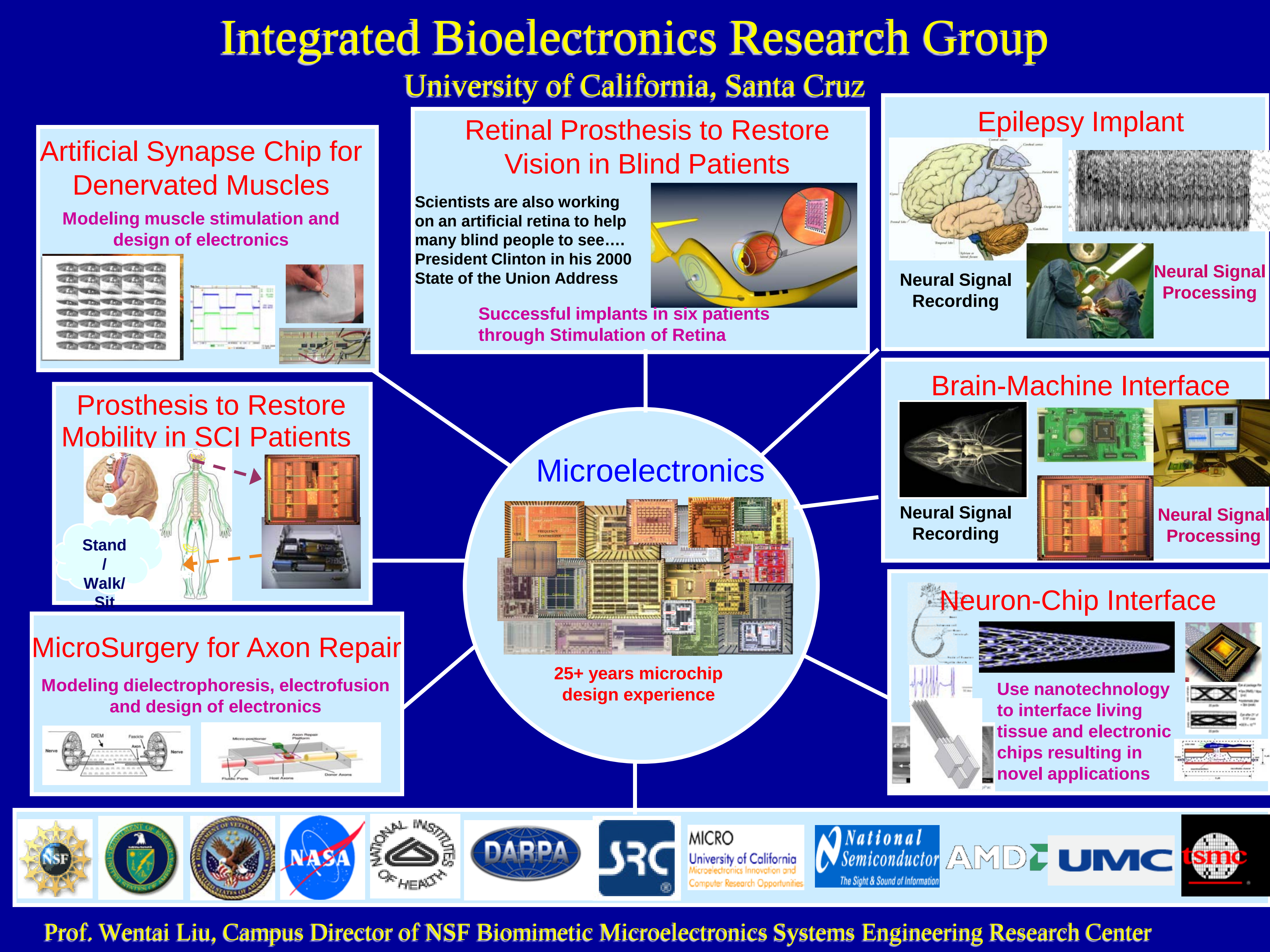


Meditronics

Biomedical Engineering

- 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





Integrated Bioelectronics Research Group
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
Epilepsy Implant
Neural Signal Recording
Neural Signal Processing
Prosthesis to Restore Mobility in SCI Patients
Stand / Walk/ Sit
Microelectronics
25+ years microchip design experience
Brain-Machine Interface
Neural Signal Recording
Neural Signal Processing
MicroSurgery for Axon Repair
Modeling dielectrophoresis, electrofusion and design of electronics
Neuron-Chip Interface
Use nanotechnology to interface living tissue and electronic chips resulting in novel applications
NSF
NASA
NATIONAL INSTITUTES OF HEALTH
DARPA
SRC
MICRO University of California Microelectronics Innovation and Computer Research Opportunities
National Semiconductor The Sight & Sound of Information
AMD
UMC
tsmc
Prof. Wentai Liu, Campus Director of NSF Biomimetic Microelectronics Systems Engineering Research Center

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, Sretavan)
Neuroscience

Nat'l Chiao-Tung University
Tsu-Chi Medical Center
(Biomimetic Center/Dr. Y.L. Hsin)
Epilepsy Implant

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

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

Arizona State Univ
(Dr. He)
Lower Limb Prosthesis

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

Stanford University
(Dr. Cockerham)
Muscle Stimulation

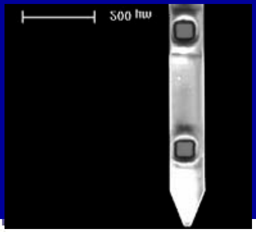
Dept. of Veteran Affairs/Cleveland Clinics
(Dr. Lin)
Spinal Cord Medicine

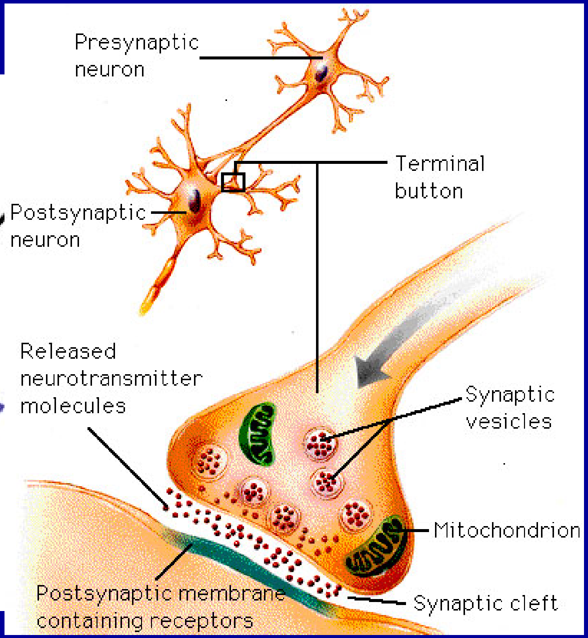
Current In-Vitro/In-Vivo Experiments in IBR Lab

- ➢ 20 member talented and active 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 and Europe (2008)
  - *Epilepsy Implant*
    - ✓ Nat'l Chiao Tung University and Tsu-Chi Medical Center (Taiwan)
  - *Bladder and bowel control for SCI*
    - ✓ Huntington Medical Research Institutes
  - *Eyelid implants (closure)*
    - ✓ Stanford University and VA-Palo Alto
  - *Eyelid implants (opening)*
    - ✓ Smith Kettlewell Eye Research Institute
  - *Brain Machine Interface*
    - ✓ *CalTech*
  - *Muscle limb implants*
    - ✓ Long Beach VA and Cleveland Clinics
  - *Cortical implants for cognition and motor control*
    - ✓ Arizona State University
  - *In-Vitro and Ex-Vivo validation for dynamic membrane modeling*
    - ✓ UCSC

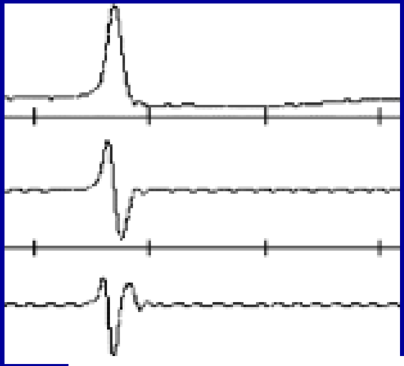
Neuron Stimulation and Signal Recording

- 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.





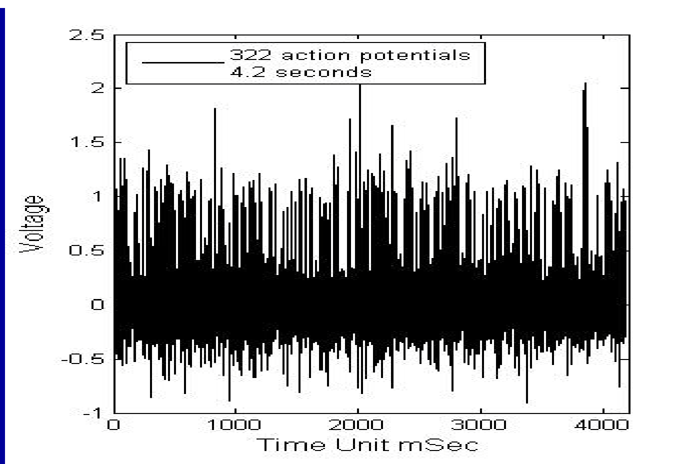
Recording:



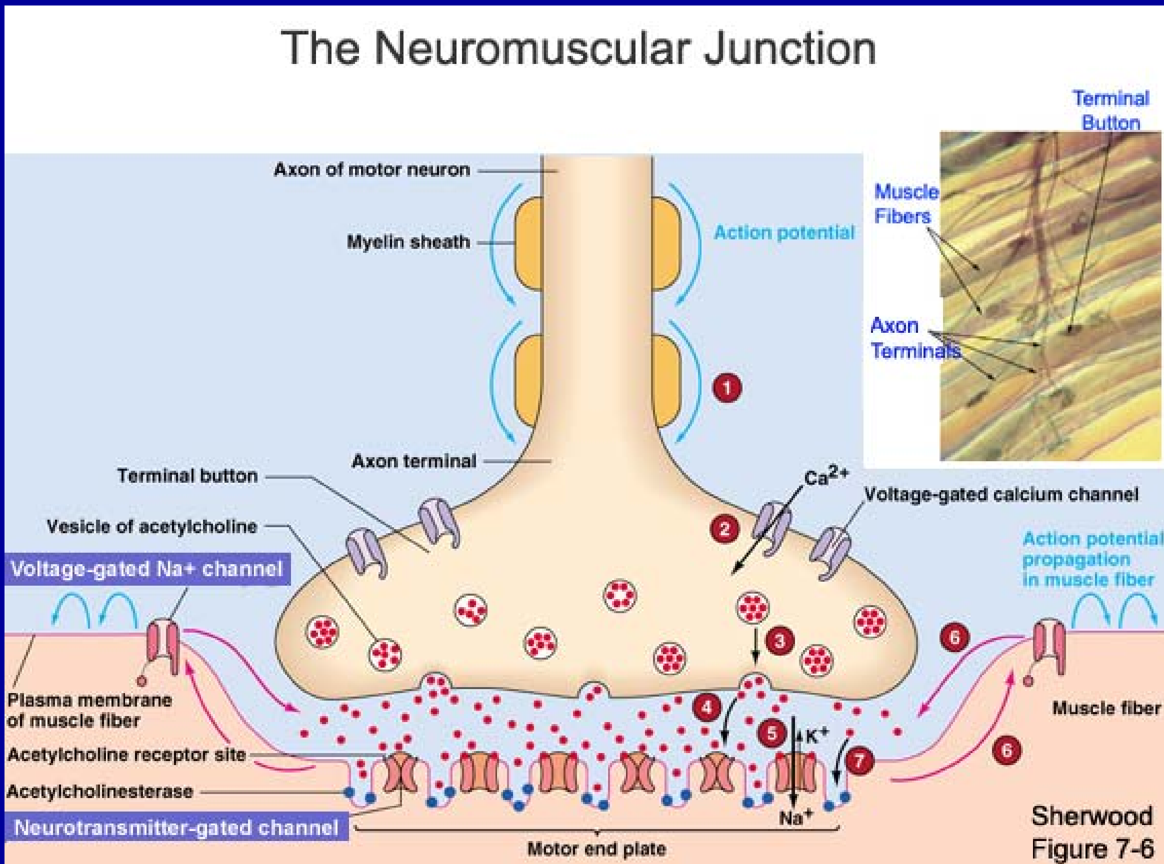
Action Potential (intracellular)

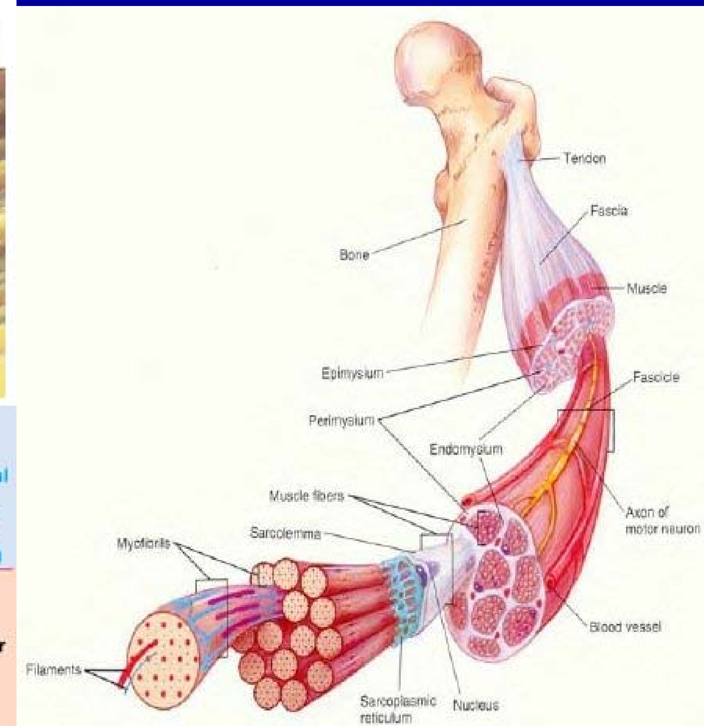
1st derivative

2nd derivative



Muscle Stimulation - Contraction and Expansion

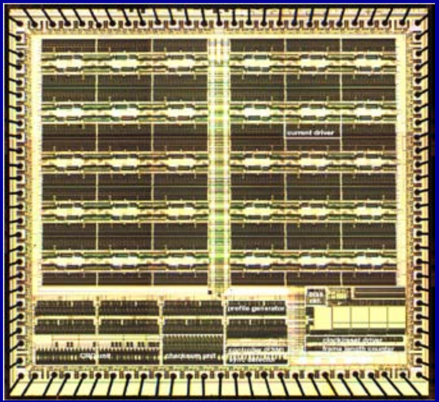


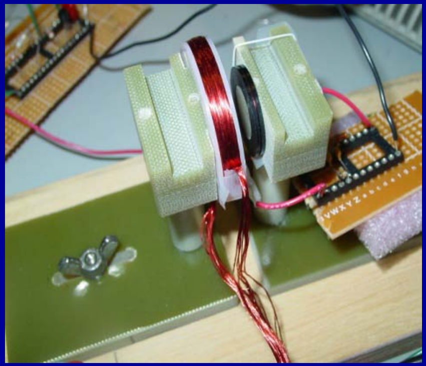


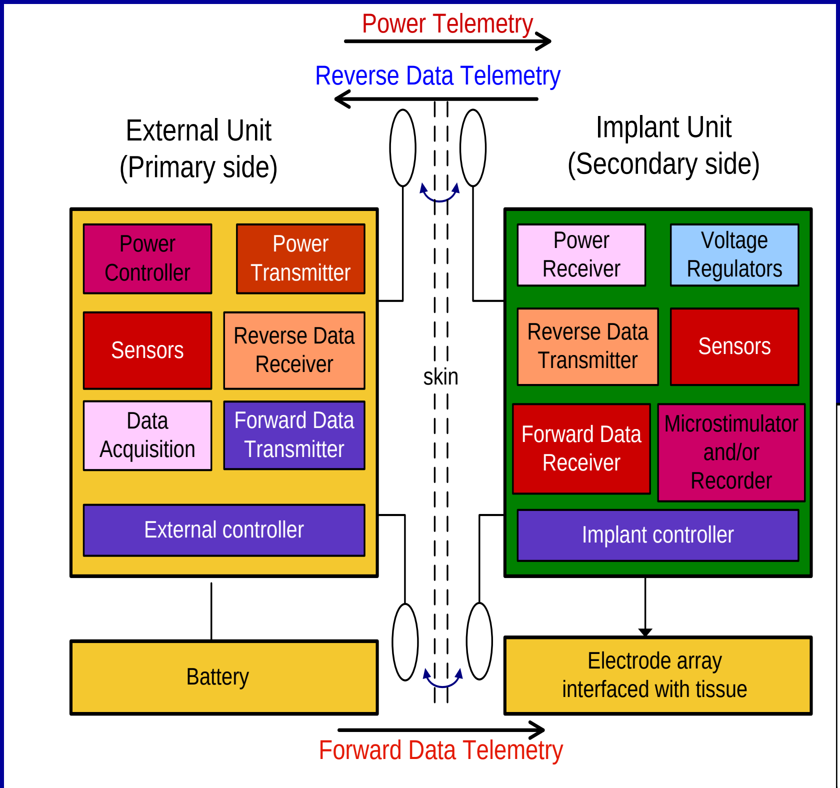
- Action potential propagates to the end plates at the buttons
- The action potential then propagates along the muscle fibers

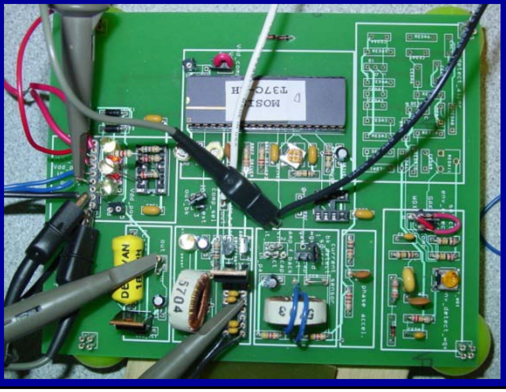
Generic Neural Interface Electronics

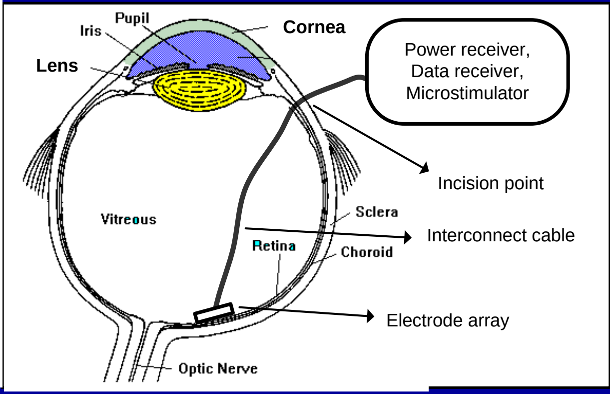
- Two major functions are ***recording*** and ***stimulation***
  - Integrated/Miniaturized Low Power Stimulator/Recorder
  - High Energy Efficiency Wireless Power Transmission
  - Wireless Bi-directional Communication
  - Closed-loop system



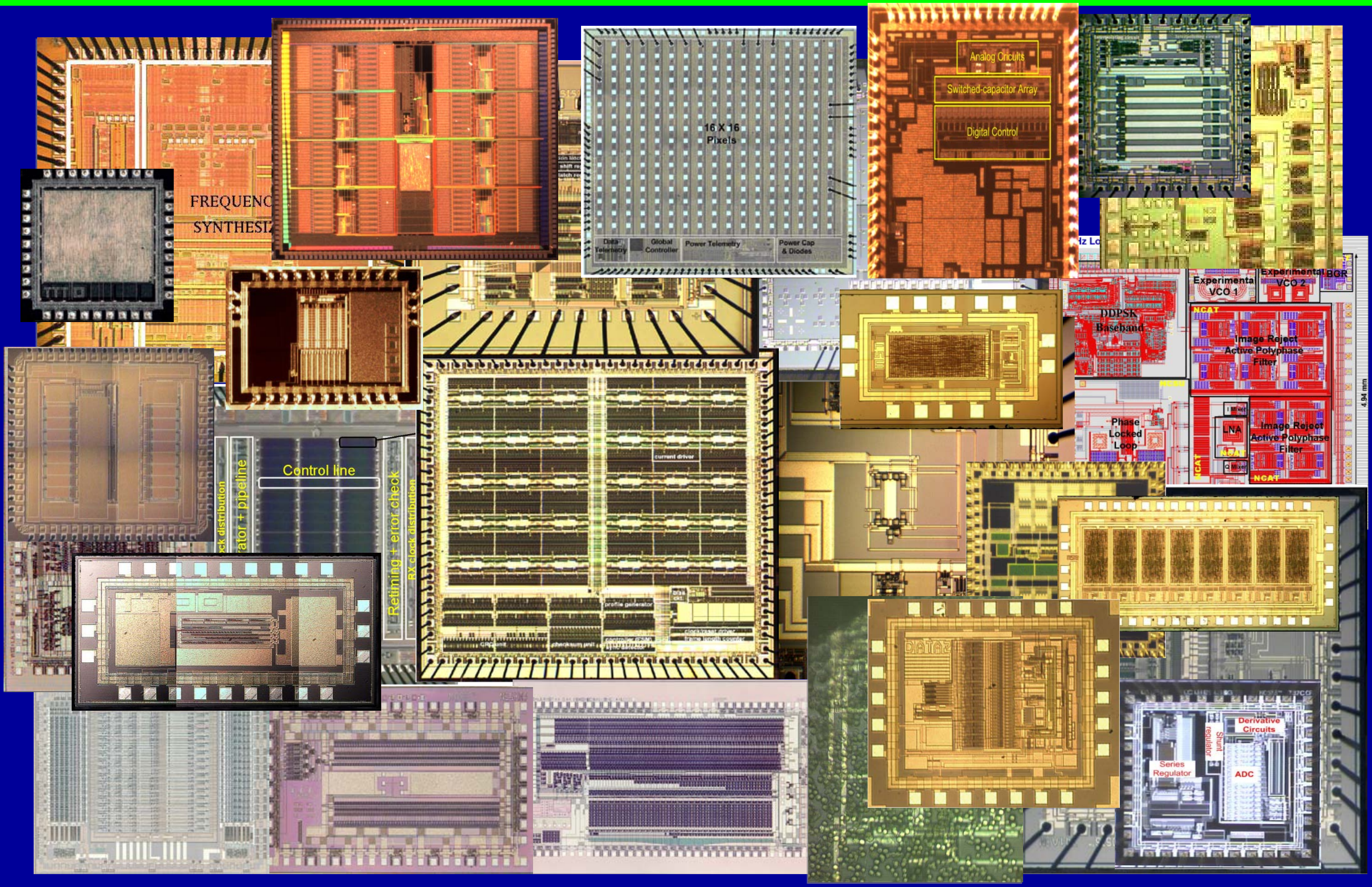




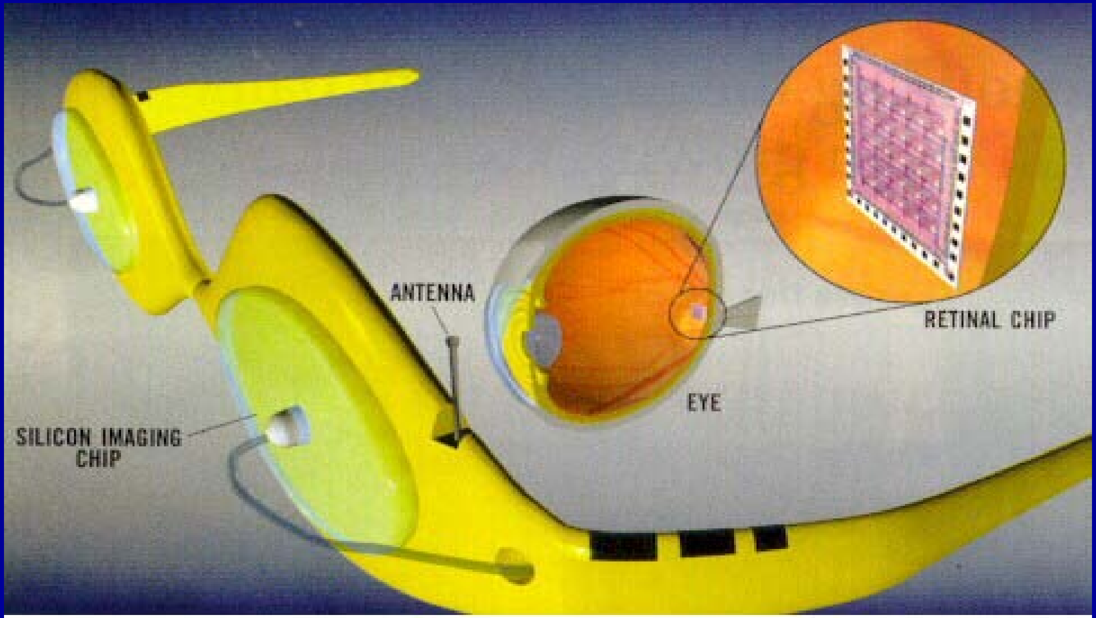




Professor Wentai Liu Group's Chip Gallery

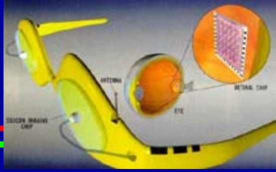


Intraocular Retinal Prosthesis



Retinal Prosthesis Project

Retinal Prosthesis



➢ To Bring Back Sight for the Blind with Retina Disease

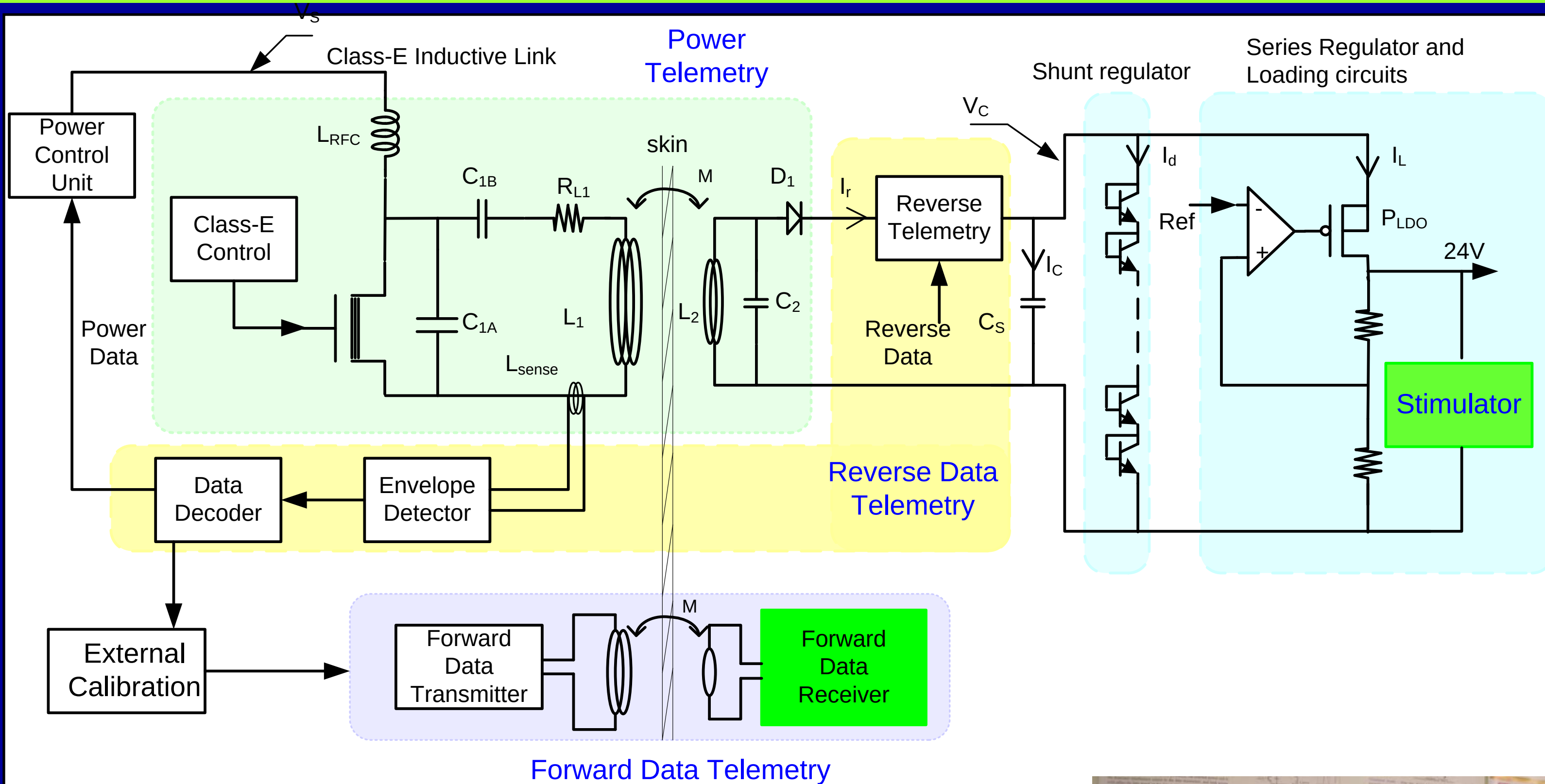
- **Stem cell approach**
- **Gene therapy approach**
- **Growth factor approach**
- **Transplantation approach**
- **Micro/nano-electronics approach - Prosthesis**

- **Retinitis Pigmentosa (RP - genetic) - 1 in 4000 incidence and 200,000 in USA, 12 millions worldwide**
- **Age-related Macular Degeneration (AMD) – 6 millions of Americans (dried AMD)**

Retinal Prosthesis -
A Neural Implant to Restore Vision

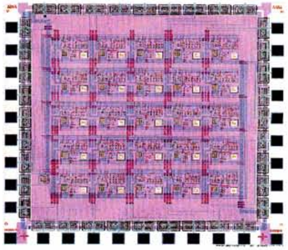
- Restore useful vision to the blind using microelectronics
  - First, restore vision that will enable unaided mobility for the totally blind
  - Second, restore reading and face recognition to the functionally/legally blind
- Project initiated in 1988 by Dr. Mark Humayun (medicine) and Dr. Wentai Liu (engineering)
- Now a multi-disciplinary multi-institutional project with over five million dollars annual funding and commercial company for product manufacturing

Dual Band Power and Data Telemetry

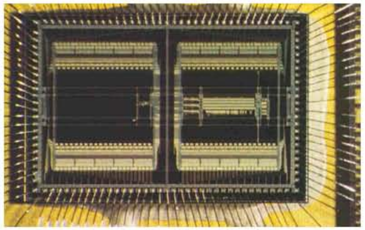


- Dual Band Telemetry
- Power Carrier: 2 MHz
- Data Carrier: 22 MHz
- Hybrid Telemetry Link achieves **both**
  - High Power Transmission Efficiency
  - High Forward Data Rate

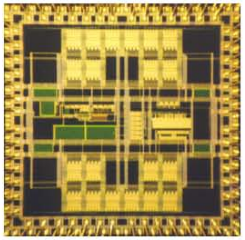
The Long Rich History…. (1991 – 2008)



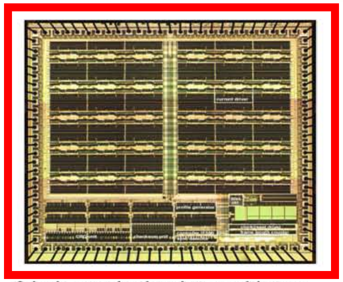
5x5 photo sensor and signal driver



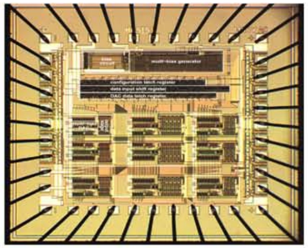
1:5 multiplexing, 4bit resolution 100 channel output stimulator using single current mirror for each channel



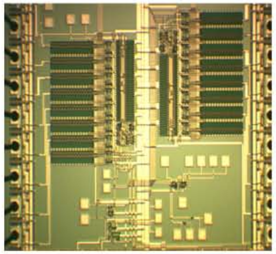
ASK demodulator with hysteresis for reliable data recovery. Achieving data rates of up to 250kb/s



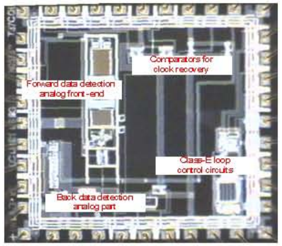
64 channel stimulator with two independent DACs per each channel creating independent anodic and cathodic pulses (A-60 core)



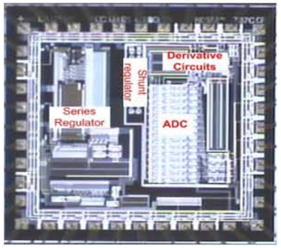
Advanced stimulator with multi bias DAC technique reducing 8-bit DAC area to 52% allowing more spatial resolution



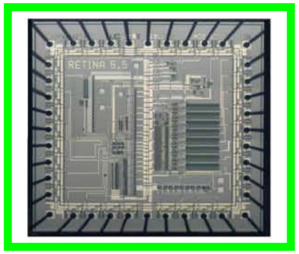
1:8 demux driver with variable gain and current limiting charge cancellation



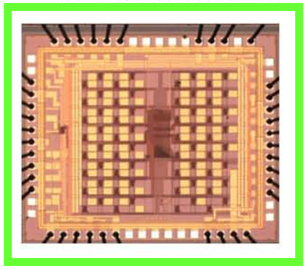
Wireless power transmitter circuits and reverse data demodulator



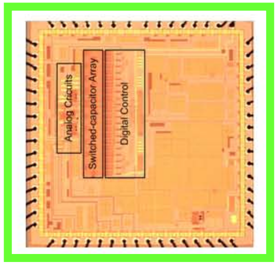
Wireless power regulation and reverse data transmitter



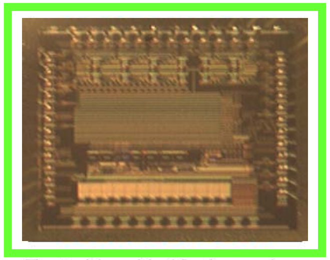
8-channel driver with 6-bit DAC with variable full scale and current limiting charge cancellation



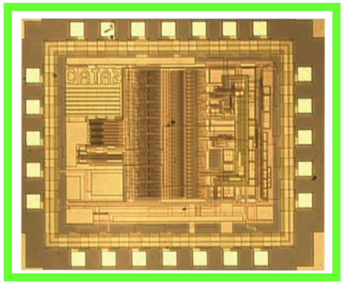
64-channel driver with 4-bit DAC with variable full scale in 5V sub-micron CMOS



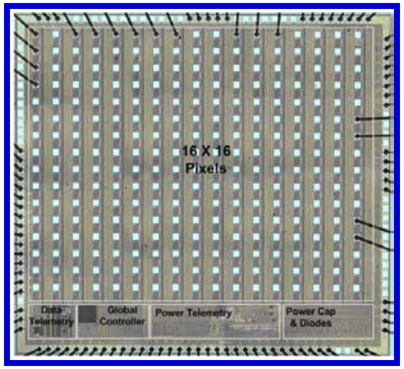
1 Mbps dual band telemetry data demodulator in 5V sub-micron CMOS



Test chip with 12-channel stimulator, CUP output pad, regulator in 32V deep sub-micron CMOS

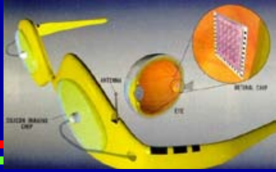


2 Mbps fully integrated dual band telemetry data demodulator in 5V sub-micron CMOS



High voltage deep sub-micron CMOS process for the first time to meet the stimulation requirements of 1000+ channels

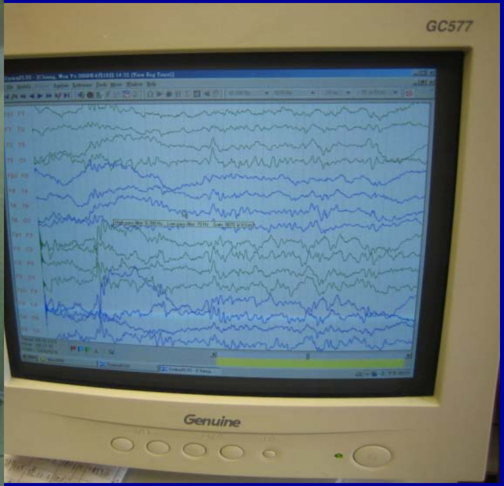
Retinal Prosthesis



First in Sight (Reading)

(First Chronic Implant in Feb. 2002)

Epilepsy Implant –
Prediction, Detection, and Intervention



Collaborators:

- Yu-Lung Hsin (MD), Tsu-Chi Medical Center, Taiwan
- Biomimetic System Research Center, Nat'l Chiao-Tung University, Taiwan

WHO - Statistics of Epilepsy

- Epilepsy is one of the most common neurological disorder and has no age, racial, social, sexual or geographical boundaries

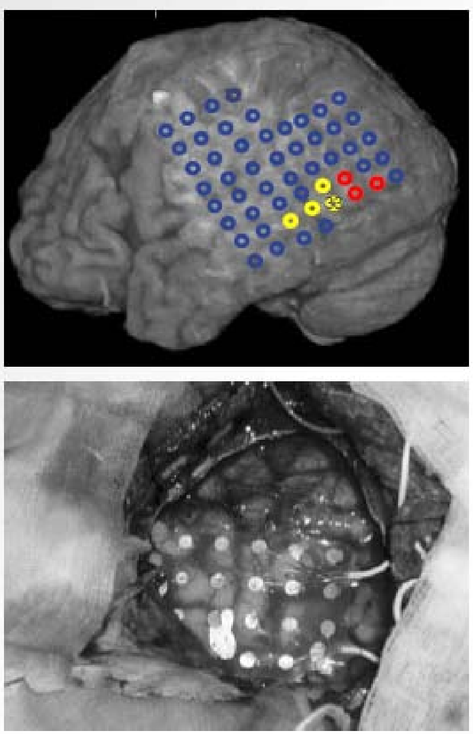
- Up to 5% of people in the world may have at least one seizure in their lives

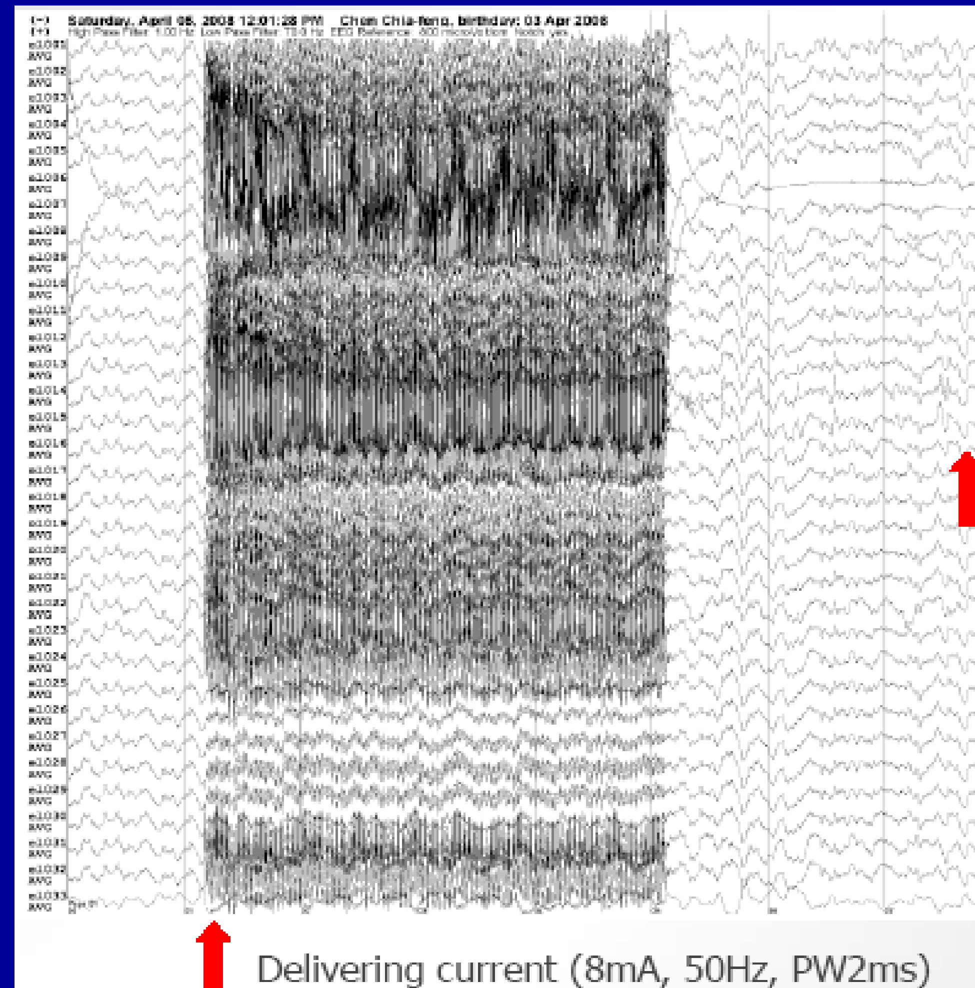
- At any one point in time, 50 million people have epilepsy, especially in childhood, adolescence and old age

- Epilepsy can have profound social, physical and psychological consequences

http://www.who.int/mediacentre/factsheets/fs165/en/

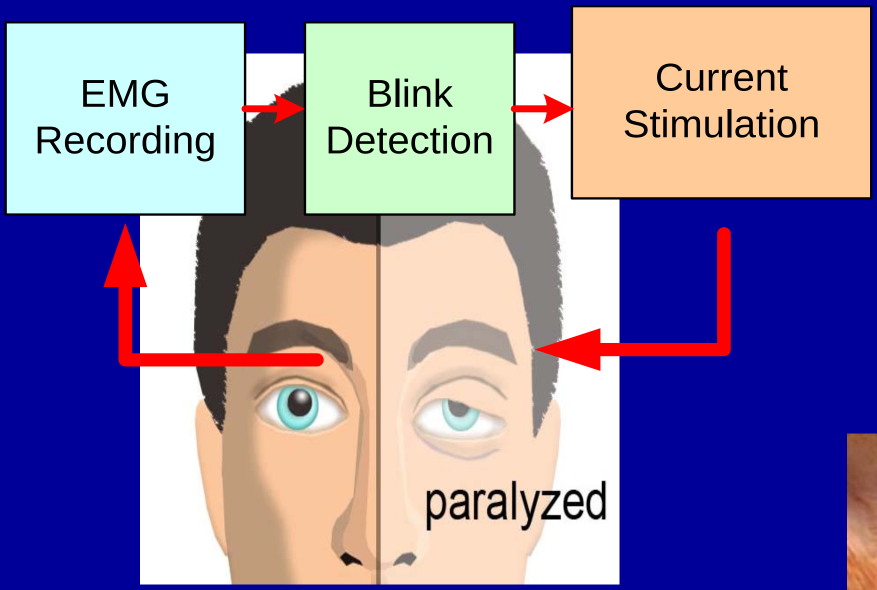
Biomimetic System for Epilepsy

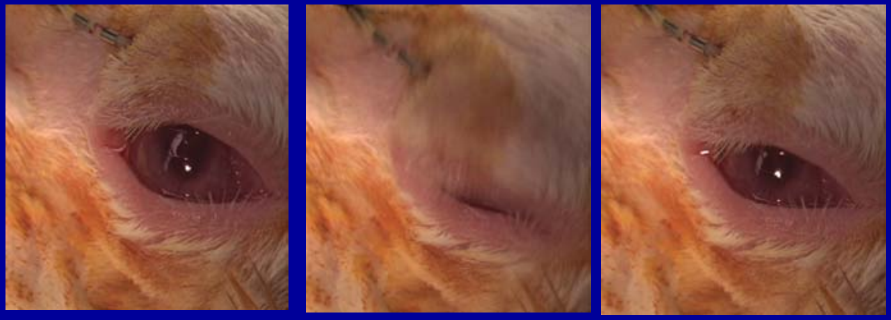




Collaborated with Tsu Chi Medical Center (Hualien, Taiwan)

Eyelid Reanimation: A Hybrid Muscle Implantable System





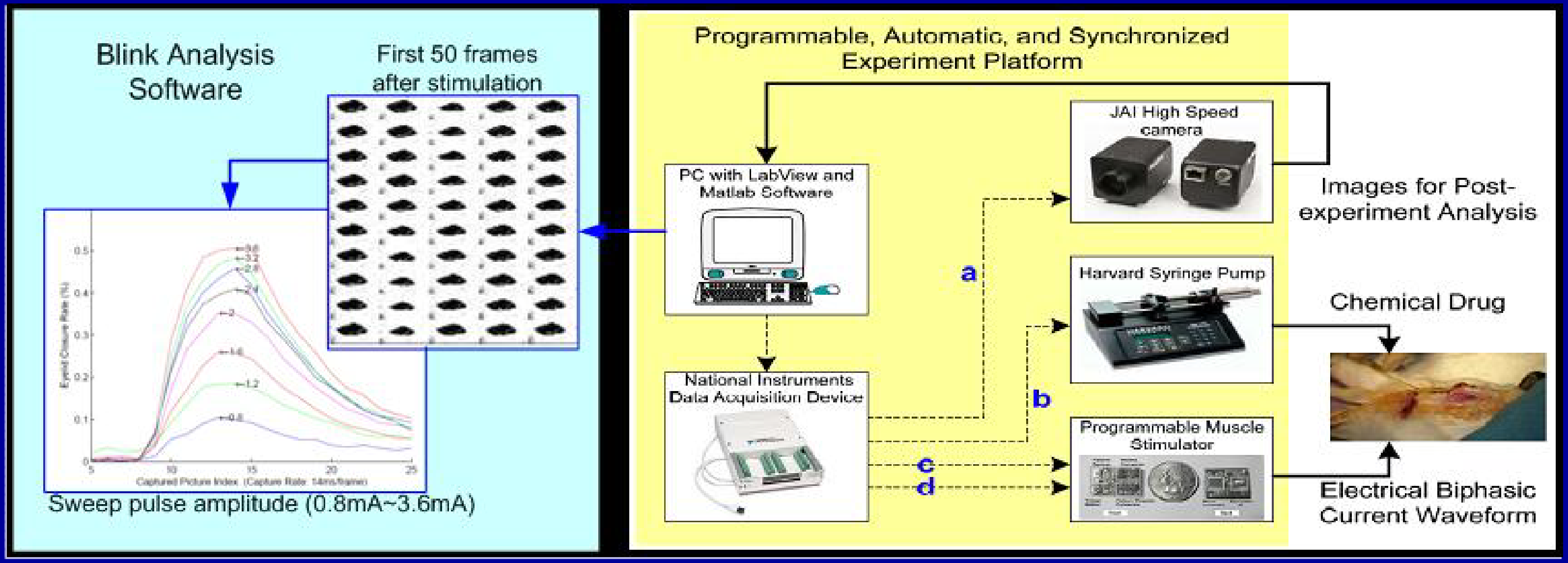
Collaborators:

- Kim Cocheram (MD), VA Palo Alto
- Juan Sandiego, Stanford University

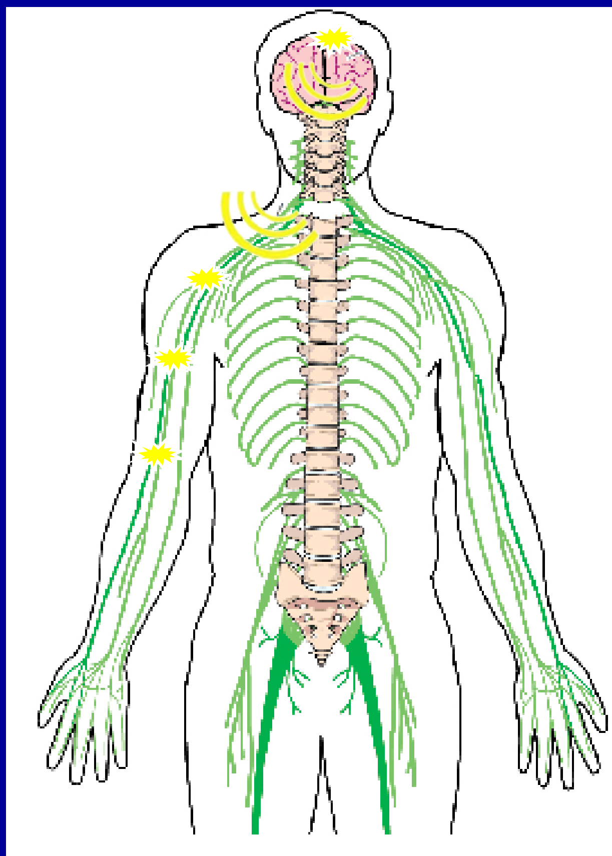
Electrochemical Stimulation Experiment

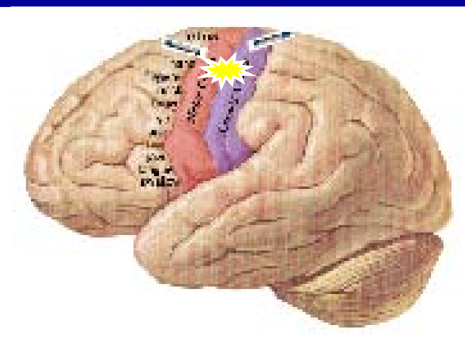
Automatic experimental environment is developed

- All experimental equipments are controlled by PC in a pre-programmed sequence
  - A National Instrument device is used as interface among PC and all equipments
  - A high speed camera is used to capture eyelid closure at 200 frame/sec
- Advantages:
  - All experiment equipments are synchronized, so the eyelid response time can be precisely measured
  - Reduce error introduced from human intervention
  - Highly improve experiment efficiency



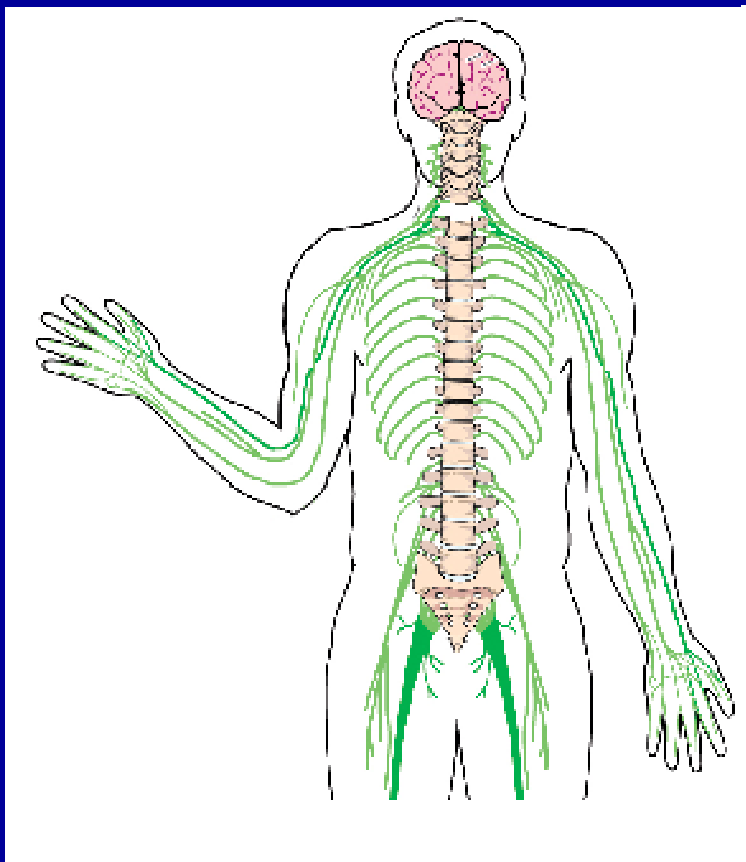
Prosthesis for Spinal Cord Injury

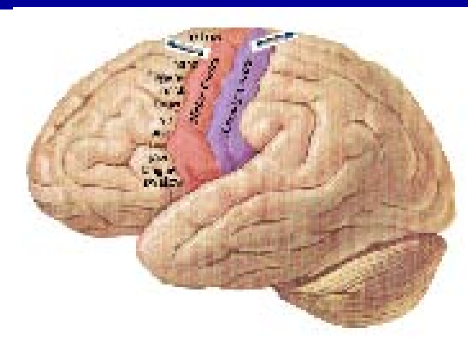




Lower Limb Control
Bladder/Vowel control

Prosthesis for Spinal Cord Injury

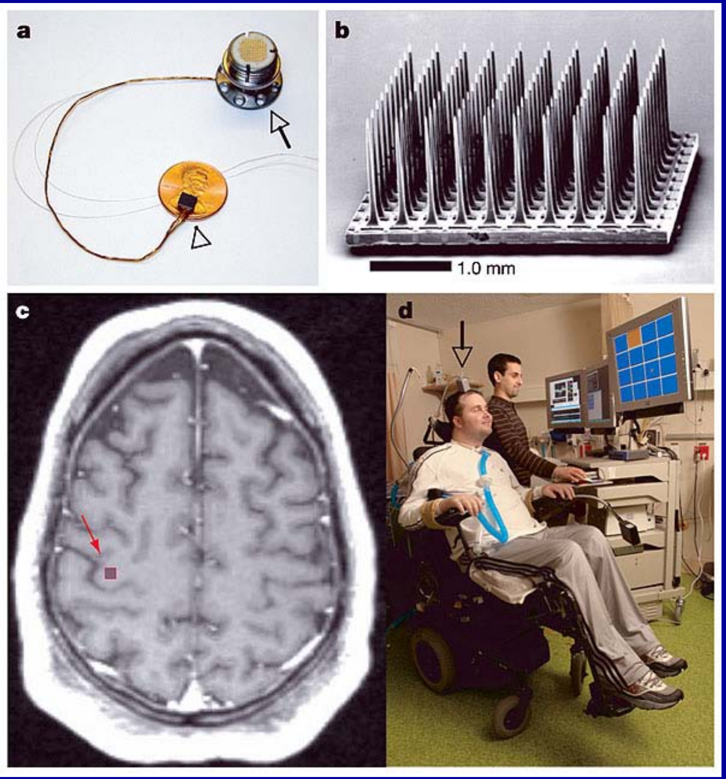


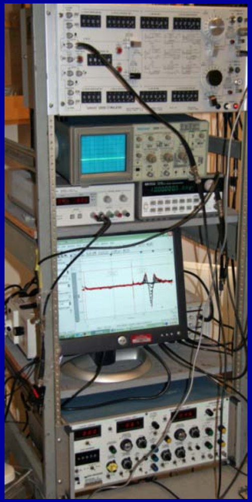


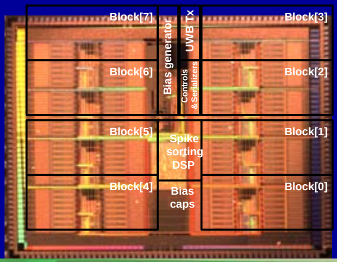
Lower Limb Control
Bladder/Vowel control

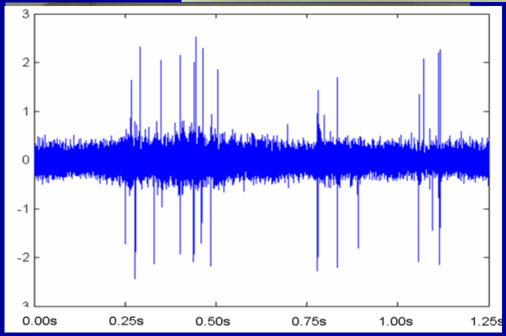
SCI: Brain Signal Recording and Processing

➢ **Wireless neural recording technology to sense signals from the brain**







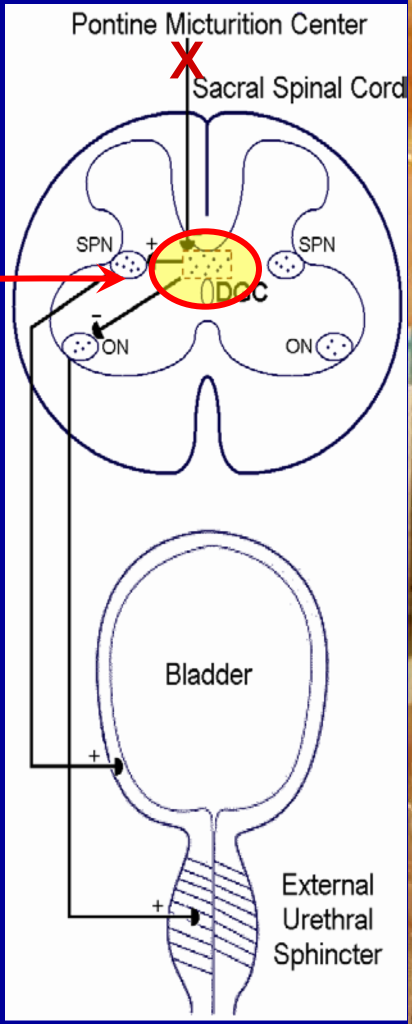


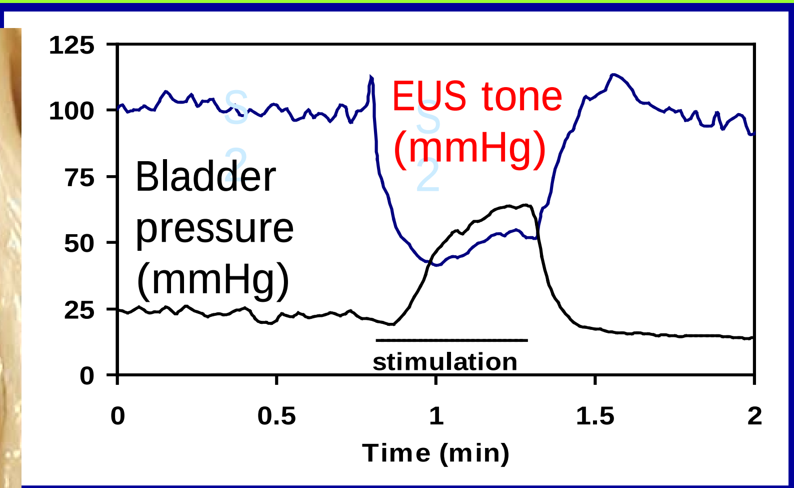
Restoring functions in patients with spinal cord injury, and other neural disorders
(arguably the biggest challenge in field of neural prosthesis)

Enable sophisticated experiments in free running animals in natural environment <u>without wires and boxes</u>
(current systems limit animal movement and number of channels)

SCI: Bladder Control

Signal from brain do not reach spinal cord after injury



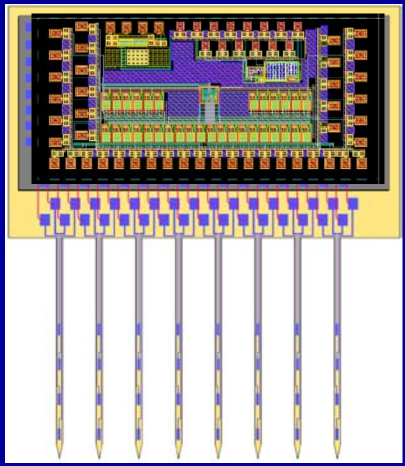


Intraspinal Microstimulation (ISMS) selectively stimulates spinal neurons for bladder control and voiding

Pikov et al., Journal of Neural Engineering, 2007

Technology needed:

- Penetrating microelectrodes
- High density stimulator

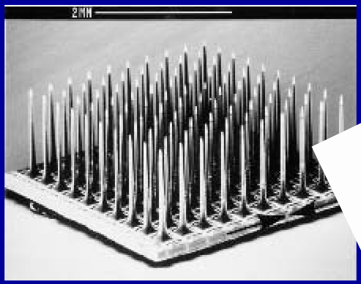


Collaboration with V. Pikov, D. McCreery
Huntington Medical Research Institutes

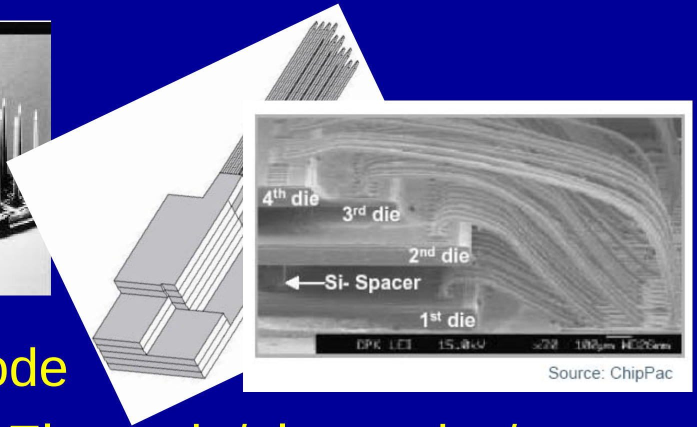
Brain-Machine Interface:

Shark Head Implant

Enabling Technology

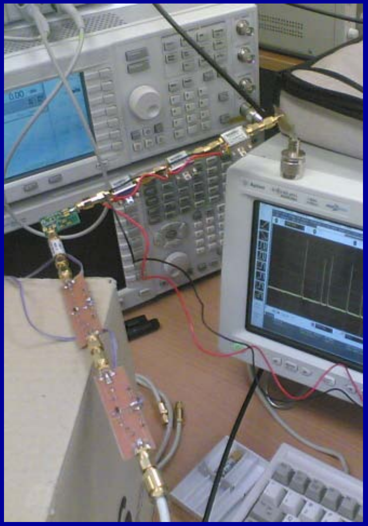


Smart Electrode

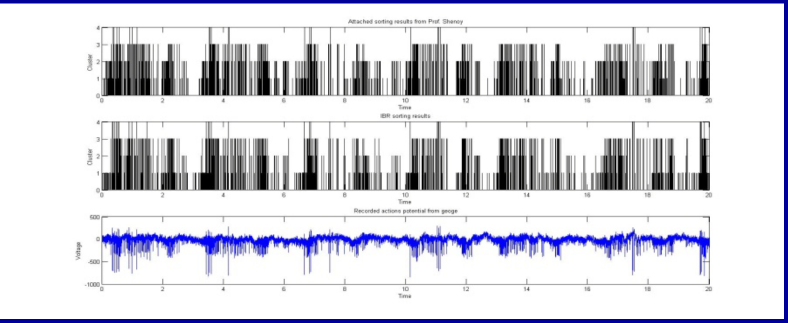


Electrode/electronics/sensor

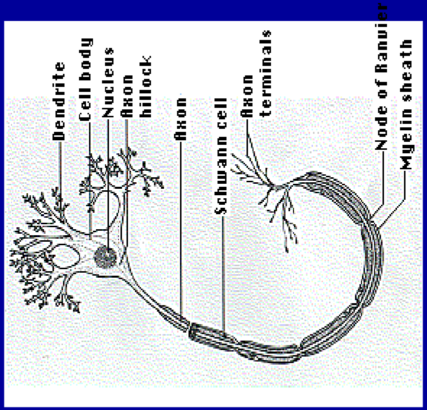
Packaging



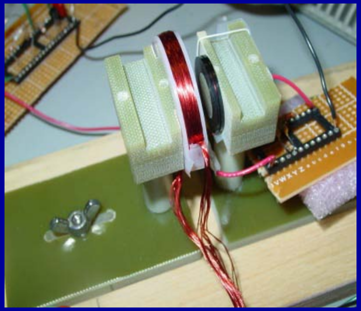
Wireless technology



Signal processing



Abiotic interface

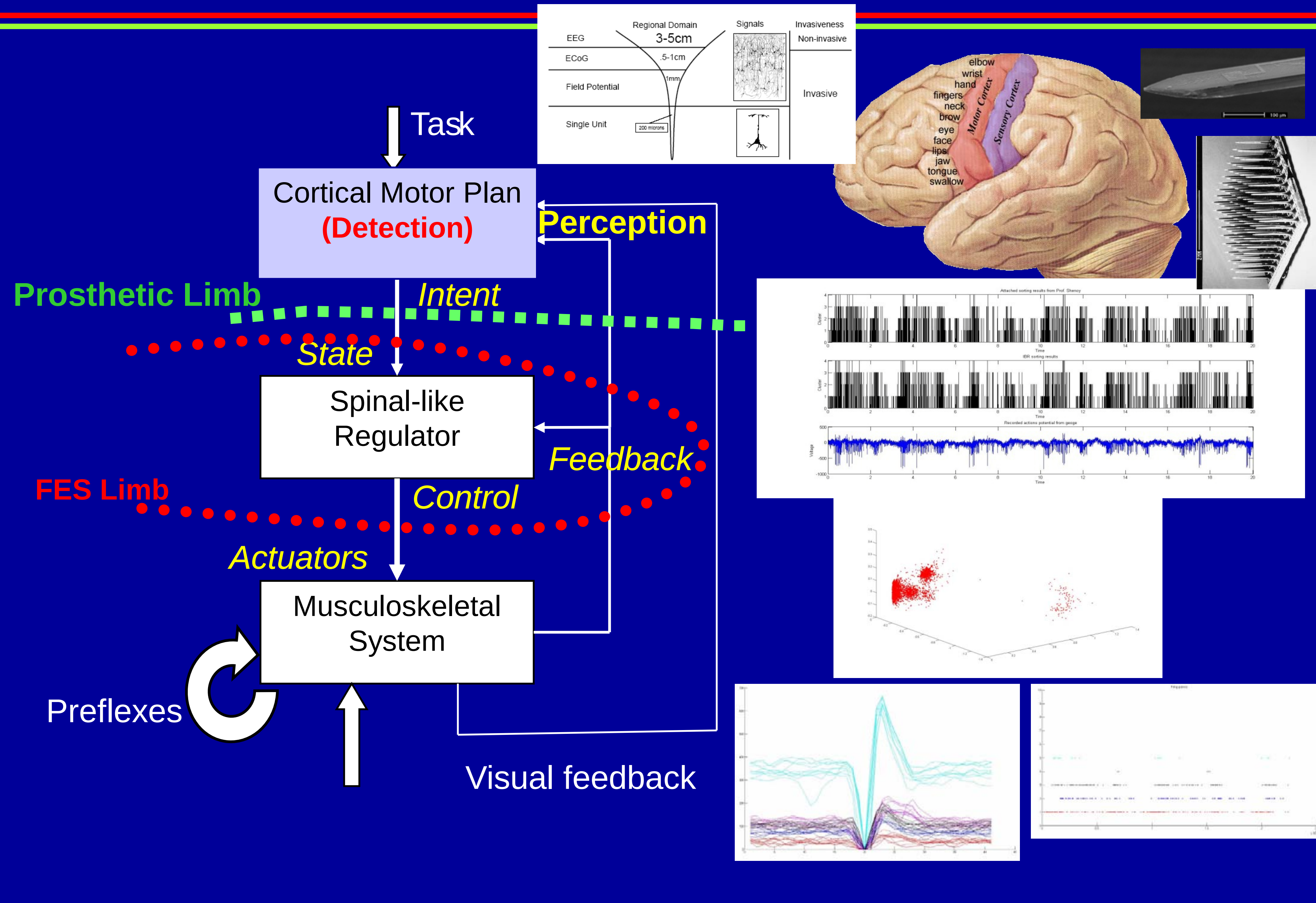


Power source

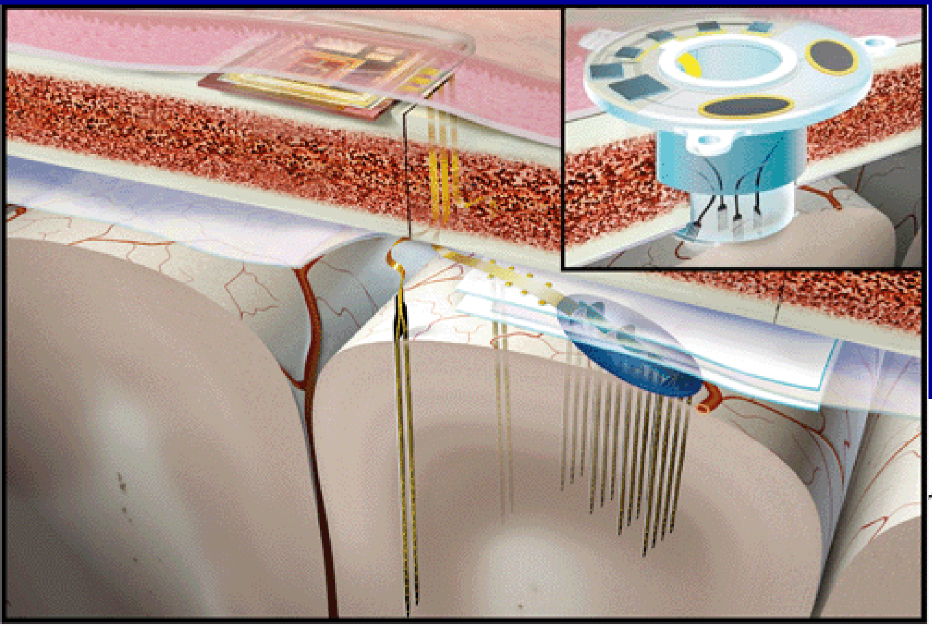
Enabling Technology

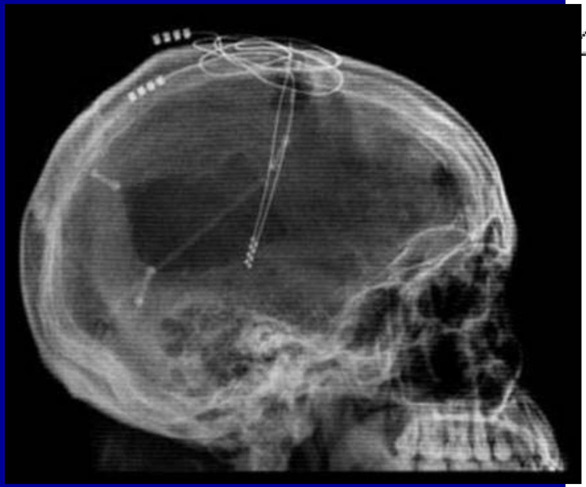
- **Miniaturization and Integration (wishful list, but some have already happened)**
  - **Smart 3D electrode with navigation and self-tune**
  - **Better Packaging**
  - **Better power source**
  - **Hybrid sensor – electrical/biochemical/optical**
  - **Sophisticated signal processing**
  - **Closed loop hybrid system**
  - **Access of a single cell in-vitro and in-vivo**
  - **Magnetic stimulation**
  - **BioSpice project**

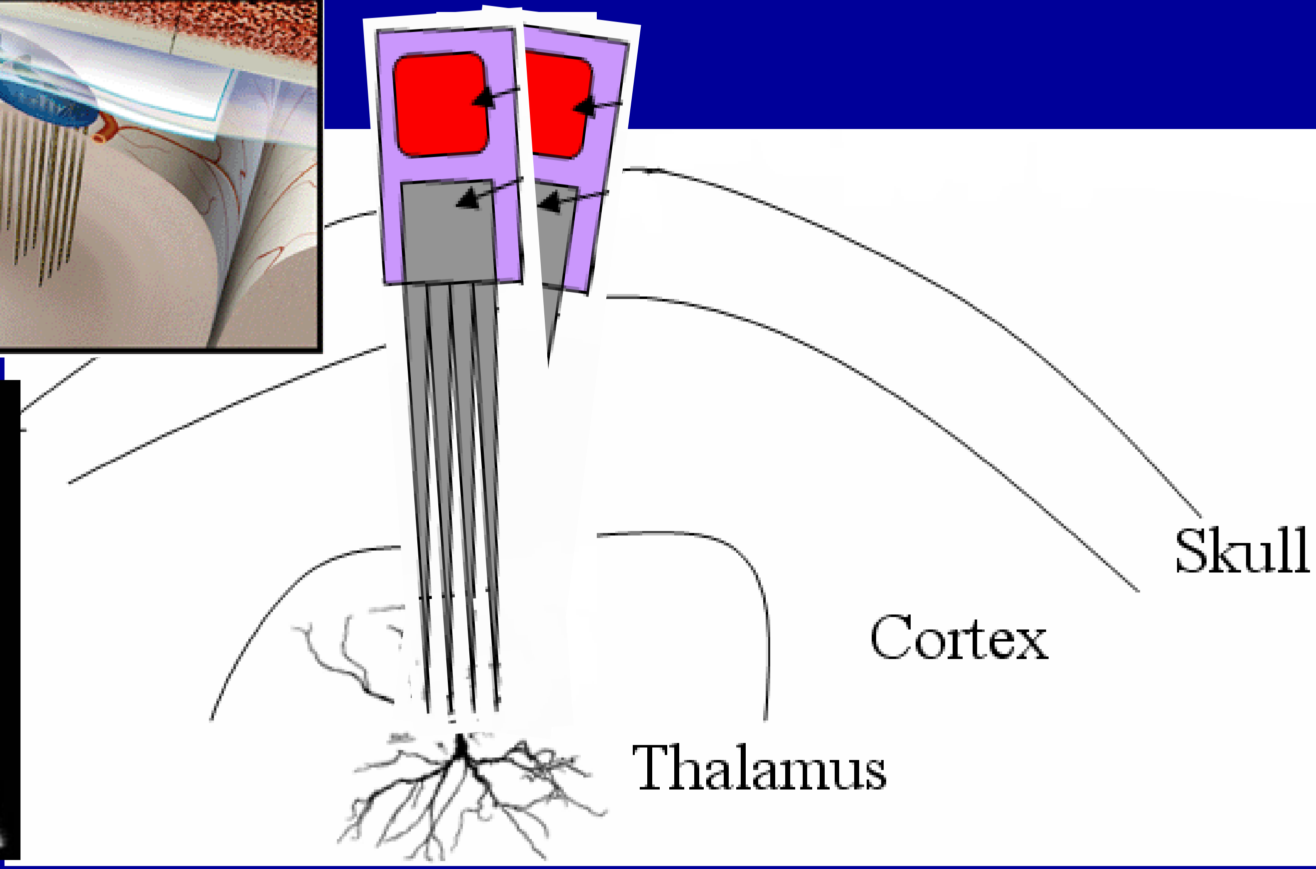
Closed Loop System: (Brain Controlled Limb)



Electrode: Self-Navigation (Fine GPS)





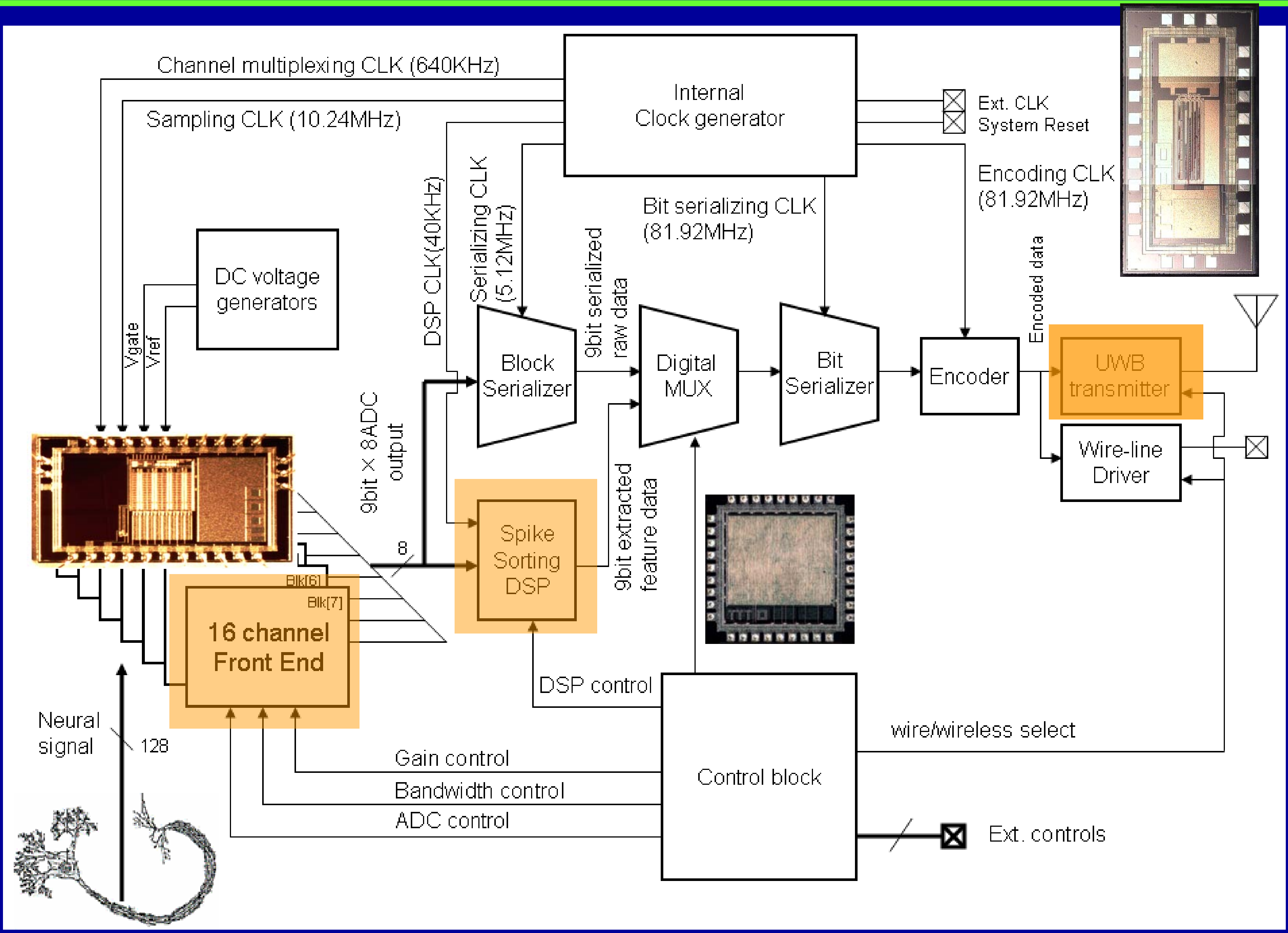


Enabling Technology – Wireless Recording

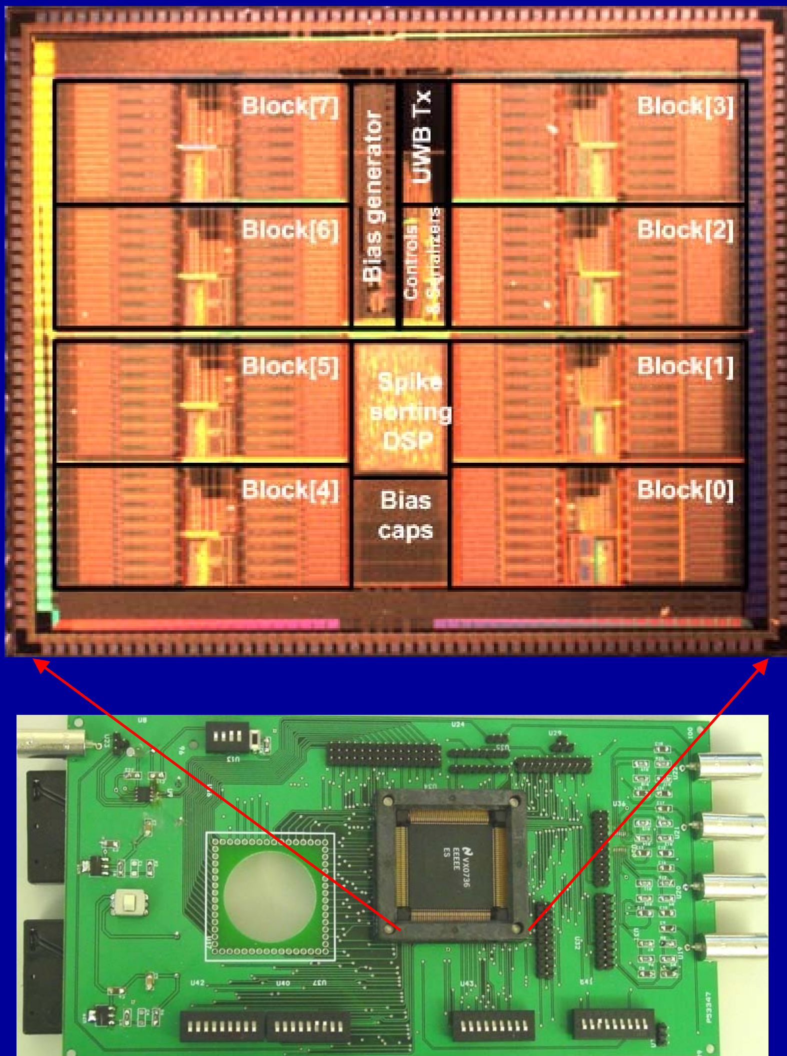
- Develop an effective and efficient neural recording/stimulation system
  - Real time (throughput and latency)
  - Robust Detection and Classification (noise and movement)
  - Wireless Telemetry (power and data)
  - Miniaturized Integrated Circuits (power and size)

- Enable complex experiments and study of new cognitive phenomena through sophisticated tools with advanced capabilities beyond existing recording systems
  - Unrestrained Behaving Animals in Natural Environment
  - Multiple Channels ranging from 10's to 100's
  - Miniaturized Wearable or Implantable Device

Chip Architecture (NEUREC4.0)



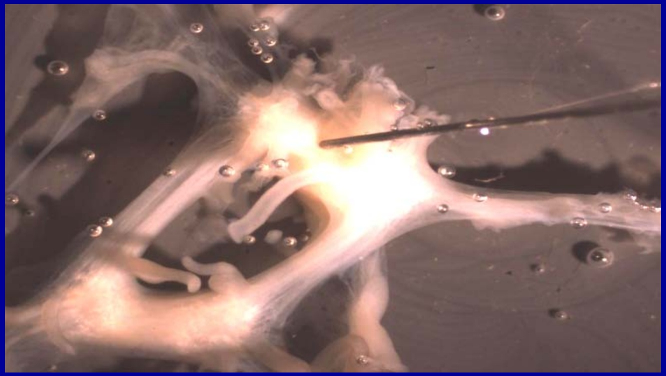
Chip Specs

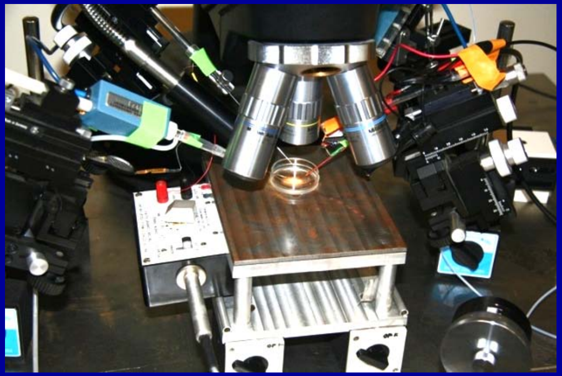


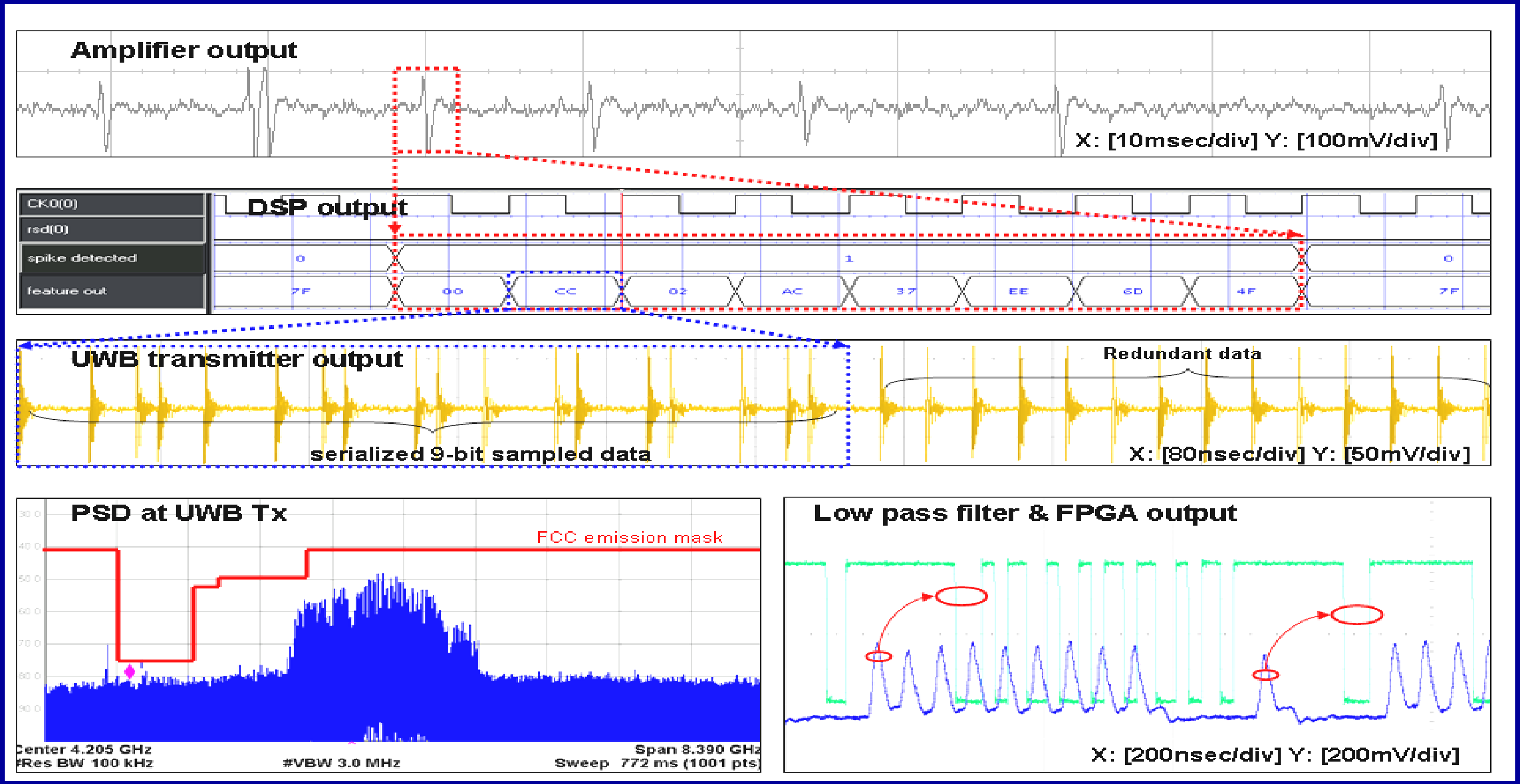
Measured performance	
Number of channels	128
Signal gain of the preamp	40dB
Input impedance (at 1KHz)	8MΩ
Input referred noise	$4.9\mu V_{rms}$
CMRR of the preamp	90dB
PSRR of the preamp	80dB
LF roll- off of the preamp	0.1Hz ~ 200Hz *
HF roll- off of the preamp	2KHz ~ 20KHz *
Signal gain of the 2^{nd} amp	17dB ~ 20dB *
ADC resolution	6 ~ 9 bits *
ADC sampling rate	640Ksample/sec
Power dissipated by DSP	0.1mW
Maximum UWB data rate	150Mbps
Power dissipated by UWB	1.6mW
Power supply level	± 1.65V
Total chip power dissipation	6.0mW
Technology	0.35 μm 4M2P CMOS
Total chip area	8.8mm× 7.2mm

* specification is programmable through external controls

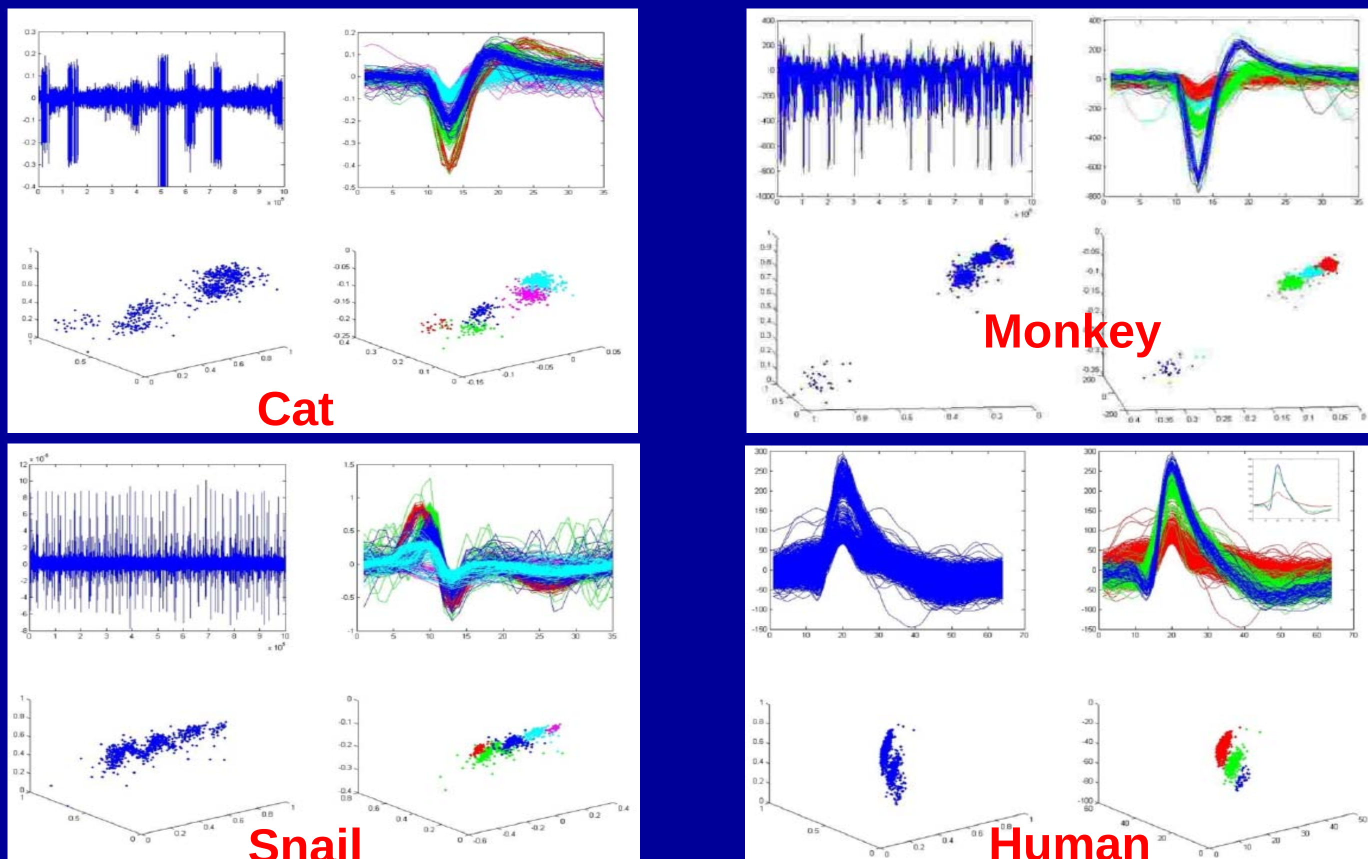
Ex-Vivo Experiments





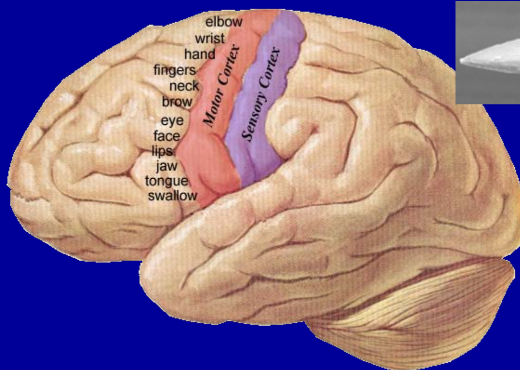


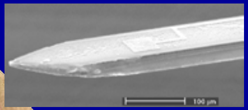
Sophisticated Signal Processing: Spike Sorting

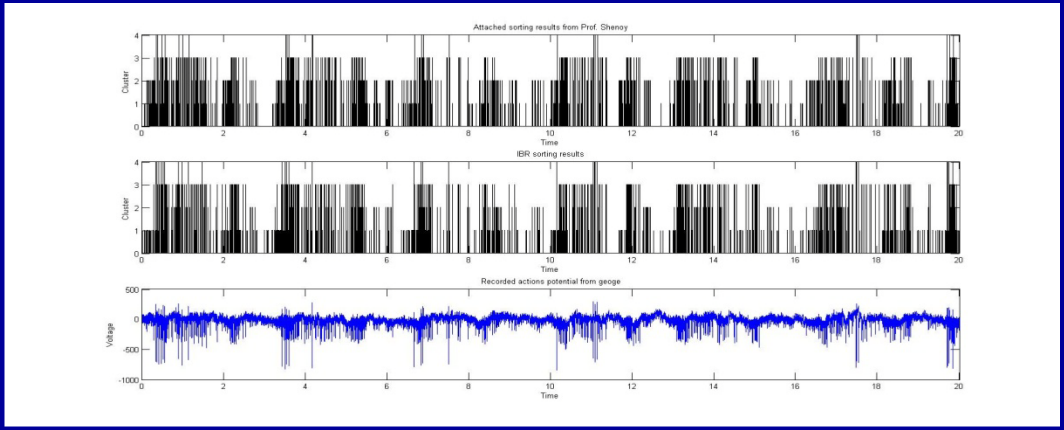


Spike Sorting: Detection and Classification

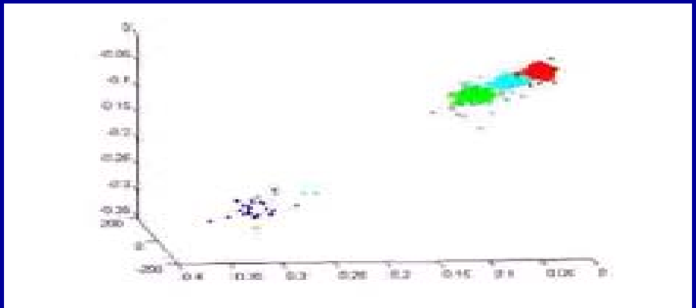
- In neural recording, an electrode may be surrounded by multiple firing neurons, and it is necessary to resolve spikes into individual neuronal sources



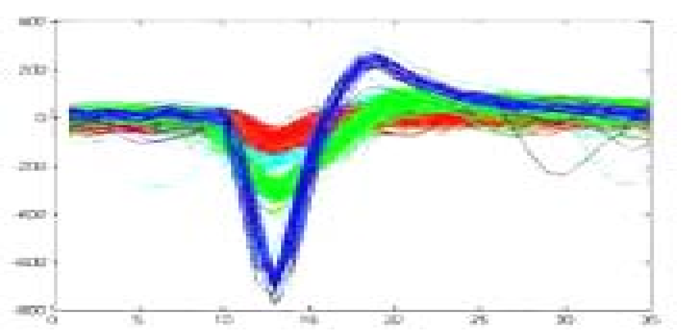




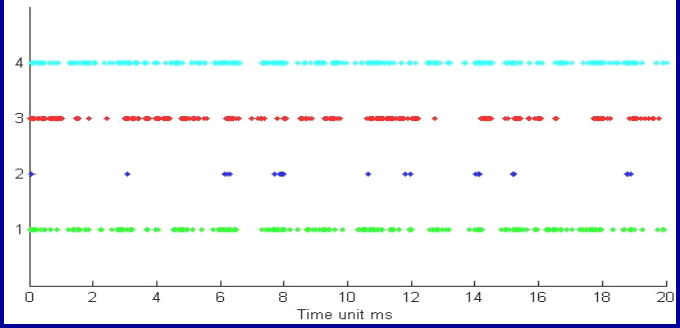
1. **Cortical Recording and Detection**



2. Spike Feature Extraction



3. Spike Classification



4. Spatial and Temporal Spike Trains

Feature Extraction Algorithm

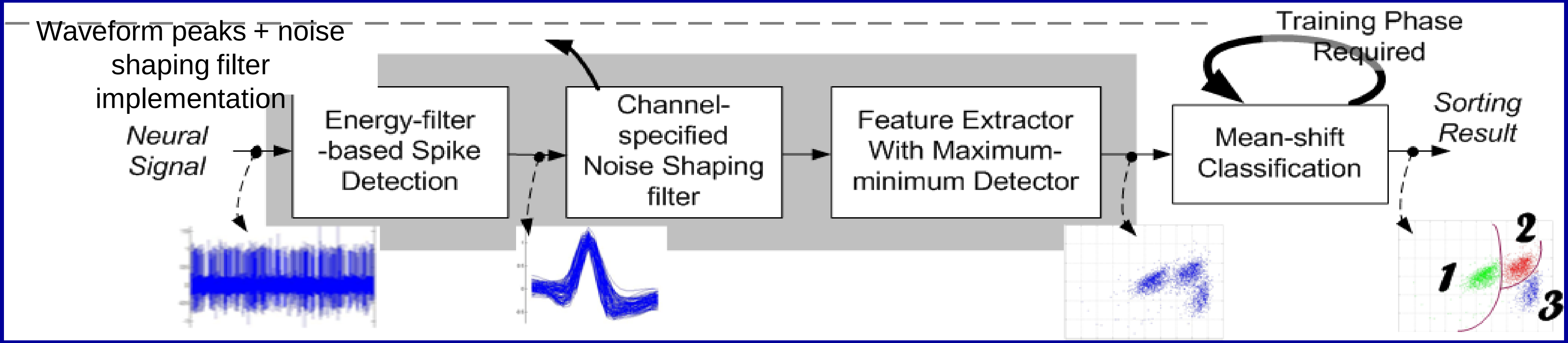
- Spike Height and Width - *Simon, 1965*
- Principal Components Analysis (PCA) - *Zumsteg ZS, 2005, Thakur, 2007*
- Wavelets - *Quian Quiroga, 2004*
- Template Matching - *Lewicki, 1994, Zhang, 2004*
- Independent Component Analysis (ICA) - *Sakurai, 2006*

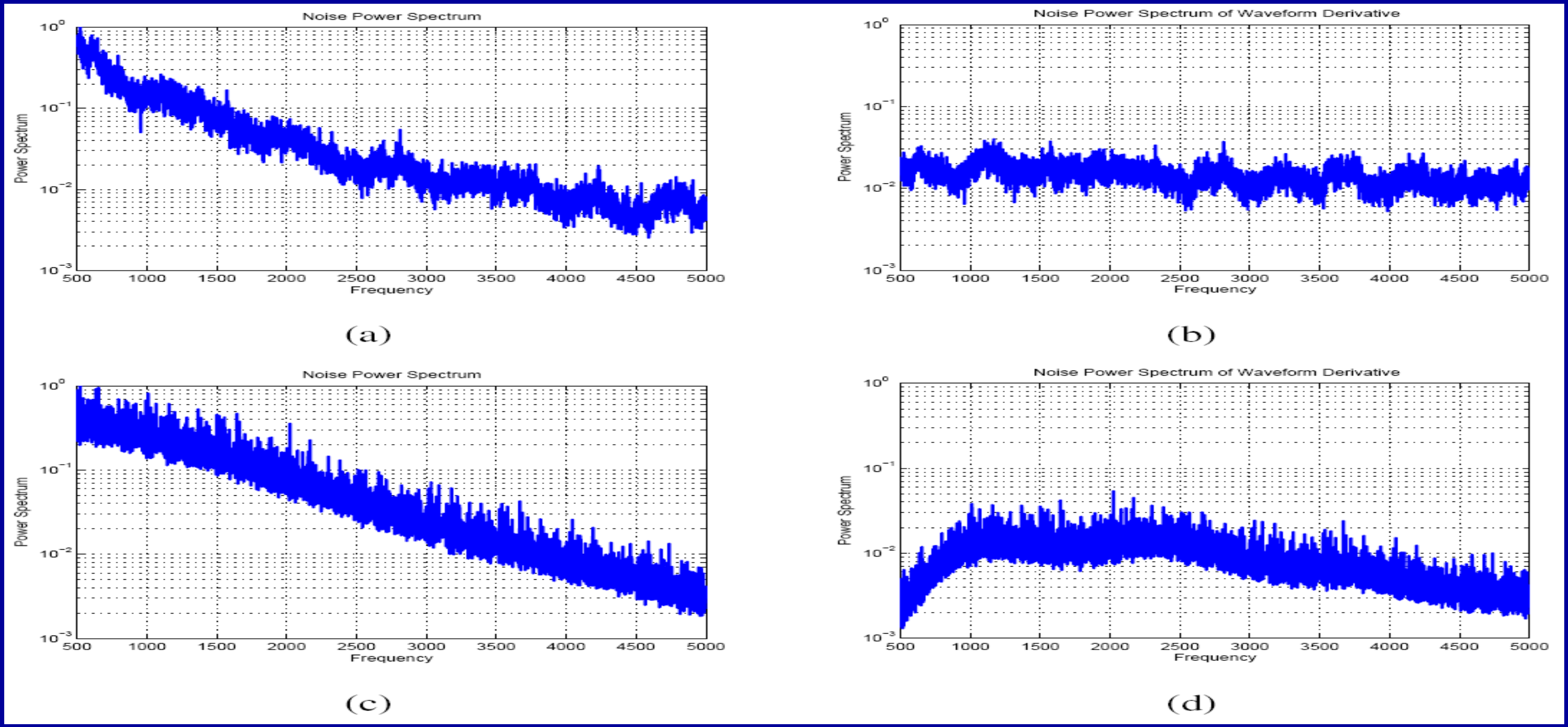
- Deficiency for spike sorting
  - Require long/frequent training for spike sorting
  - No on-chip implementation of classifier

➢ Looking for On-the-Flying or Minimal Training Sorting Algorithm which is possibly miniaturized

Derivative or Sample Selection based followed by Evolving Mean Shift (EMS) Classifier – Z.*Yang and W. Liu* 2008

Noise Spectrum Shaping using Derivative





Feature Extraction: Sample Selection

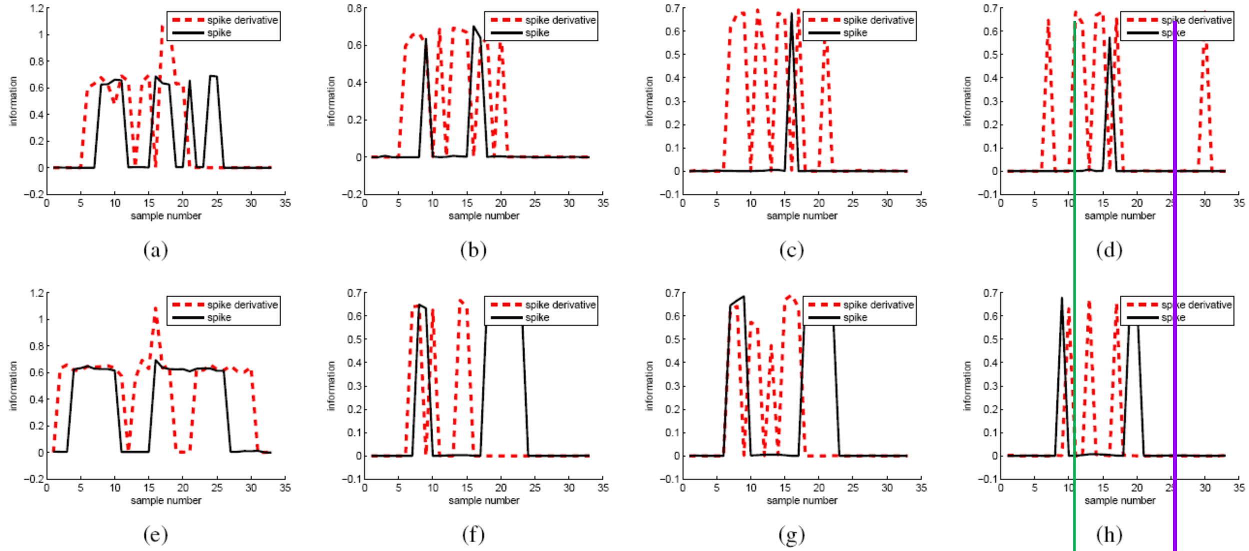
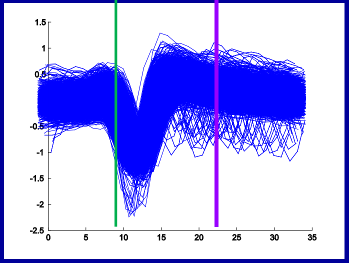


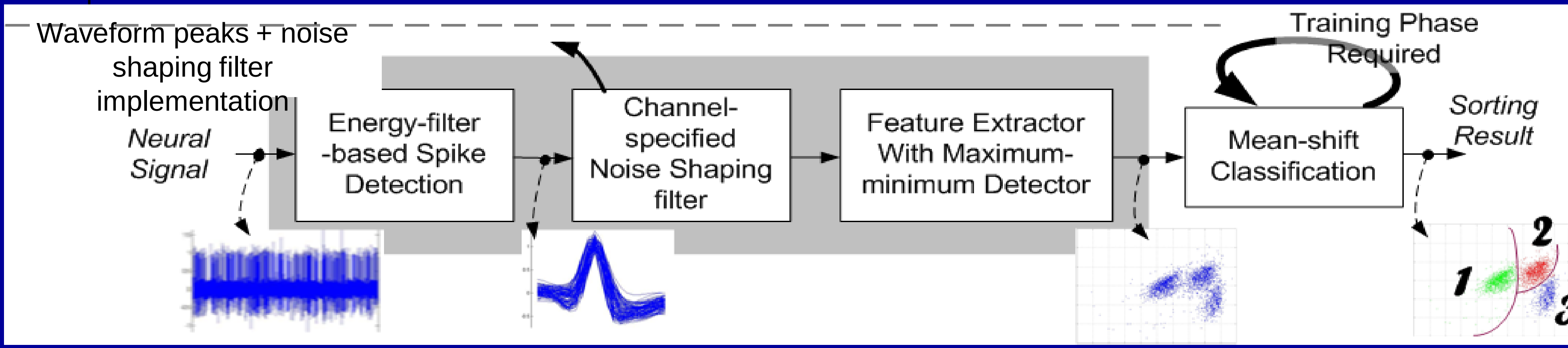
Fig. 3. (a) - (h) information carried by samples from spikes and their derivatives. X axis is the sample number and Y axis is the estimated entropy. The black solid line and red dotted line represent the sample information from spikes and their derivatives, respectively.

$$info_j = -\sum_{p_q > p_0} p_q ln(p_q)$$

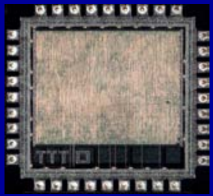


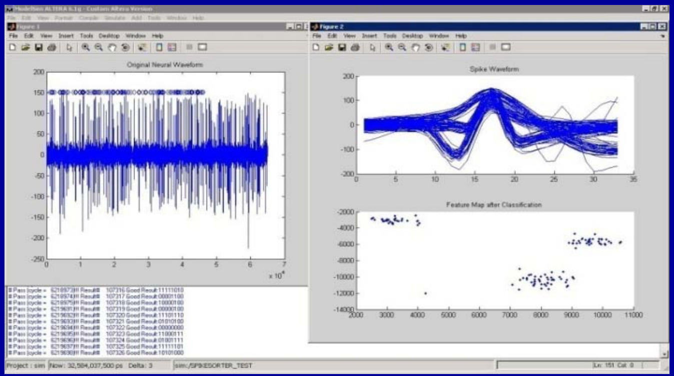
- Different sample point contain different amount of information

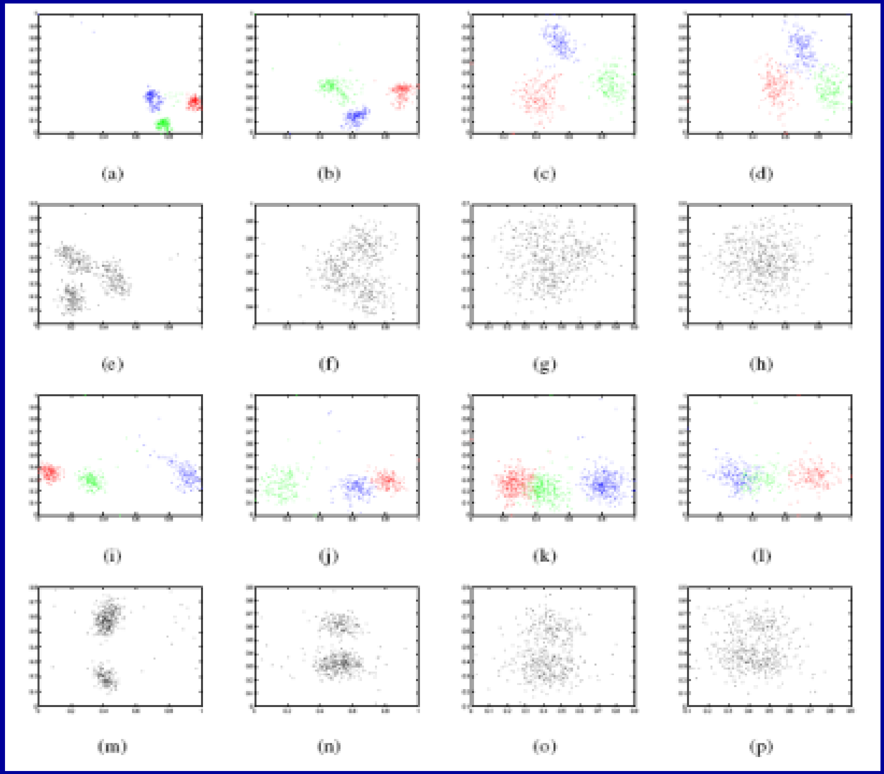
Prototype with Customized Sorting Chip



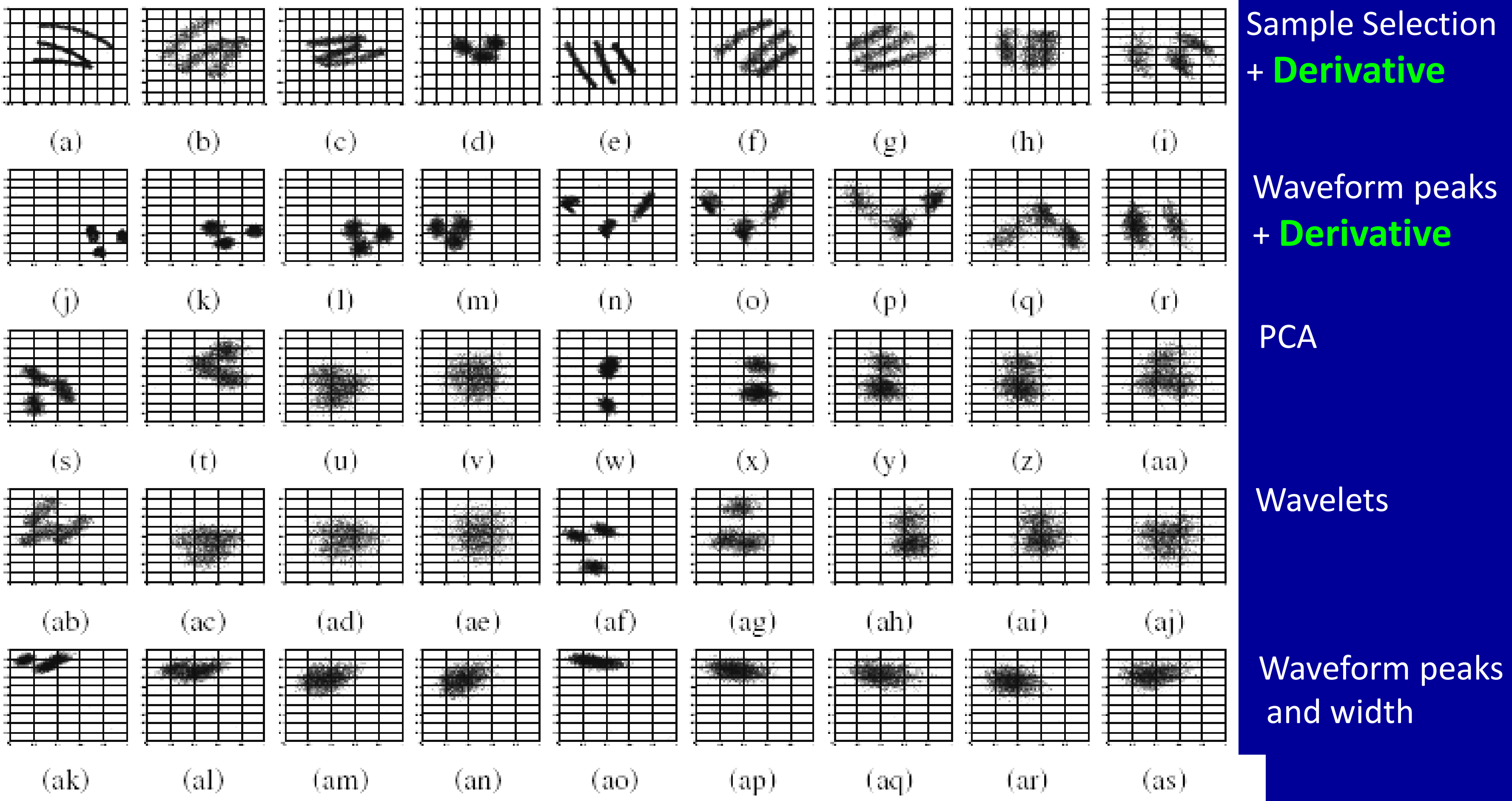
Custom software





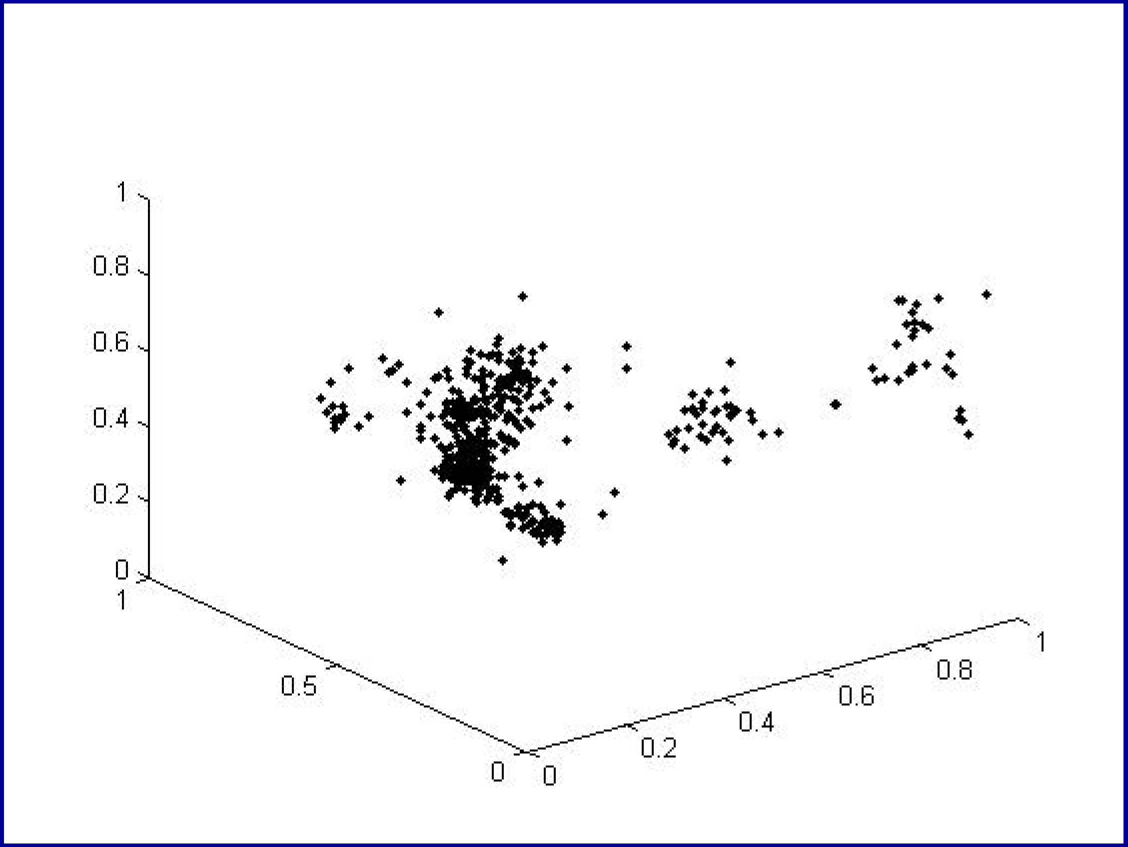


Performance Comparison

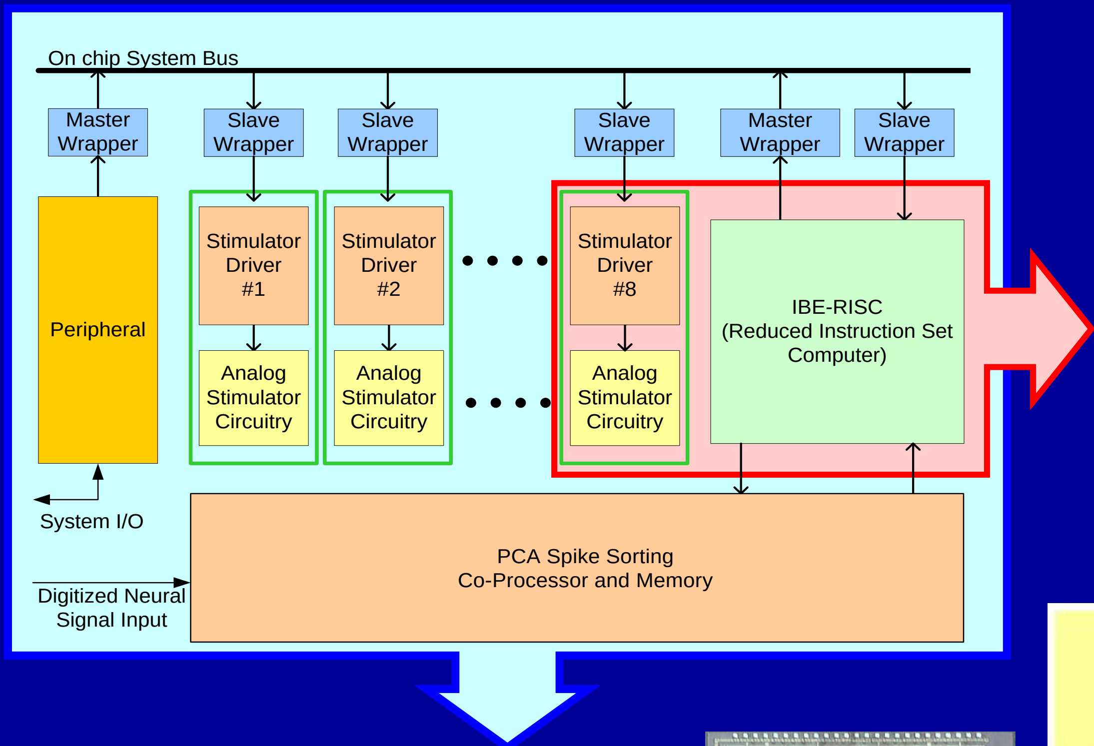


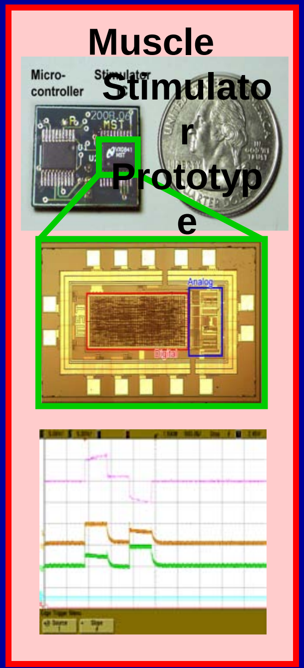
Sequence Number	1	2	3	4	5	6	7	8	9
Informative Samples + Derivative	98%	98%	98%	97%	98%	99%	97%	92%	95%
peaks+Derivative	98%	98%	97%	95 %	98 %	98 %	93%	91%	75%
PCA	98%	89%	60%	55%	98%	78%	80%	69%	55%
Wavelets	92%	91%	82%	57%	97%	68%	51%	49%	40%
Spike Peaks	34%	34%	35%	34%	36%	37%	36%	36%	35%

Evolving Mean Shift Classifier

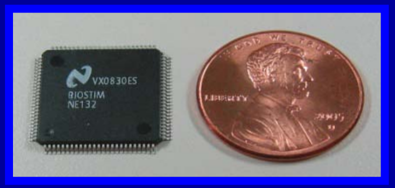


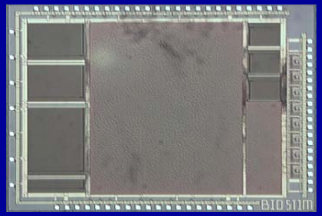
Integration of Neural Signal Processor and Stimulator

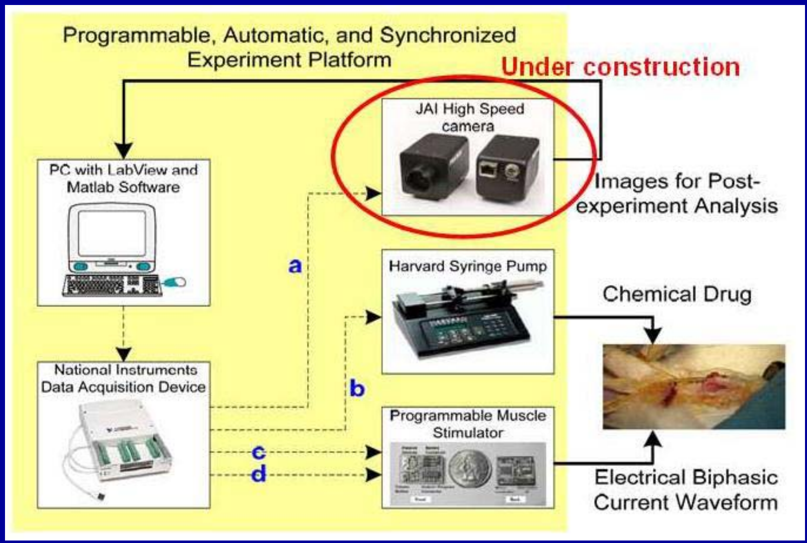




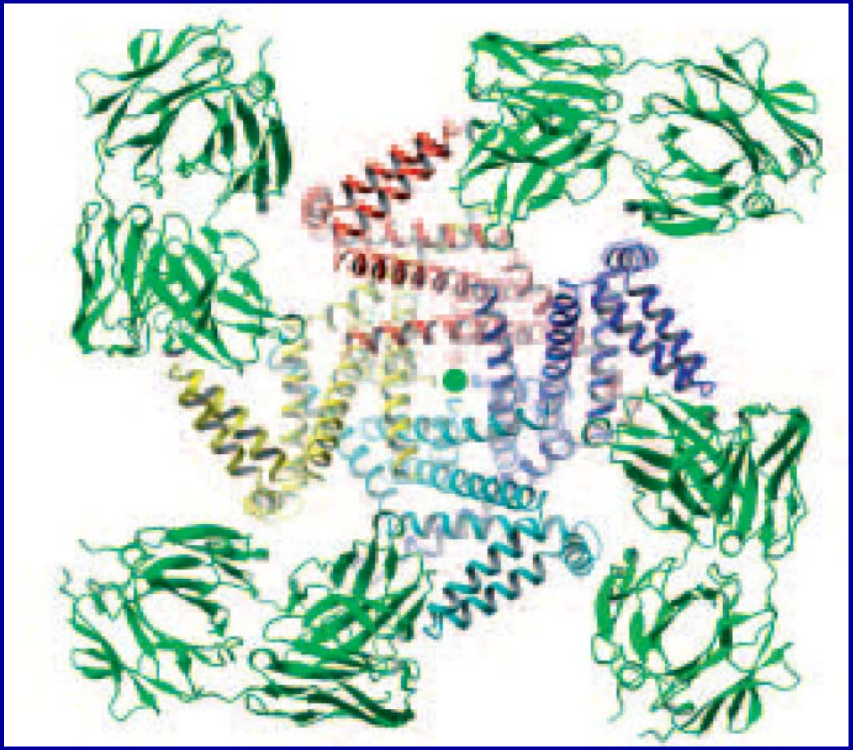
Fully Integrated Platform IC





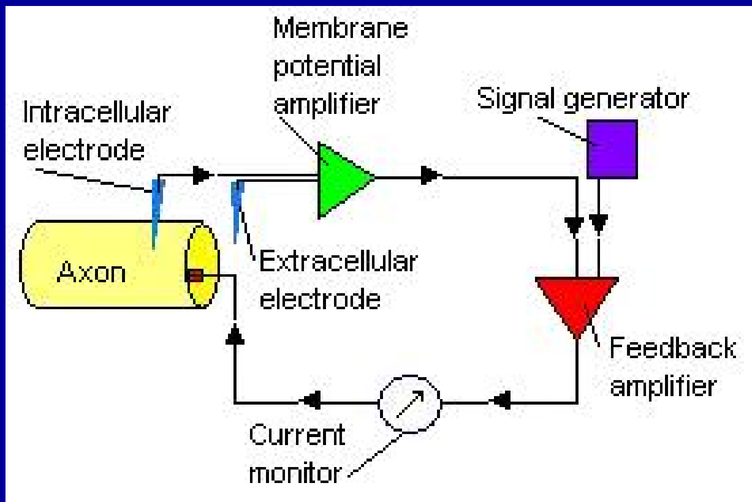


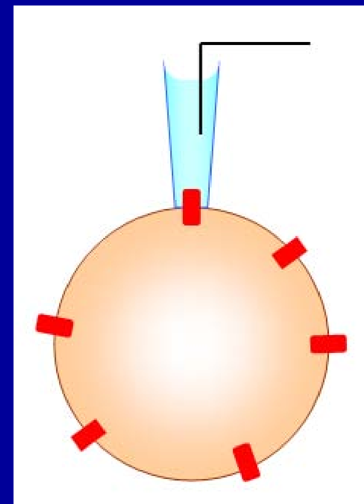
Understanding of an Ion Channel

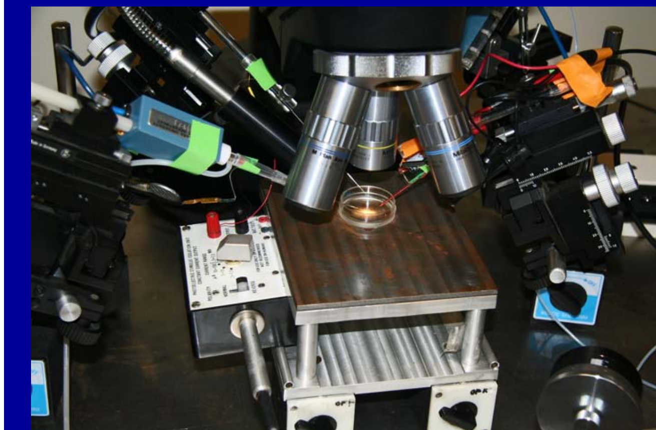


From R. MacKinnon (Nobel Laureate)

Intracellular Recordings



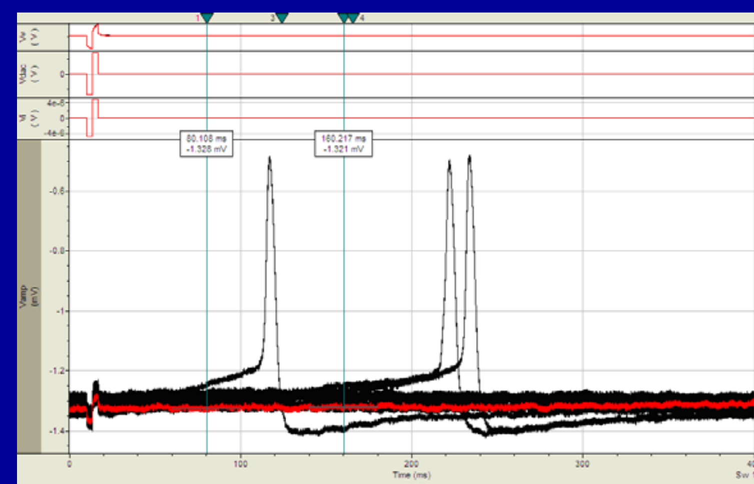




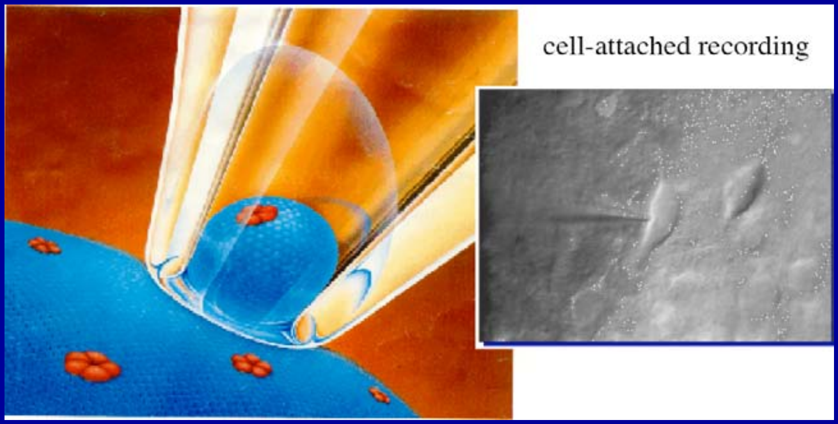
- Extracellular microelectrodes generally record superimposed neural responses from multiple neurons

- Intracellular recordings provide very localized membrane responses.

- Essential to quantify individual neuron's response to specific stimulus



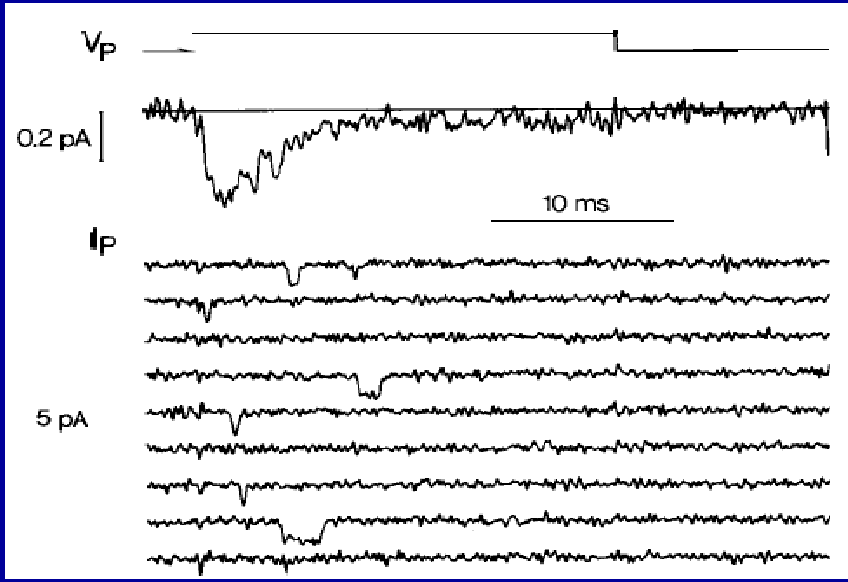
Patch Clamp Recording

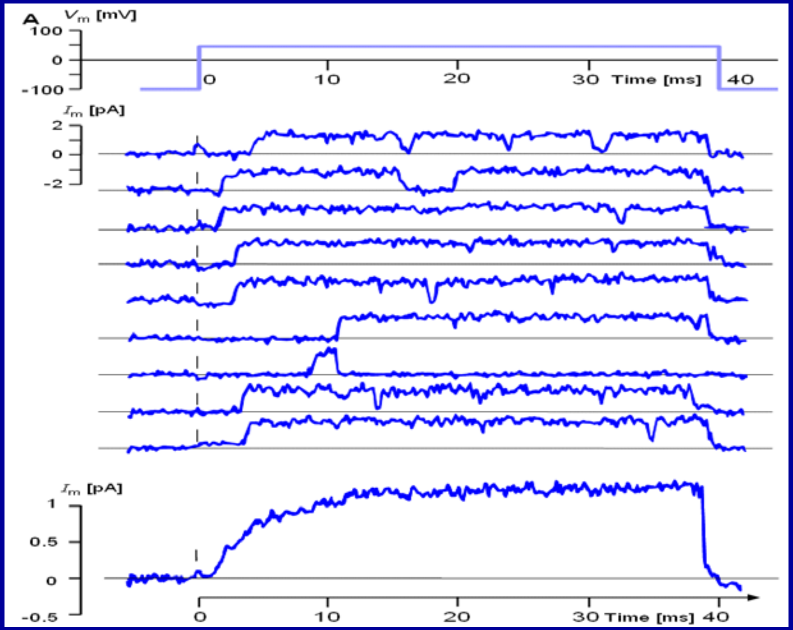


➢ Individual channel's response are stochastic in nature.

K+ channel

Na+ 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

➢Model work at Liu's Lab

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

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

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

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*

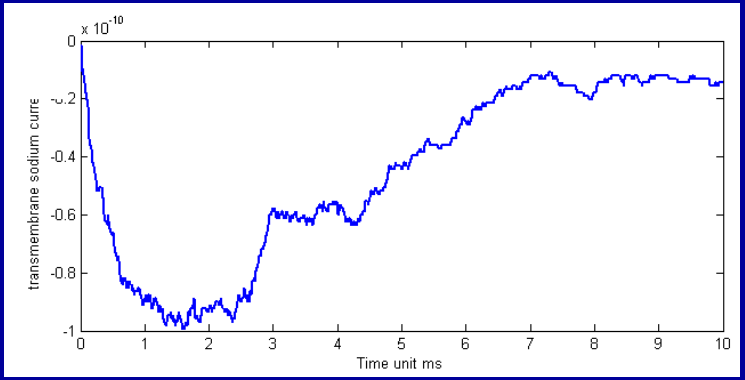
R_{zy} *: transferring rate from rest to activation*

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

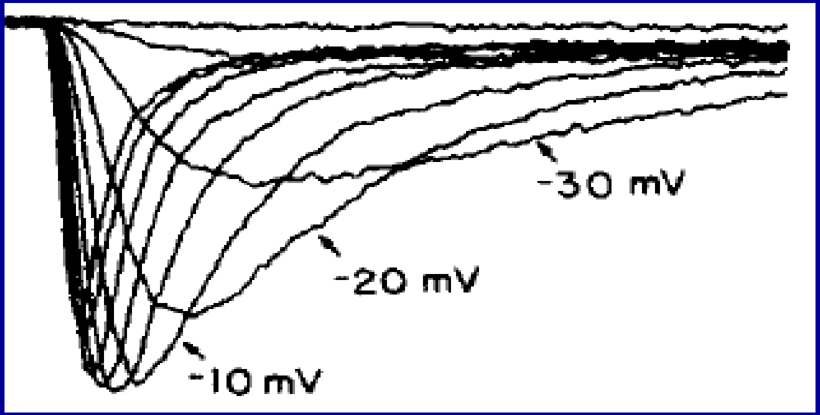
$$t_{peak} = (\ln\tau_2 - \ln\tau_1)/(\tau_1^{-1} - \tau_2^{-1});$$

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

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



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

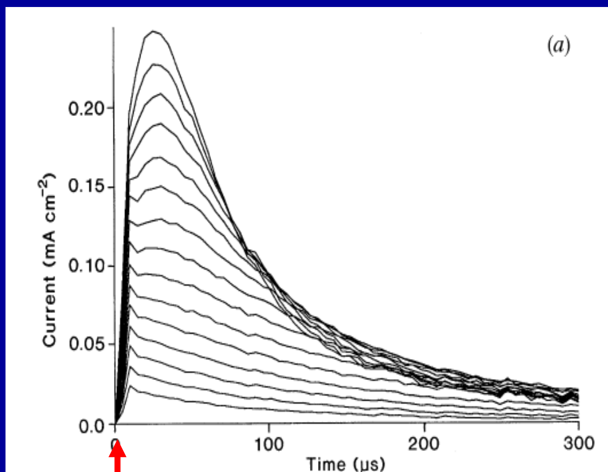


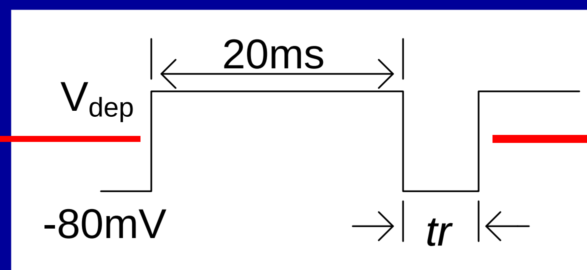
Experimental Results

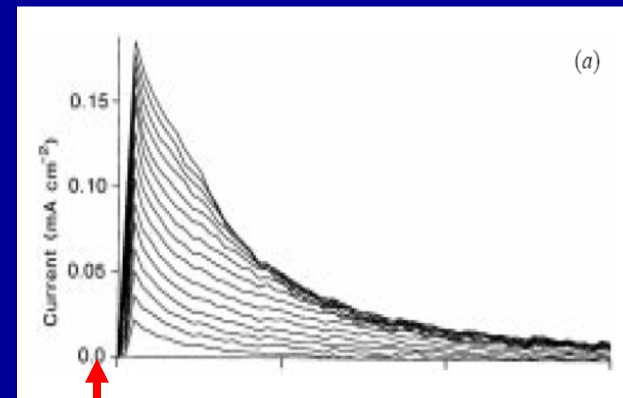
Moran,O. and Conti, F. "Sodium ionic and gating currents in mammalian cells" European Biophysics Journal, 1990

Transmembrane Gating Current

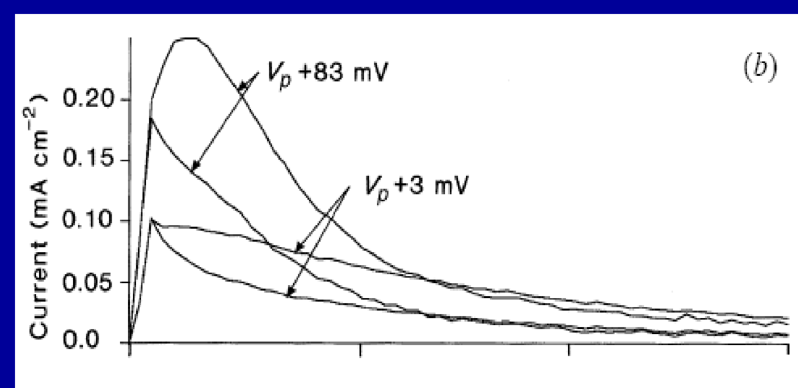
R. D. Keynes. and F. Elinder, "On the slowly rising phase of the sodium gating current in the squid giant axon," The Royal Society 1998







➢ **Liu's Lab**

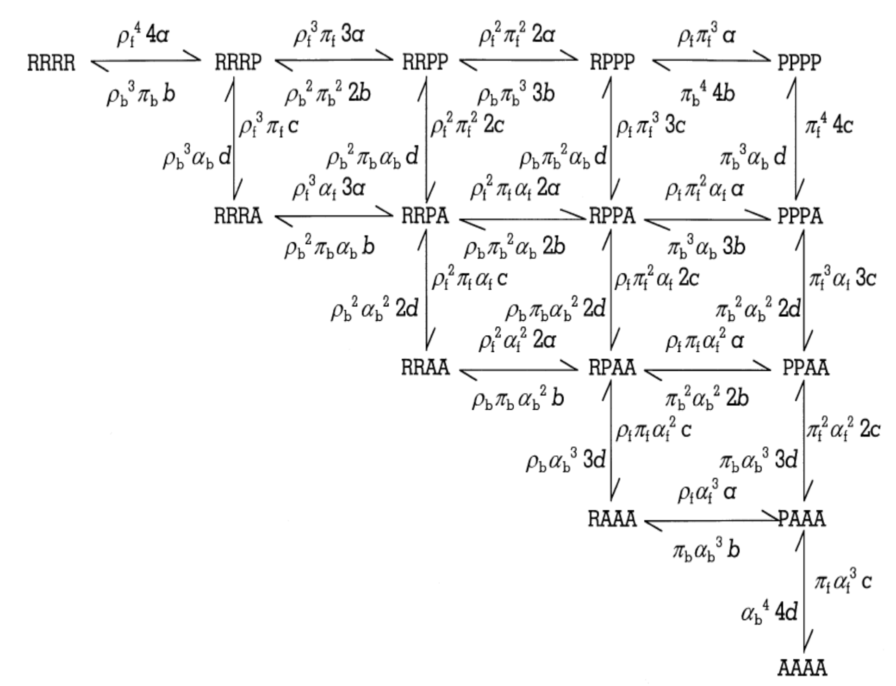


Transmembrane Current Components?

- 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

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

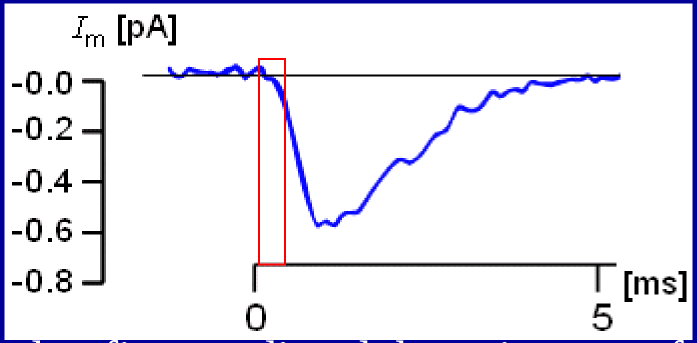
$$k_b(V) = k_{eq} e^{\frac{-z(1-\beta)(V_m - V_0)F}{RT}}$$

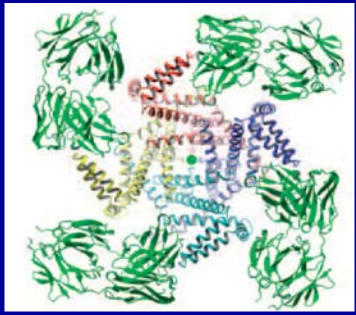
β □ $(0.6, 0.8)$

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

Measurement of Gating Current

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





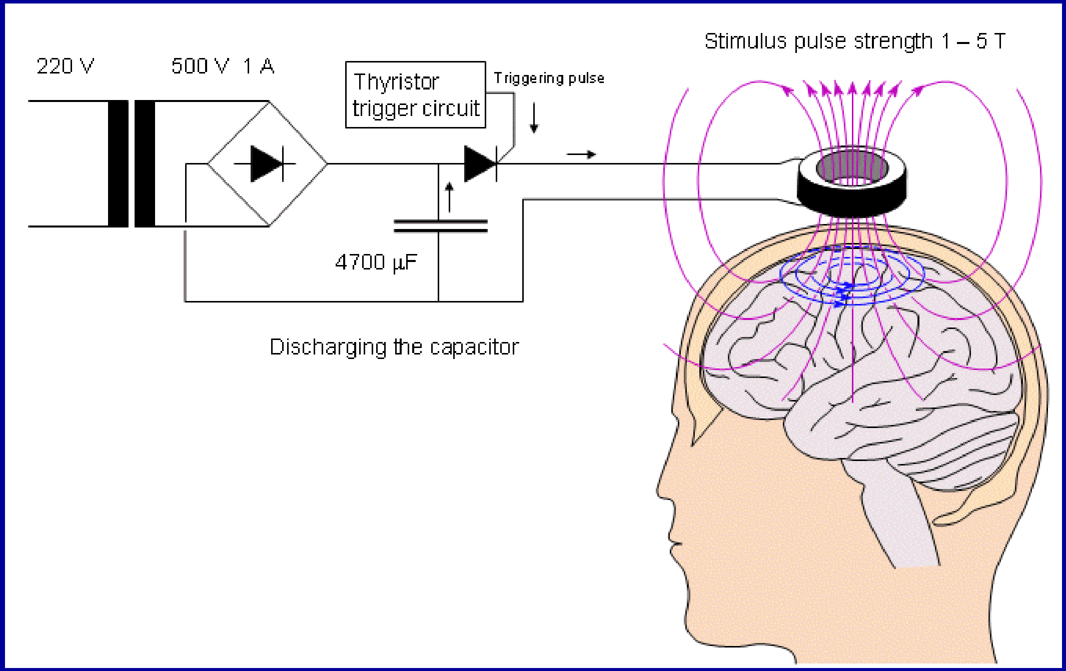
- Alan Hodgkin and Andrew Huxley first predicted the existence of the transmembrane sensors and HH model was proposed accordingly. The transmembrane current is an average macro scope one. The sensors are proved to be charged proteins and responding to the transmembrane voltage changes. (Nobel Prize in Medicine, 1963)
- Bert Sakmann and Erwin Neher measured an individual ionic channel current by using voltage 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:

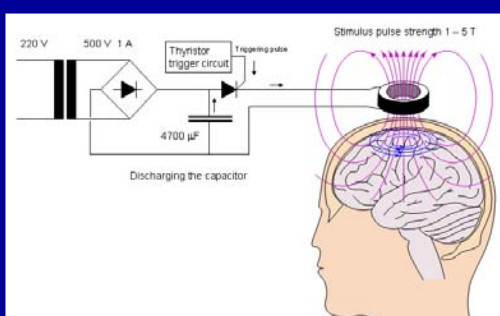
- I_{gate} is a small transient current due to protein motion. To detect a single channel protein current composed of 12e charge proteins, the recording bandwidth is >1MHz with a signal amplitude of 100fA.
- The transmembrane voltage is required to be stabilized in 10us in order to filter out the effect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

Magnetic Field Electrode and Stimulation

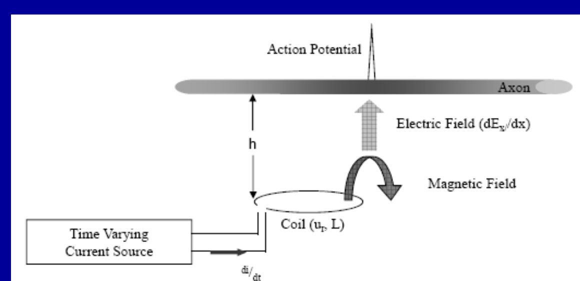
(No protein encapsulation problem as occurred in electrical field electrode)



- Magnetic stimulation
  - Noninvasive
  - Treatment for neurologic/psychiatric disorders:
    - Stroke, Parkinson's disease, dystonia, Tinnitus, depression, hallucination
- Major challenges
  - Large current to create magnetic field ~0.5 tesla in the cortex; or current to create electric field ~10V/m or E field derivative ~10,000V/m^2 for activating neurons in vitro
  - Coil design (appropriate geometry parameters, inductance value ~tens uH, high Q)
  - Supporting electronics (ramp current through inductive load, up to10,000V output, up to 10^8 A/s slew rate for large coil)
  - Penetration depth (~ coil radius)
  - Spatial selectivity

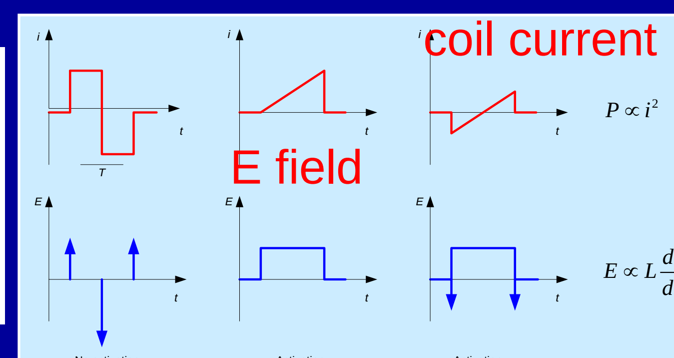


conceptual figure targeting cortex

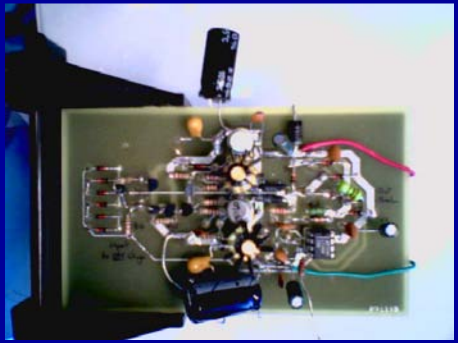


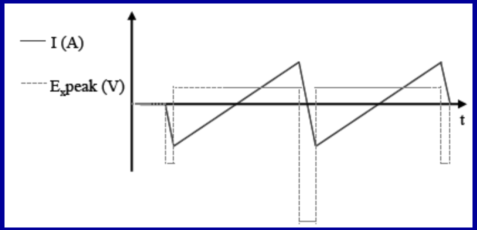
Conceptual figure targeting axons in vitro

poor inefficient good

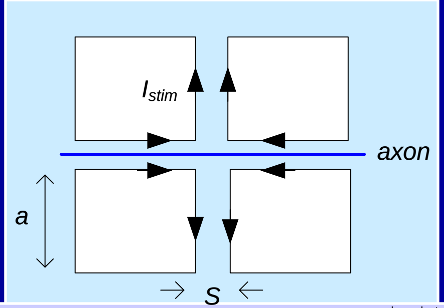


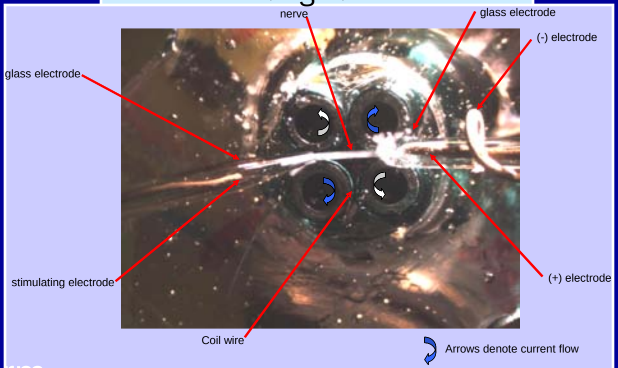
Stimulation protocols





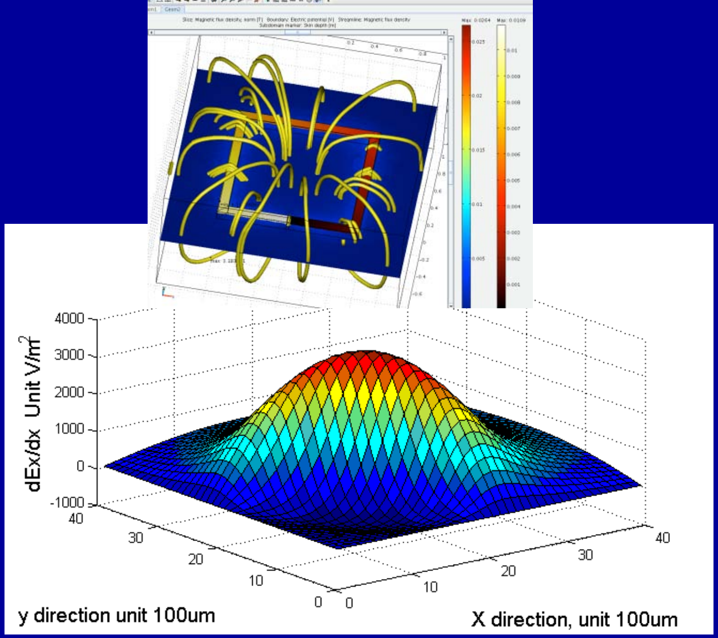
Circuit & ramp current waveform
slew rate: 10^5 A/sec
supply +-15V
bandwidth 100KHz
only drive small coil





Quad Ferrite Core, 1mm cores, N=20

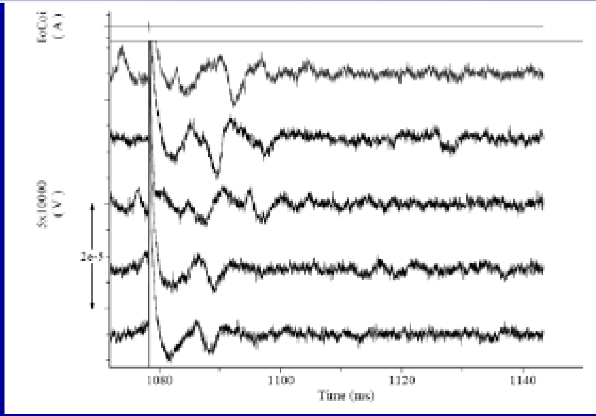
Quad coil setup, 20uH,
R~1Ohm, coil radius ~1mm,
penetrate depth ~ hundreds um



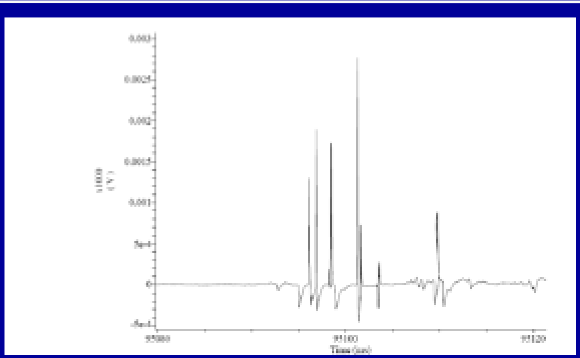
Magnetic field and tangential E field simulation

$$\lambda^2 \frac{\partial E_x}{\partial x} = -\lambda^2 \frac{\partial^2 V_m}{\partial x^2} + \tau \frac{\partial V_m}{\partial t} + V_m$$

Neuron preparation:
H. Aspersa circumoesophageal ring



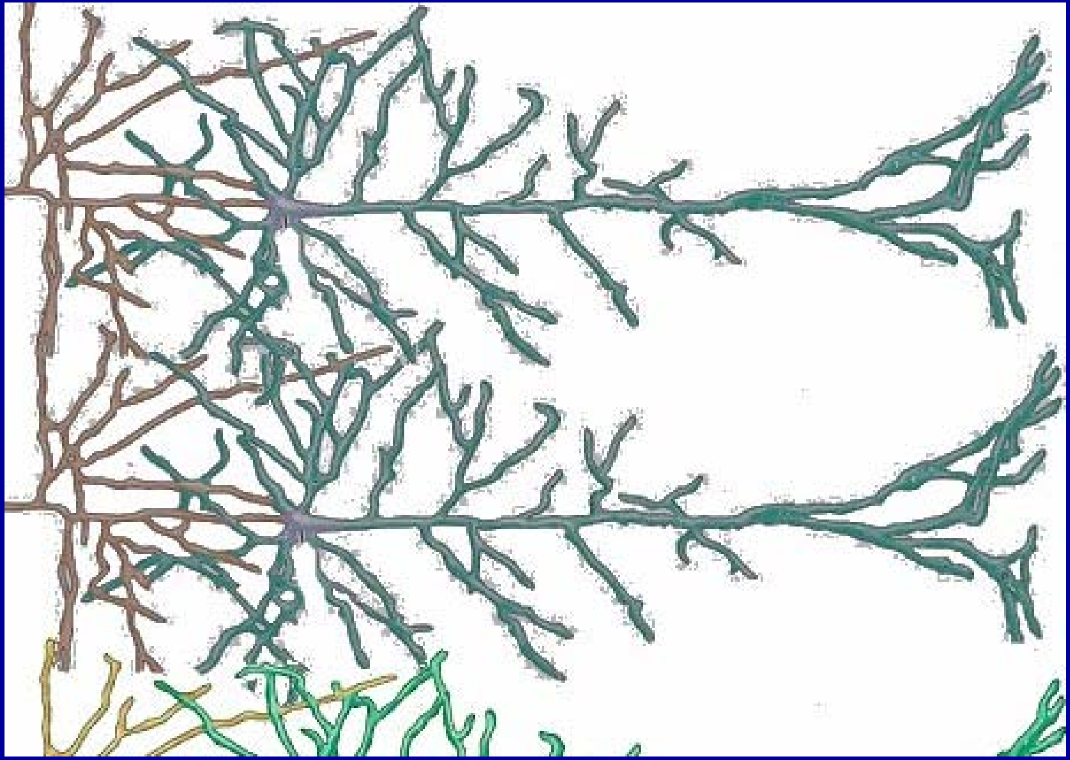
Magnetically triggered single action potentials using *H. Aspersa neurobiological preparation (each trace represent one trail).*



Magnetically triggered single action potentials using *P. Clarkii neurobiological preparation.*

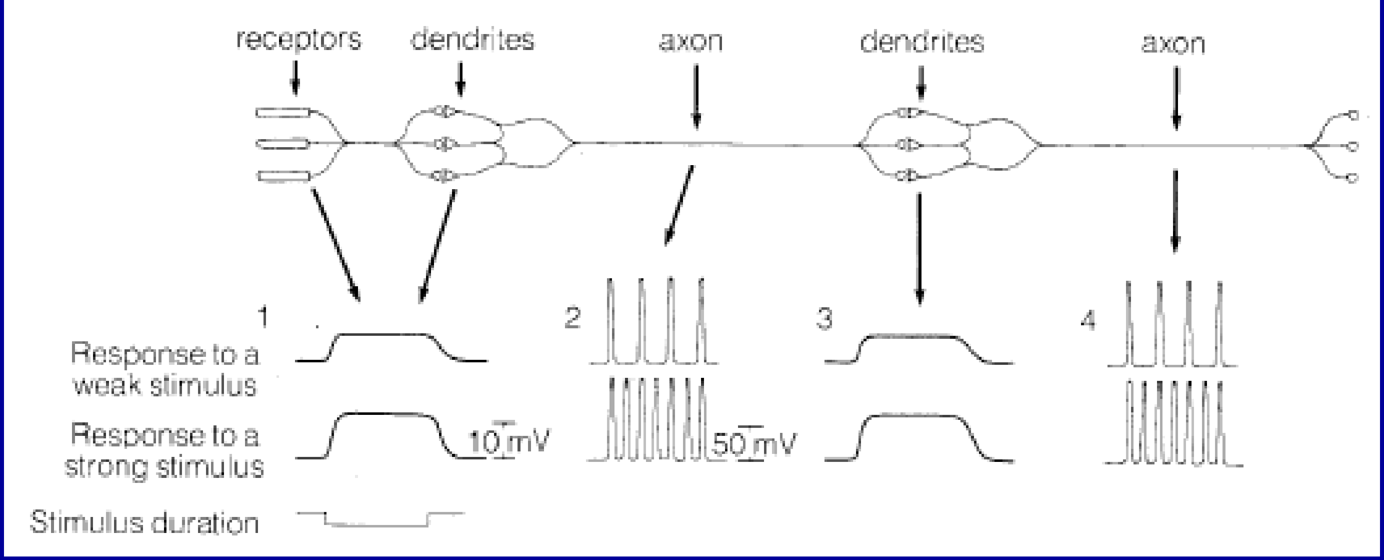
(Basham, E., Yang, Z. and Liu, W. 08)

Access of a Single Cell In-Vitro and In-Vivo



BioSpice Project for Neuroscience

- A Spice-like simulator consists of
  - **Elements and models (type and geometry)**
  - **Connections and signals (mode of level and pulse)**
  - **Signal processing and matrix algorithms**



(Figure taken from John Dowling, *The Retina*, Harvard University Press, 1987)

Concluding Remarks

- Many applications with biomimetic systems

- Enabling Technology for integrated and miniaturized biomimetic SYSTEM that can be deployed in experimental and clinical settings

  - Wireless EEG cap for epilepsy implant- a 128-channel 6-mW neural recording chip with programmable parameters, on-chip spike sorting and UWB telemetry has been designed, fabricated and tested

  - Wireless Stimulator -A 256-channel +/-12V single chip for retinal prosthesis with power receiver, data receiver, analog drivers and digital controllers has been designed and fabricated

- Many other enabling technologies are needed to develop

- However, manufacturing grade integrated hermetic packaging is the key to realize implantable systems