Advanced Neural Implants and Control

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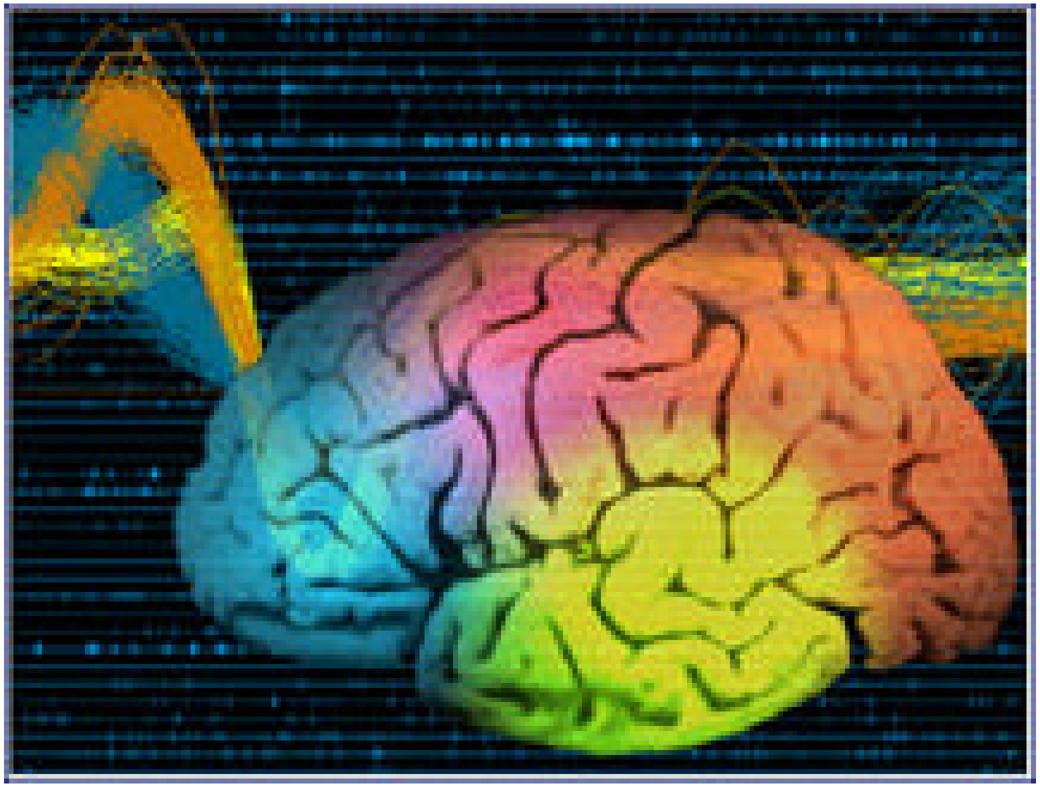

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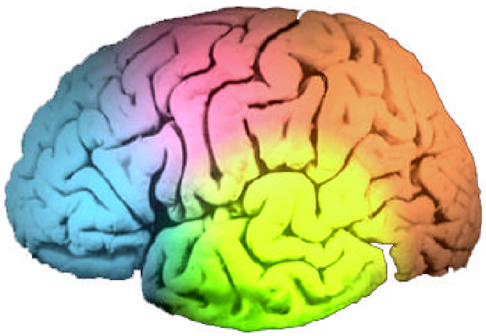
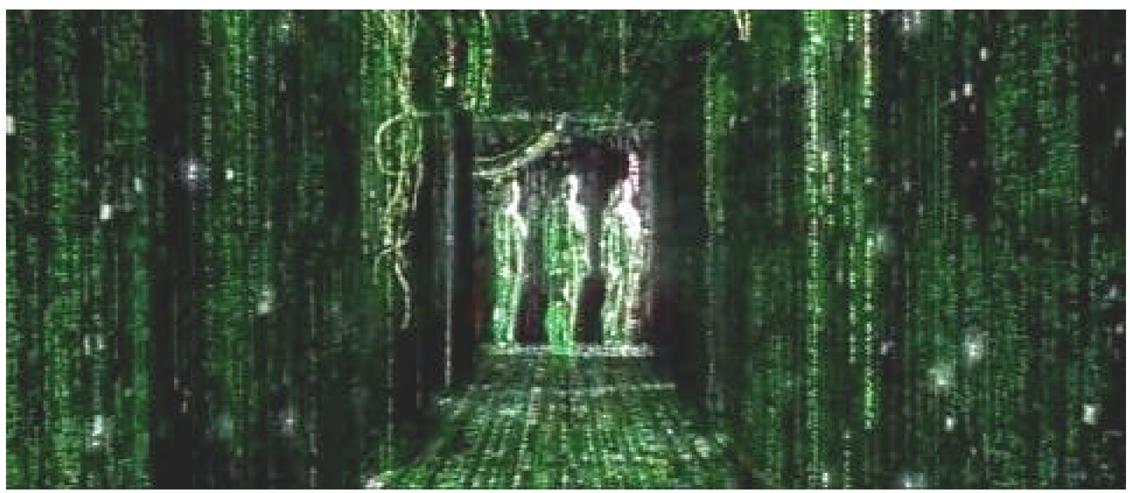
The Underlying Premise…



The ability to engineer reliable, high-capacity direct interfaces to the brain and then integrate these into a host of new technologies will cause the world of tomorrow to be much different than that of today.



However…

- There are some serious scientific barriers between where we stand today and where we can stand in the future.
  - How do we establish permanent and reliable interfaces to selected areas of the central nervous system?
  - How do we use these interfaces to directly and reliably communicate at high rates with the brain?

Applied Neural Implants and Control

Project Director
Kipke (BME)

Advisory Committee
Raupp, Hoppensteadt, Farin

Systems Science & Signal Processing
He (BME)
Hoppensteadt (Math & EE)
Kipke (BME)
Si (EE)

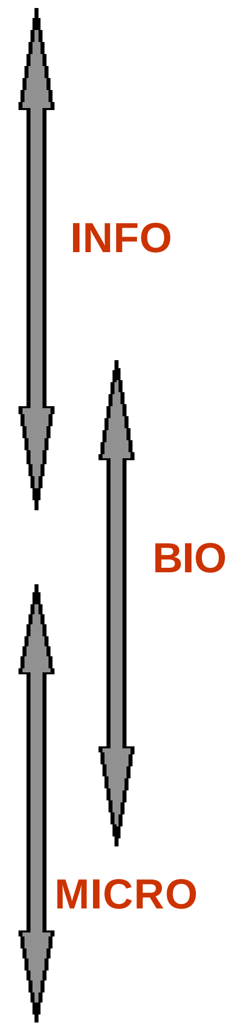
Visualization & Modeling
Farin (CSE)
Nelson (CSE)
Razdan (CSE)
Smith (Math)

Neural & Tissue Engineering
Kipke (BME)
Massia (BME)
Panitch (BME)
Rousche (BME)

Tissue Culture & Analysis
Capco (Bio)
Massia (BME)
Pauken (Bio)

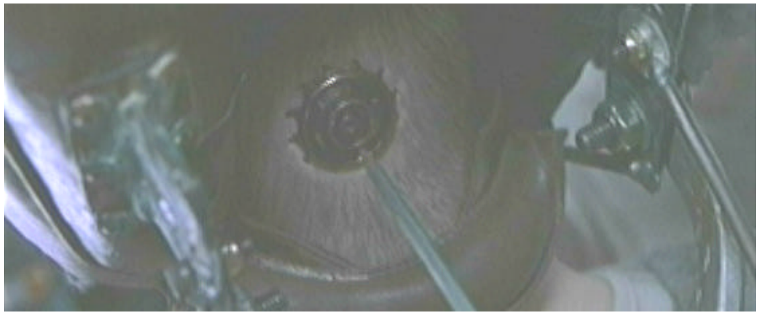
Materials Synthesis & Bioactive Coatings
Ehestraimi (BME)
Massia (BME)
Panitch (BME)
Raupp (ChemE)

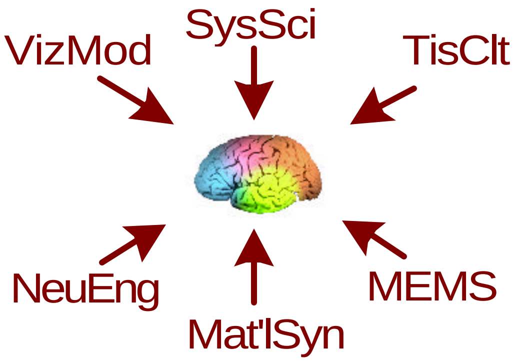
MEMS
Shen (EE)
Pivin (EE)
Li (EE)



Primary Goals of the BIO:INFO:MICRO Project

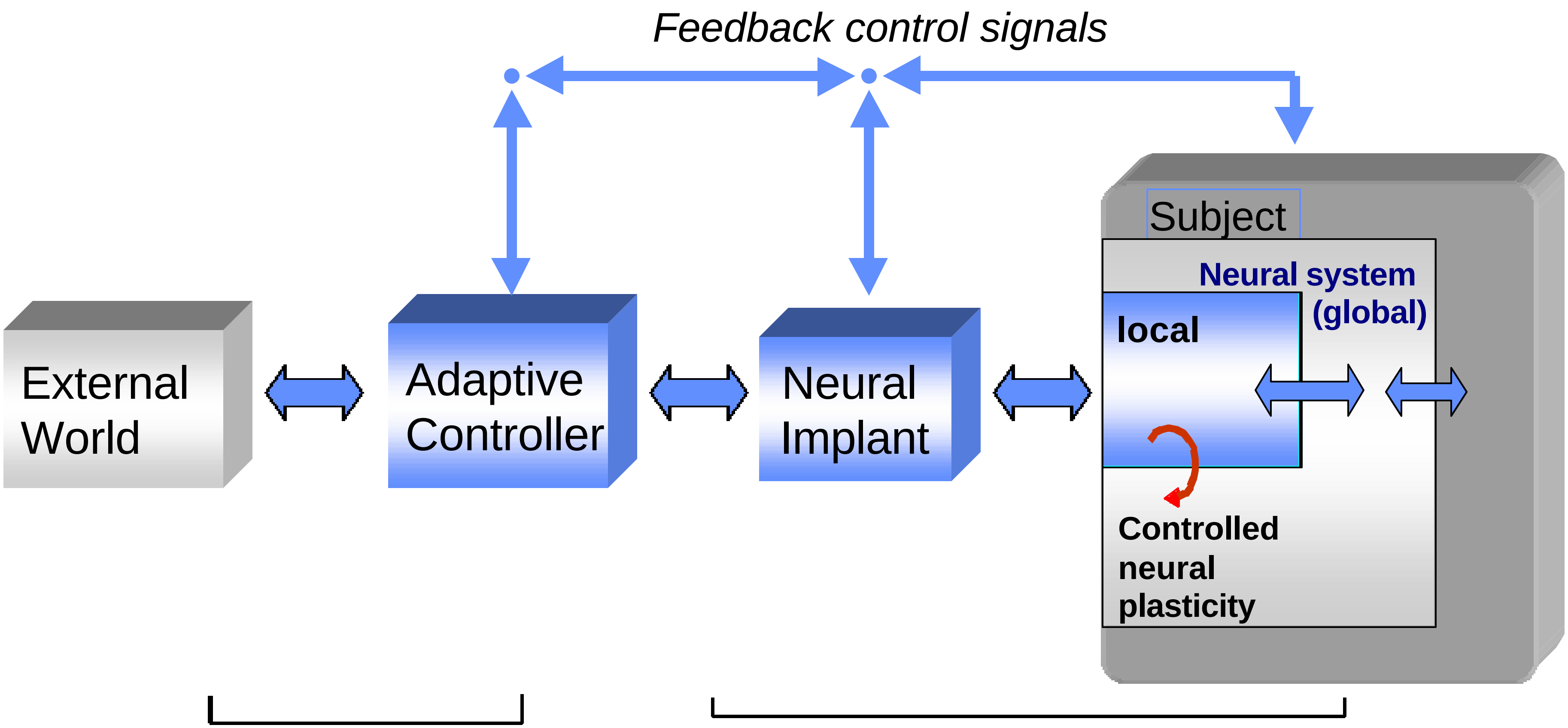
- Develop new neural implant technologies to establish *reliable*, *high-capacity*, and *long-term* information channels between the brain and external world.





- Develop real-time signal processors and system controllers to *optimize* information transmission between the brain and the external world.

Systems-level Approach…



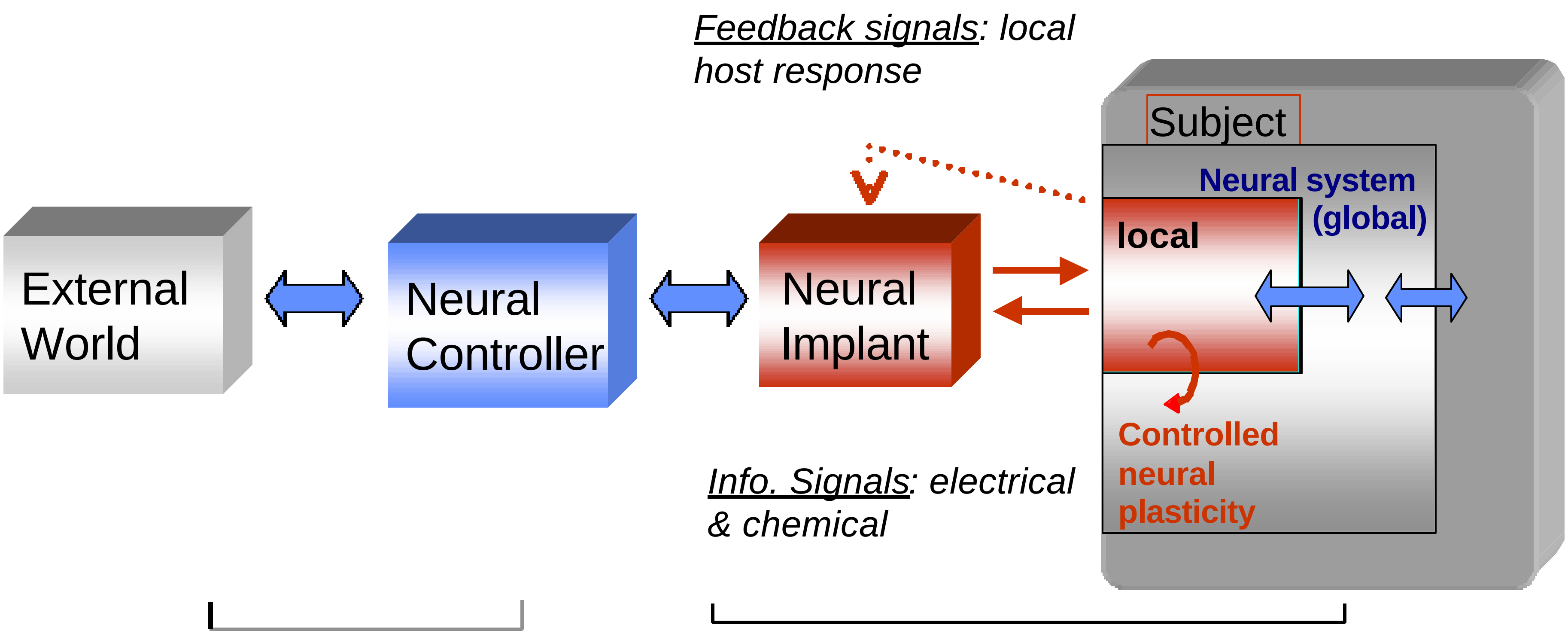
__Objective 2:__ *Optimize Adaptive Controller*

__Objective 1:__ *Optimize neural interface*

Topics

- ☒ *Project overview*
- ❑ Towards the Development of Next-Generation Neural Implants (BIO, MICRO, and INFO)
- ❑ Bioactive Coatings to Control the Tissue Responses to Implanted Microdevices
- ❑ Modeling the Device-Tissue Interface
- ❑ Direct Cortical Control of an Actuator
- ❑ Neural Control of Auditory Perception
- ❑ Wrap-up

Focus on Next-Generation Neural Implants

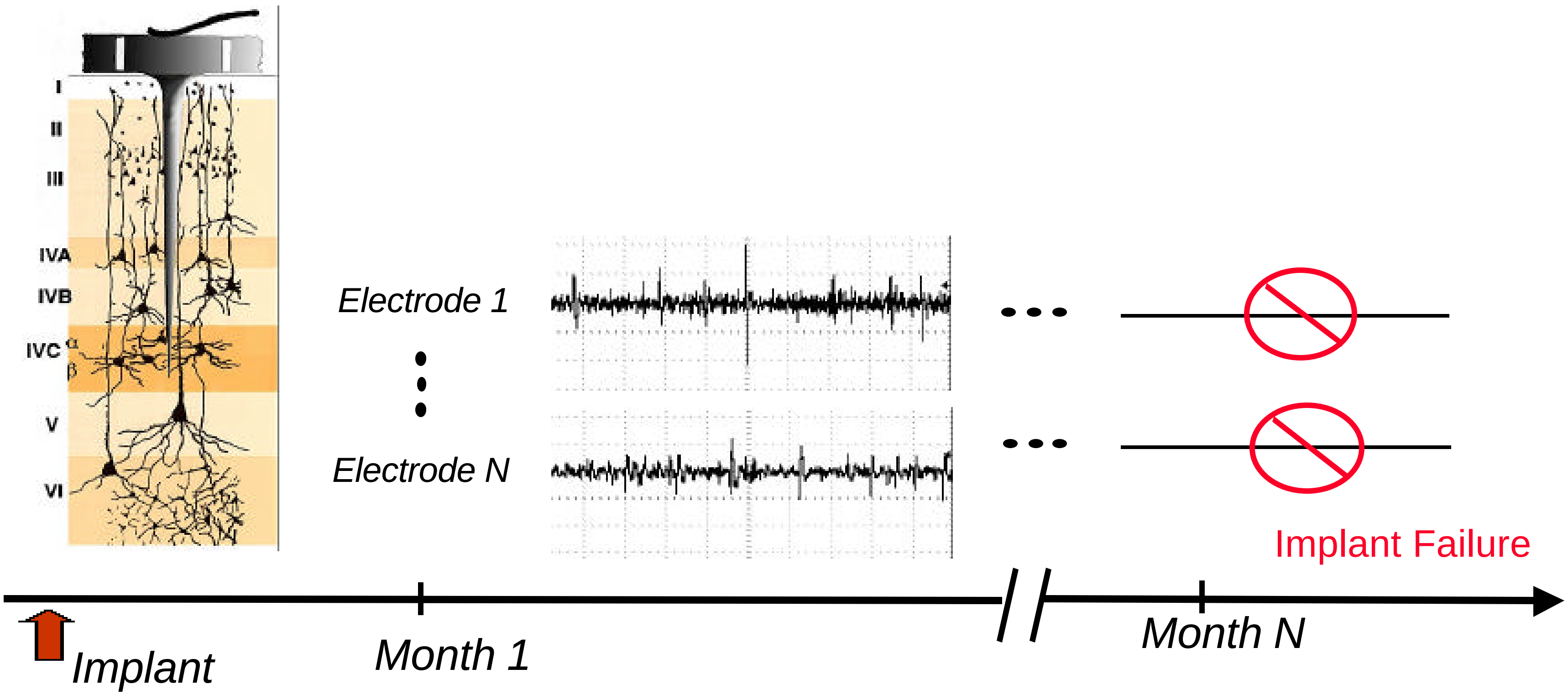


Objective 2: *Optimize Adaptive Controller*

Objective 1: *Optimize neural interface to achieve reliable, two-way, high-capacity information channels. …and "self-diagnostic"*

Fundamental Problem of Implantable Microelectrode Arrays

- Brain often encapsulates the device with scar tissue
- Normal brain movement may cause micro-motion at the tissue-electrode interface
- Proteins adsorb onto device surface
- Useful neural recordings are eventually lost



3rd-Generation Neural Implants

Technology Spectrum

1st-generation

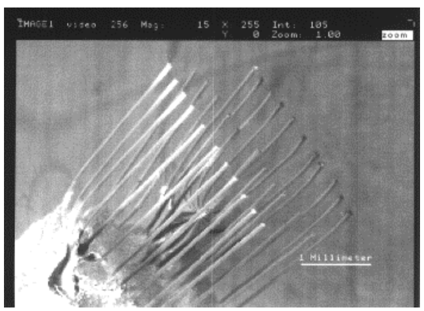
Microwires

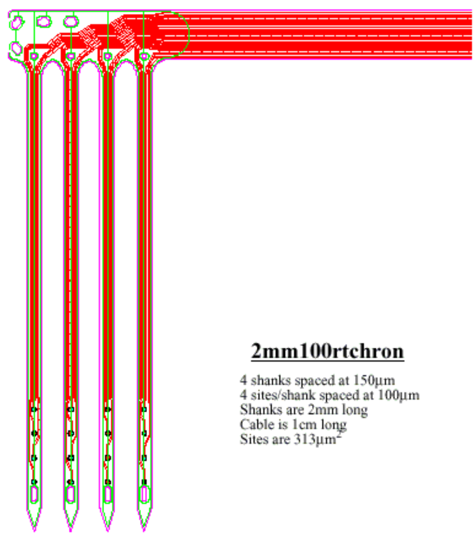
2nd-generation

Silicon arrays

3rd-generation

Neural Implants



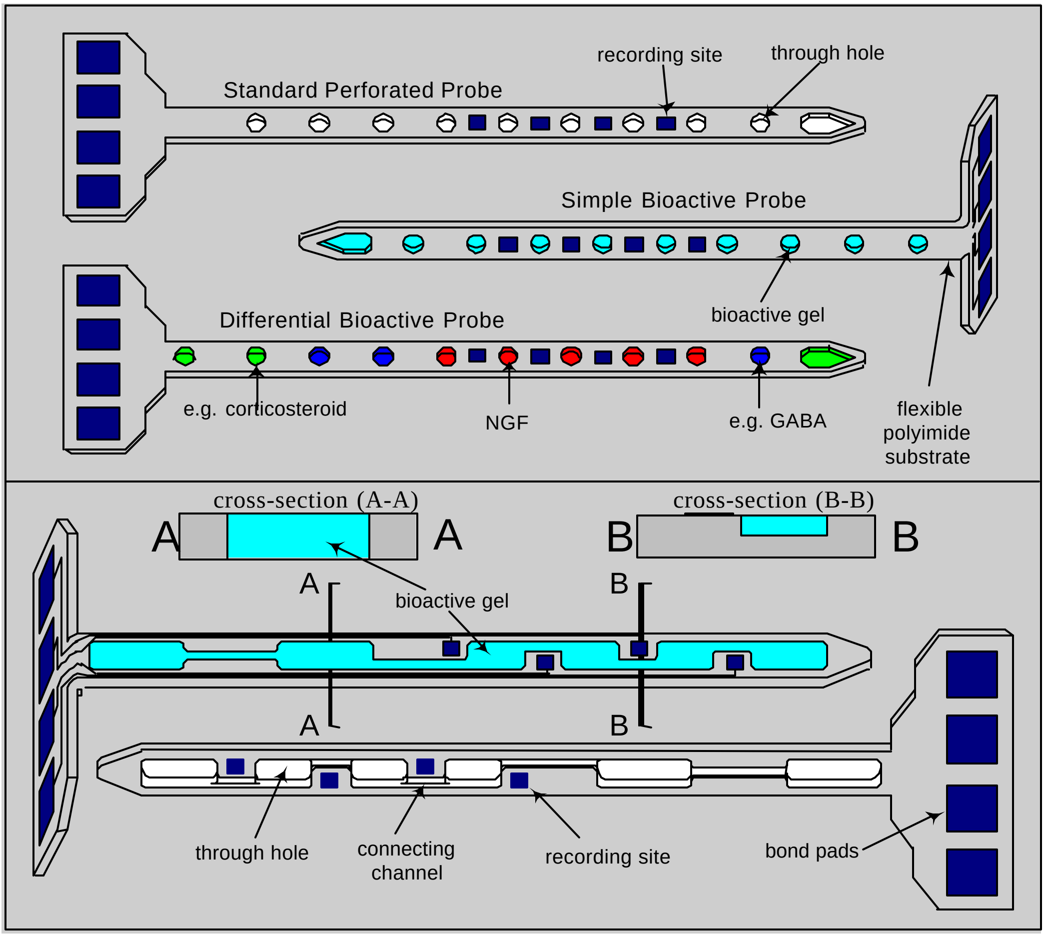


Desired Properties

- Very high channel count (<1000)
- Bioactive coatings
- Flexible
- Engineered surfaces
- Controlled biological response
- Integrated electronics

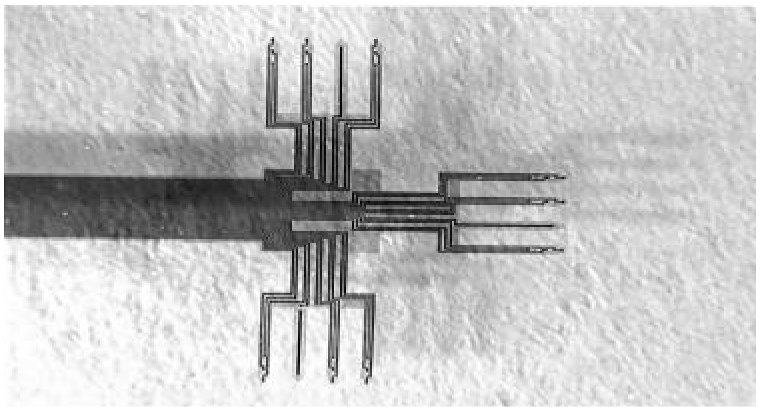
“Brain-centered” Design of Neural Implants

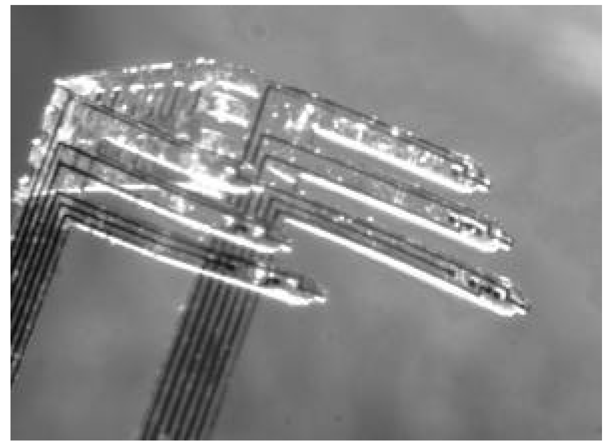
Initial conceptual designs

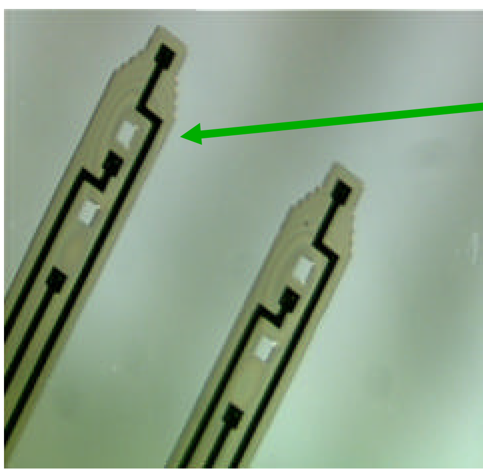


Polymer-substrate Neural Implants

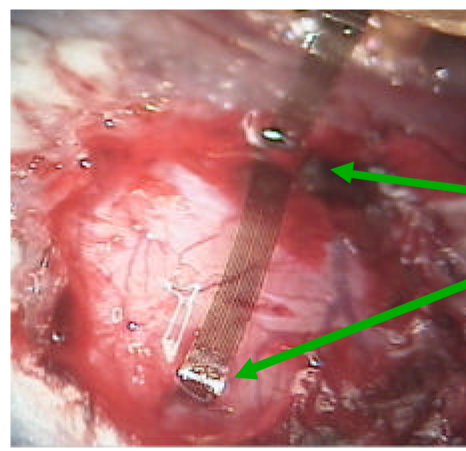
- 2-D planar devices can be bent into 3-D structures
- Increases insertion complexity







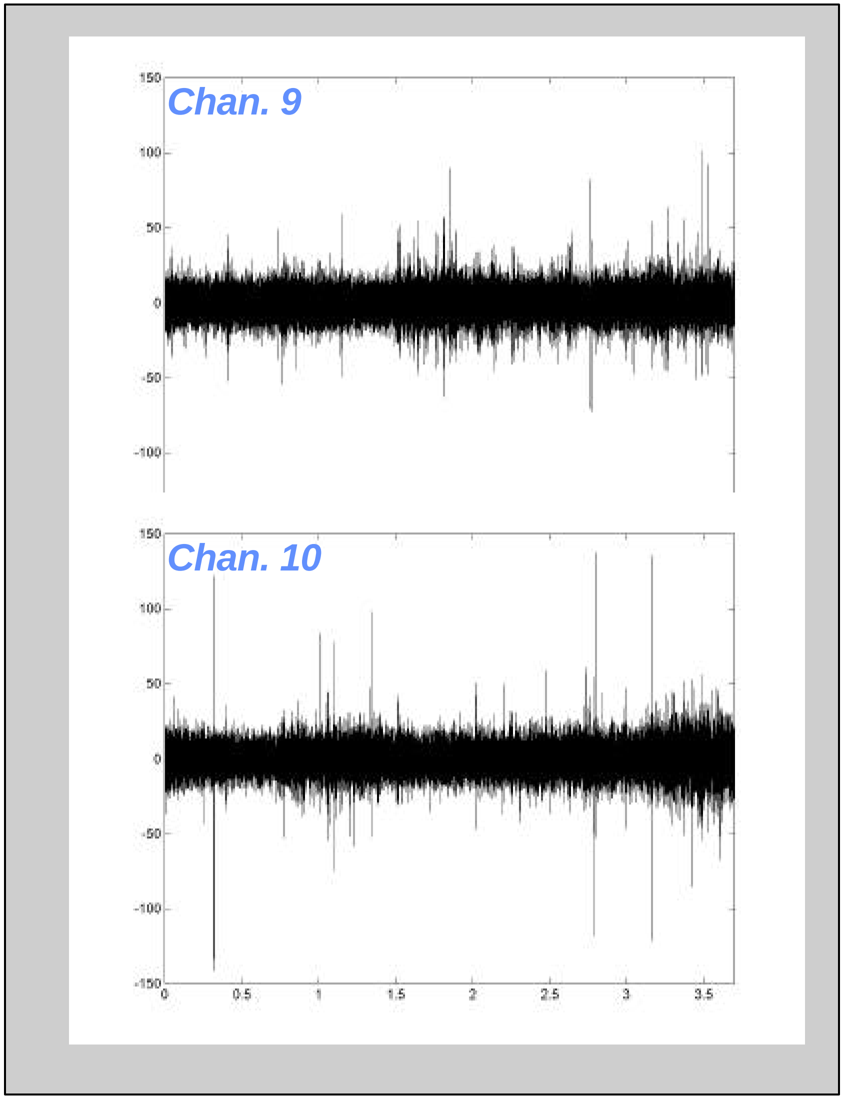
Holes to promote integration with neuropil



90 degree angles

Recordings From Polymer-substrate Neural Implants

One Day Post-op

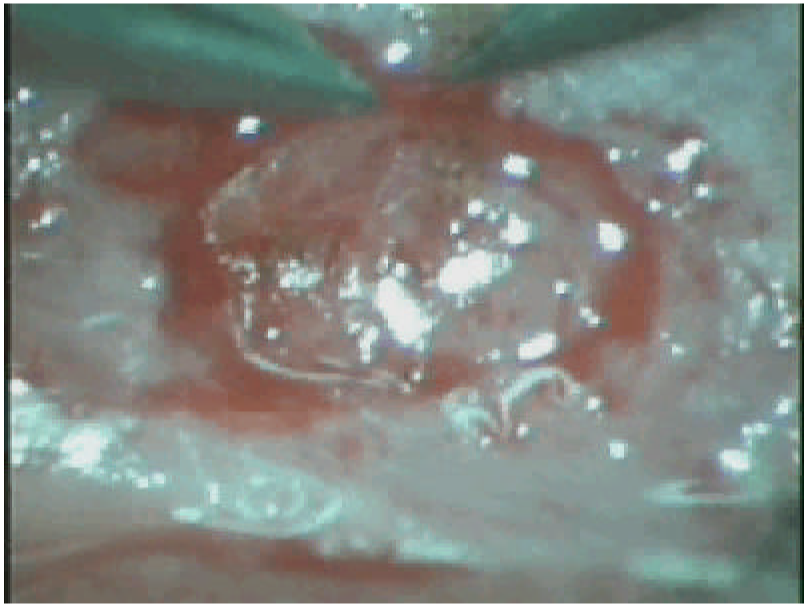


Lost most unit activity after 7 days – Most likely due to failure to properly close dural opening.

Flexible Neural Implants Present Surgical Challenges

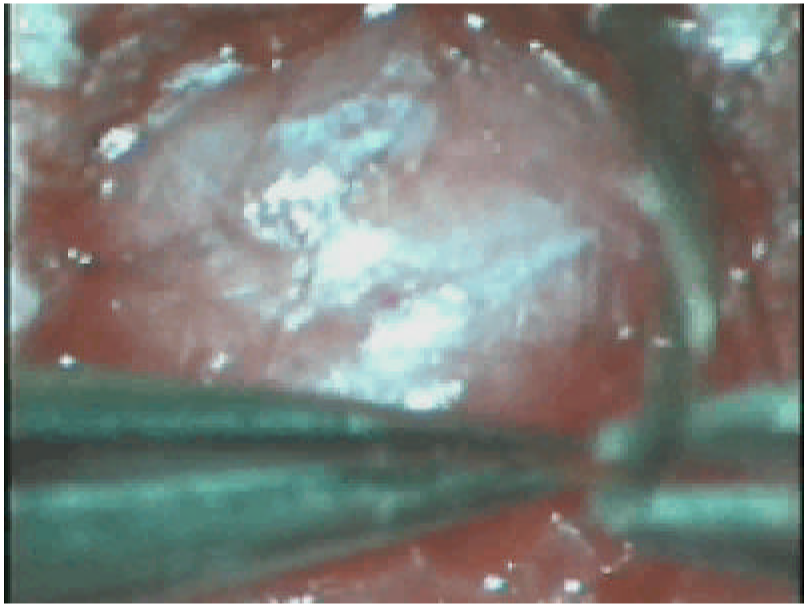
- While the “micro-motion” hypothesis suggests that flexible neural implants should be more stable, the same flexibility presents significant new surgical challenges.

“Difficult” insertion



Rdr2, 9-00

“Easy” insertion

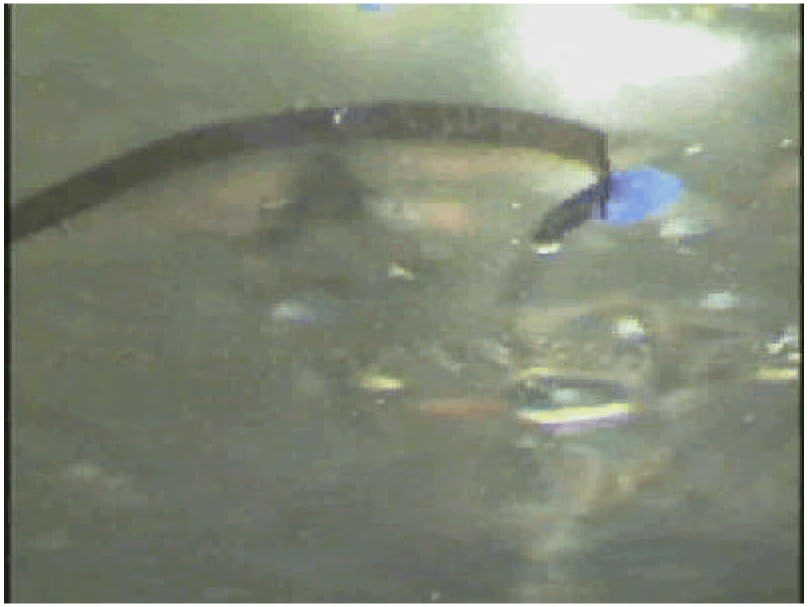


Rdr3, 9-00

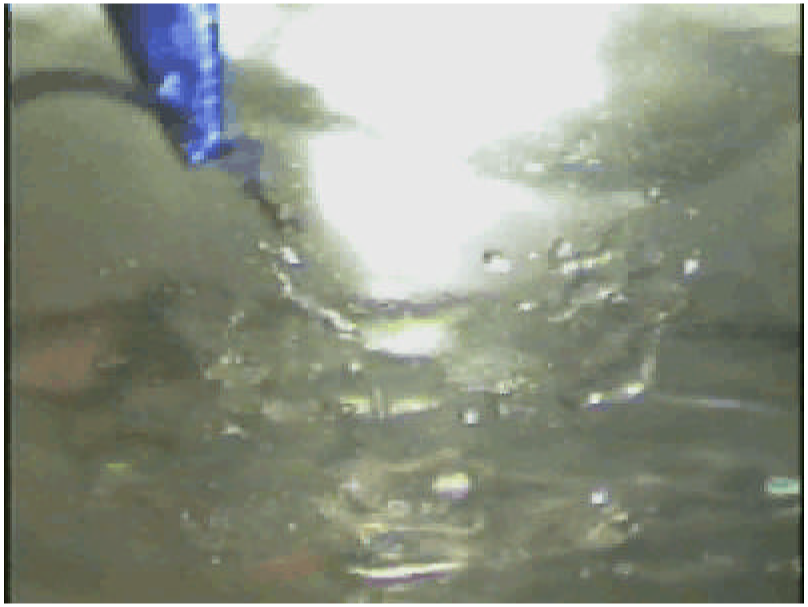
Using Dissolvable Coatings to Stiffen the Neural Implant

- Dip-coat microdevice with polyethylene glycol (PEG)
  - Provides mechanical stiffening prior to implant
  - Quickly dissolves when in contact with tissue

First insertion of coated microdevice into gelatin -- Device easily penetrates material

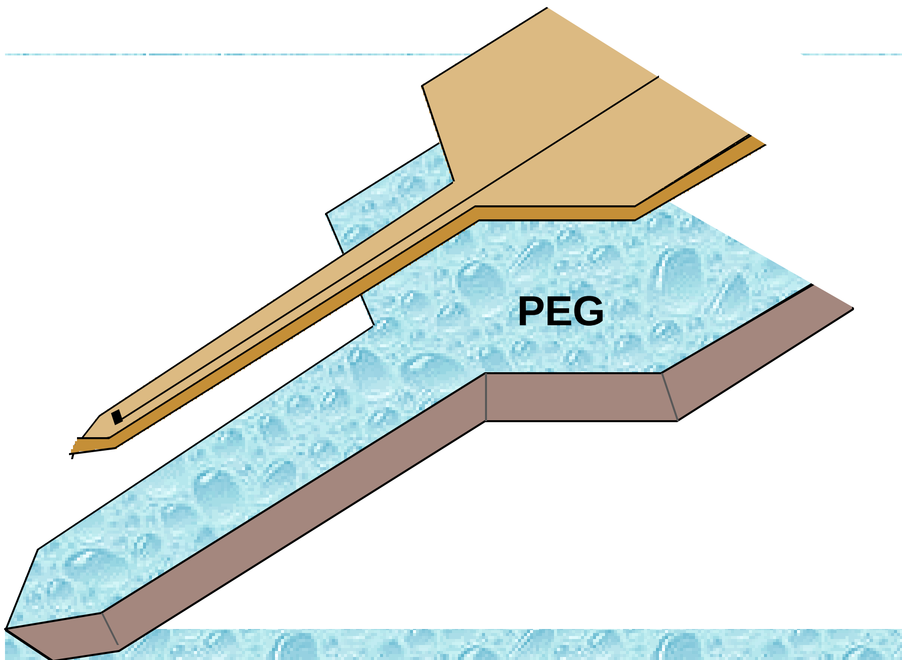


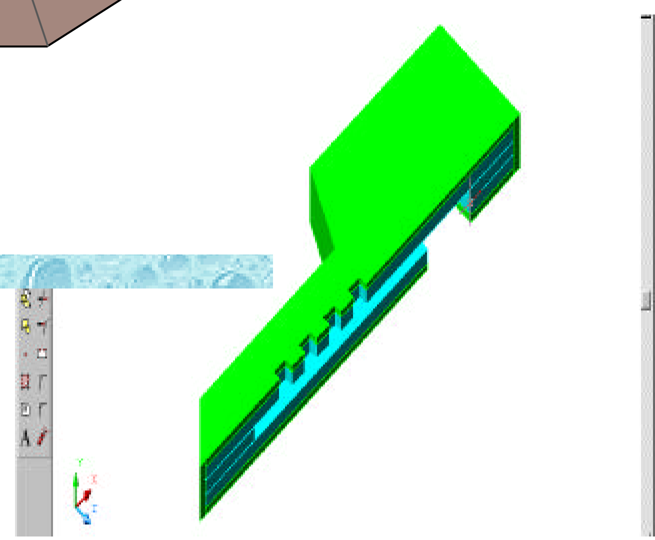
Second insertion of coated microdevice into gelatin – The device is too flexible to penetrate material because the PEG has dissolved.

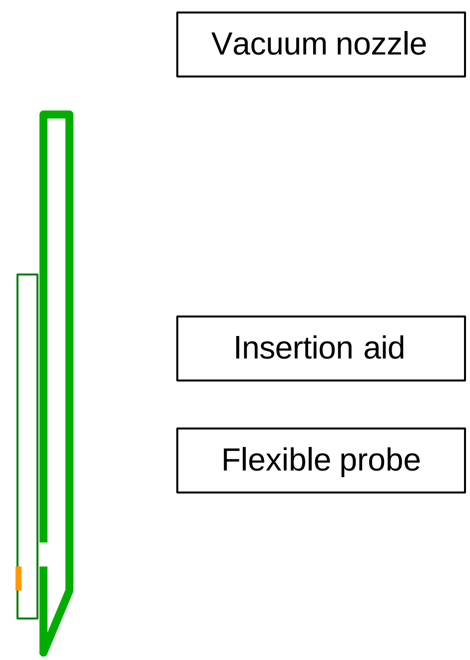


Micromachined Surgical Devices

Silicon Knife/Inserter







Vacuum Actuated Knife/Inserter

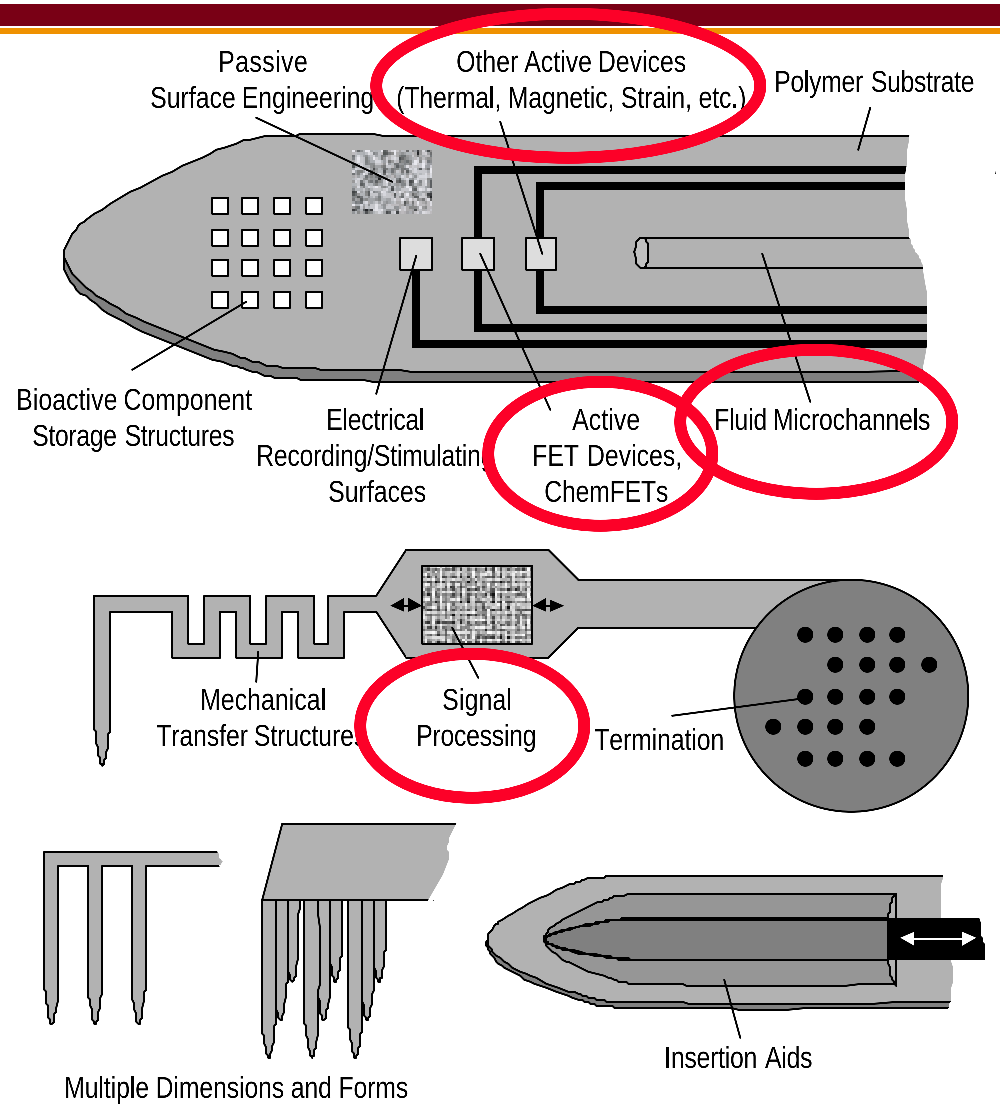
Exploratory Functionality

- Magnetic/thermal stimulation
- Drug delivery channels
- Active micro-manipulation of probes

Currently...

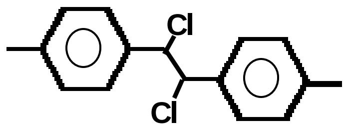
Internal Review

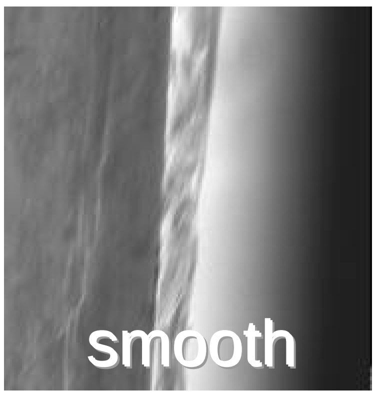
Feasibility Studies



Implant Coatings and Surface Modifications

Parylene-N,C





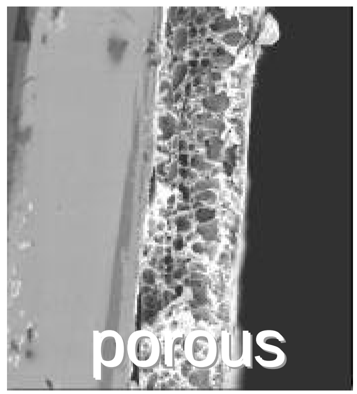
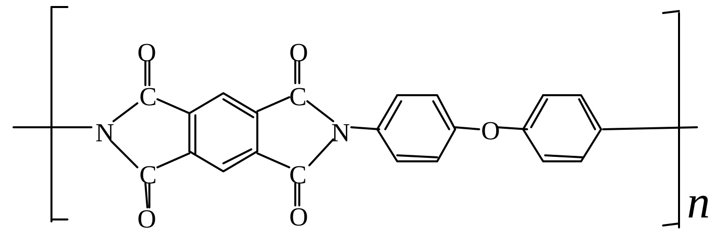
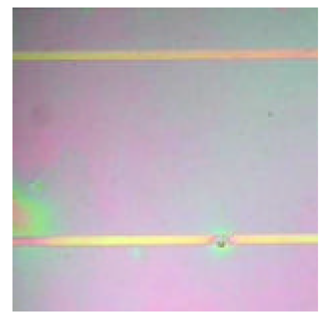
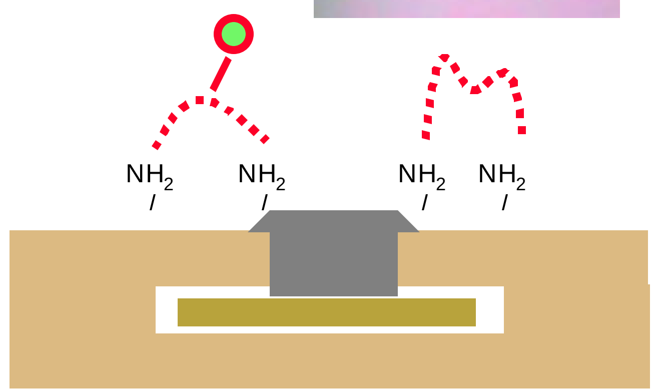


Photo-crosslinked Polyimides



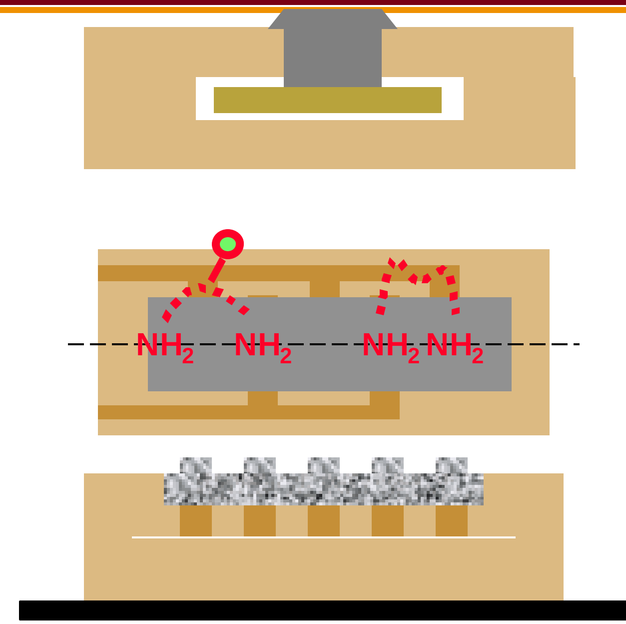


Surface Plasma Treatments
(NH_3 - Amination)



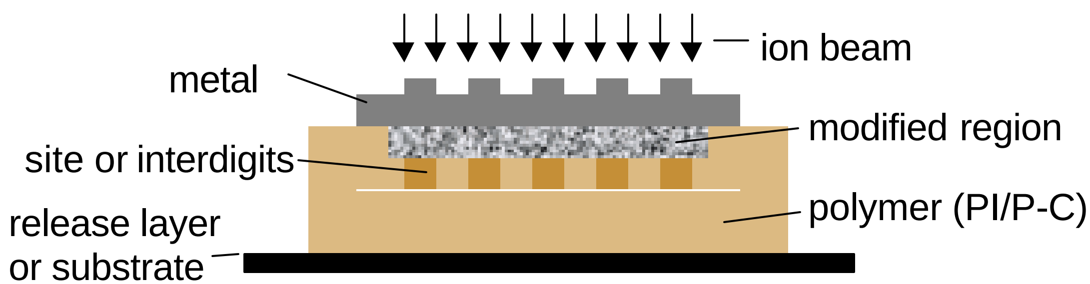
Advanced Neuro-Device Interfaces

Passive



Chemical/Electronic
Amplification

Active



Silicon FETs?

Topics

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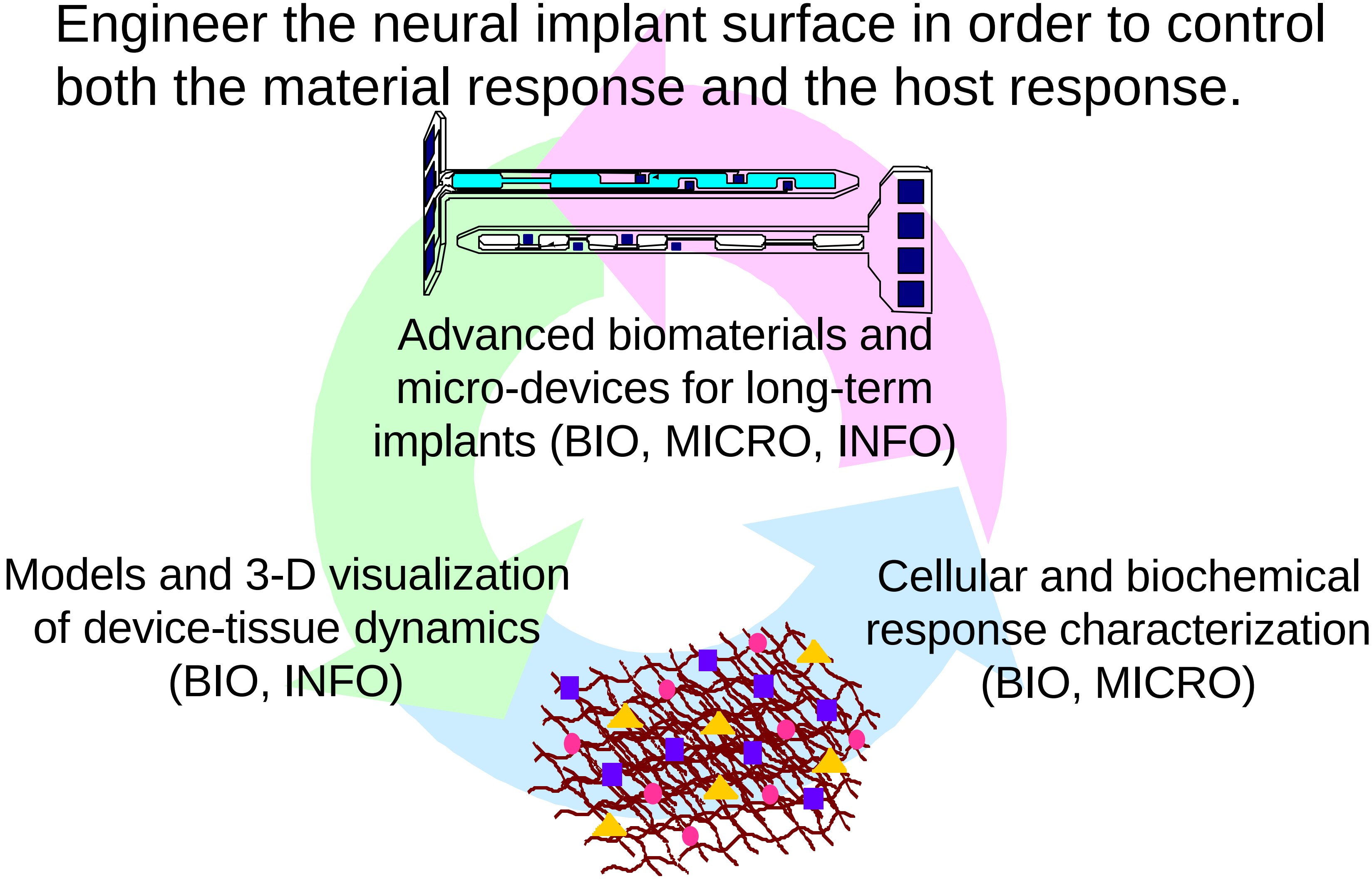
Approach

Engineer the neural implant surface in order to control both the material response and the host response.



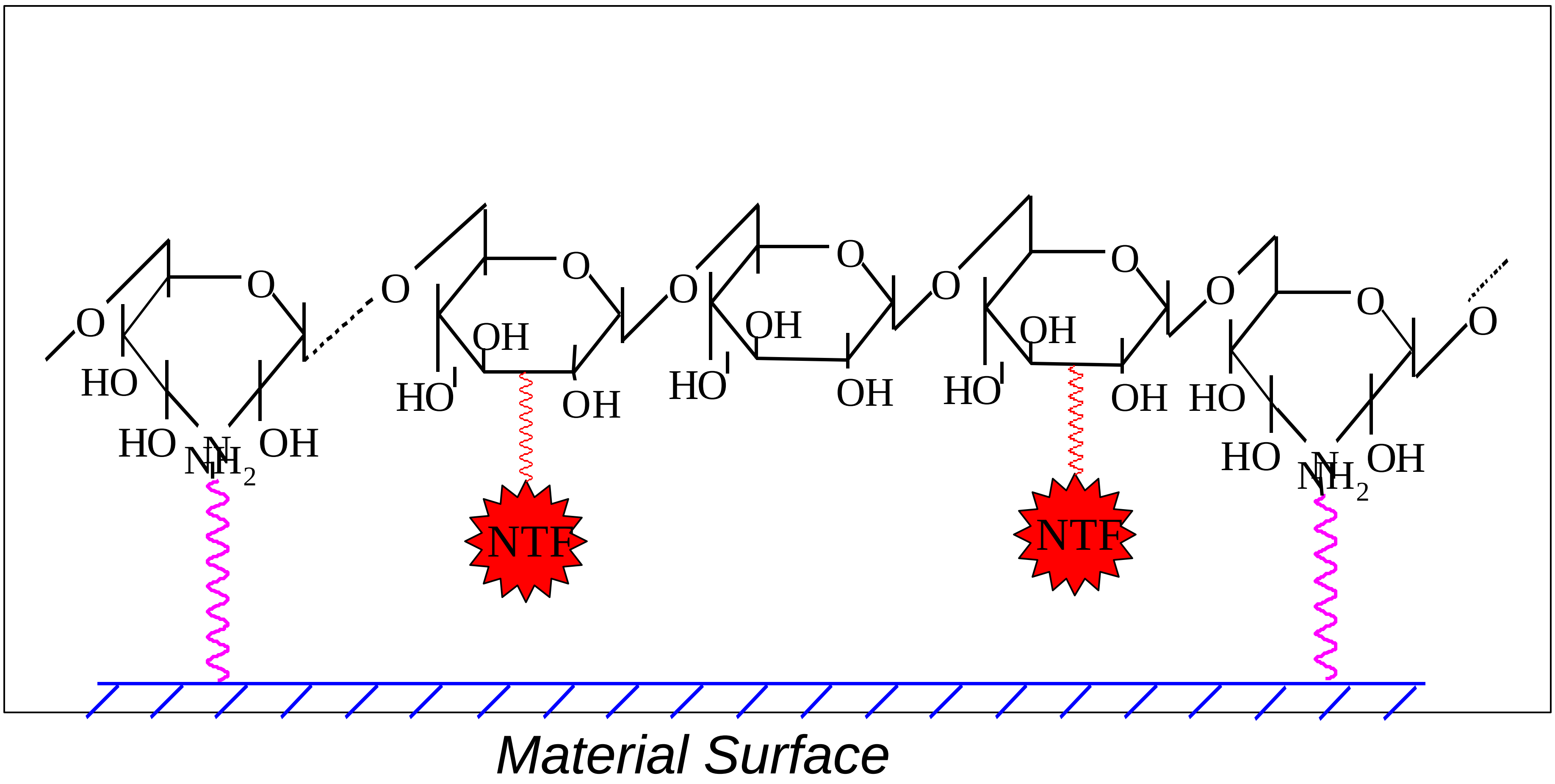
Factors Limiting Chronic Soft Tissue Implants

- Inability to control cellular interactions at biomaterial-tissue interface
- Initial adsorption of biological proteins
  - Non-selective cellular adhesion
- Unavoidable "generic" foreign body reactions
  - Inflammation
  - Fibrous capsule formation

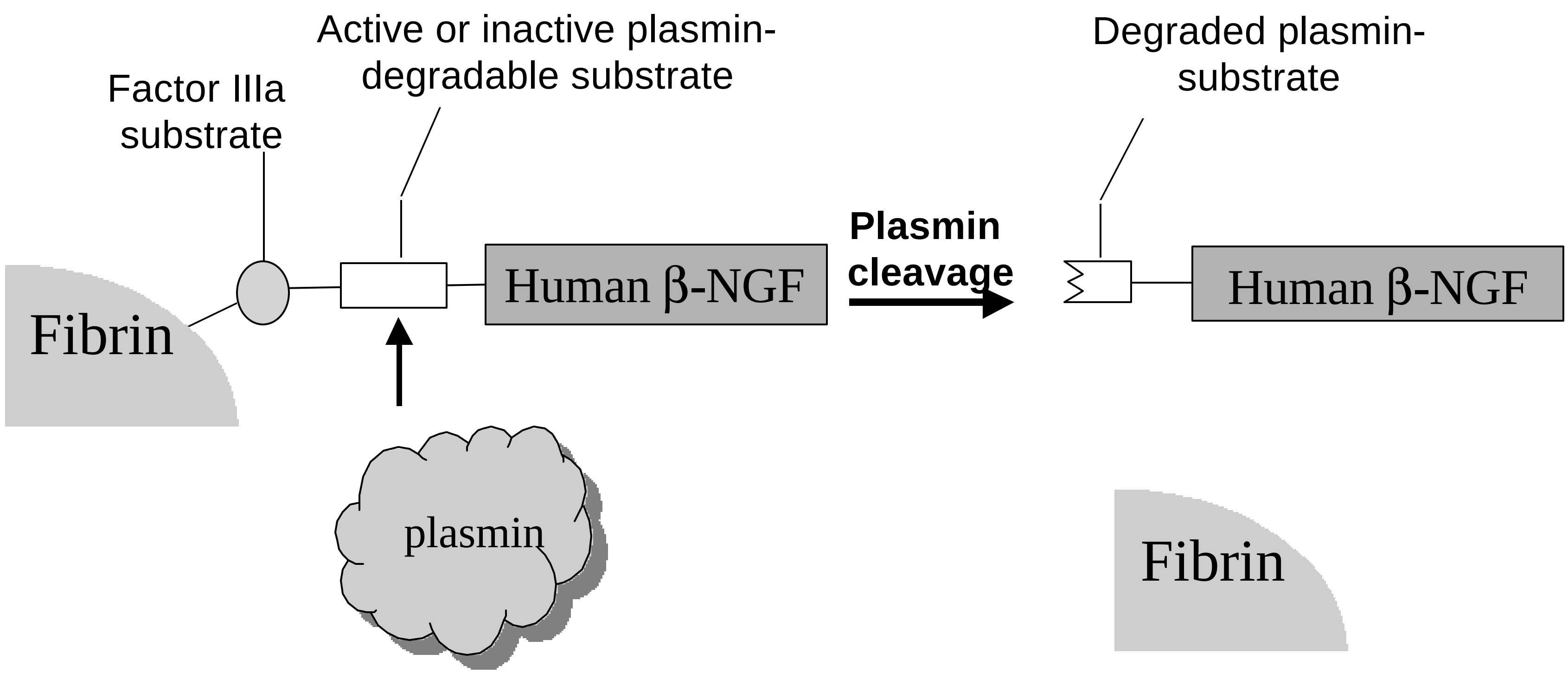
Potential Solution

- Engineer surface for minimal protein adsorption and selective cell adhesion
  - Cell-resistant polymer coatings
    - Synthetic: Polyethylene Glycol, Polyvinyl Alcohol
    - Natural: Polysaccharides, Phospholipids
  - Surface immobilization of biologically active molecules
    - Mimic biochemical signals of extracellular matrix
    - Cell binding domains for integrin receptors

Biomimetic Surface Modification

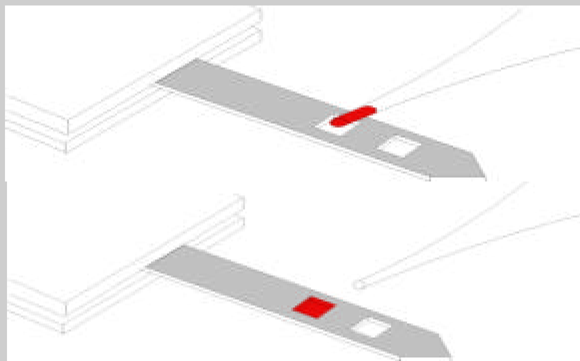


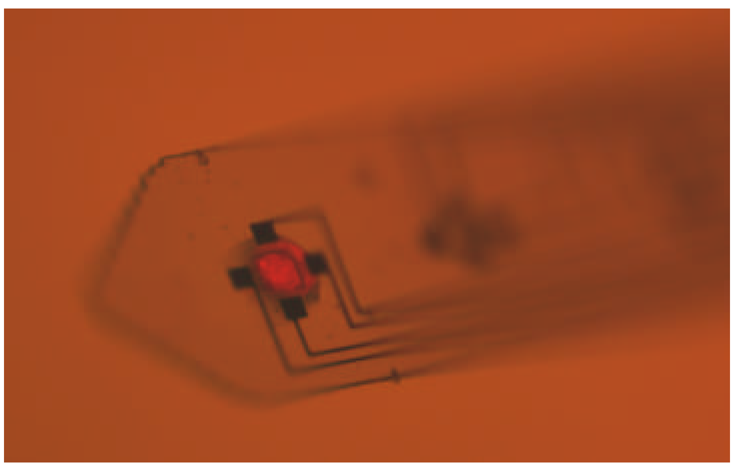
Recombinant NGF Fusion Protein



Bioactive Functionality

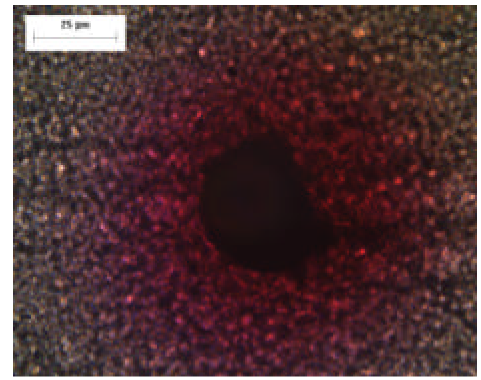
Methods

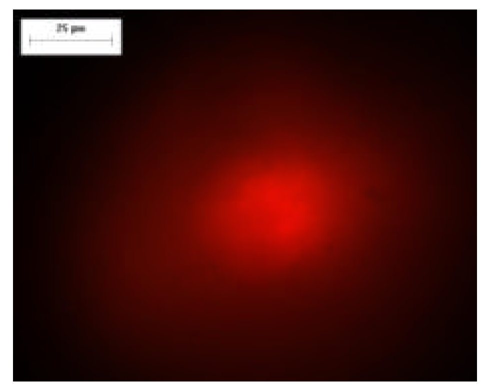


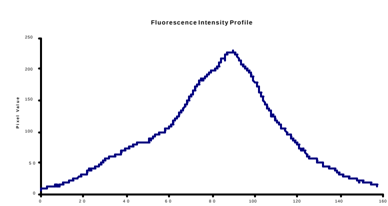


NeuroTrace™ DiI tissue-labeling paste, inverted fluorescent microscope with FITC/rhodamine filter cube

6-hour diffusion in rat cortex







Topics

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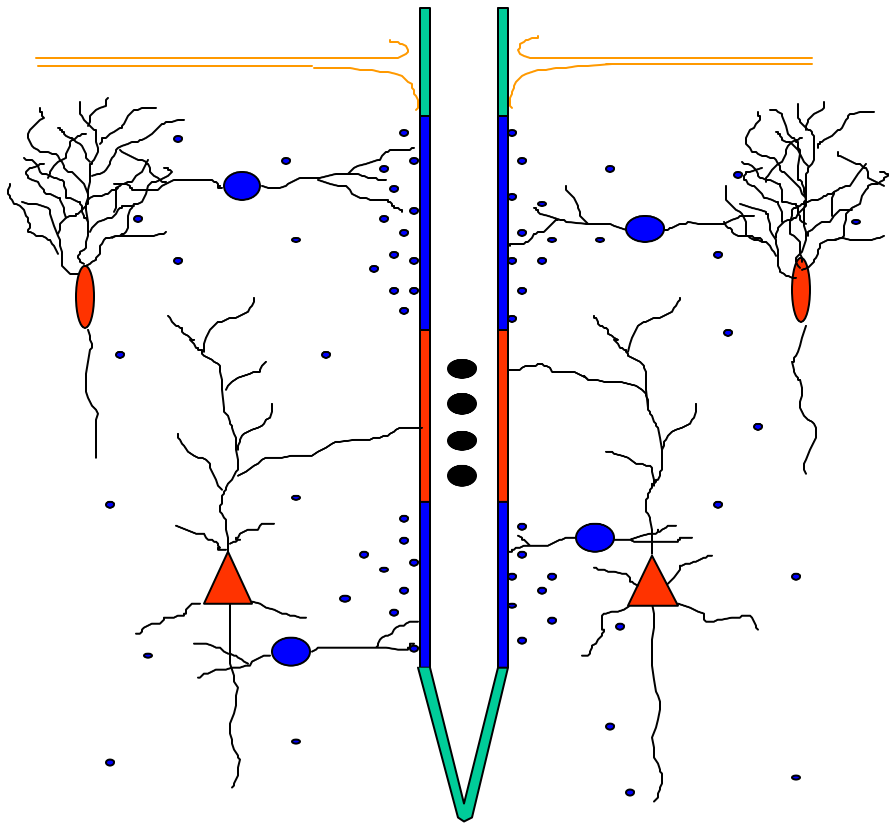
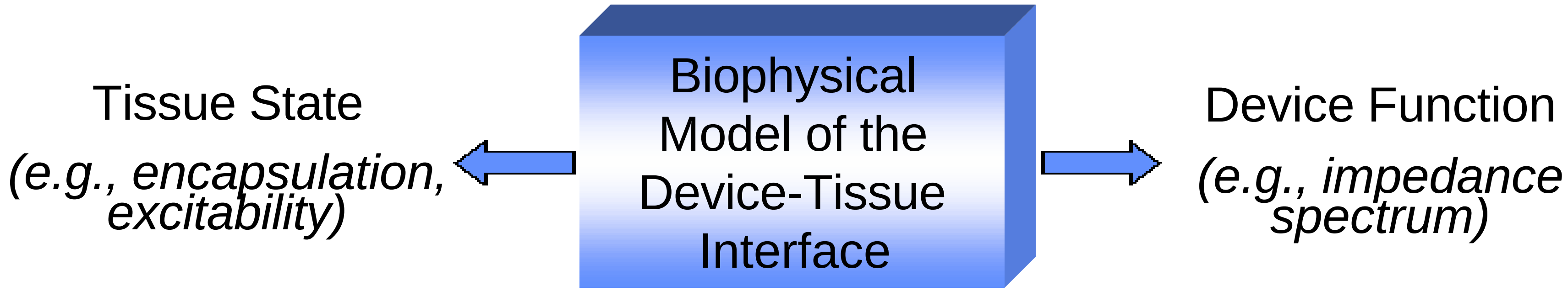
The Device-Tissue Interface

Neural Interface:

Micro-device, Neurons, Glia, Extracellular Space

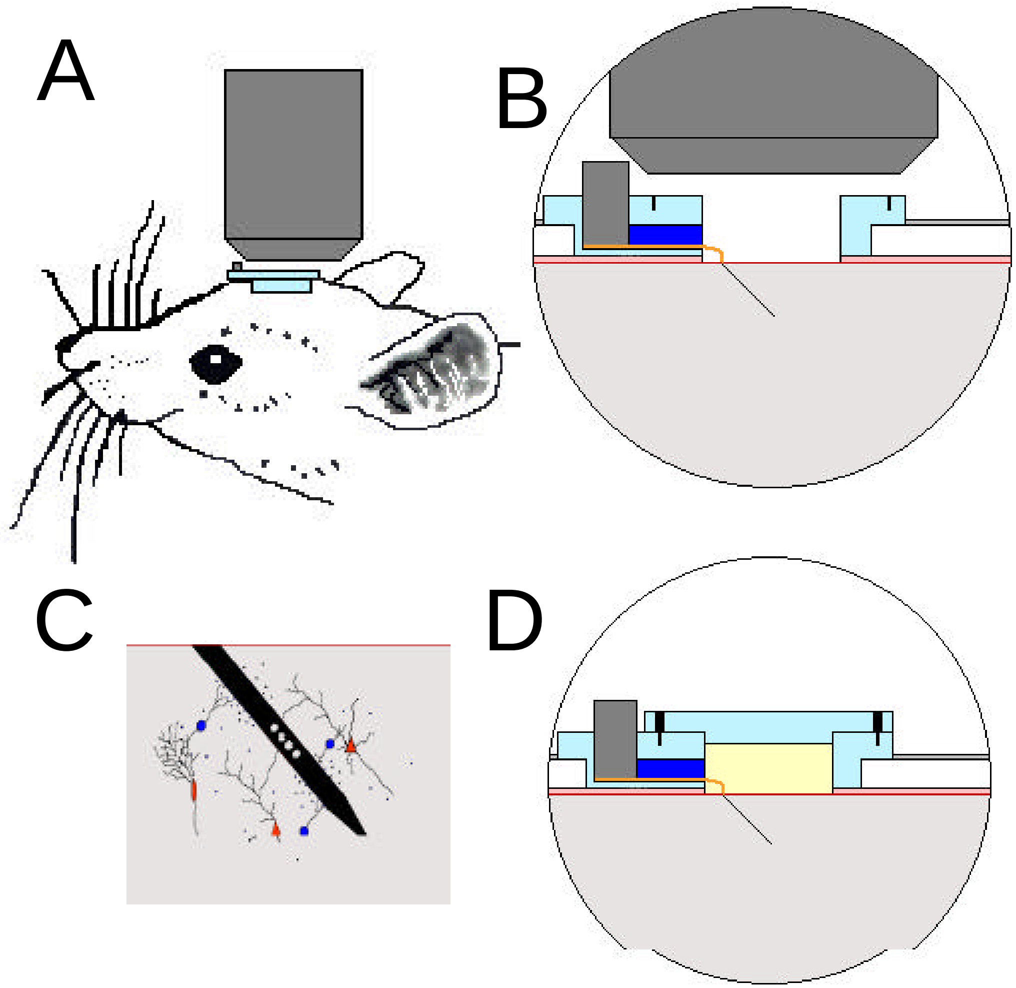


The Goal is to Characterize, Predict, and Control the Device-Tissue Interface

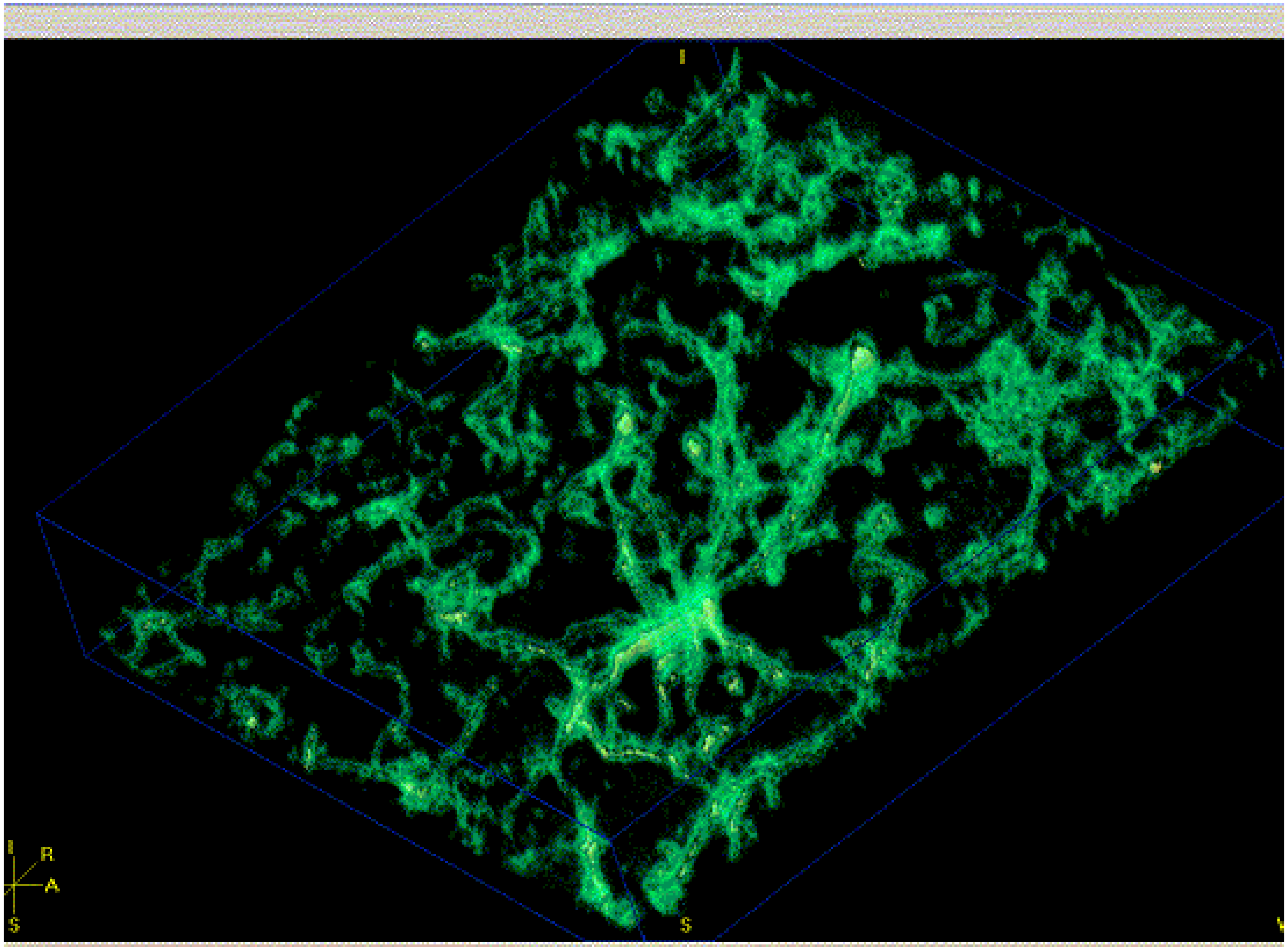


- Integrate bioelectrical, histological and biochemical data
- Optimize electrode specifications

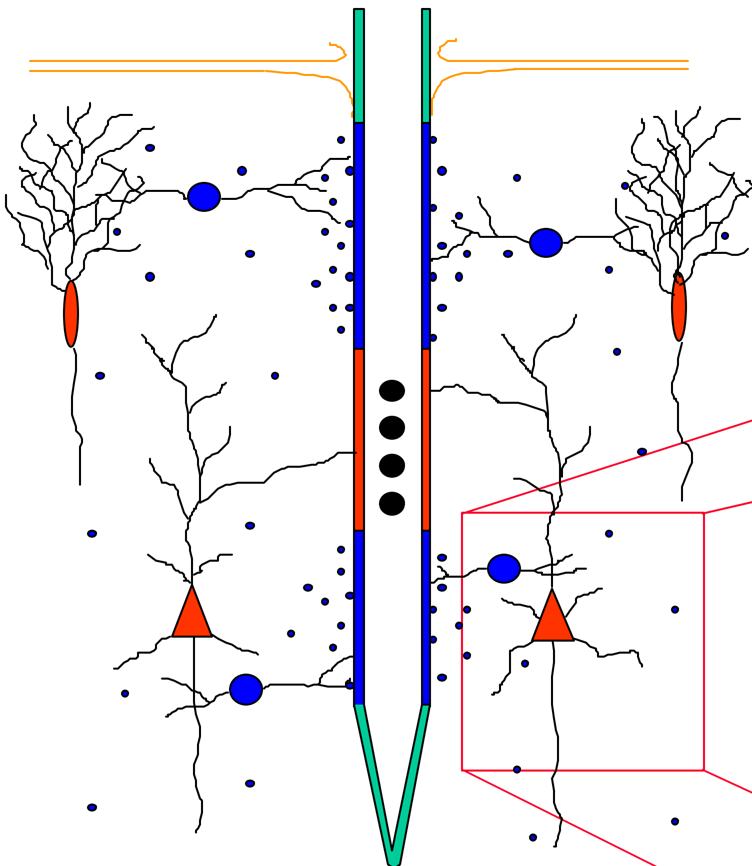
Visualization of the Chronic Device-Tissue Interface With Confocal Microscopy



In vivo Visualization of the Chronic Device-Tissue Interface



Multi-Domain Continuum Model



- Tissue is two (or more) coupled volume-conducting media
- Electrode is boundary condition

At each "point" $\vec{r}$ in space:

volume fraction $f_{e/i}(\vec{r})$

potential $\Phi_{e/i}(\vec{r},t)$

conductivity tensor $G_{e/i}(\vec{r})$

membrane parameters

a, C, g_L, etc.

Equations for a Multi-Domain Continuum Model

Volume conductor equations (conservation of current)

$$-f_e \nabla \cdot \left(G_e \nabla \Phi_e \right) = + \sum_i I_{mem_i} + I_{app}$$

$$-f_i \nabla \cdot \left(G_i \nabla \Phi_i \right) = - I_{mem_i} \qquad i = \text{index over intracellular domains}$$

Membrane potential(s) and membrane current(s)

$$V_i = \Phi_i - \Phi_e \qquad I_{mem_i} = a_i \left(C_i \frac{\partial V_i}{\partial t} + I_{ion_i} \right)$$

$\Phi_{e/i}$ = potential (mV)

$G_{e/i}$ = conductivity (mS/cm)

$f_{e/i}$ = volume fraction

a_i = surface to volume ratio (cm^{-1})

I_{mem_i} = membrane current (mA/cm^3)

I_{app} = applied current (mA/cm^3)

V_i = membrane potential (mV)

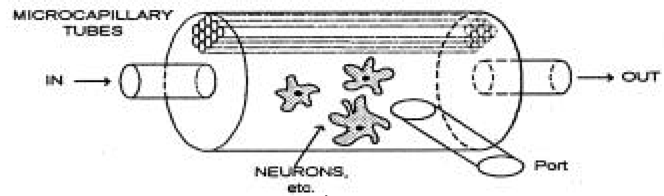
C_i = membrane capacitance (mF/cm^2)

I_{ion_i} = membrane current (mA/cm^2)

Levels of Modeling

Numerical	Analytical
Multiple intracellular domains	A single intracellular domain
Voltage-dependent conductances	Passive membrane conductance
$I_{ion_i} = \sum_j \bar{g}_{ij} \prod_k q_{ijk} \left(V_i - E_j \right)$ $\frac{\partial q_{ijk}}{\partial t} = -\frac{q_{ijk} - q_{ijk}^{\infty}\left(V_i\right)}{t_{ijk}\left(V_i\right)}$	$I_{ion} = g_L \left(V - E_L \right)$
Complex electrode geometry	Simple electrode geometry
Tissue inhomogeneous and anisotropic	Tissue assumed homogenous and isotropic
under construction	*much progress*

Bi-domain Model for the Microcapillary Bioreactor

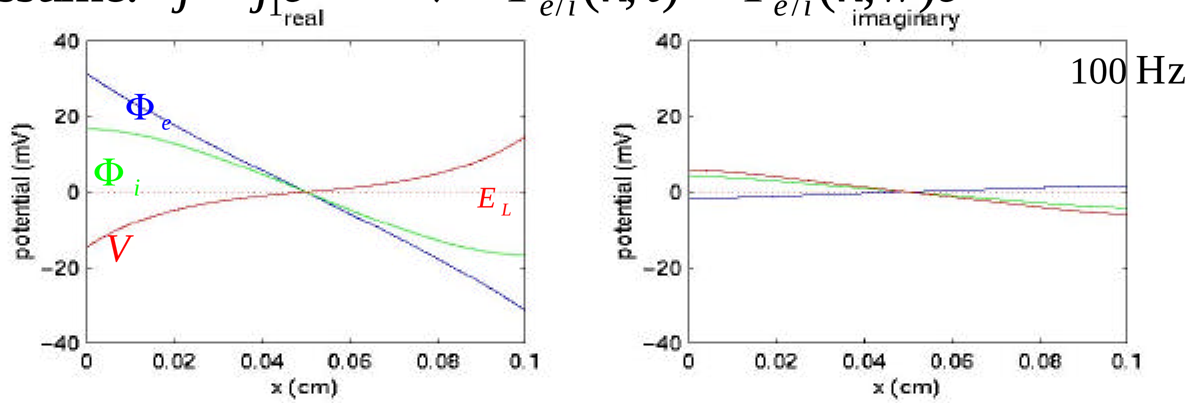


Write BCs and assume: $j = j_1 e^{iwt} \Rightarrow \Phi_{e/i}(x,t) = \Phi^1_{e/i}(x;w)e^{iwt}$

Calculate profiles

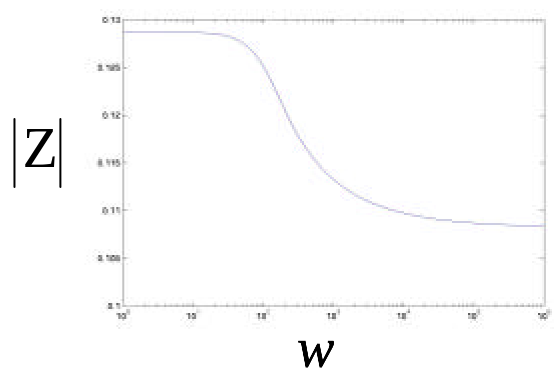
$\Phi^1_{e/i}(x;w)$

in bioreactor



...and impedance...

$$Z(w) = \frac{\Phi^1_e(L;w) - \Phi^1_e(0;w)}{j_1}$$



...and predict $Z(w)$

as tissue parameters

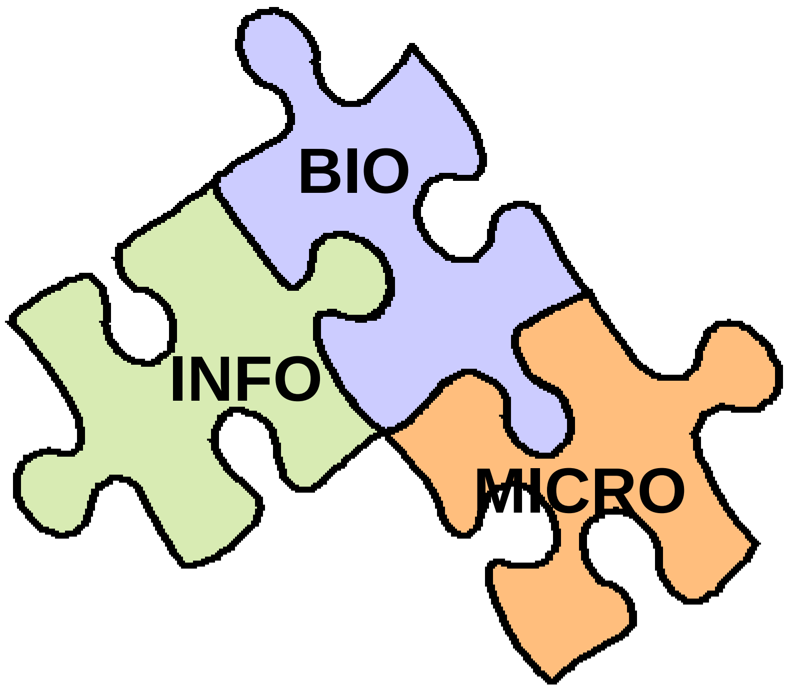
$f_{e/i}, G_{e/i}, a, C, g_L, E_L$

are experimentally

manipulated

Recap

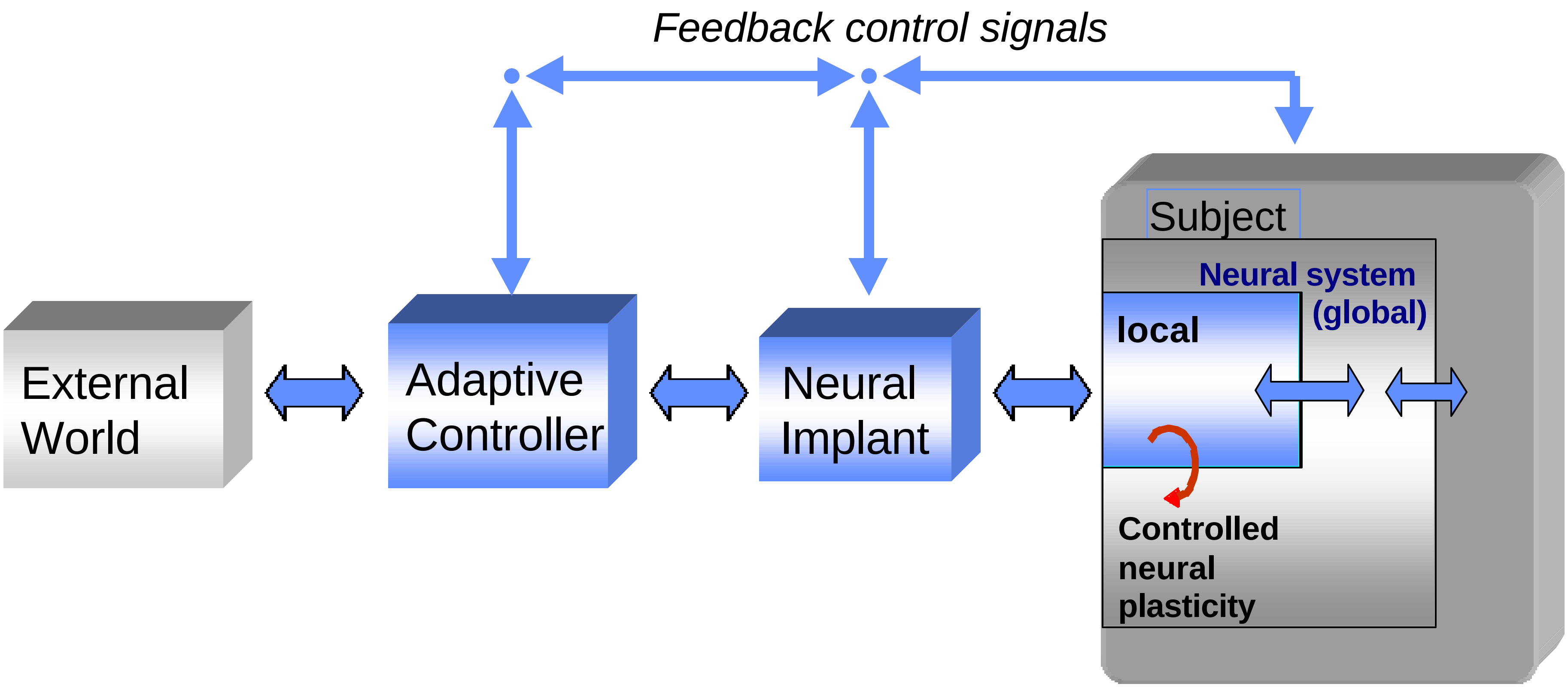
- Focused & integrated effort
  - *BioMEMS…Neural Engineering…Materials… Computational Neuroscience…Cellular Biology…Visualization*
- Why are we so excited?
  - We have the very real potential of characterizing the biological responses to neural implants ***and*** then engineering new classes of microdevices to provide a permanent high-capacity interface to the brain



Why the BIO, INFO, and MICRO Program?

- Wide-open Challenges
  - Characterizing and modeling the biological (cellular and chemical) responses around a neural implant
  - Controlling the dynamic biological responses around a neural implant.
  - Designing, fabricating, and using “advanced” neural implants
- Collaboration Possibilities
  - Additional functionalities for implantable microdevices of the class that we are working on.
  - Exploring fundamentally new types of tissue-device interfaces.
  - Complementary studies of the neural interface (experimental and analytical)
  - Confocal microscopy of the neural interface
  - Sharing technologies, procedures, insights, etc…
  - *New emergent ideas…*

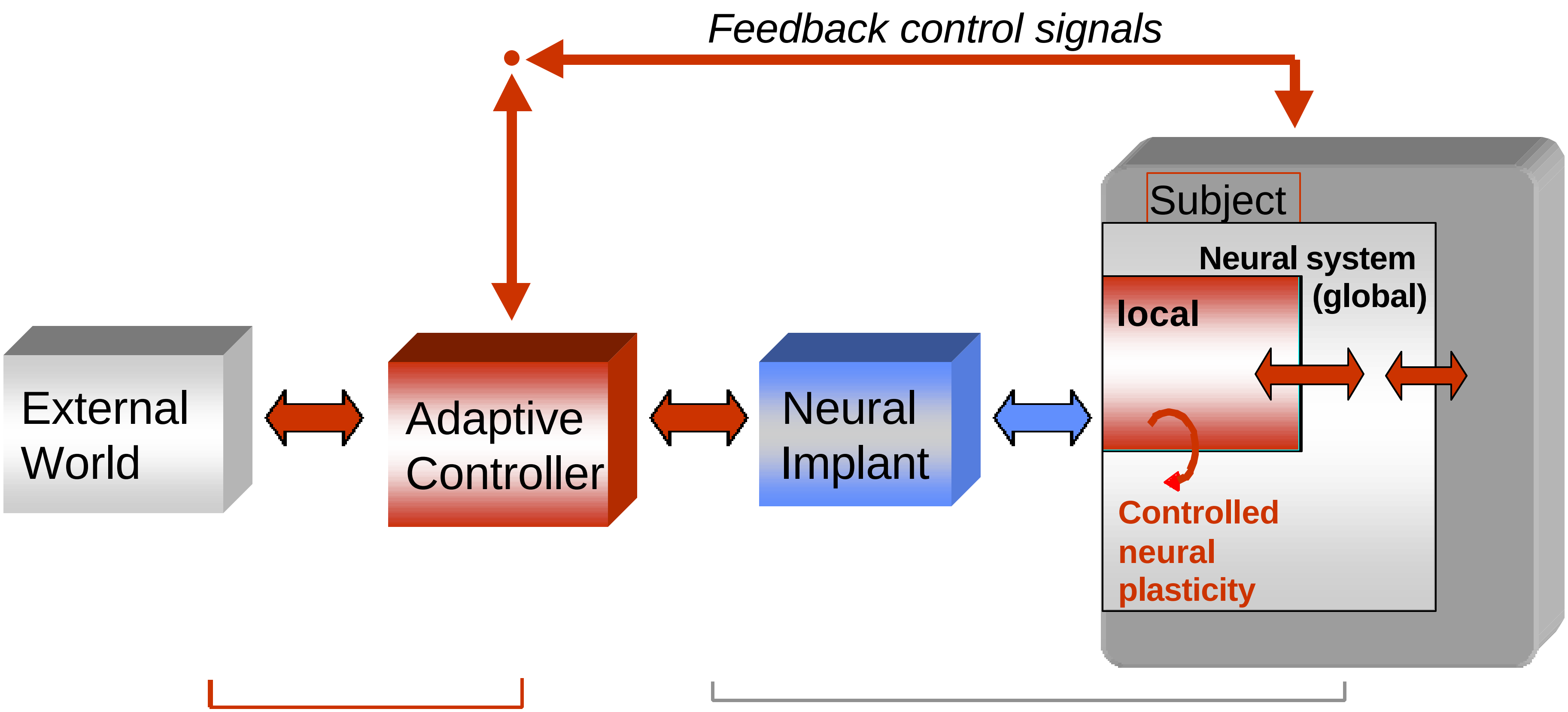
Systems-level Analysis of Advanced Neuroprosthetic Systems



***__Objective 2:__* Optimize Adaptive Controller**

***__Objective 1:__* Optimize neural interface**

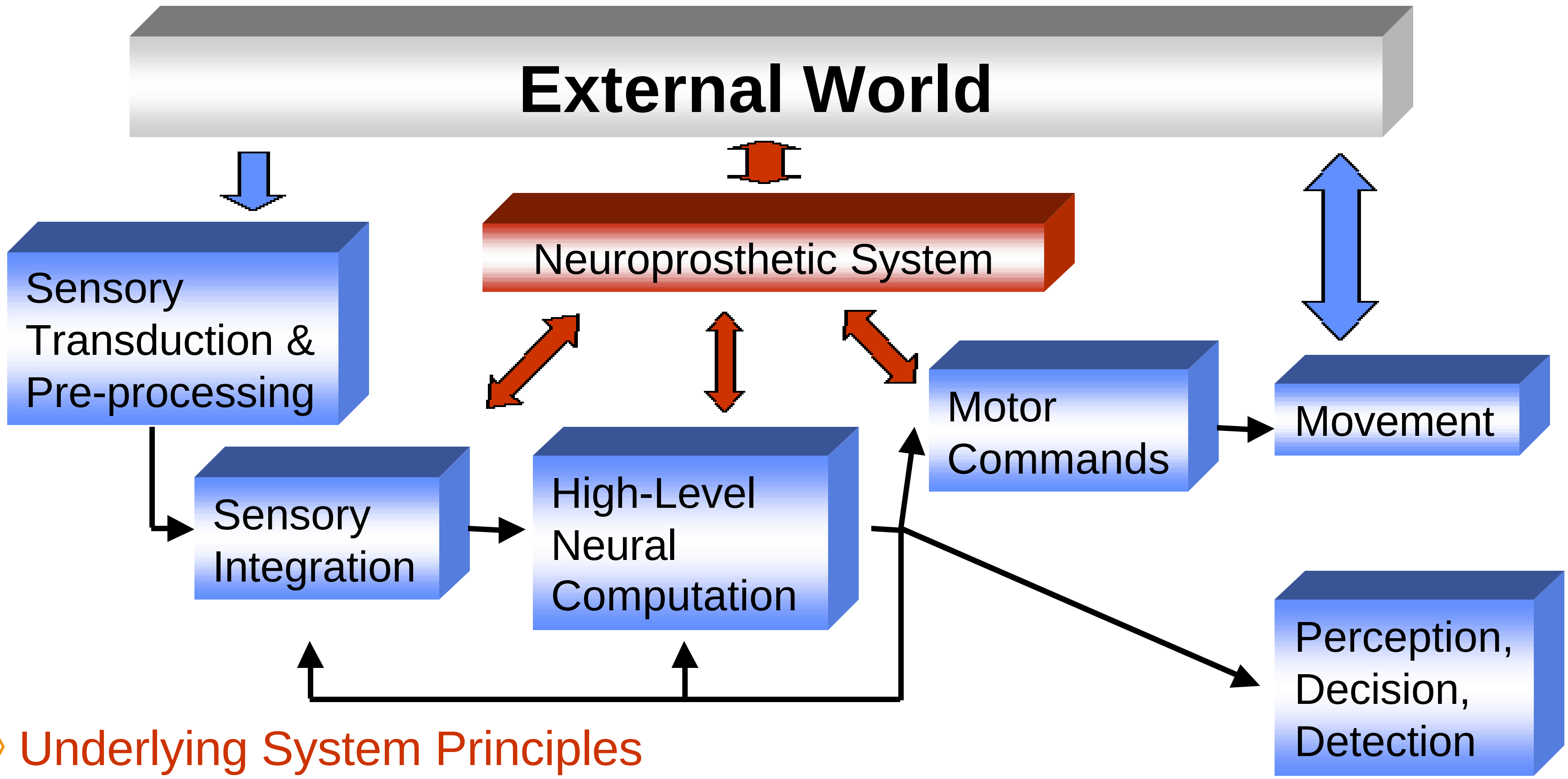
Systems-level Approach for Advanced Neuroprosthetic Systems



Objective 2: ***Develop adaptive controller to optimize system performance.***

Objective 1: *Optimize neural interface*

Advanced Neuroprosthetic Systems



◊ Underlying System Principles

- **Two-way communication** with targeted neural systems
- Harness **neural plasticity** to our advantage
- Appropriately **balanced "wet-side" and "dry-side" computation**

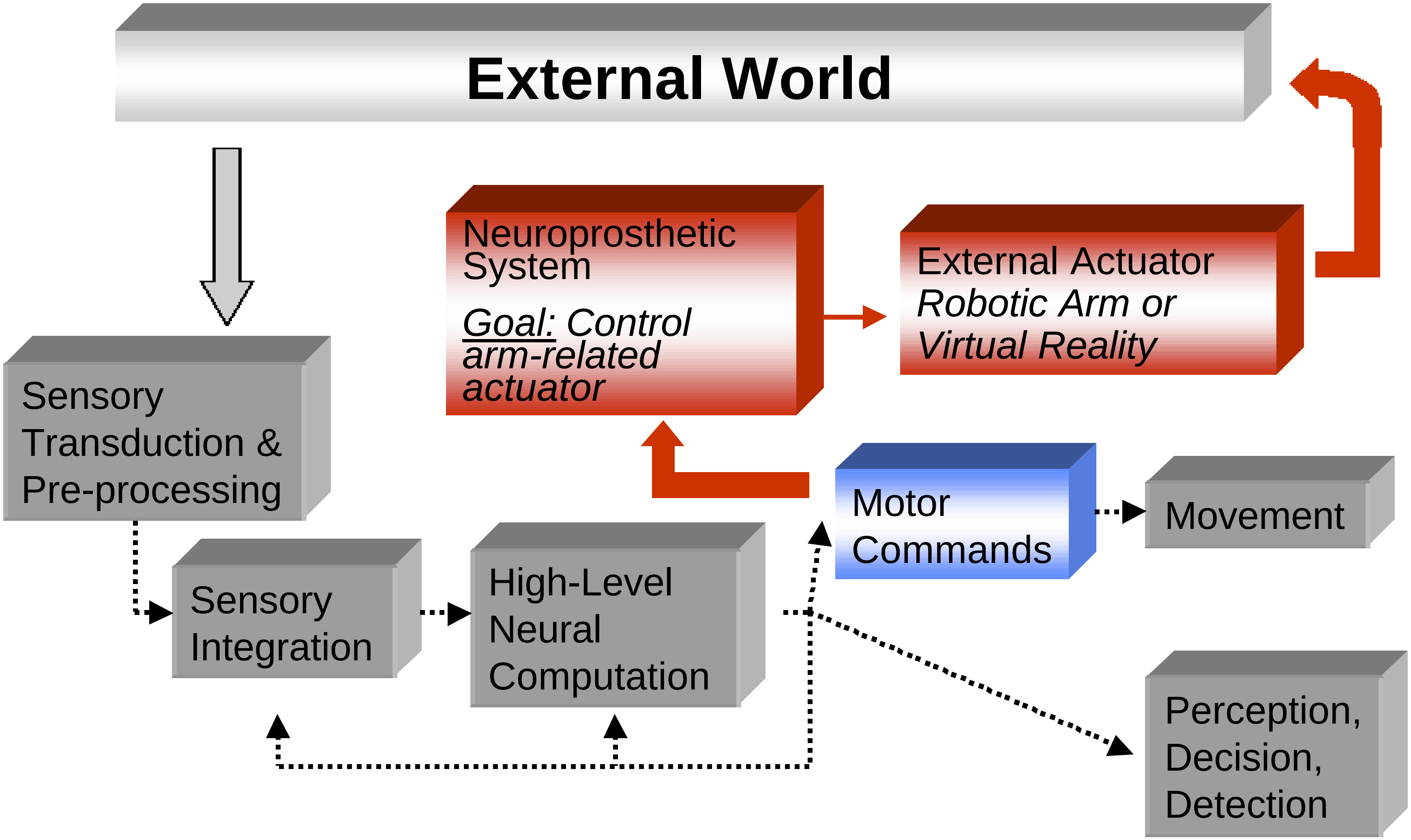
Approach

- Four Project Areas
  - Direct neural control of actuators
  - Detection of novel sensory stimuli through monitoring neural activity
  - Neural control of behavior
  - Investigate signal transformations from ensembles of single neurons to local field potentials to EEG.

Topics

- ☒ *Project overview*
- ☒ *Towards the Development of 3rd-Generation Neural Implants (BIO, MICRO, and INFO)*
- ☒ *Bioactive Coatings to Control the Tissue Responses to Implanted Microdevices (BIO, MICRO, and INFO)*
- ☒ *Modeling the Device-Tissue Interface (BIO, MICRO, and INFO)*
- ❑ Direct Cortical Control of a Motor Prosthesis (BIO, MICRO, and INFO)
- ❑ Neural Control of Auditory Perception
- ❑ Wrap-up

Direct Cortical Control of Actuators



Fundamental Questions

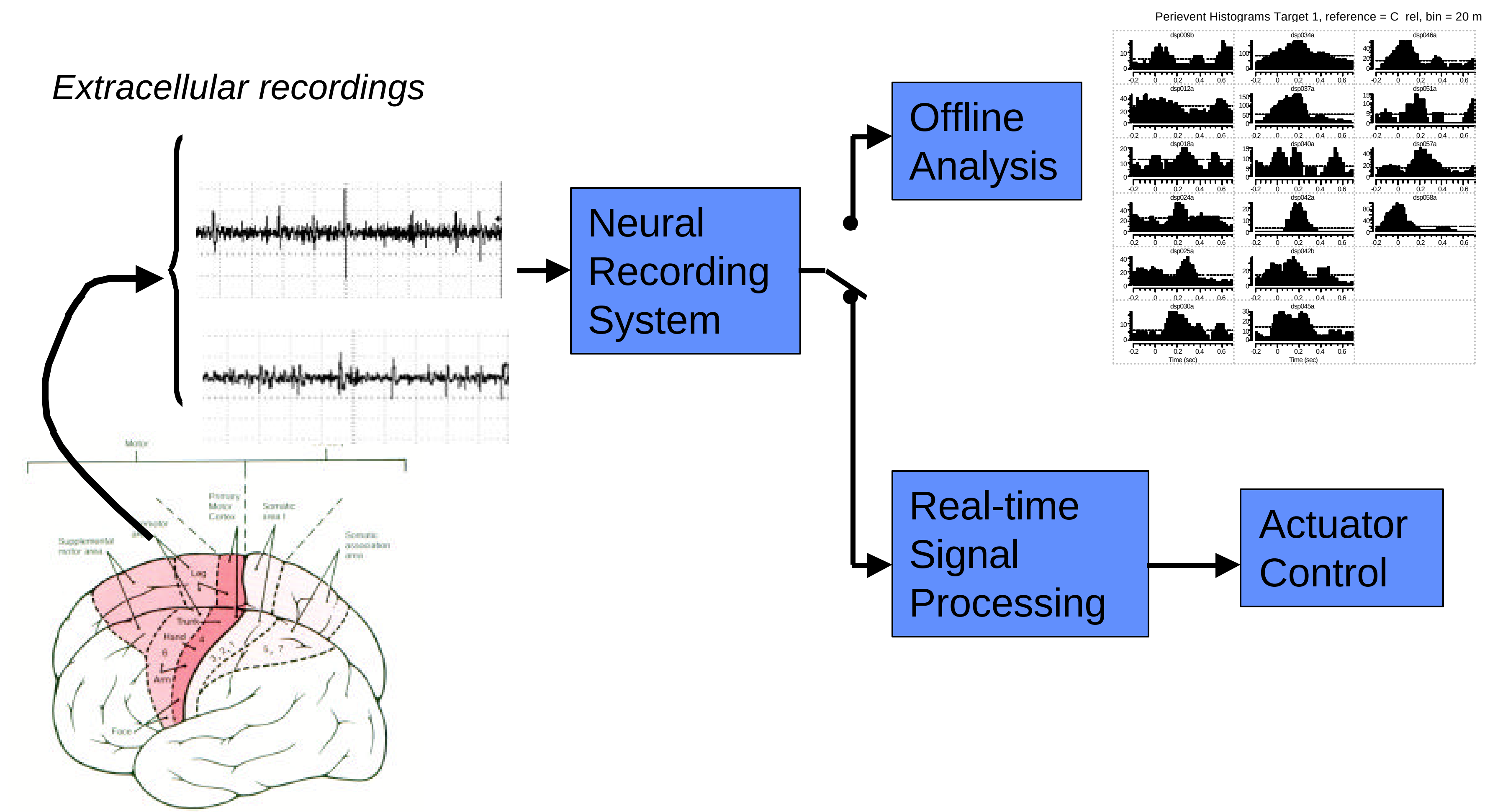
- What are “optimal” real-time signal processing strategies for precise 3-D control of external, arm-related actuators in the presence of sensory distractions and/or physical perturbations to the arm?
- To what extent can we use composite neural signals [neuronal (unit) recordings, local field potentials, and brain-surface recordings] for control signals?
- How do we take advantage of inherent or controlled neural plasticity in order to optimize system performance?

Experimental Preparation

- Train monkeys to perform tracking and/or reaching tasks.
- Record cortical responses with multichannel neural implants.
- Measure arm movement in 3-D space.

Chronic Neural Recordings

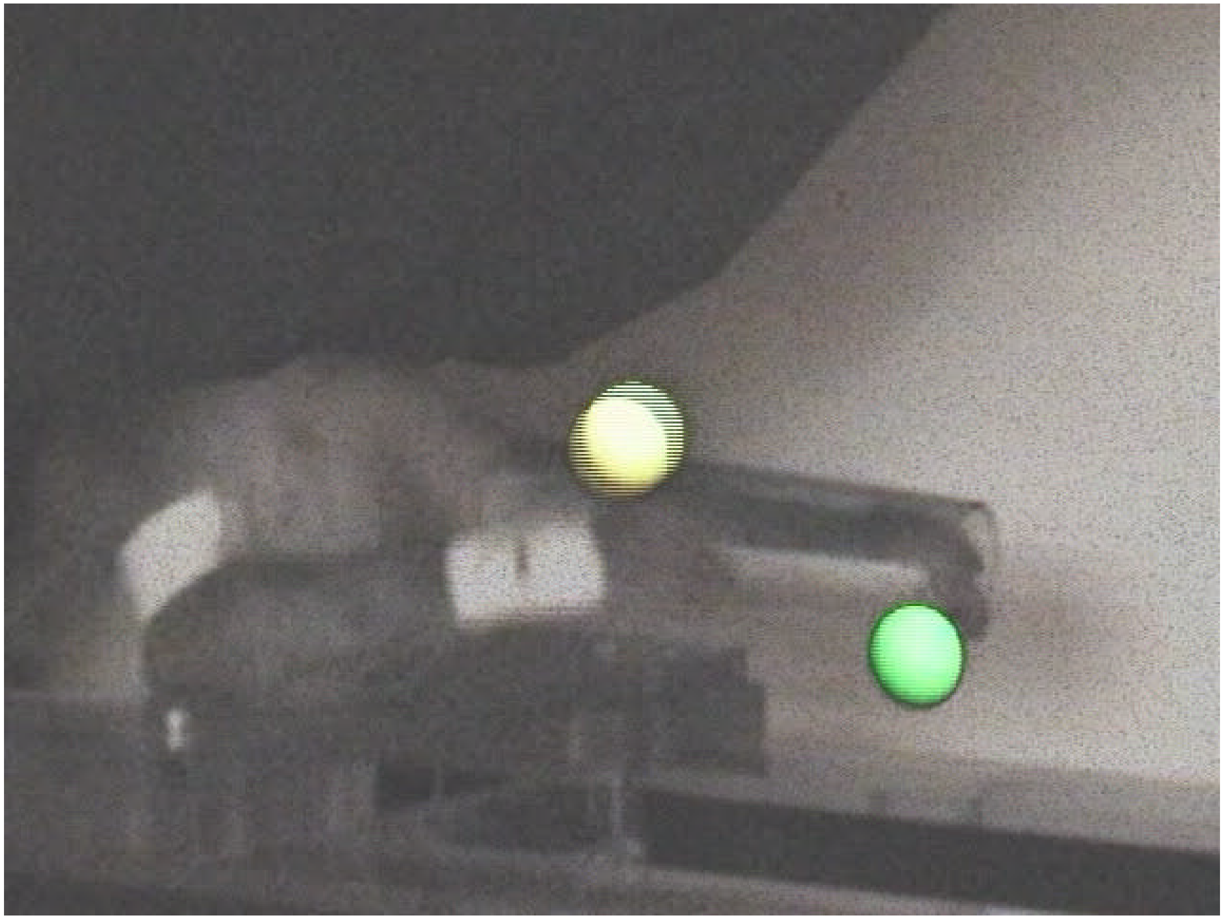
- Multi-channel neural implants in motor and sensorimotor cortical areas.
- Eventually: Sub-dural electrodes for local potentials



Direct Cortical Control of Movement

Green ball: Target

Yellow ball: Actual hand position, or hand position estimated from cortical responses



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Topics

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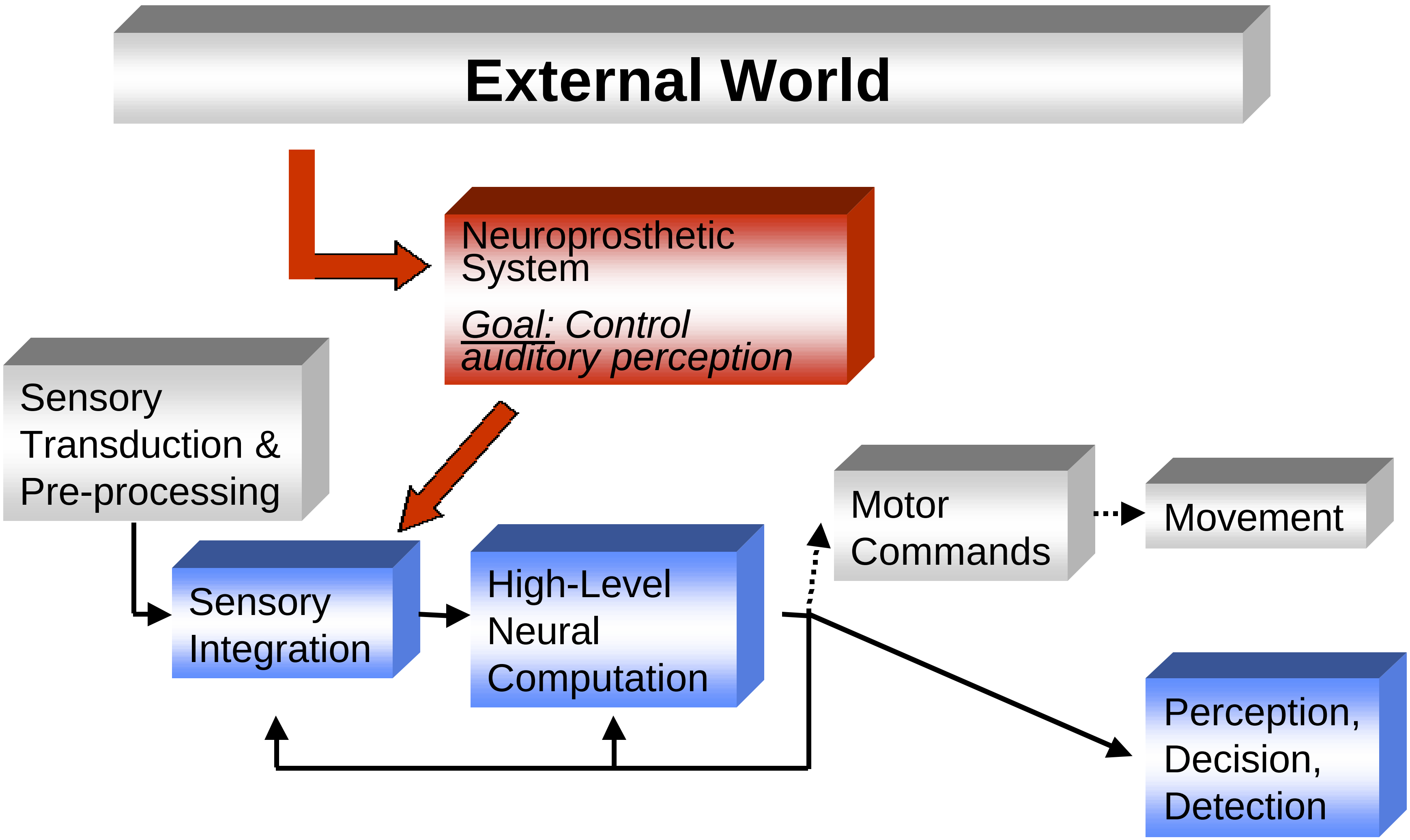
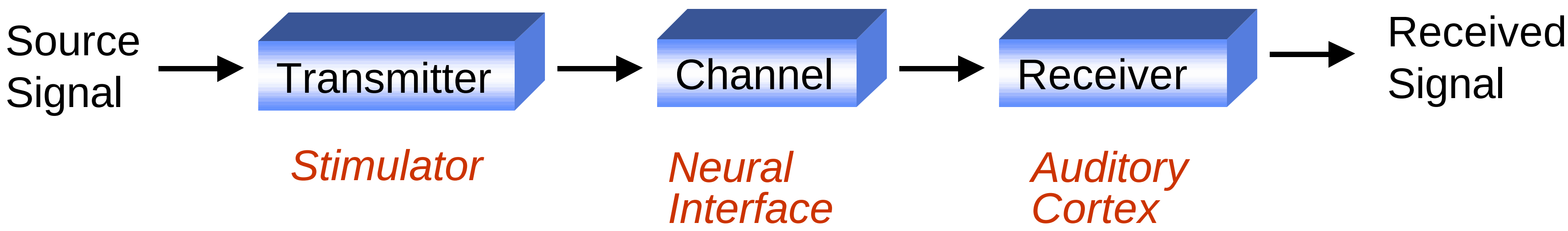
Neural Control of Auditory Perception



Fundamental Questions

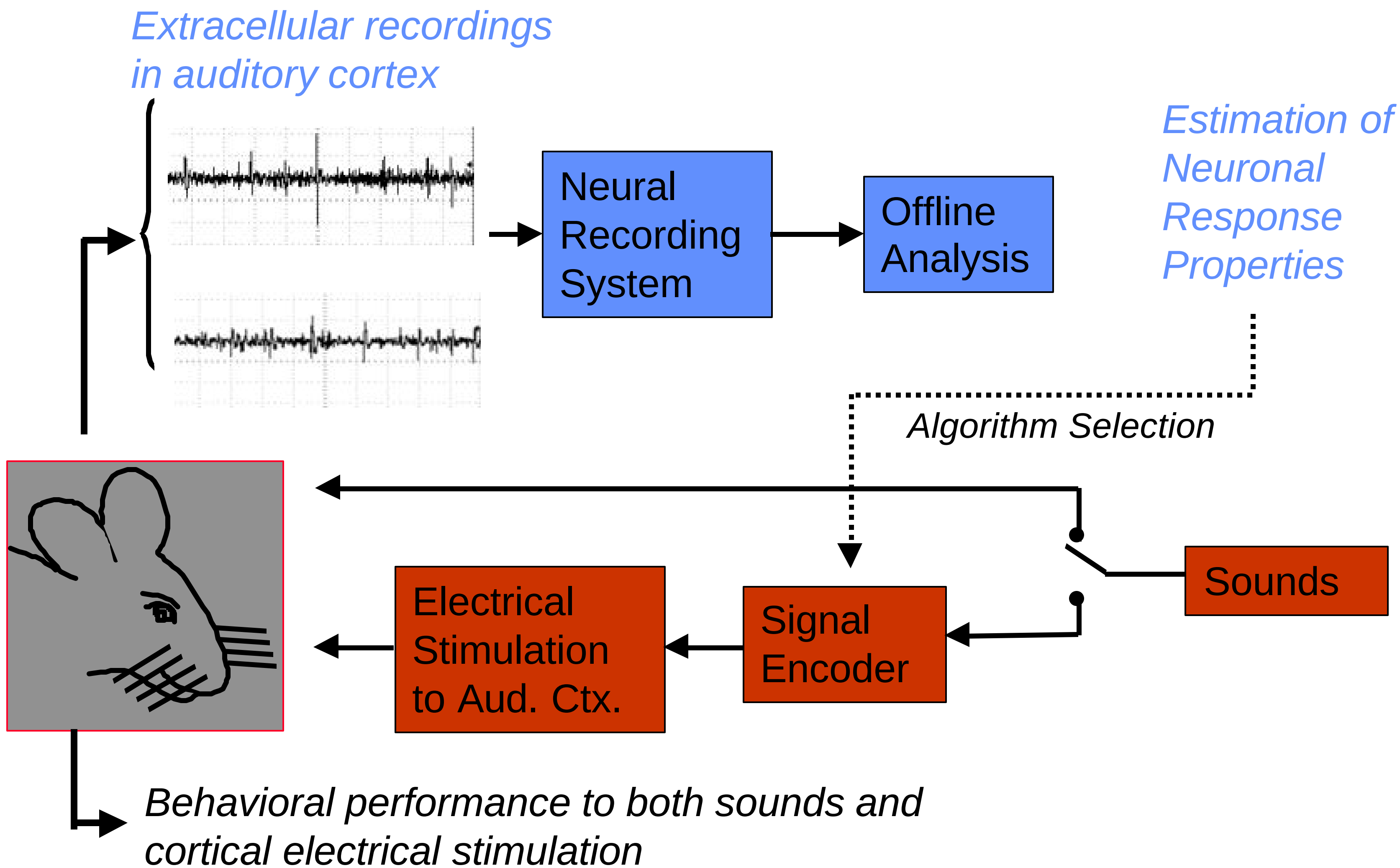
◊ To what extent can we control auditory-mediated behavior using intra-cortical microstimulation (ICMS) through the neural interface?



◊ What are the information transmission characteristics of the multichannel neural implant in high-level cortical areas using ICMS?
  - Channel capacity (bits per second)
  - Channel reliability
  - Channel resolution
- How can we optimize information transmission
  - Implant designs, Neural implant locations, Signal encoding strategies, Controlled neural plasticity

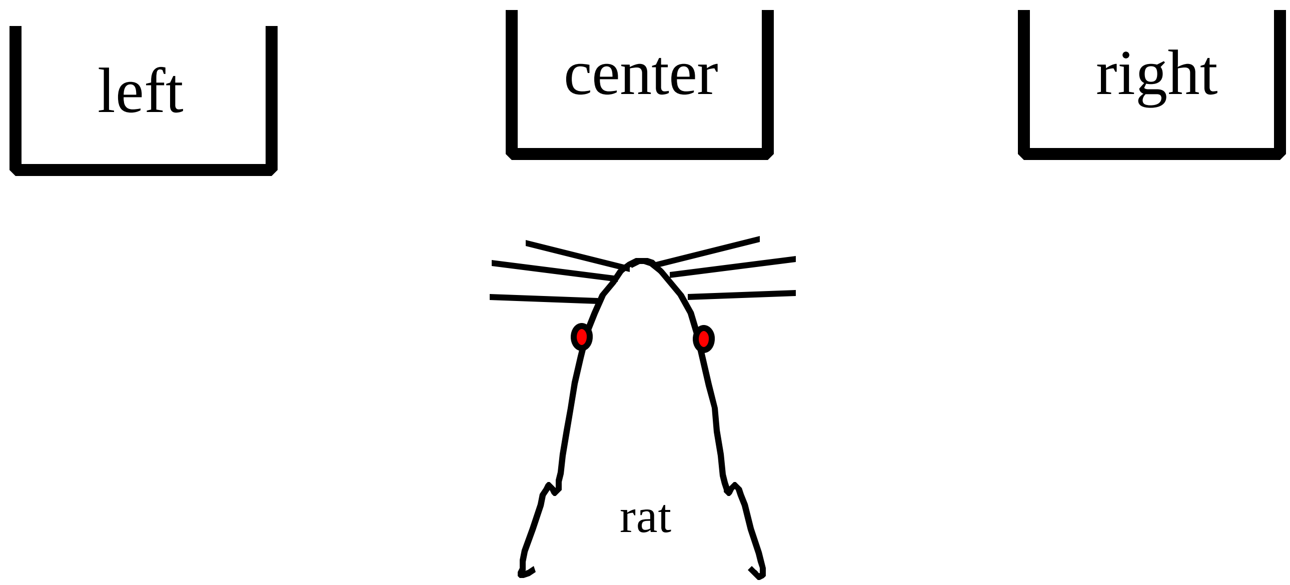
Chronic Neural Recordings

- Multi-channel neural implants in primary auditory cortex



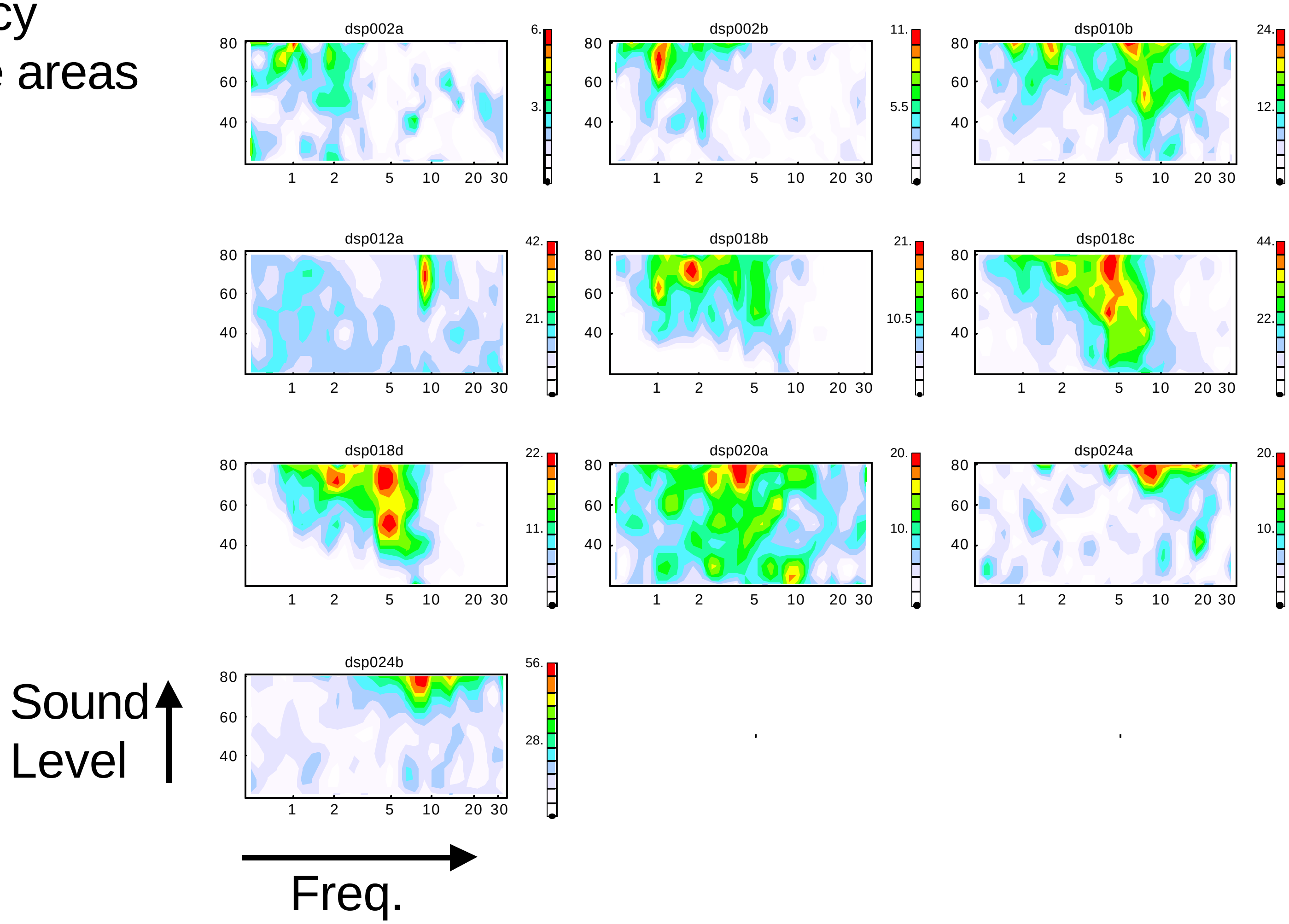
Auditory Behavior

- Lever-press sound or ICMS discrimination task
- Center paddle hit starts trial, 2-tone pair presented
- Reward obtained by signaling the correct stimulus sequence



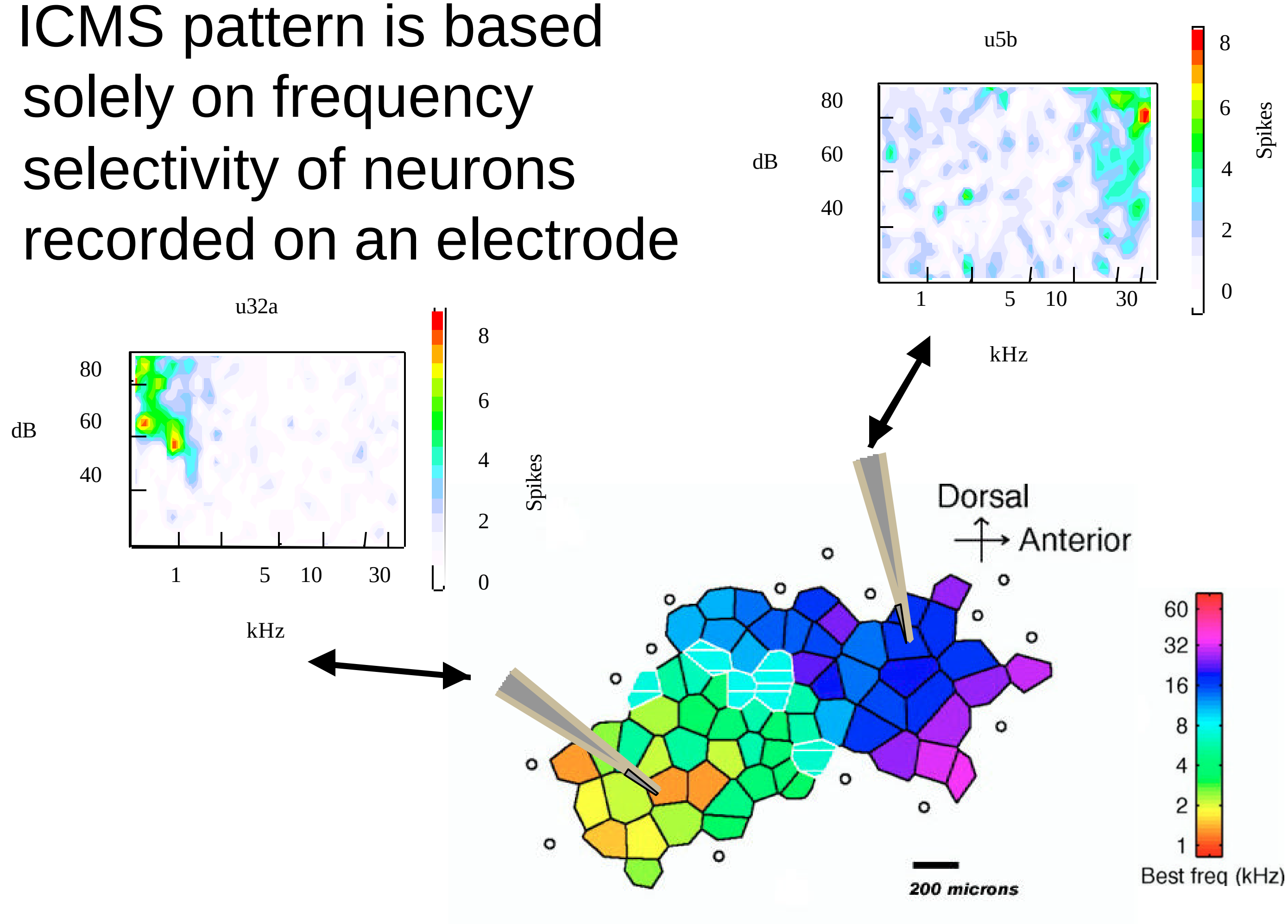
Frequency Selectivity in Auditory Cortex

Frequency response areas

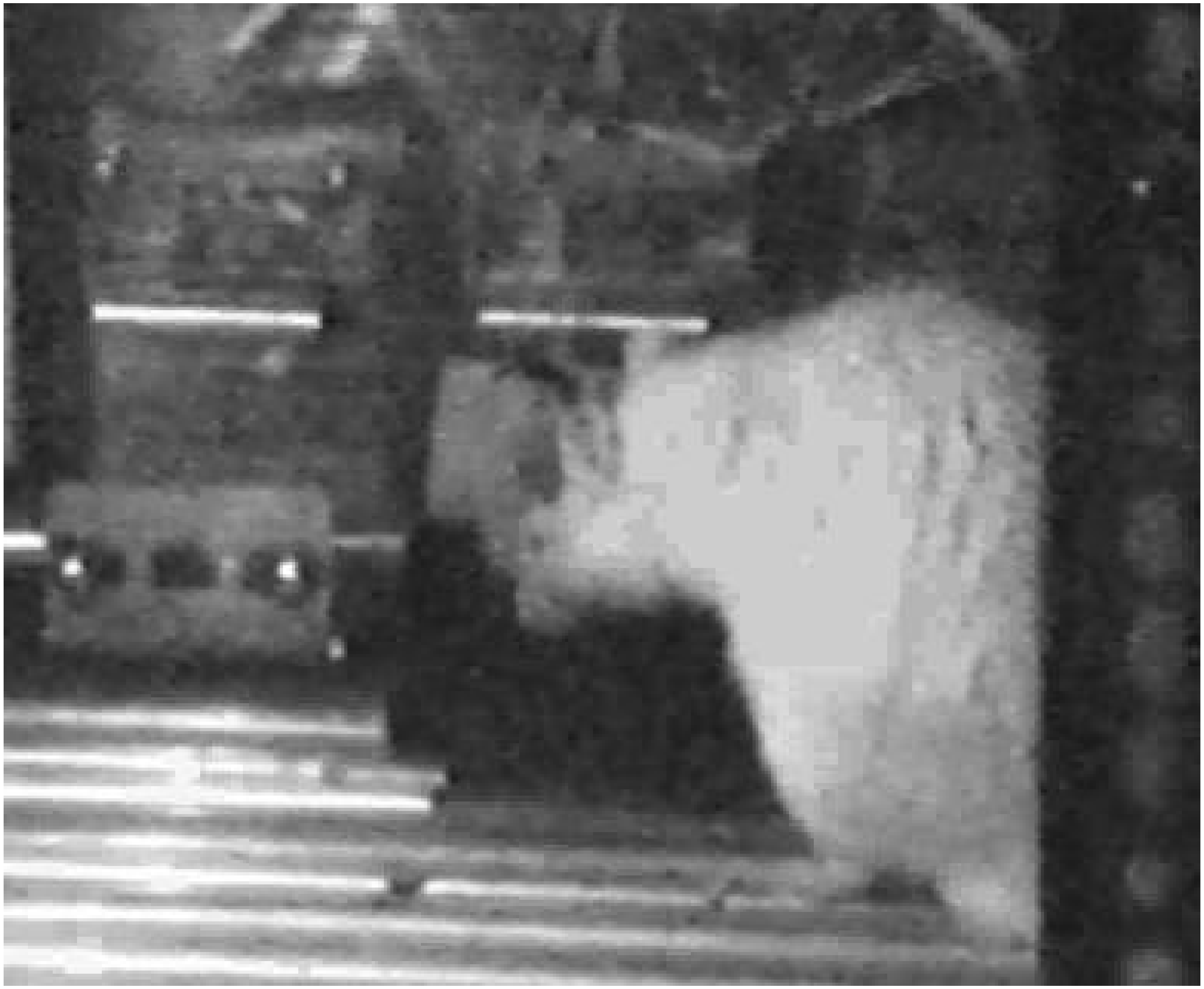


Signal Encoding Algorithm: Frequency Selectivity

ICMS pattern is based solely on frequency selectivity of neurons recorded on an electrode



Behavioral Performance



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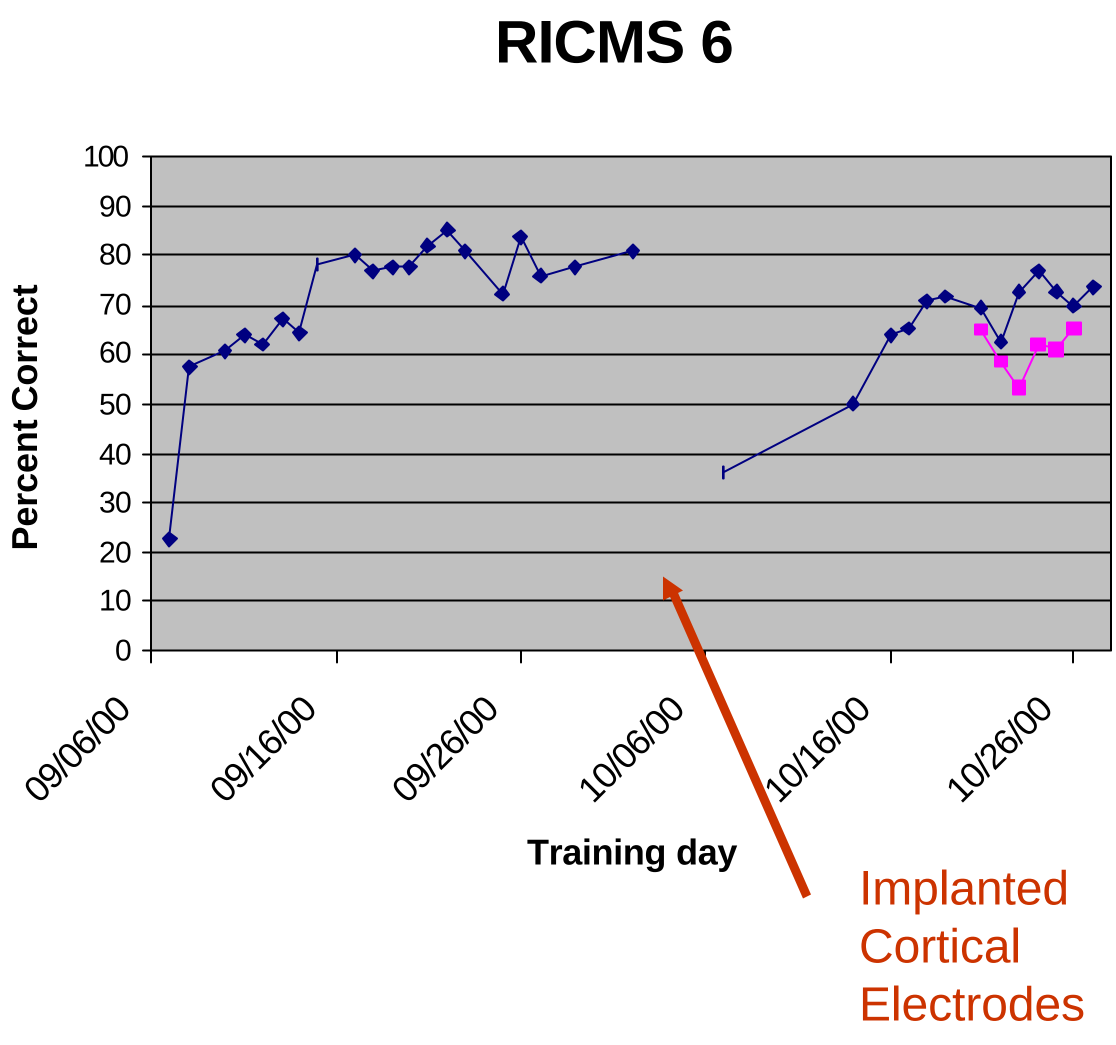
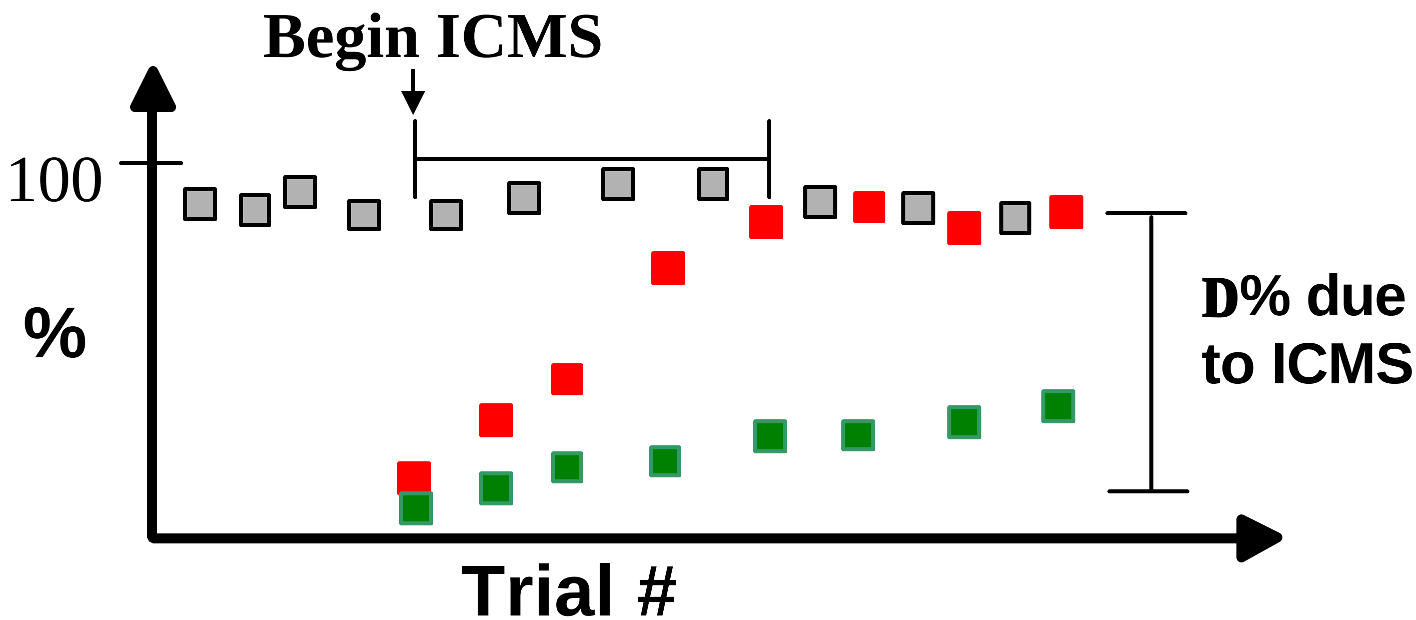
Rat Behavioral Performance



Expected Results to ICMS Stimuli

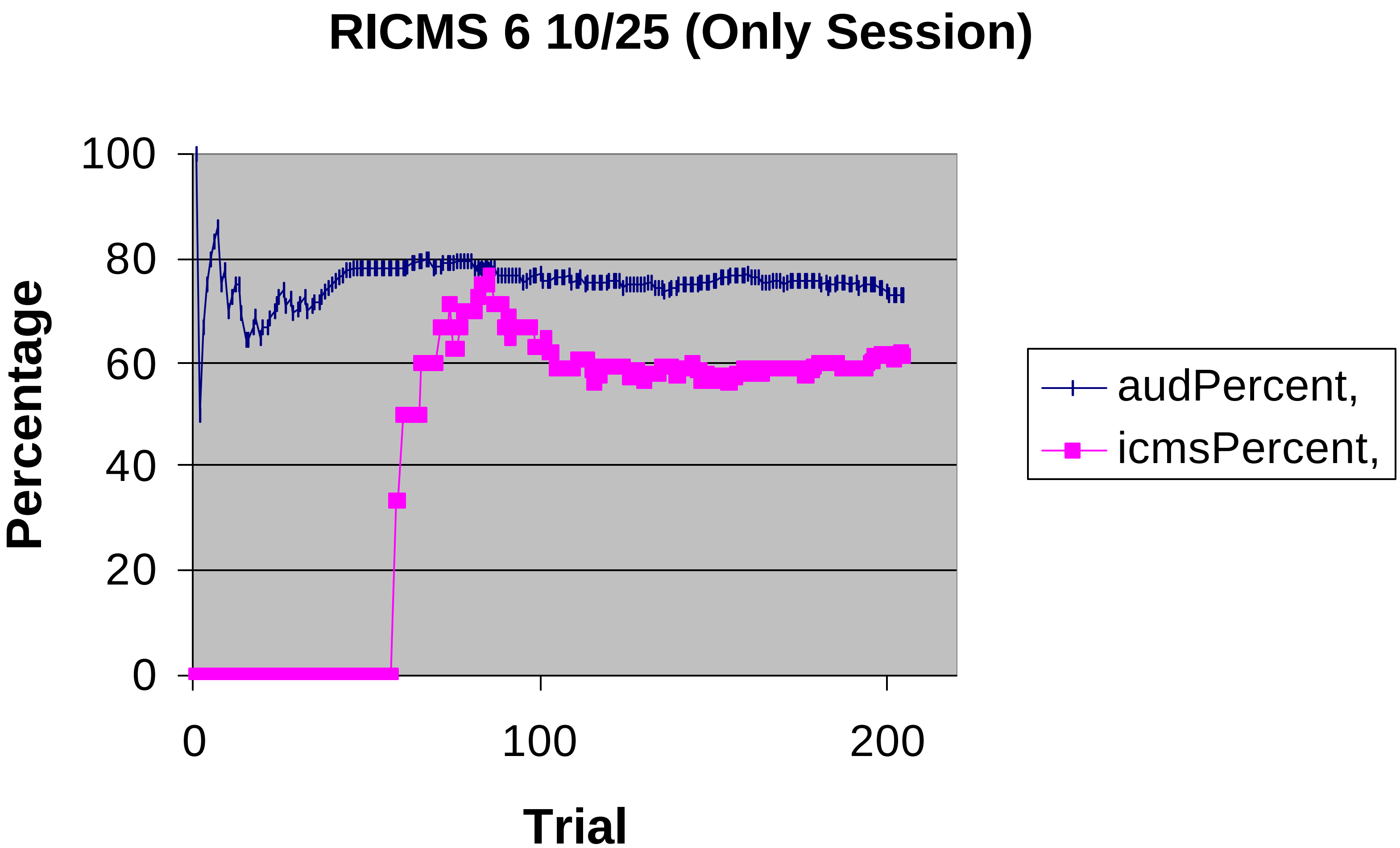


Auditory trial =

ICMS Algorithm1 =

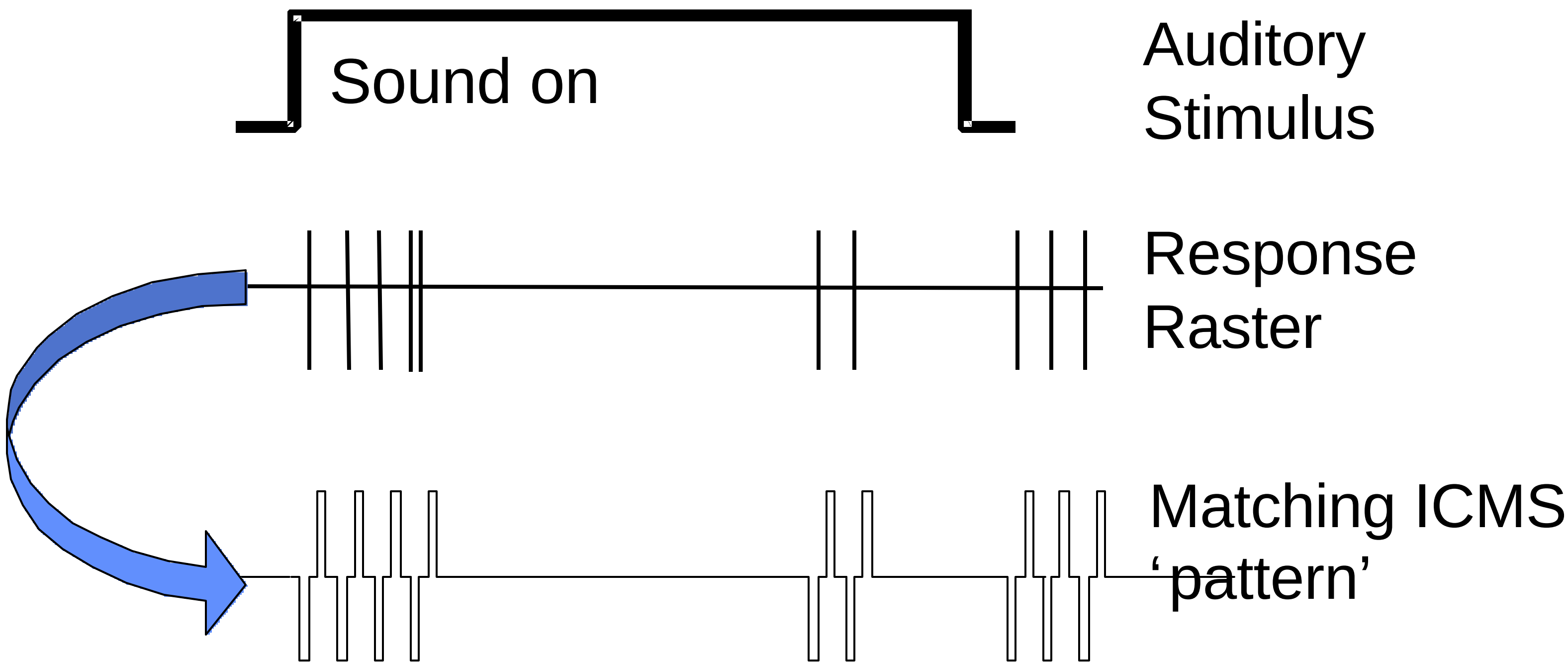
ICMS Algorithm2 =

Behavioral Curve



Alternative Signal Encoding Algorithm: *Cortical Activation Pattern*

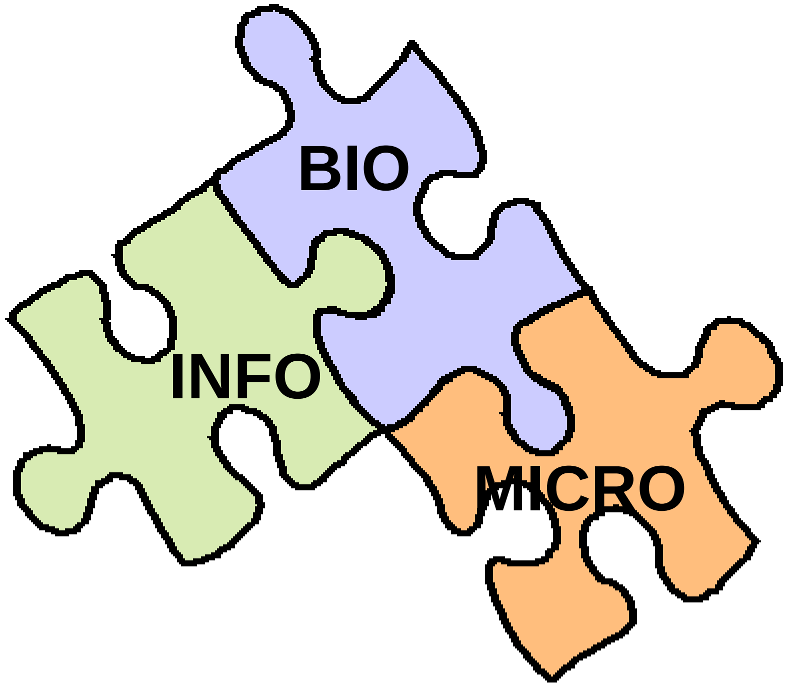
For a given electrode, the unit firing pattern is used as a template for ICMS delivery



***Procedure is simultaneously duplicated on each active electrode

Recap

- Focused & integrated effort
  - *Neural Engineering…Signal Processing…Systems Neurophysiology…Visualization*
- Why are we so excited?
  - We have the very real potential of developing new classes of neuroprosthetic systems to explore our ability to interact directly with the brain.



BIO, INFO, and MICRO…

- Wide-open Challenges
  - Appropriate mathematical constructs for describing neural encoding and decoding.
  - Advanced data visualization techniques for understanding this new class of neural data.
  - Understanding signal transformations as a function of the spatial and temporal scale of the neural data.

- Collaboration Possibilities
  - Exploring new signal encoding and decoding strategies for particular neuroprosthetic applications.
  - Sharing technologies, procedures, insights, etc…
  - *New emergent ideas…*

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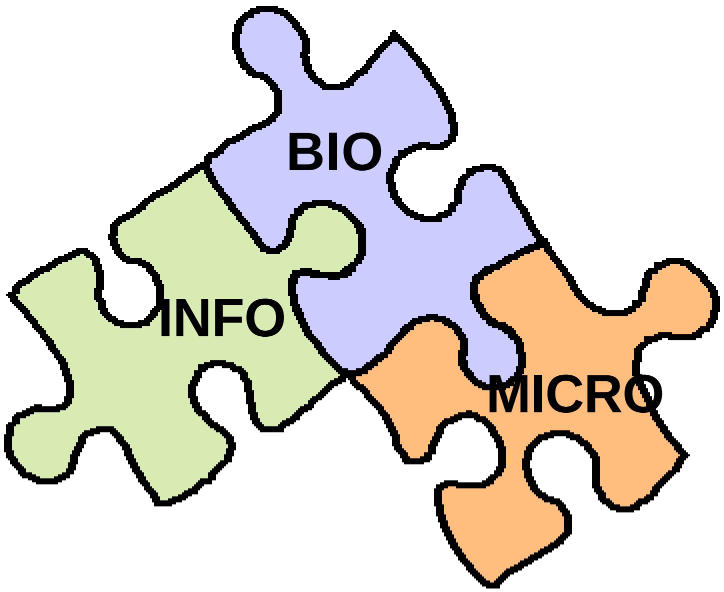
Project Challenges

- Scientific
  - Overcoming engineering and scientific hurdles.
  - Identifying and fostering strategic alliances with appropriate external groups.
  - Crossing disciplines

- Management
  - Strategic planning
  - Resource allocation
  - Open and effective communication among the diverse project team
  - Team-building: Maintaining enthusiasm, energy, and focus after the initial “honeymoon” period

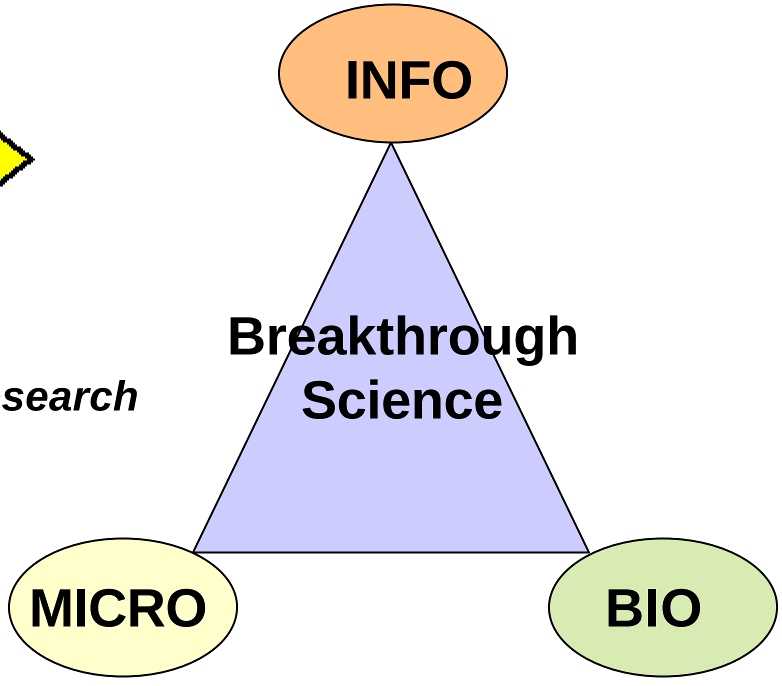
"Insanely Intense Interdisciplinary" Research

"pieces of a puzzle"



- *Hard work*
- *Open minds*
- *Honesty*
- *Top-notch research*

"easy synergism"



What Does the Future Hold?

"Perhaps within 25 years there will be some new ways to put information directly into our brains. With the implant technology that will be available by about 2025, doctors will be able to put something like a chip in your brain to prevent a stroke, stop a blood clot, detect an aneurysm, help your memory or treat a mental condition. You may be able to stream (digital) information through your eyes to the brain. New drugs may enhance your memory and fire up your neurons."

-- *Dr. Arthur Caplan,*
Director of the Center of Bioethics,
University of Pennsylvania
Arizona Republic, Dec 27, 1998.

Acknowledgments

- ASU Colleagues
  - 13 co-PI's, 5 research faculty, numerous graduate and undergraduate students.
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