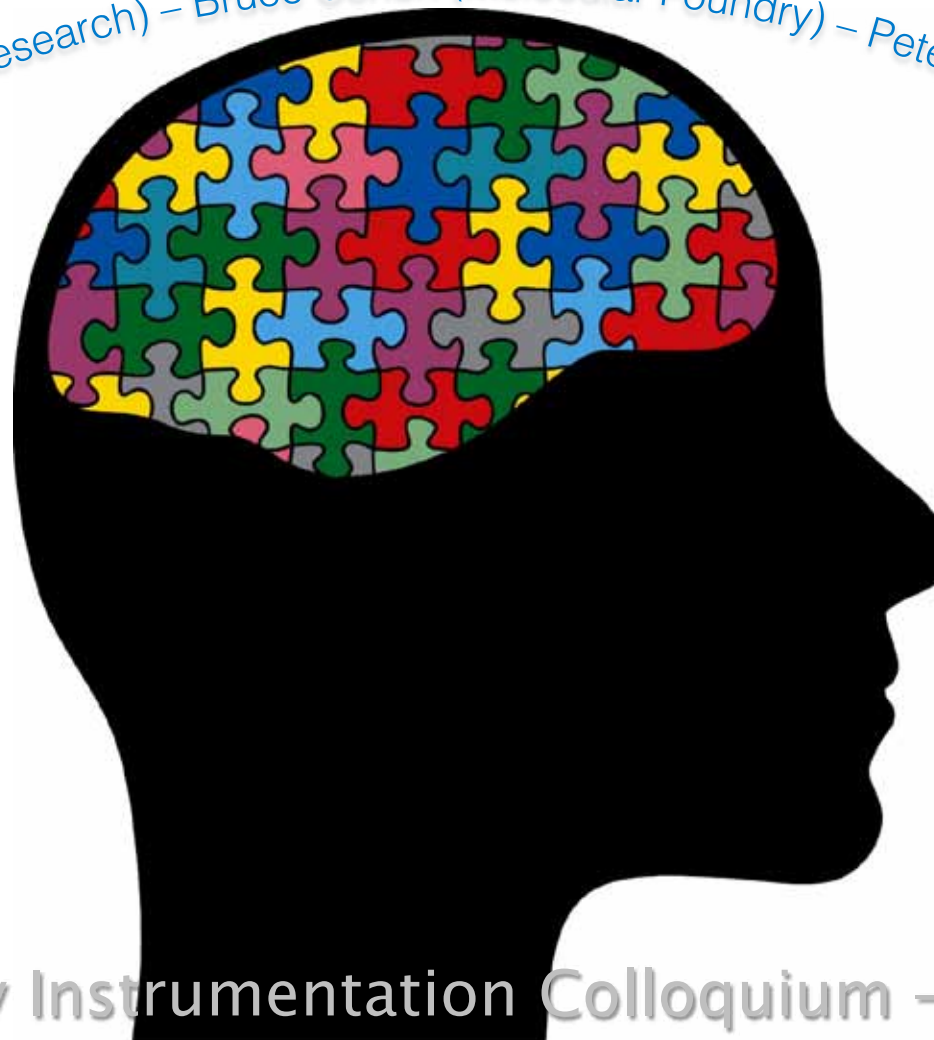


# BRAIN

## ultimate Interdisciplinary Instrumentation



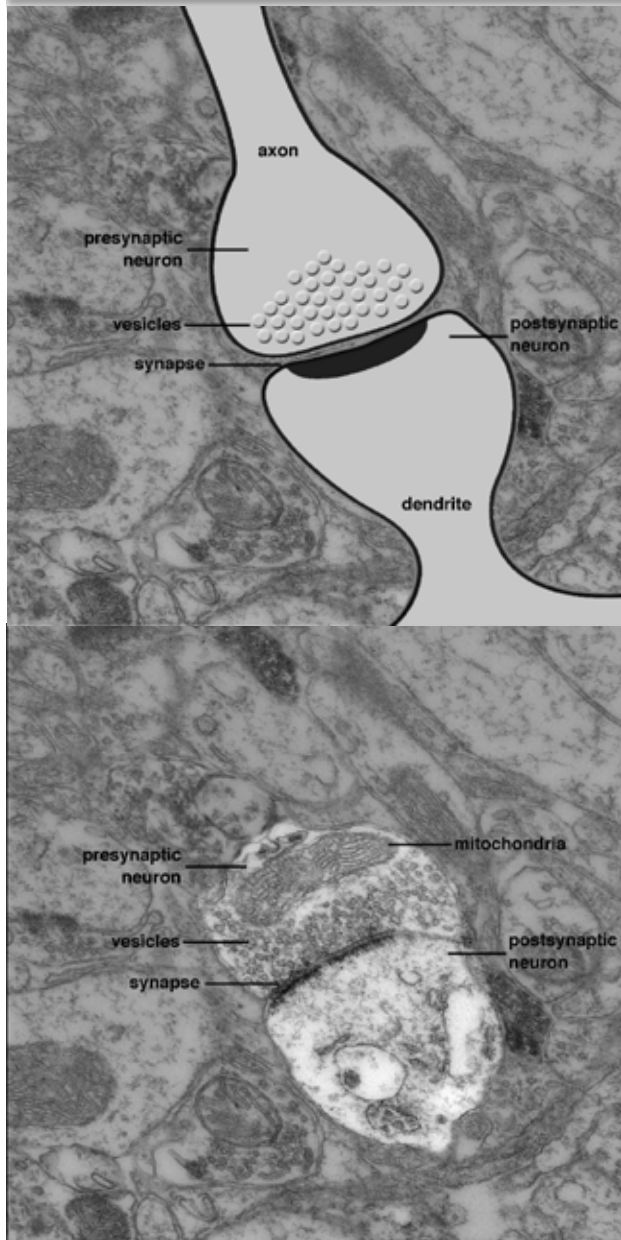
Carl Zeiss  
Brain Section  
Microscope  
(circa 1907)

# A FLOP?

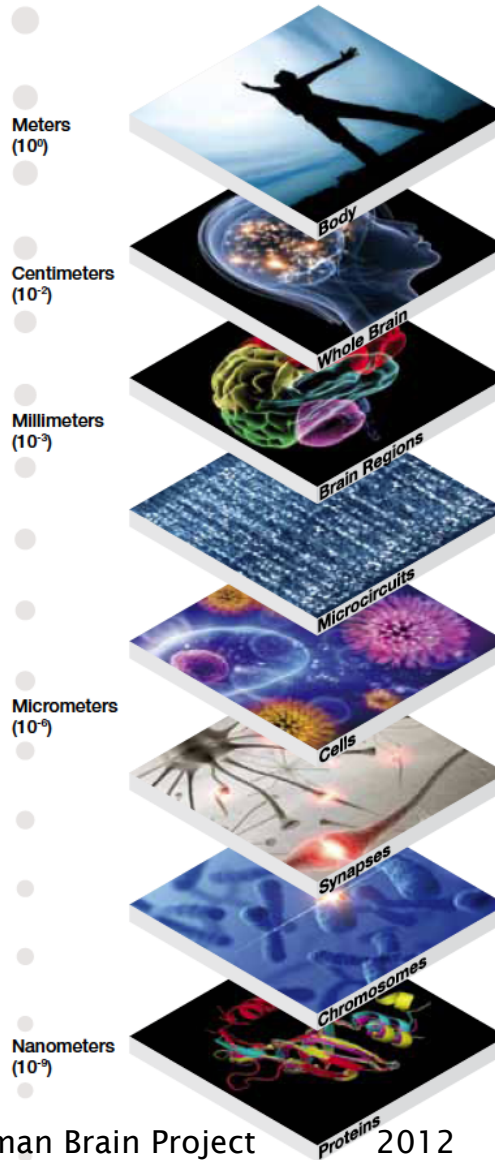


Processors	$10^5$	~1	$10^{11}$	Neurons
Connections	$10^{14}$		stors	
Clock Speed	$10^{15}$	10-LOTS	$10^{15}$	Synaptic
Volume	2		AM	$10^{-9} - 10^{-5}$
Weight	$10^8$		2	
Power	$10^5$		3	
	$1.6 \times 10^6$		~20	

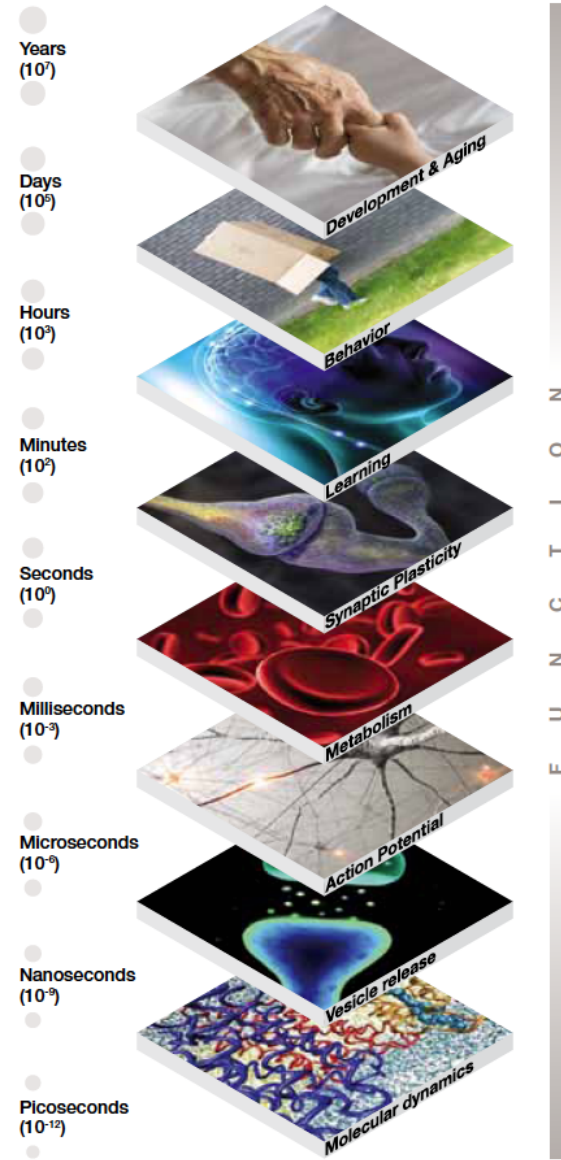
# A "Multiscale" Problem



## Spatial Scales



## Time scales



S T R U C T U R E

F U N C T I O N

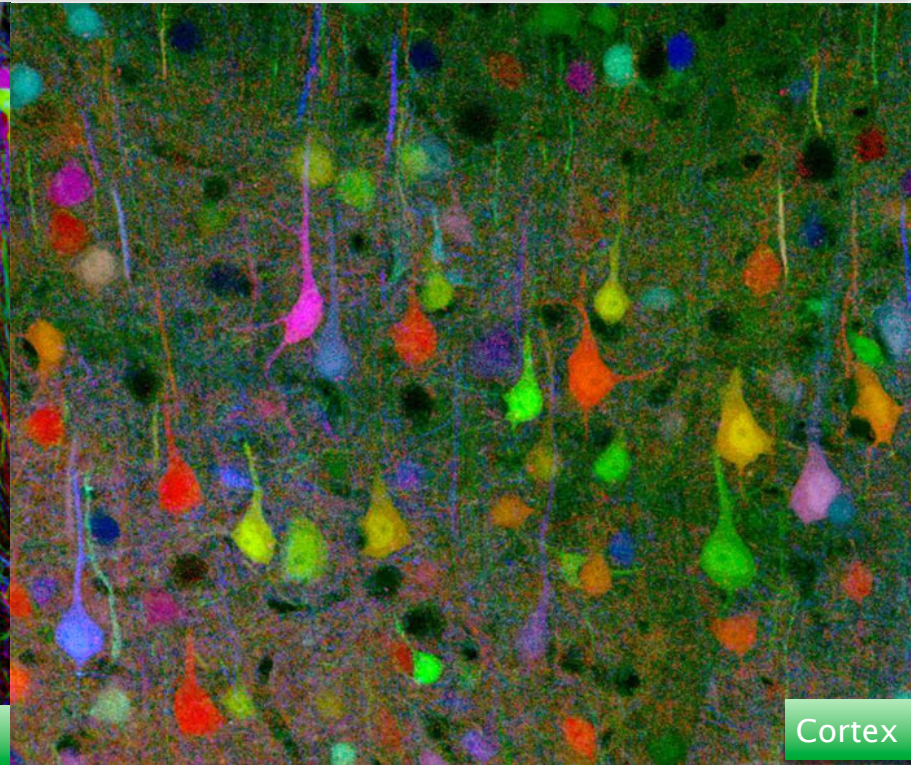
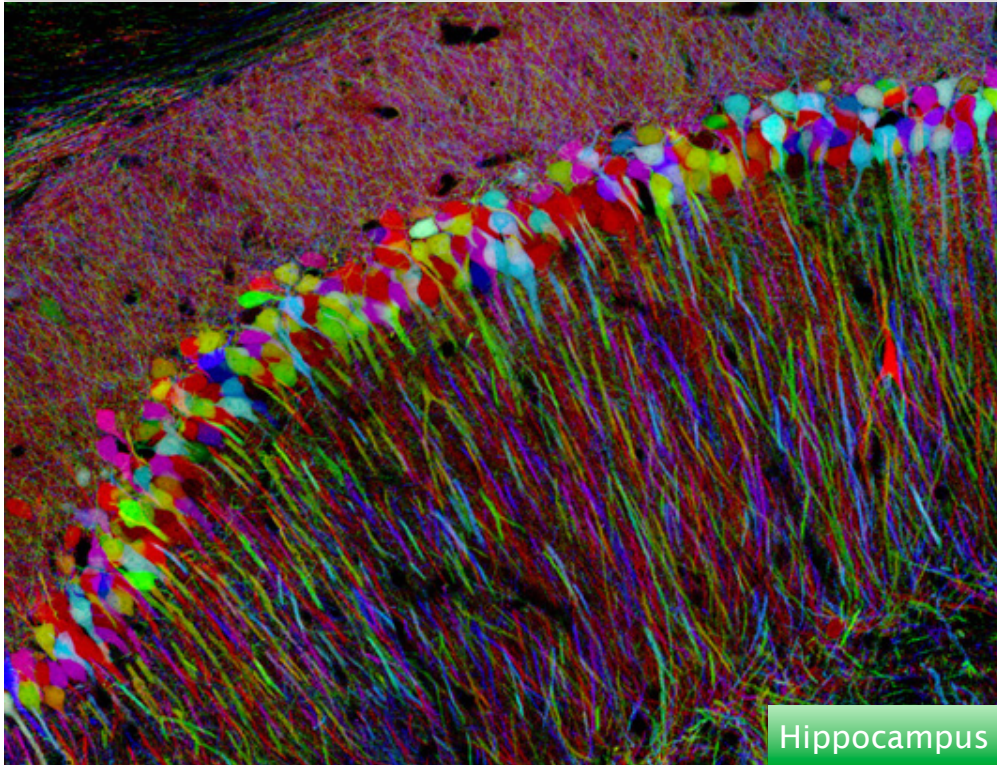
# Daunting



NO USER SERVICEABLE  
PARTS INSIDE



# but...



- Length scale  $\mu\text{m}$  (s)
- Micro / Nano technology to the rescue?



# BRAIN Initiative

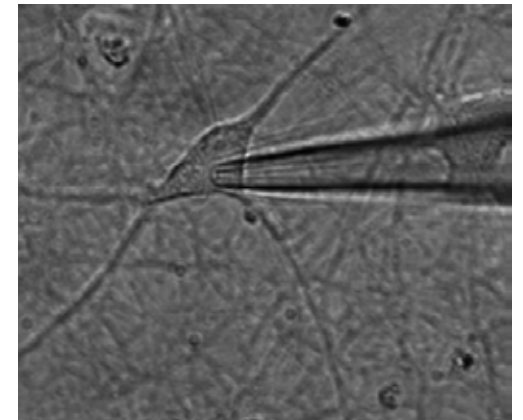
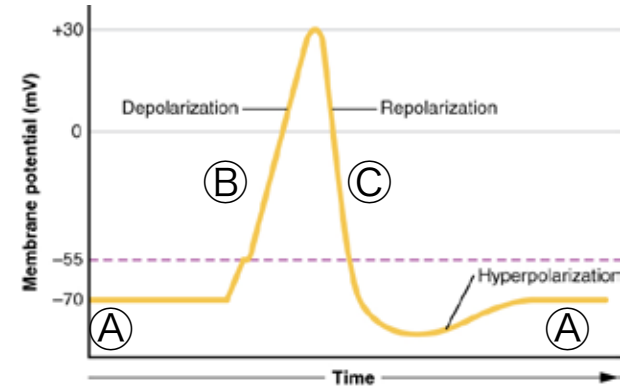
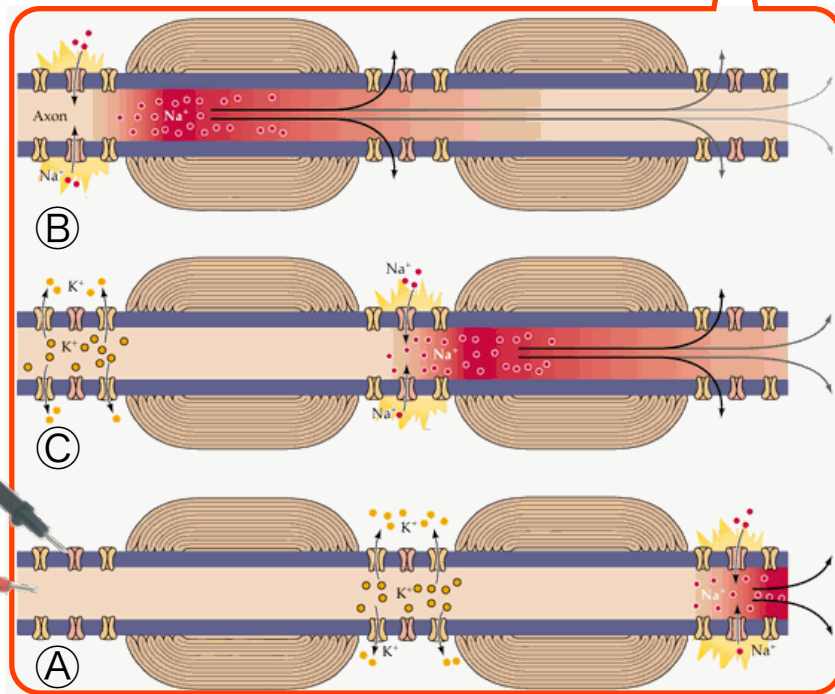
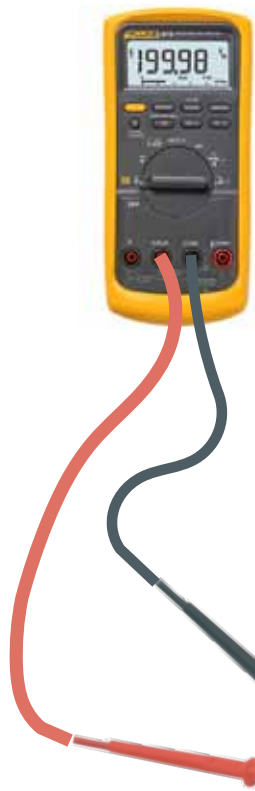
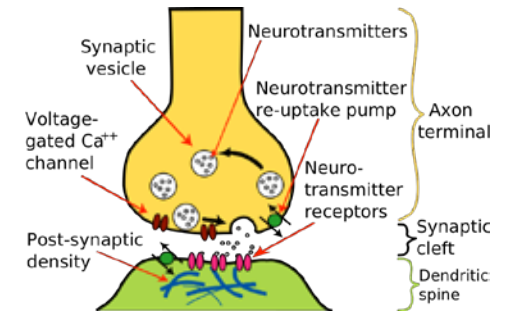
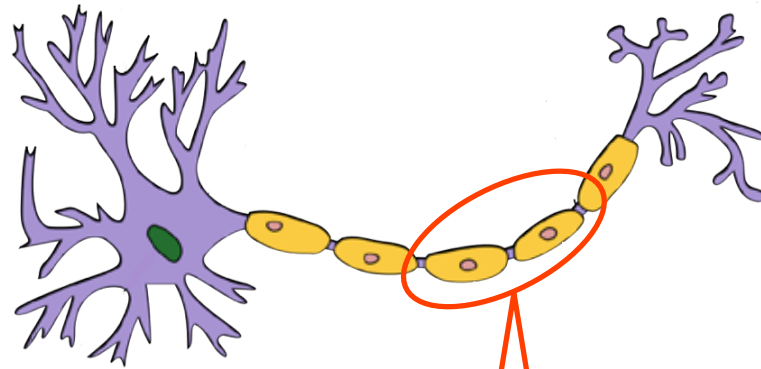


- Presidential Initiative

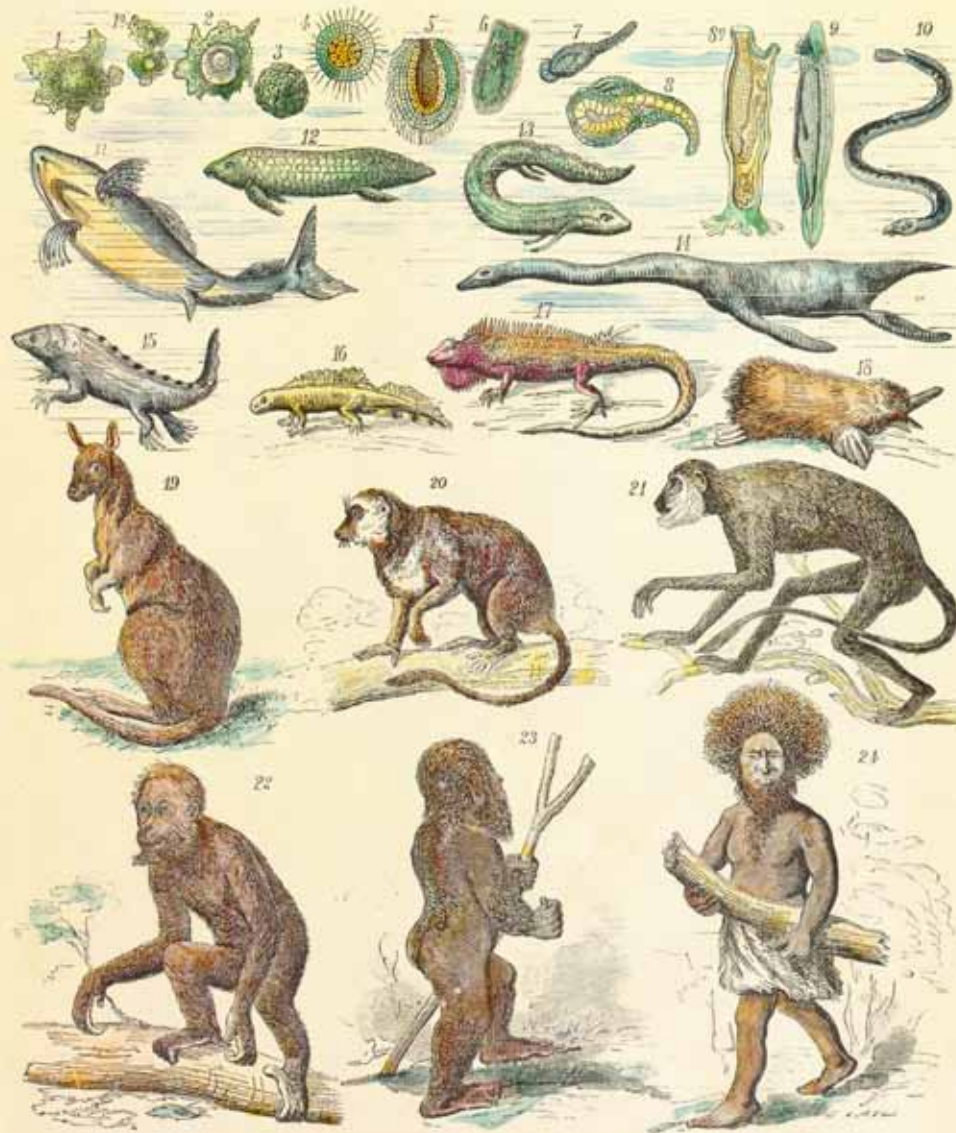
- April 2013
- “The BRAIN Initiative will accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact at the speed of thought.”

“Grand Challenge” – observe 1 million neurons, on ms timescale with “markedly reduced invasiveness”

# Shielded Coaxial Waveguide (with capacitance reduction) Nature is an Electrical Engineer?



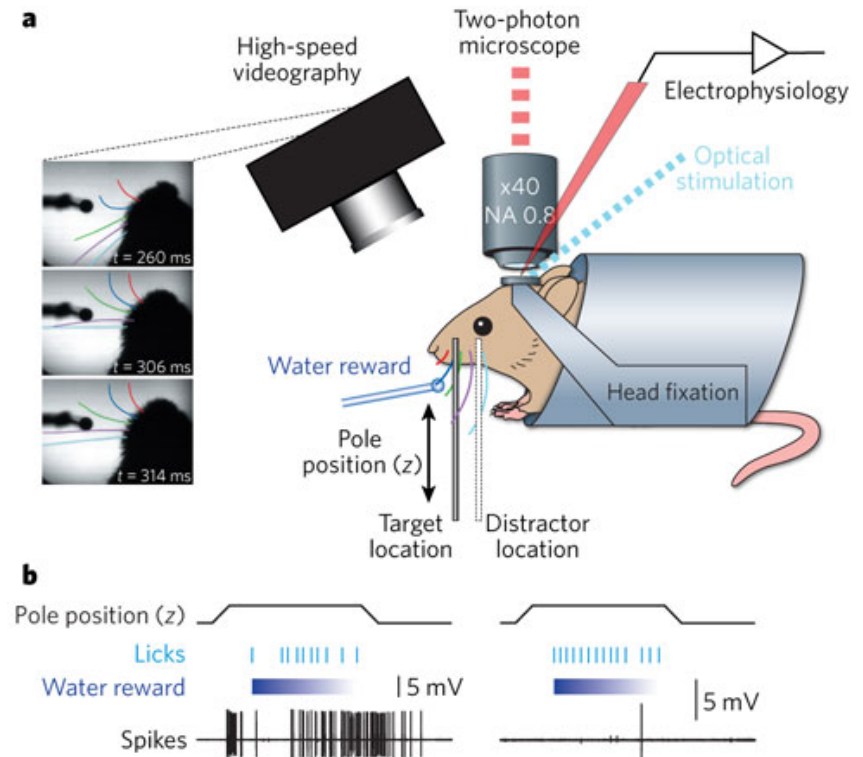
# “Non-Invasive”



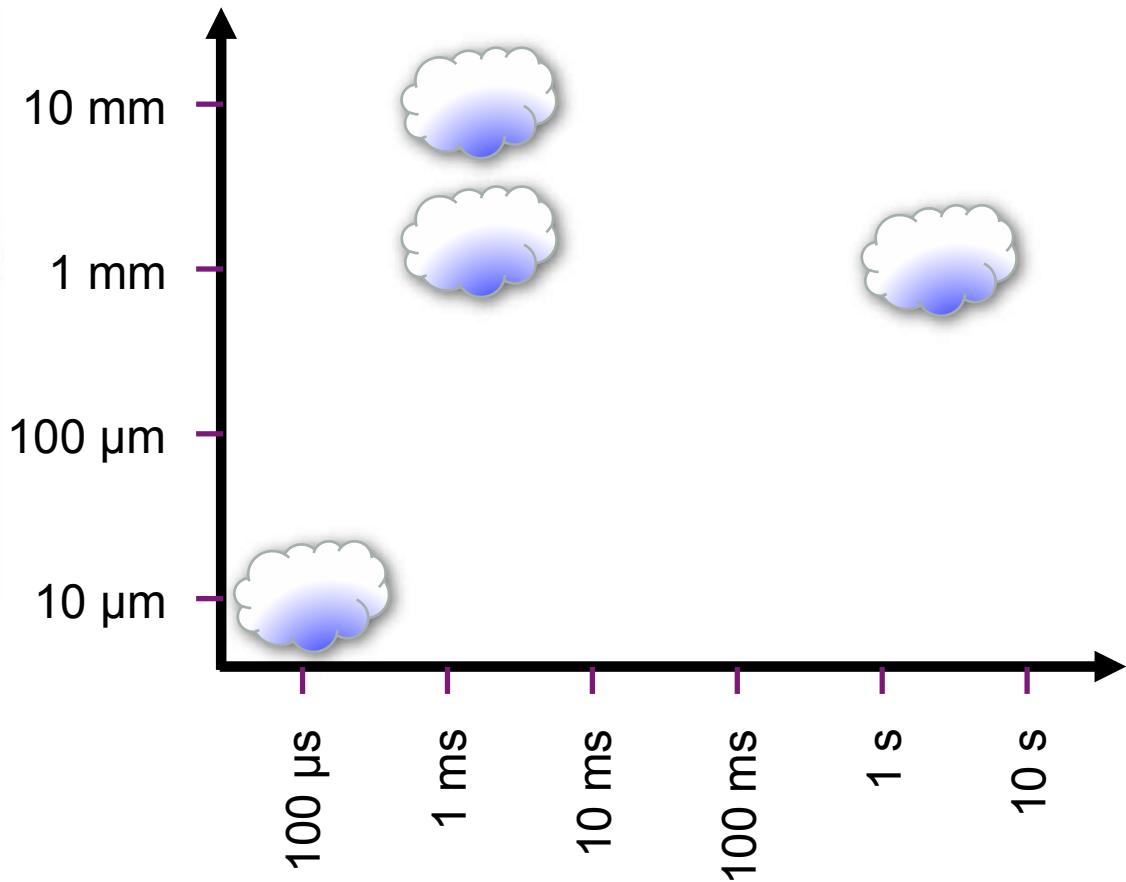
THE MODERN THEORY OF THE DESCENT OF MAN.

“Grand Challenge” – observe 1 million neurons, on ms timescale with “markedly reduced invasiveness”

- Not for you?
- Study model systems.



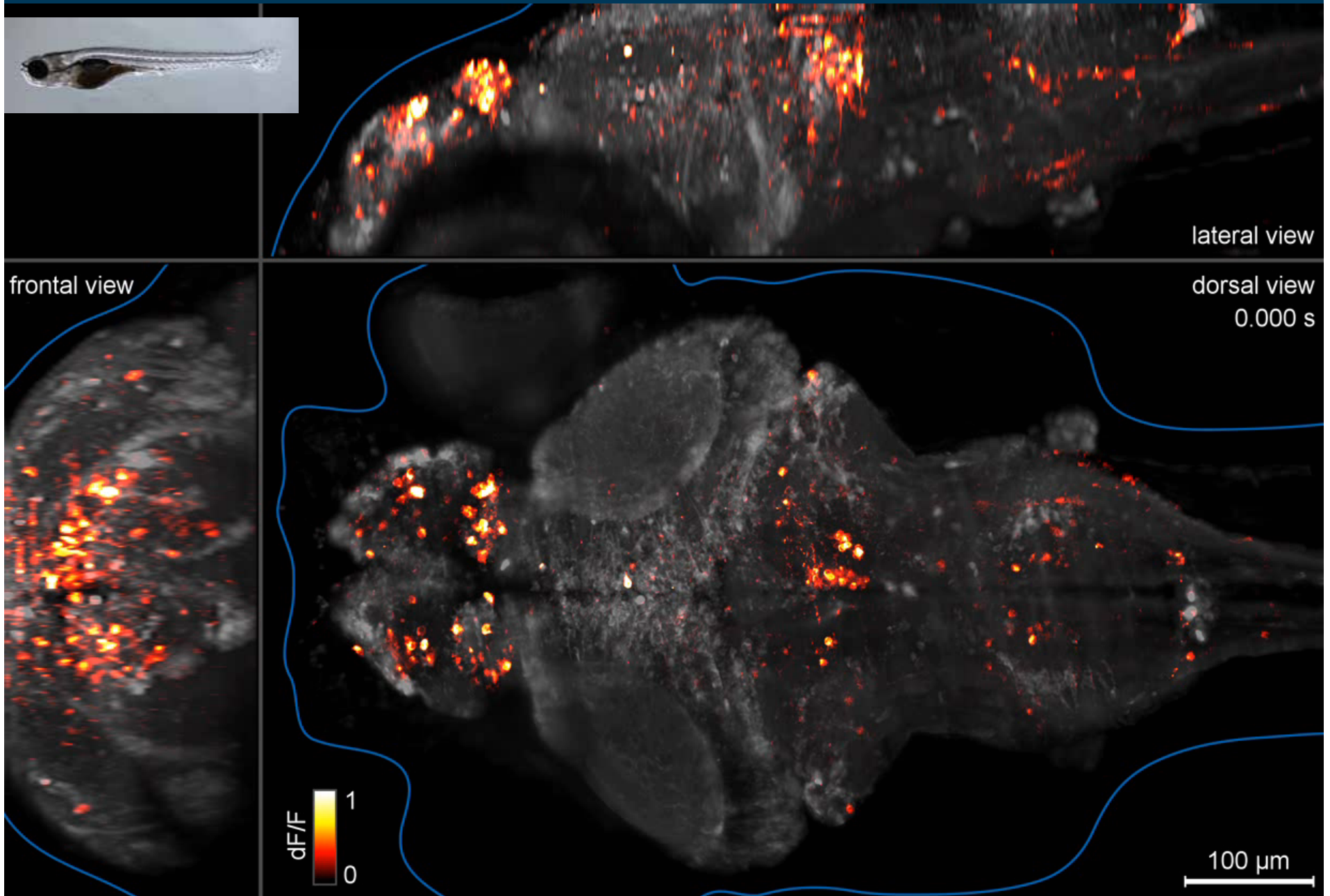
# (some) Current Human Neuroscience Tools



- and in 3D
- and non-invasive
- and and and
- +other current methods (PET, MEG, ...)



# Optical Sensors of Neuronal Activity



# Technique (and Needs)

## Stunning successes

- **Optically active:**

- Sensors (report activity)
- Actuators (stimulate or silence neurons: *Optogenetics*)

- Many techniques

- **Improved microscopies?**

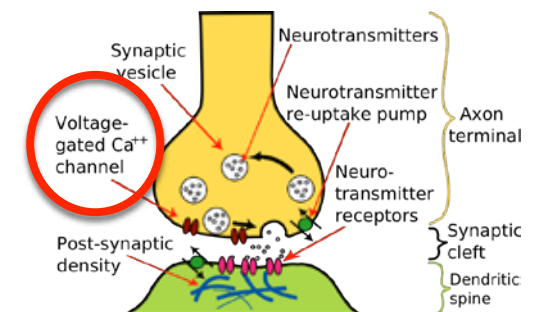
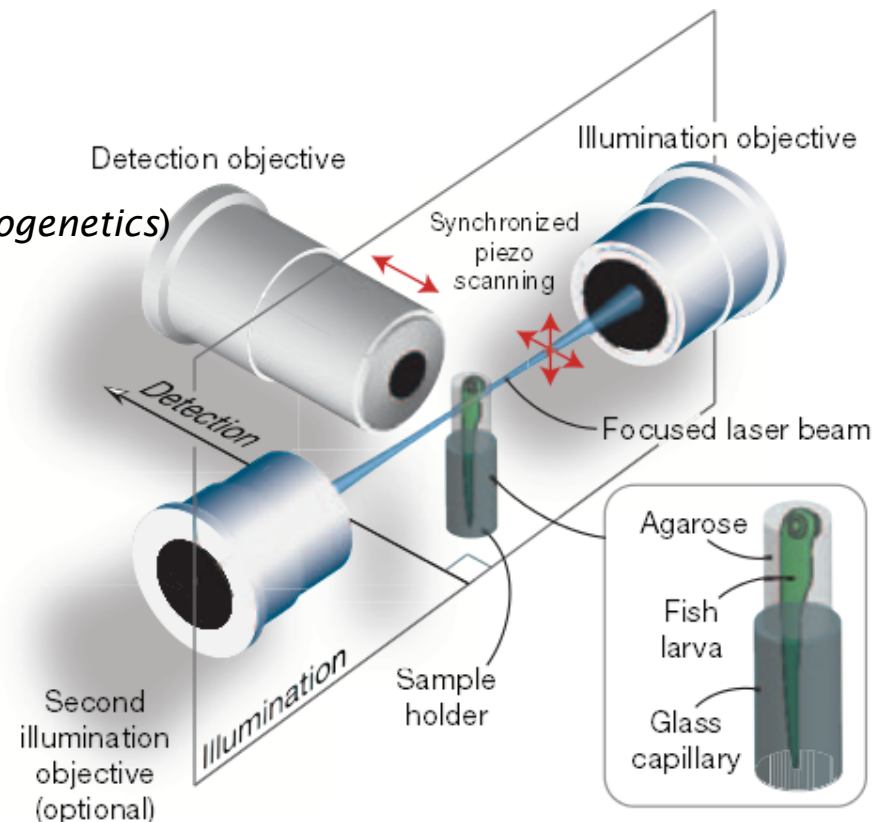
- Deeply penetrating NIR wavelengths
- Single neuron resolution
- Photoacoustic
- Live animal capabilities

- **Calcium indicators**

- Genetically targetable
- Optical properties can be tailored
- Amenable to two-photon techniques

- **Better sensors?**

- Other ions ( $\text{Na}^+$ ,  $\text{K}^+$ )
- Neurotransmitters
- Improved voltage sensors

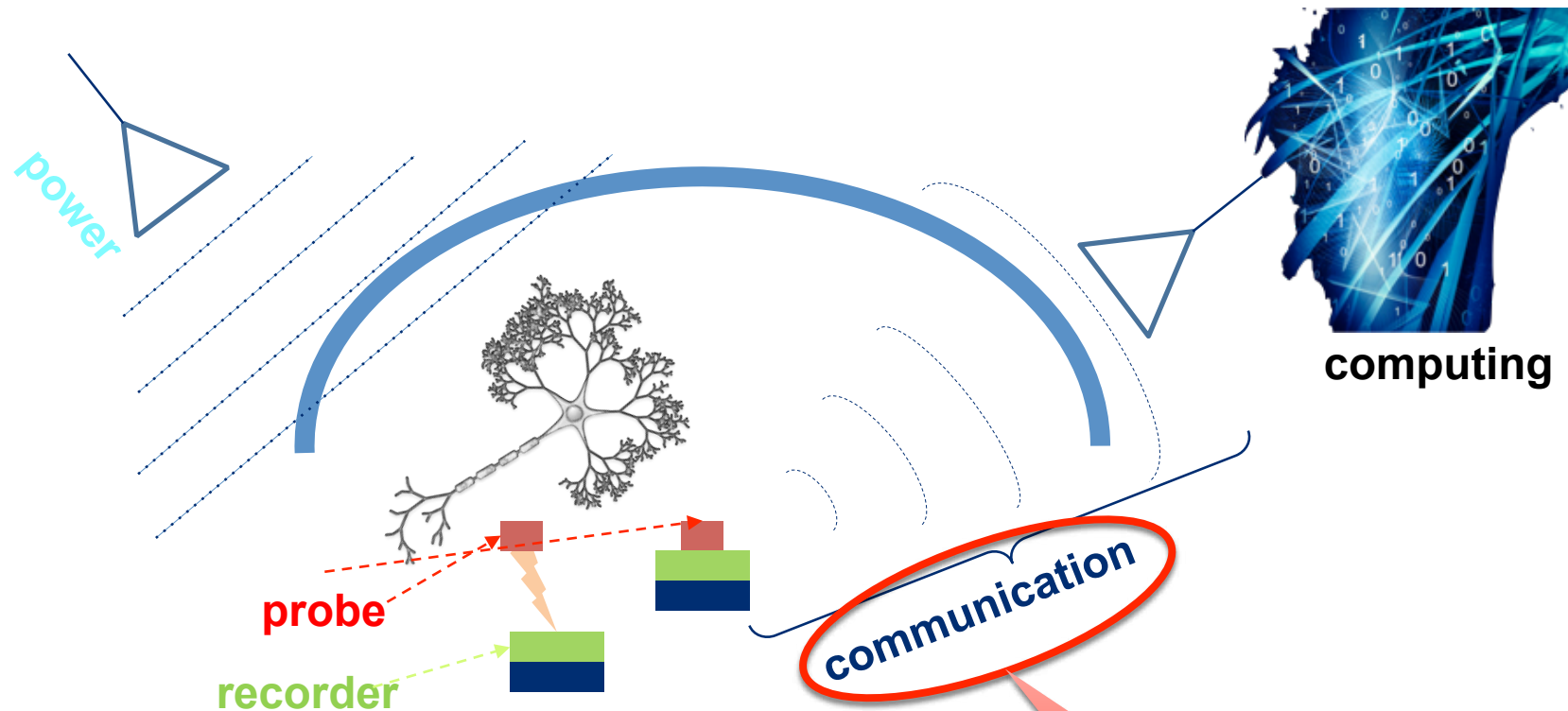


# Many Ways to use Light



- **CLARITY** (Clear, Lipid-exchanged, Acrylamide-hybridized Rigid, Imaging/immunostaining compatible, Tissue hYdrogel)
- Renders tissue transparent
- Replaces lipids with hydrogel

# Tools to Track Neurons — What's Needed?



“**probe**” – detector or transducer of neuronal activity (electrical, optical, chemical ...)

“**recorder**” – receives information from “probe”, “communicates” the information (perhaps, position ...)

“**communication and data acquisition system**” – means for transferring information to the outside world, and capturing it; potential power source

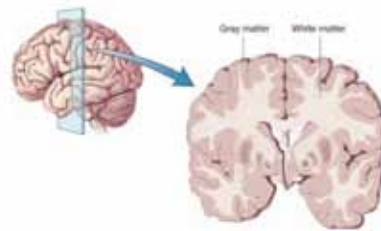
“**computing**” – processing the acquired data

This is the problem

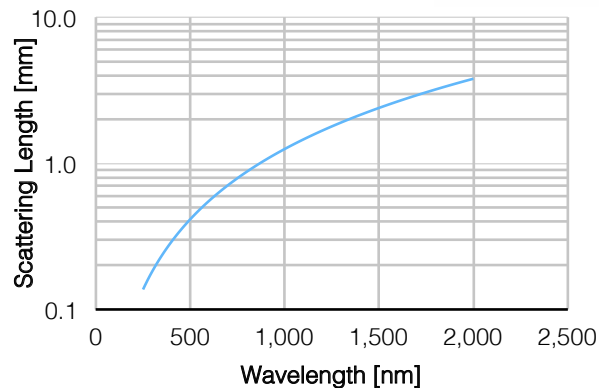
# Communication

- **Optical**

- Penetration depth\*
  - Large variation\* in absorption



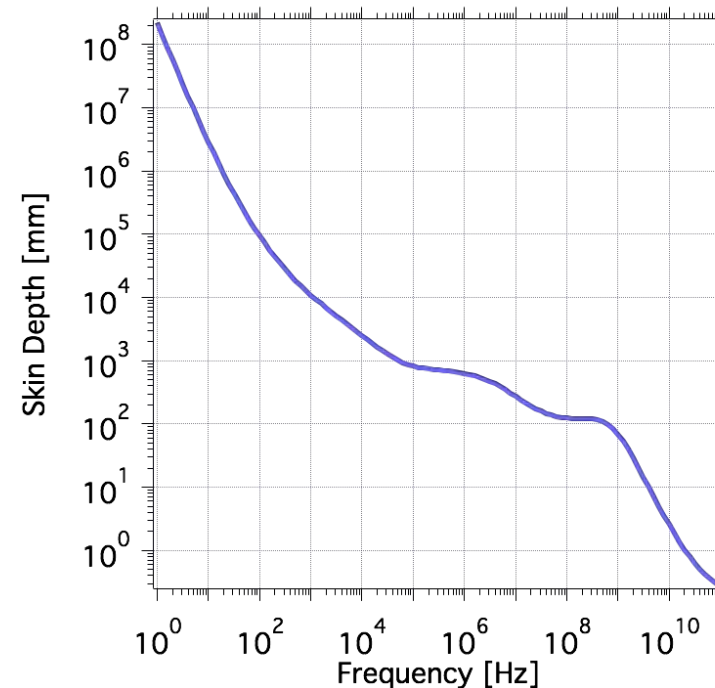
- Scattering\*



- Optical sensors and actuators prefer visible light
- Depth
- Scanning

- **Electrical**

- Skin depth\*

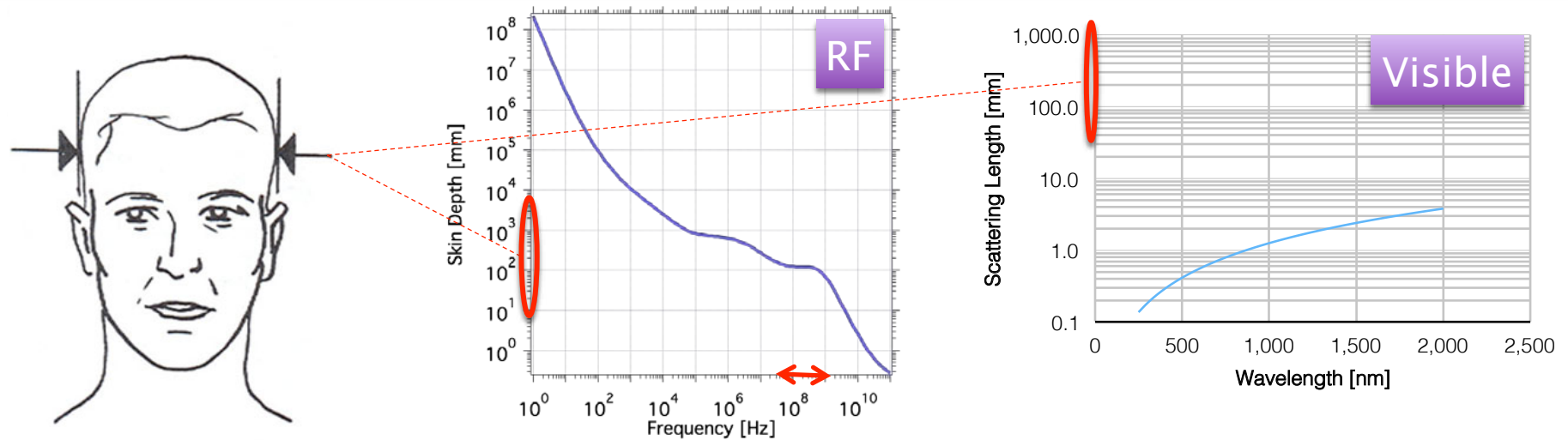


- **Acoustic**

- Ultrasound - 10s MHz

\*Variation (tissue, bone, ...) in all of these values

# An Inconvenient Truth



“Grand Challenge” – observe 1 million neurons, on ms timescale with “markedly reduced invasiveness”

- It's true: we are really thick-headed!
- Simultaneous **3D, spatial, temporal** resolution “challenging”
- $10^6 \times 10^3$  Hz ( $\rightarrow > 10^3$  Hz)  $\times$  \_ bits = (*many*) GHz BW
  - Not light, sound or RF

# How to

- Goals: 3D,  $N = 10^6$ ,  $t = 1$  ms, ( $x = \_ \mu\text{m}$ )
- **Nano-Archeologist** – tag neuronal activity *ex post facto*
  - 3D ✓  $N$ ?  $t$  ✗  $x$ ? (✓ in principle)
- **Nano-Tweeter** – optogenetics
  - 3D ✗  $N$  ✗  $t$ ?  $x$  ✓
- **Nano-Reporter** – microelectronic reporter (analog)
  - 3D ✗  $N$ ?  $t$  ✓  $x$ ?
- **Nano-Detective** – microelectronic reporter (digital – only if neuron fired)
  - 3D?  $N$  ✓  $t$  ✓  $x$ ?



# Not so Easy

- Goals: 3D,  $N = 10^6$ ,  $t = 1$  ms, ( $x = \_ \mu\text{m}$ )
- **Nano-Archeologist** – tag neuronal activity **ex post facto**
  - 3D ✓  $N$  ?  $t$  ✗  $x$  ? (✓ in principle)
  - + microscopy (EM ...)
- **Nano-Tweeter** – optogenetics
  - 3D ✗  $N$  ✗  $t$  ?  $x$  ✓
- **Nano-Reporter** – microelectronic reporter (analog)
  - 3D ✗  $N$  ?  $t$  ✓  $x$  ?
- **Nano-Detective** – microelectronic reporter (digital – only if neuron fired)
  - 3D ?  $N$  ✓  $t$  ✓  $x$  ?

No 3D ✓  $N$  ✓  $t$  ✓  $x$  ✓



The Partnership used a simple advertisement showing an egg in a frying pan, similar to this photo, suggesting that the effect of drugs on a brain was like a hot pan on an egg.

Can't fry your brain:  $\Delta T \sim 1^\circ\text{C}$

Can't blow your mind:  $\Delta V/V \sim \%$



# “BRAINseed”

**UCSF**

University of California  
San Francisco

- Clinical
- Neuroscience

**Berkeley**  
UNIVERSITY OF CALIFORNIA

- Neuroscience
- Technology



**BERKELEY LAB**  
Lawrence Berkeley National Laboratory

- Technology
- Scale

## Tri-Institutional Partnership BRAIN R&D Initiative to support innovative neurotechnology



**Berkeley**  
UNIVERSITY OF CALIFORNIA

**UCSF**  
University of California  
San Francisco

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### NEWS & ANNOUNCEMENTS

New Partnership Launches with Meeting at Berkeley Lab  
April 1, 2014

To unite the research strengths of Berkeley Lab, UC Berkeley and UC San Francisco, the three institutions recently announced the formation of the Tri-Institutional Partnership as a means to promote collaborative research among the three institutions.

The partnership's first venture will seed collaborative research projects in neurotechnology. The project was formally launched earlier this year with the announcement of a peer-reviewed competition for teams among the participating institutions to catalyze bold, potentially transformative research in neurotechnology at scale.

On March 13, more than 90 researchers from all three partners convened at Berkeley Lab for "Proposers' Day," to learn more about the seed program, the opportunities provided by President Obama's **BRAIN initiative**, and especially to share their research ideas and forge new collaborations.



"Bringing people together across disciplines is difficult, and across institutions even more so," said Graham Fleming, Vice Chancellor for Research at Berkeley. "But the impressive turnout of researchers across all three institutions and the energy in the room demonstrates the level of excitement they share in addressing the neurotechnology challenges posed in the BRAIN initiative."

"I was happy to see such a tremendous turnout for our first Proposer's Day. Our scientists were joined by 23 scientists from UC SF and 28 from UC Berkeley," said Berkeley Lab Deputy Director Horst Simon. "This demonstrates to me that the Bay Area scientific community is ready for the tri-institutional partnership in order to address new and interdisciplinary scientific challenges."

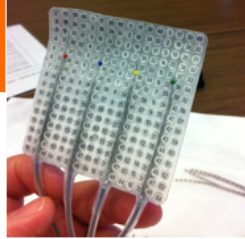
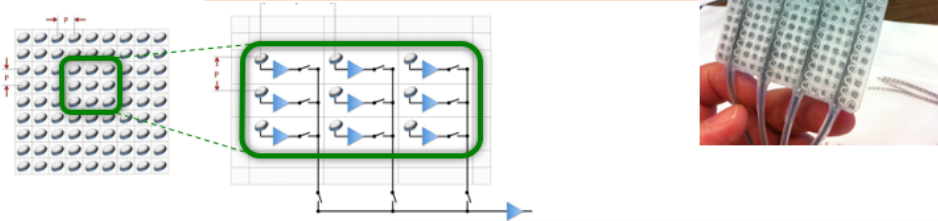
Successful "seeds" of the regional program will be calibrated on technical excellence, innovation, and the substantive involvement of the collaborative partners across multiple disciplines. To ensure impact, each project must have a clear path from concept to the development of a competitive proposal for outside funding.

Go [here](#) to learn more about the Tri-Institutional Partnership and the BRAIN R&D seed-funding project to support innovative neurotechnology.

# Very High Density Electroocortigraphy

Eddie Chang (UCSF), Fritz Sommer (UCB), Peter Denes, Kris Bouchard (LBNL)

State of the art - 256 electrodes  
 <10 electrodes / cm<sup>2</sup>  
**Improve to 10<sup>4</sup> electrodes / cm<sup>2</sup>**



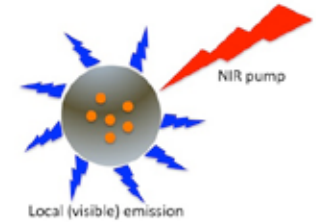
- Analysis *already* complex
- **If successful, data ↑ 10<sup>3</sup>**
- HPC
- Format, portal, ...



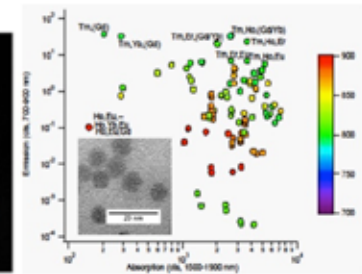
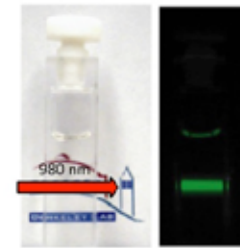
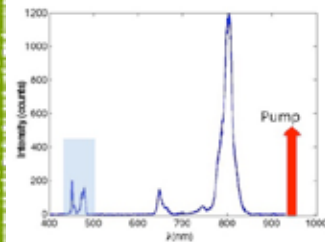
# Nanocrystal Light Bulbs

Bruce Cohen (LBNL), Chris Chang (UCB), Charles Craik (UCSF), Robert Edwards (UCSF), Ehud Isacoff (UCB)

- Tether-less light bulbs (injectable)
- Synthesis of nanocrystals that convert NIR light to visible, to activate nearby sensors and photoswitches
- NIR pump provides
  - Deep-tissue penetration
- UNCPs:



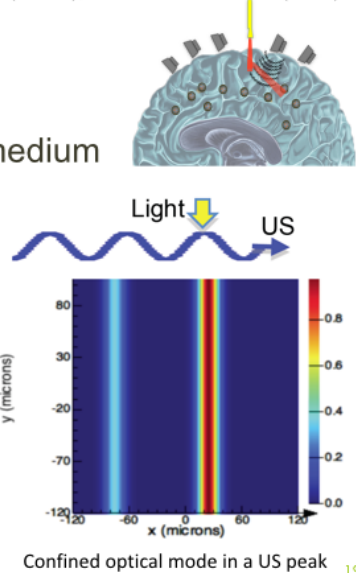
Emission wavelength...



# Acousto-optic 'Virtual' Waveguides

P. James Schuck (LBNL), M. Reza Alam (UCB), Vikaas Sohal (UCSF), Michel M. Maharbiz (UCB)

- Ultrasound : Pressure waves
  - Modulating optical properties of medium
- In-tissue light confinement
- Reconfigurable trajectory of light
- Fast reconfiguration
- Can penetrate the skull
- Low loss
- Medically-safe modality
- **Non-invasive**

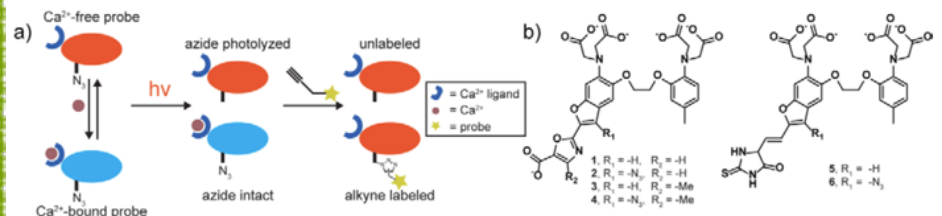
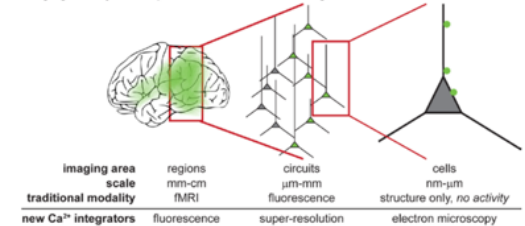


# Ca<sup>2+</sup> Dosimeters

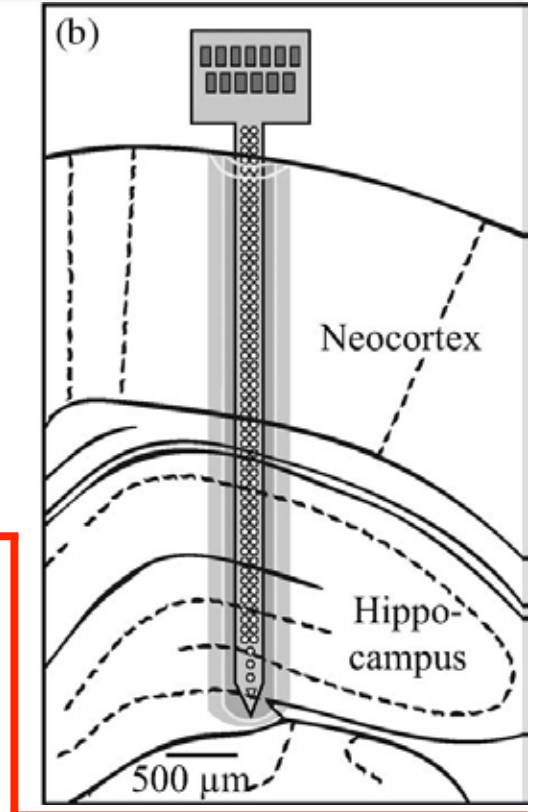
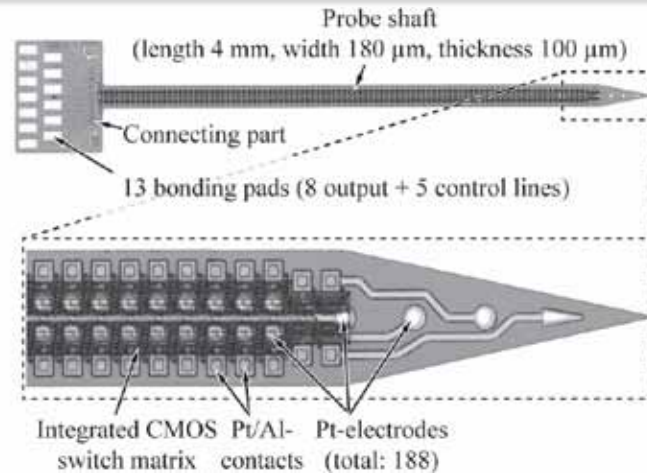
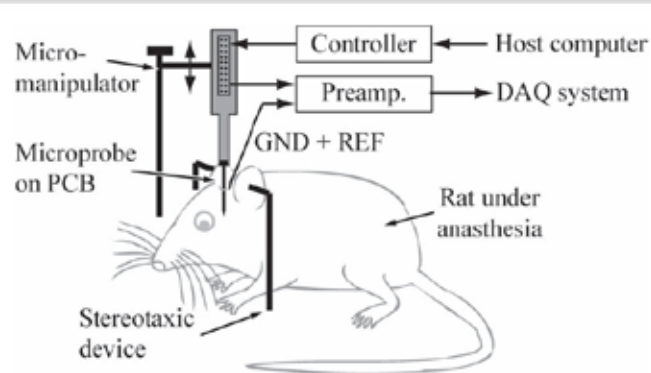
Pamela denBesten (UCSF), Terumi Kohwi-Shigematsu (LBNL), Evan Miller (UCB)

- Probes which remember Ca<sup>2+</sup> concentration
- Cover multiple length scales
- (post hoc)
- 3D reconstruction of activity across entire brain regions with cellular resolution

Imaging Activity at Multiple Scales with New Ca<sup>2+</sup> Integrators

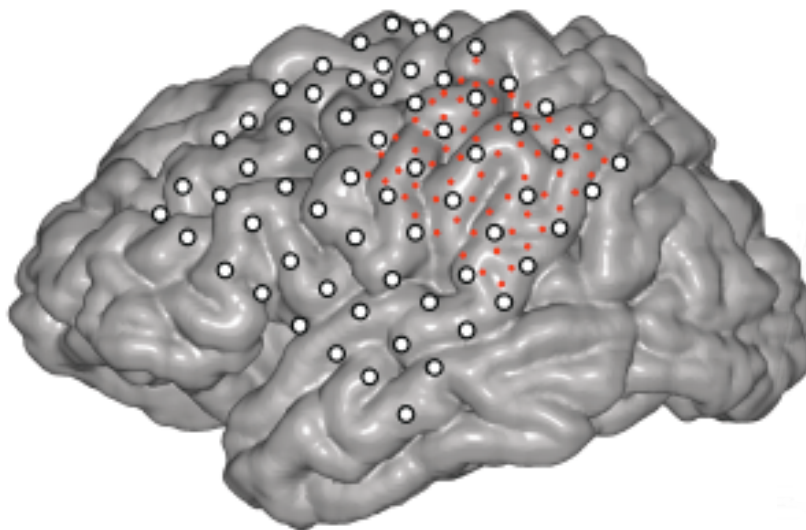


# Electrical Recording

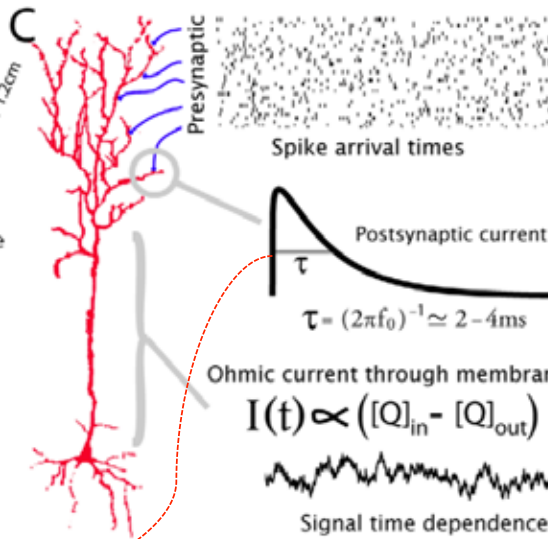
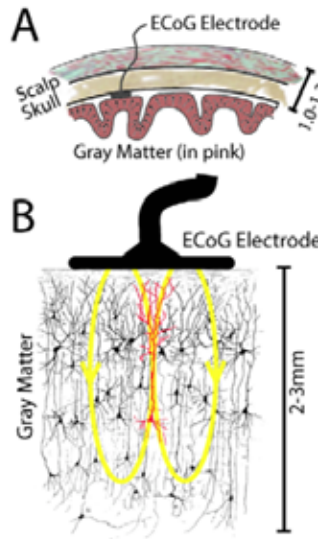
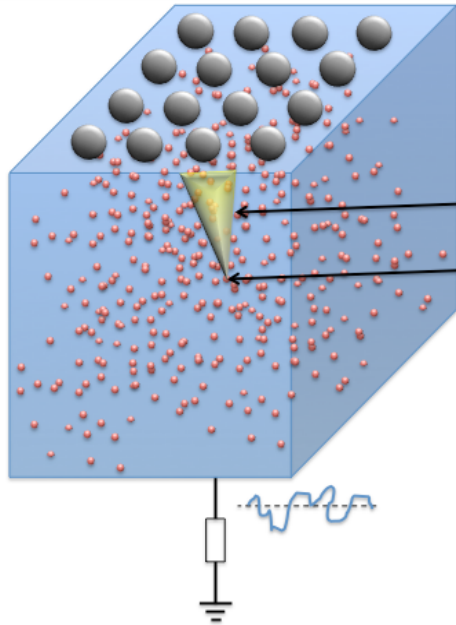


*Somewhat invasive*

*Somewhat less invasive*



# Problem Statement



$$P(f) \sim A$$

$$P(f) \sim A \frac{1}{1 + (f/f_0)^2}$$

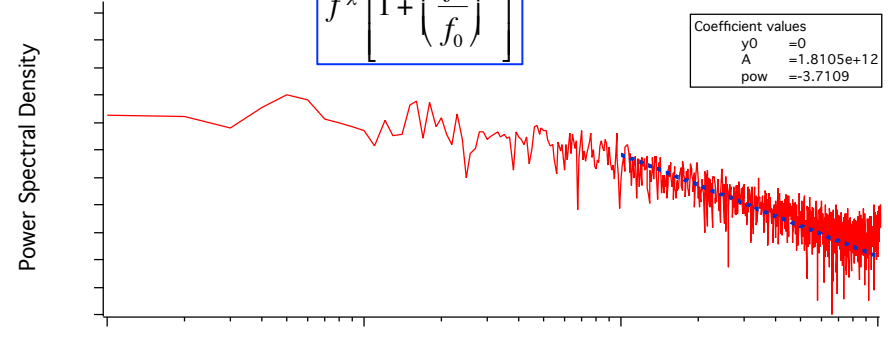
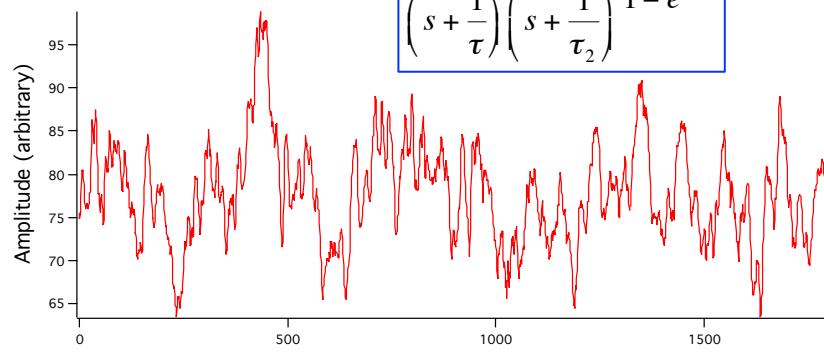
$$P(f) \sim A \frac{1}{1 + (f/f_0)^2} f^{-2}$$

$$\frac{1}{\left(s + \frac{1}{\tau}\right) \left(s + \frac{1}{\tau_2}\right)}$$

$$\frac{1}{\left(s + \frac{1}{\tau}\right) \left(s + \frac{1}{\tau_2}\right)} \frac{1}{1 - e^{-sT}}$$

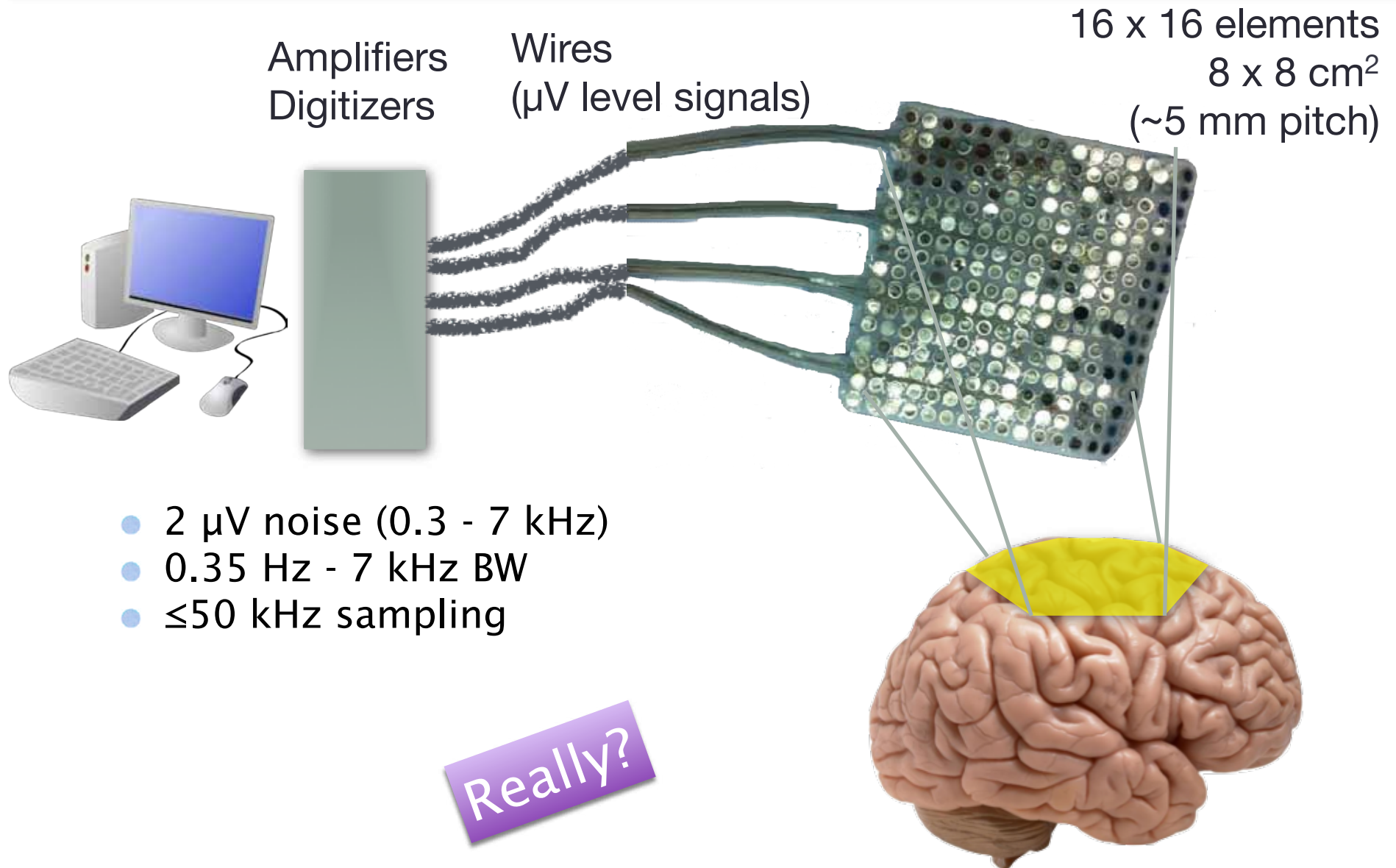
$$\frac{1}{f^\alpha \left[1 + \left(\frac{f}{f_0}\right)^2\right]}$$

Coefficient values	
y0	=0
A	=1.8105e+12
pow	=-3.7109



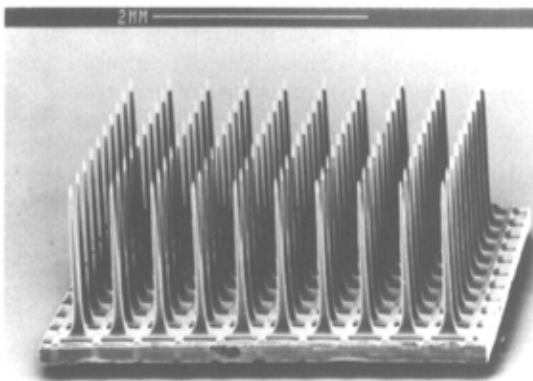
Under 1 electrode:  $10^N$  ( $N=4+$ ) neurons with  $\sim 10^4$  synapses

# State-of-the-Art (Human)

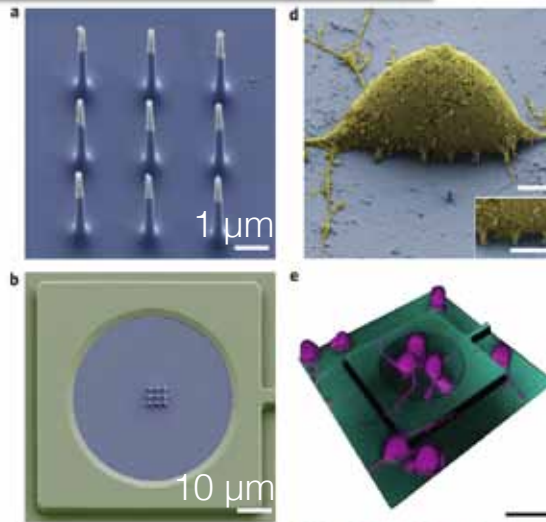


# Sophisticated Electrodes

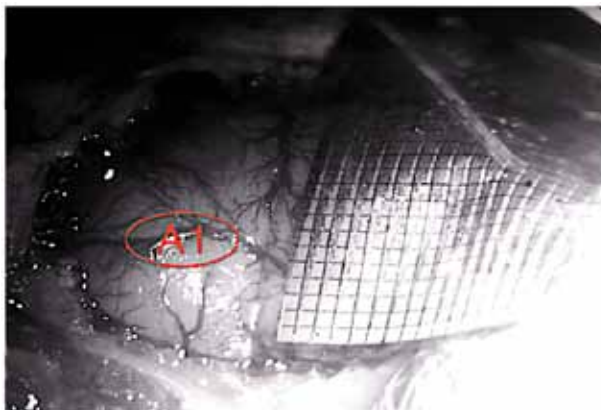
## Passive - 1 wire/electrode



Utah Array (Si - 1990s)



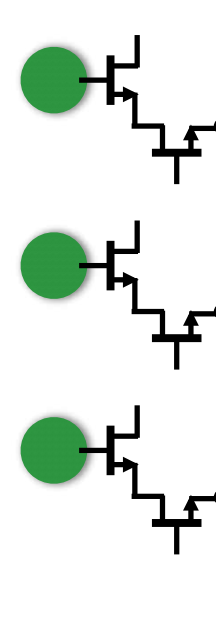
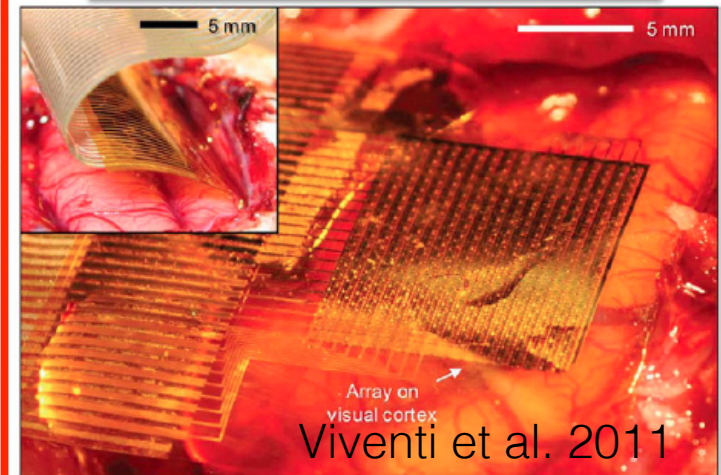
Robinson et al. 2012



Berkeley Array (paralyne)  
semi-transparent



## Multiplexed - SNR



TFT on Kapton  
500 μm pitch



# “Obvious” Solution

- Passive –  $10^6$  electrodes =  $10^6$  wires
- Multiplexed – fewer wires, but S/N degradation
- **Problem is to get  $10^6$  signals off the brain**
- Put amplifier behind each electrode
- Target:  $100\ \mu\text{m}$  “pixel”
- $4\ \text{mW}/\text{cm}^2 \rightarrow 400\ \text{nW}/\text{pixel}$  (“very hard”)

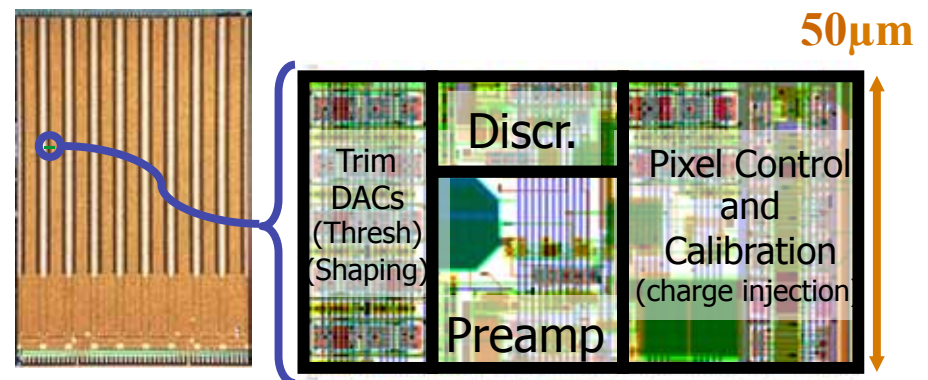
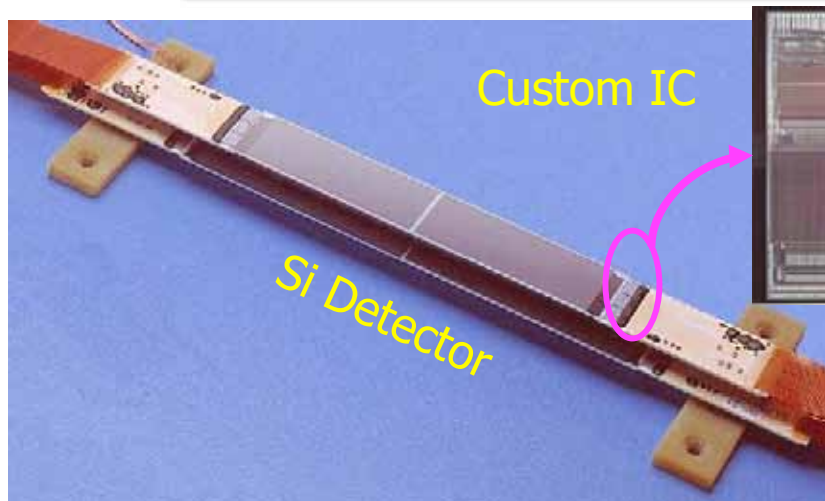
$\mu\text{V}$  noise  $\rightarrow \mu\text{W(s)}$  power

$$V_n \approx \sqrt{\frac{4kT}{g_m} \times BW}$$

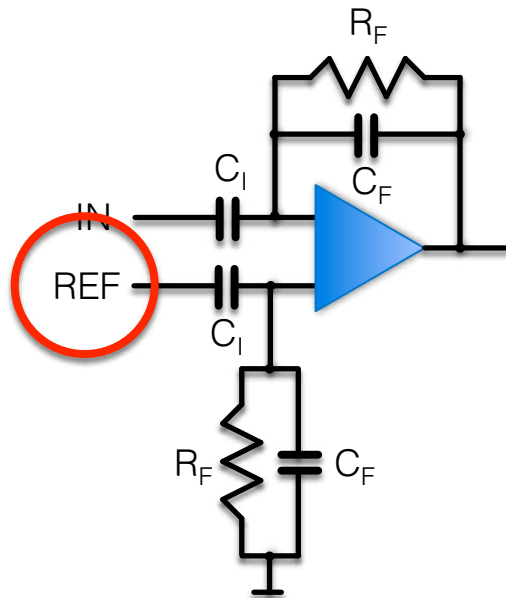
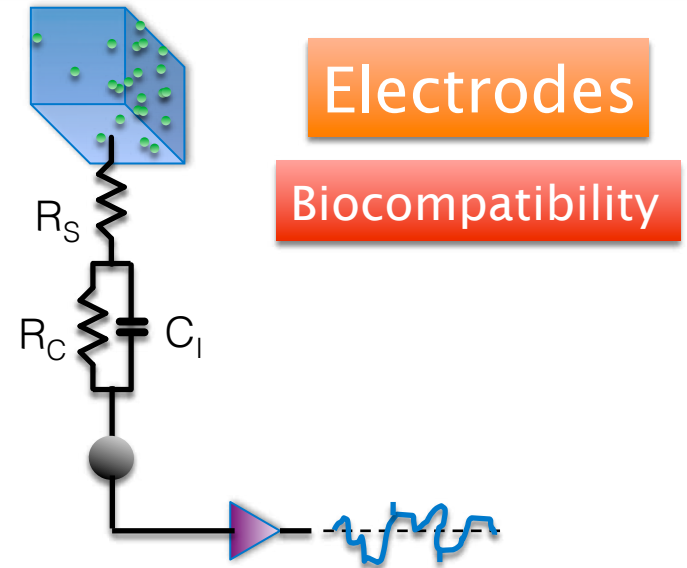
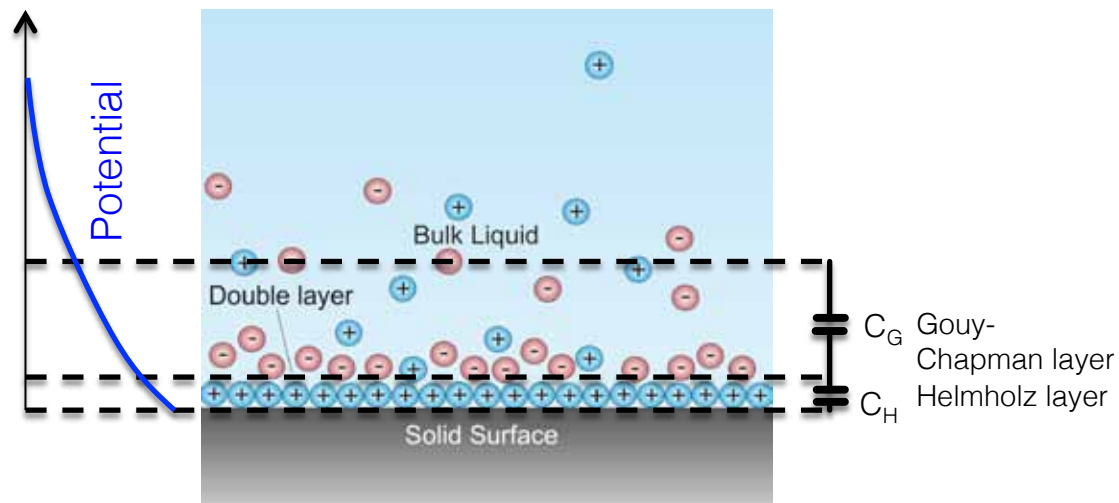
$$g_m \xrightarrow{WI} \frac{I_D}{nU_T}$$

$$V_n \approx \frac{2\ \text{nV}}{\sqrt{I_D}}$$

HEP analogy: “strip” (1D) and “pixel” (2D) detectors



# Getting the Signal



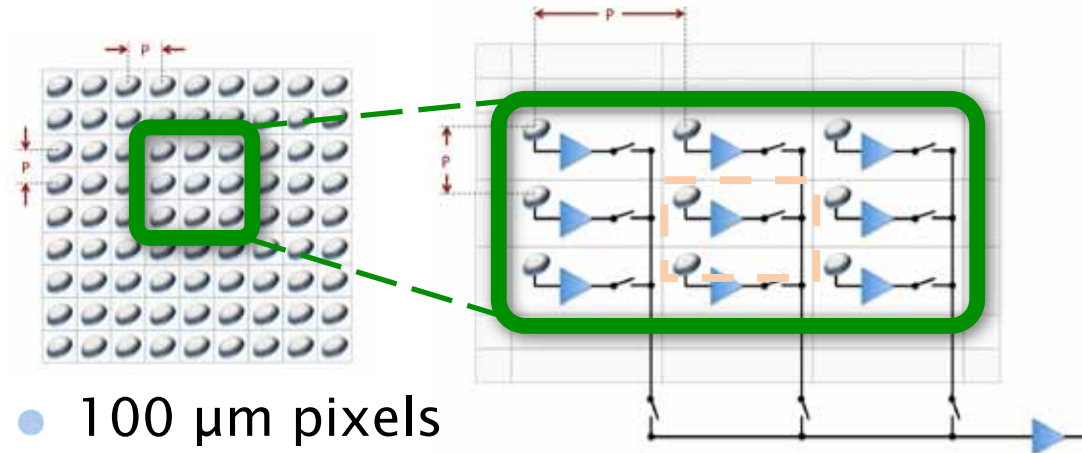
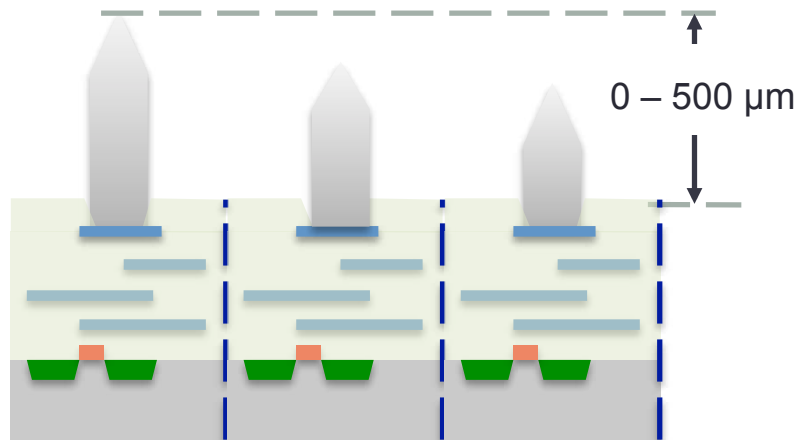
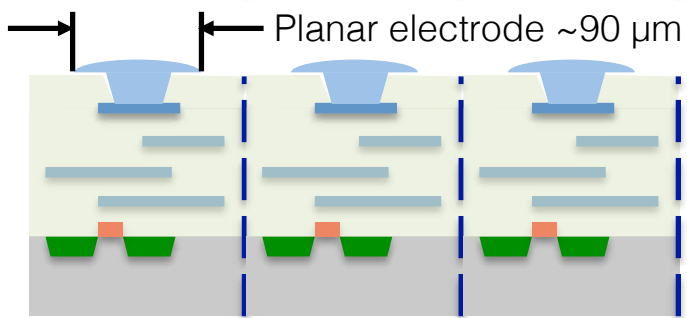
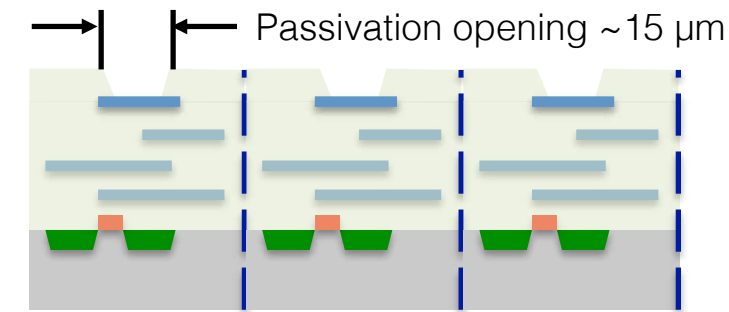
Most typical:

- AC-coupled
- Gain =  $C_I/C_F$
- $\tau_{LF} = R_F C_F$
- e.g.  $C_I = 10$  pF, Gain = 100  $\rightarrow C_F = 100$  fF
- $\tau_{LF} \sim$  Hz  $\rightarrow R_F = 1$  T $\Omega$
- (and, CMOS generally  $\sim 1$  fF/ $\mu\text{m}^2$ )

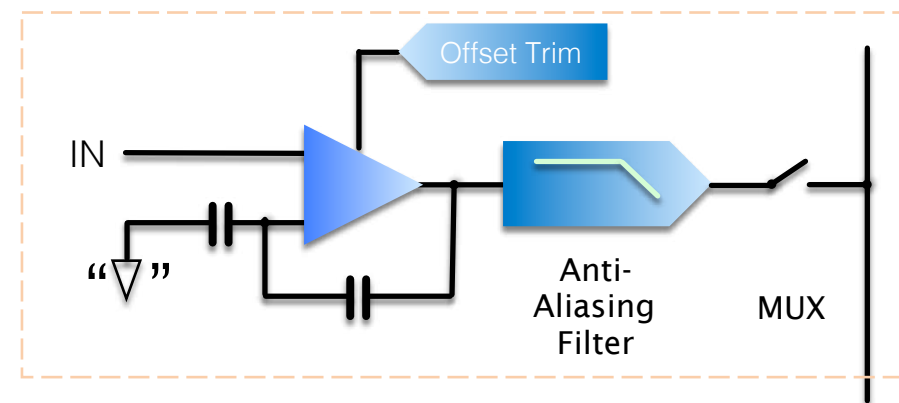
100  $\mu\text{m}^2$



# e-chip



- $100 \mu\text{m}$  pixels
- $20 \text{ kHz}$  / pixel
- 1 wire / 1,000 pixels
- Grow electrodes on chip
  - (or bump bond chip to array)



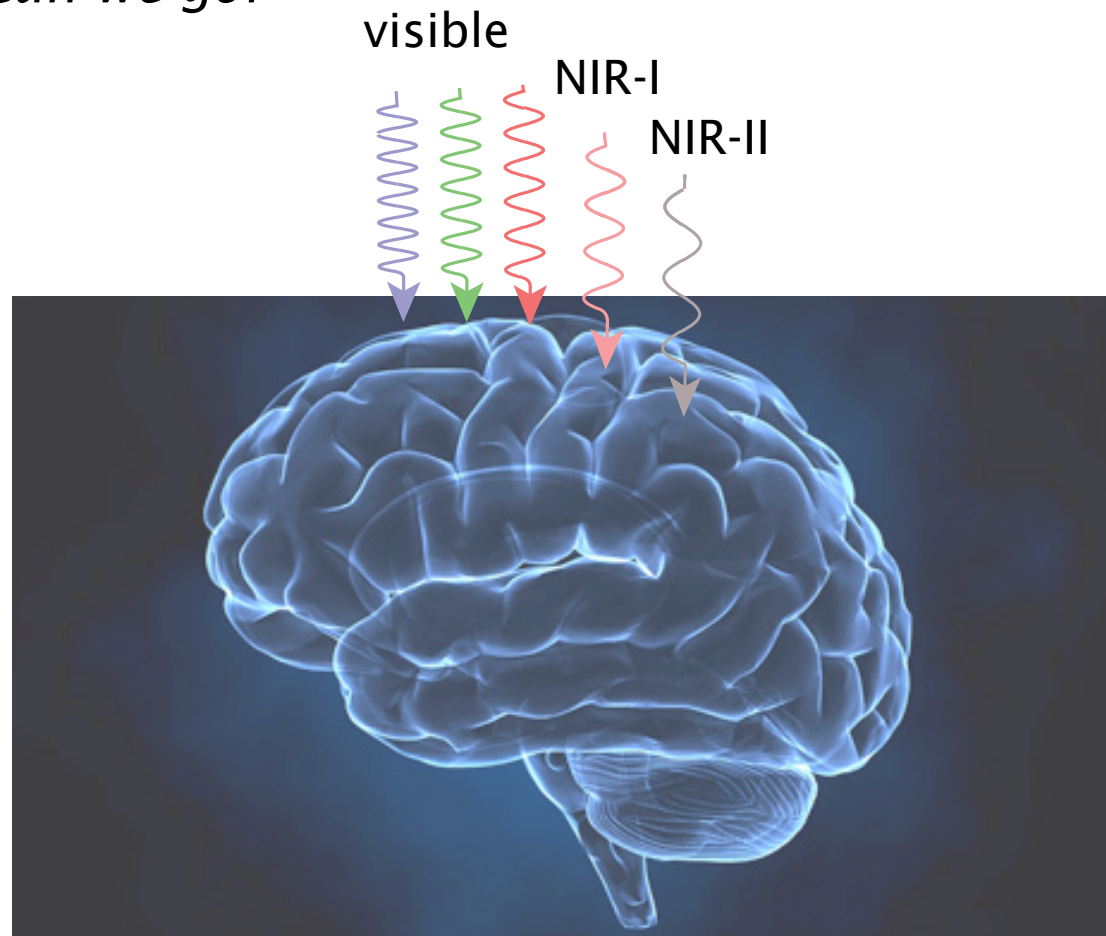
Later - an app for this

**BRAIN**seed

# Interrogating the Brain with Light



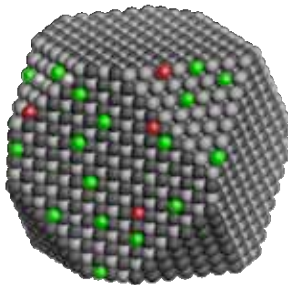
*How deep can we go?*



[mouse optogenetics](#)

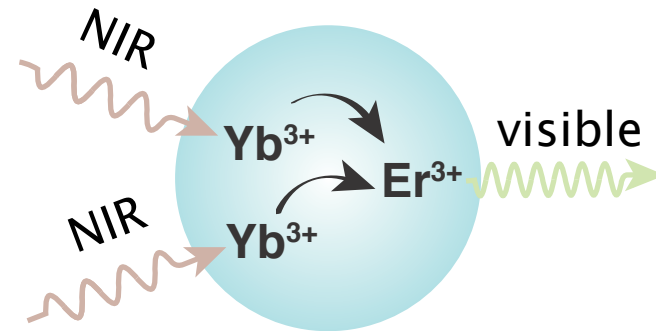
# Nanocrystals as Optical Transducers

## UCNP

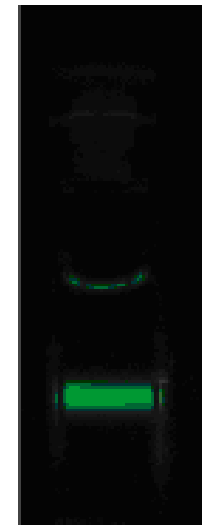


- 20%  $\text{Yb}^{3+}$  - *sensitizer*
- 2%  $\text{Er}^{3+}$  - *emitter*
- $\text{NaYF}_4$  - *host matrix*

*...require new light sources and detectors*



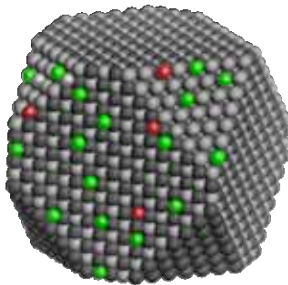
980 nm  
~



**BRAINseed**

# Nanocrystals as Optical Transducers

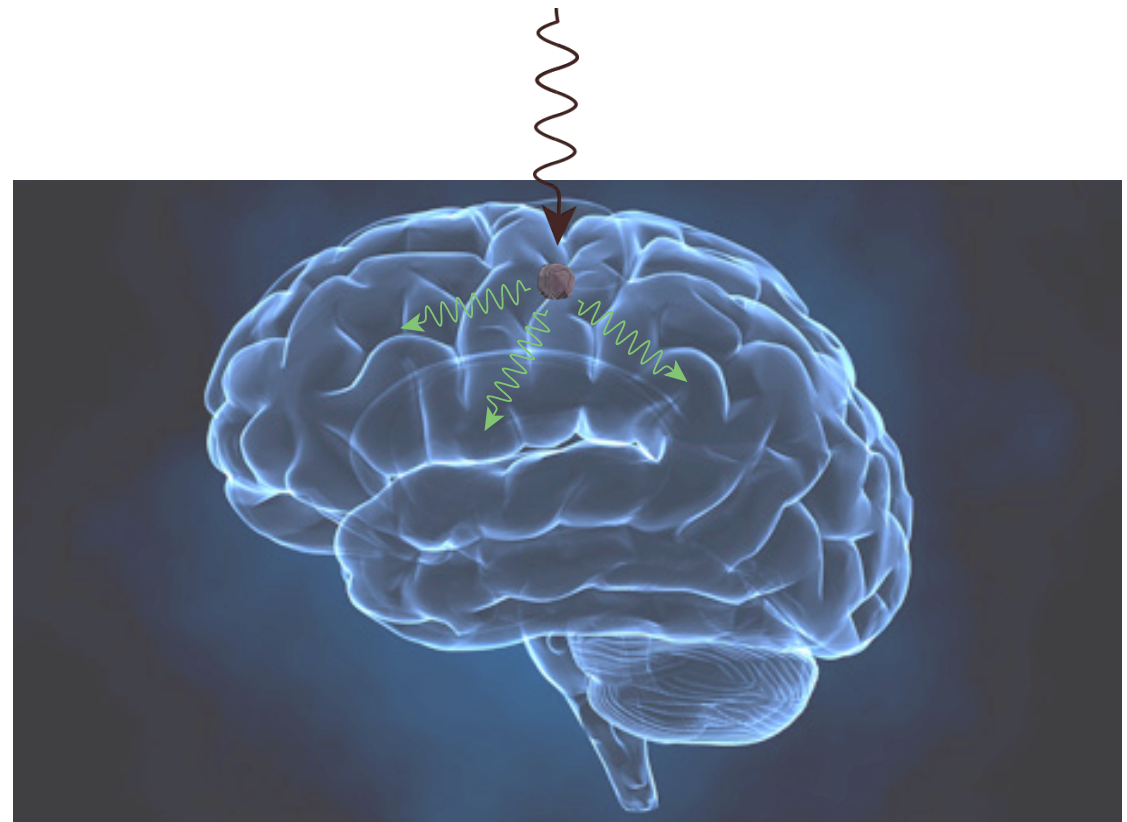
UCNP



## *Wish list*

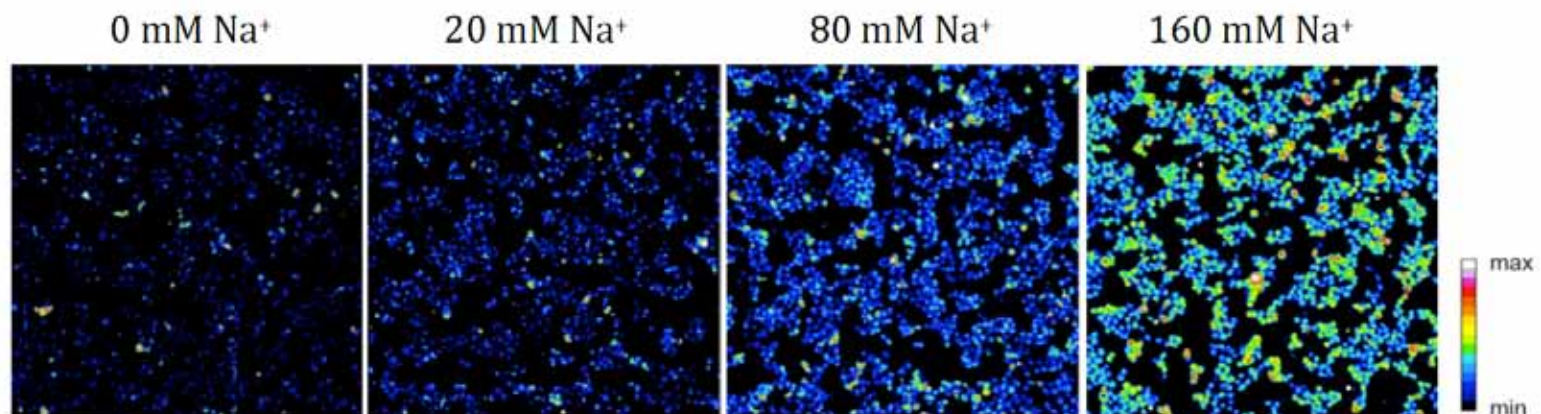
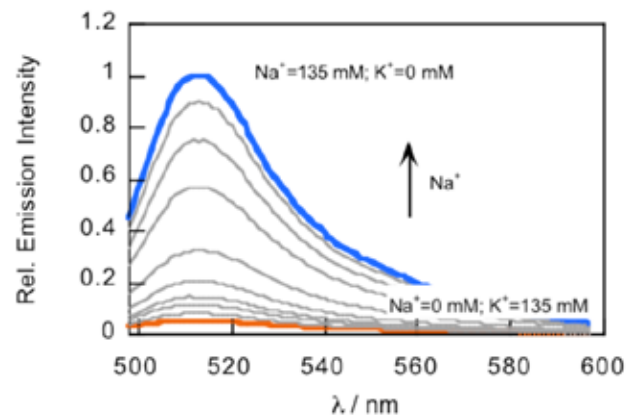
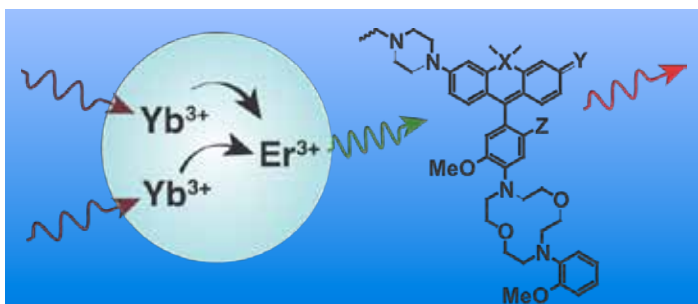
- cw NIR lasers!
- better IR detectors!
- acoustic imaging microscope!

NIR-I (700 – 1200 nm)



# Sensing Na<sup>+</sup> ions with NIR light

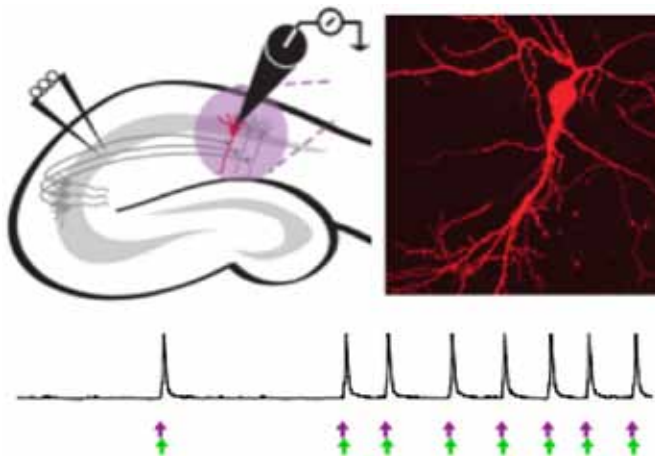
with Chris Chang, UCB/LBNL



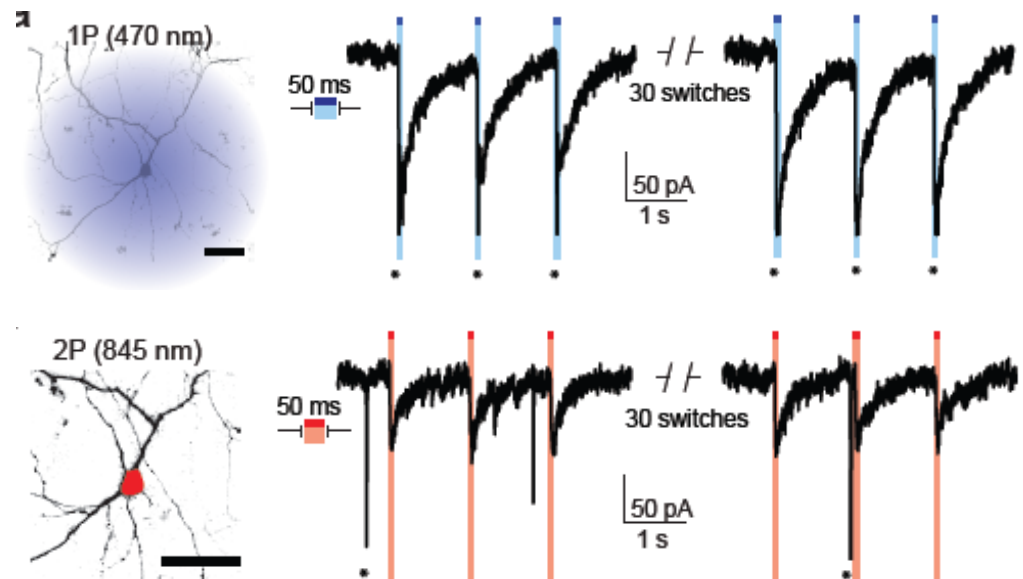
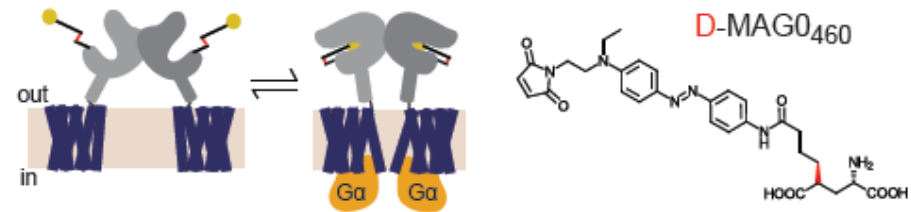
# Activating neurons with NIR light

*with Udi Isacoff, UCB/LBNL*

Light-activated neuronal firing:

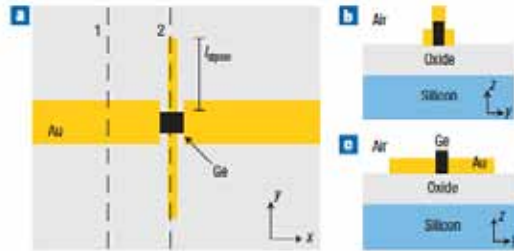
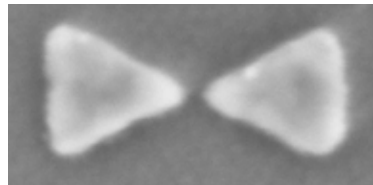
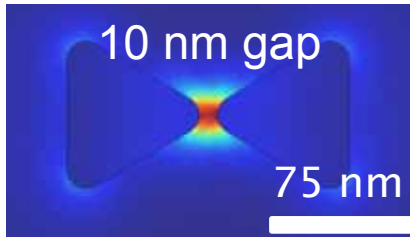


Shifting to NIR wavelengths:

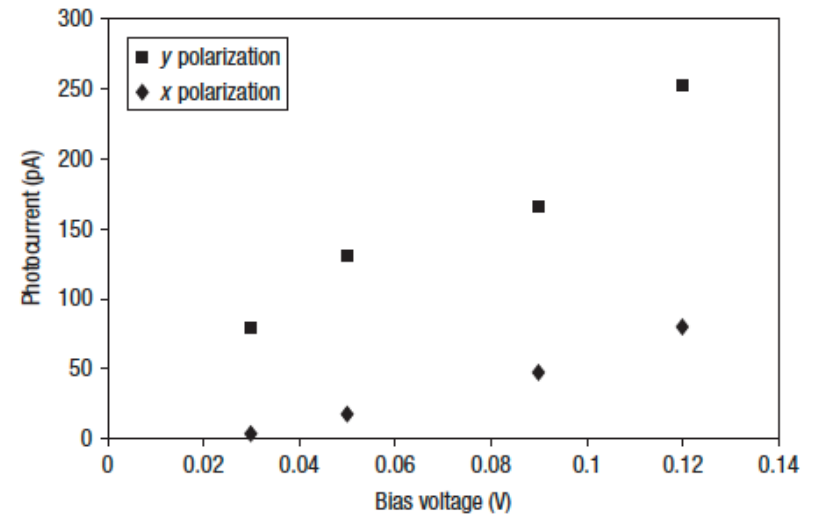


# Nanotech-inspired Approaches

## Plasmonic optical antennas - as single photon detectors (or re-radiators)

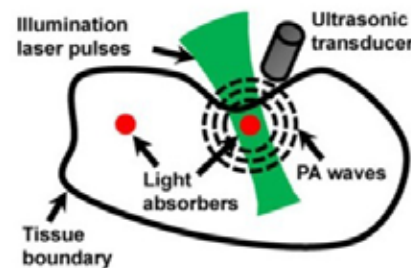


- $\mu\text{m}$ -scale device
- est. 5 aF capacitance
  - $1 e^-/5 \text{ aF} = 160 \text{ mV}$



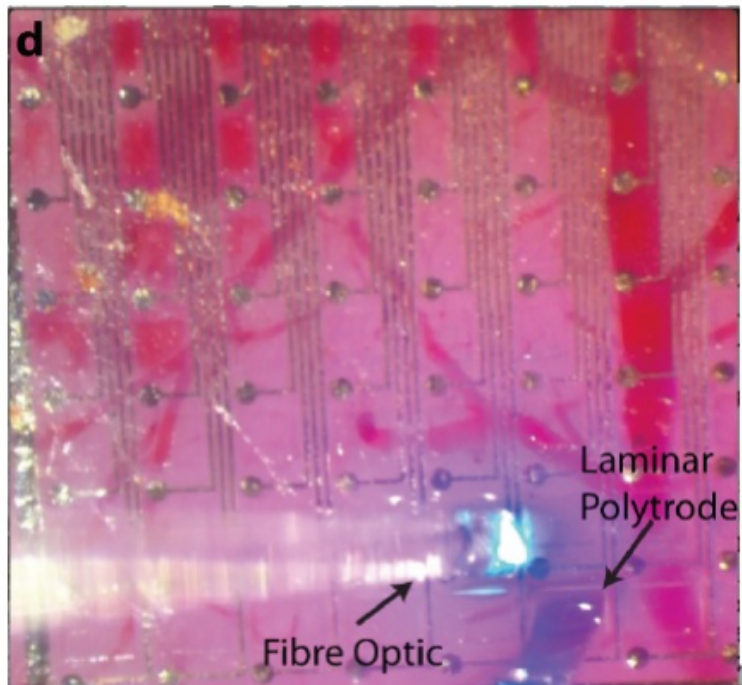
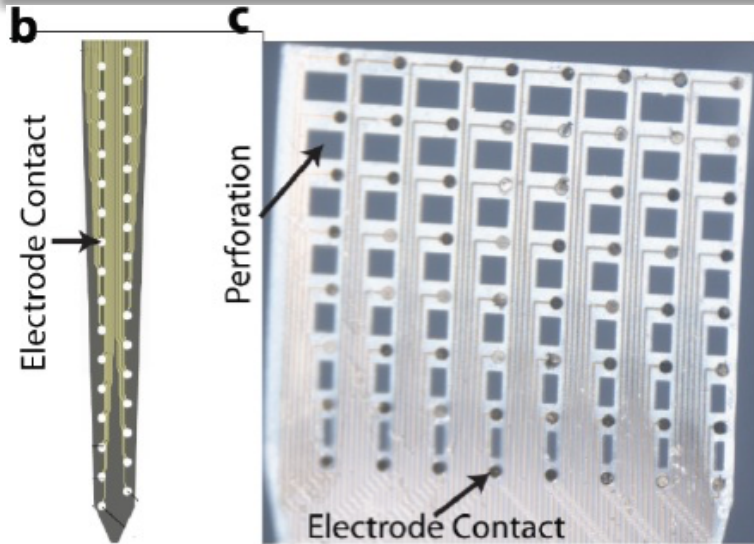
A few technical details remain

## Micro-cantilevers as (photo) acoustic (ultrasound) sensors



Tang, L. et al. Nanometre-scale germanium photodetector enhanced by a near-infrared dipole antenna. Nature Photon 2, 226–229 (2008).

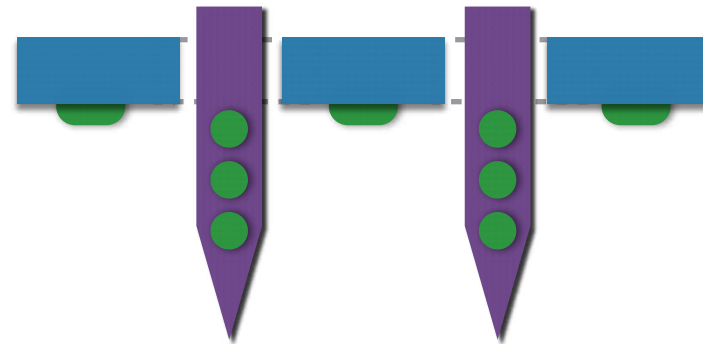
# Excitation and Sensing



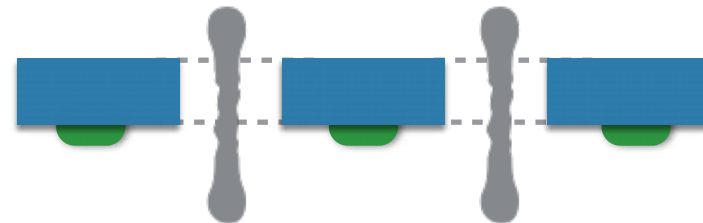
- Electrical Excitation



- Surface + Depth



- Optical excitation





# An App



~~Available on the~~  
App Store

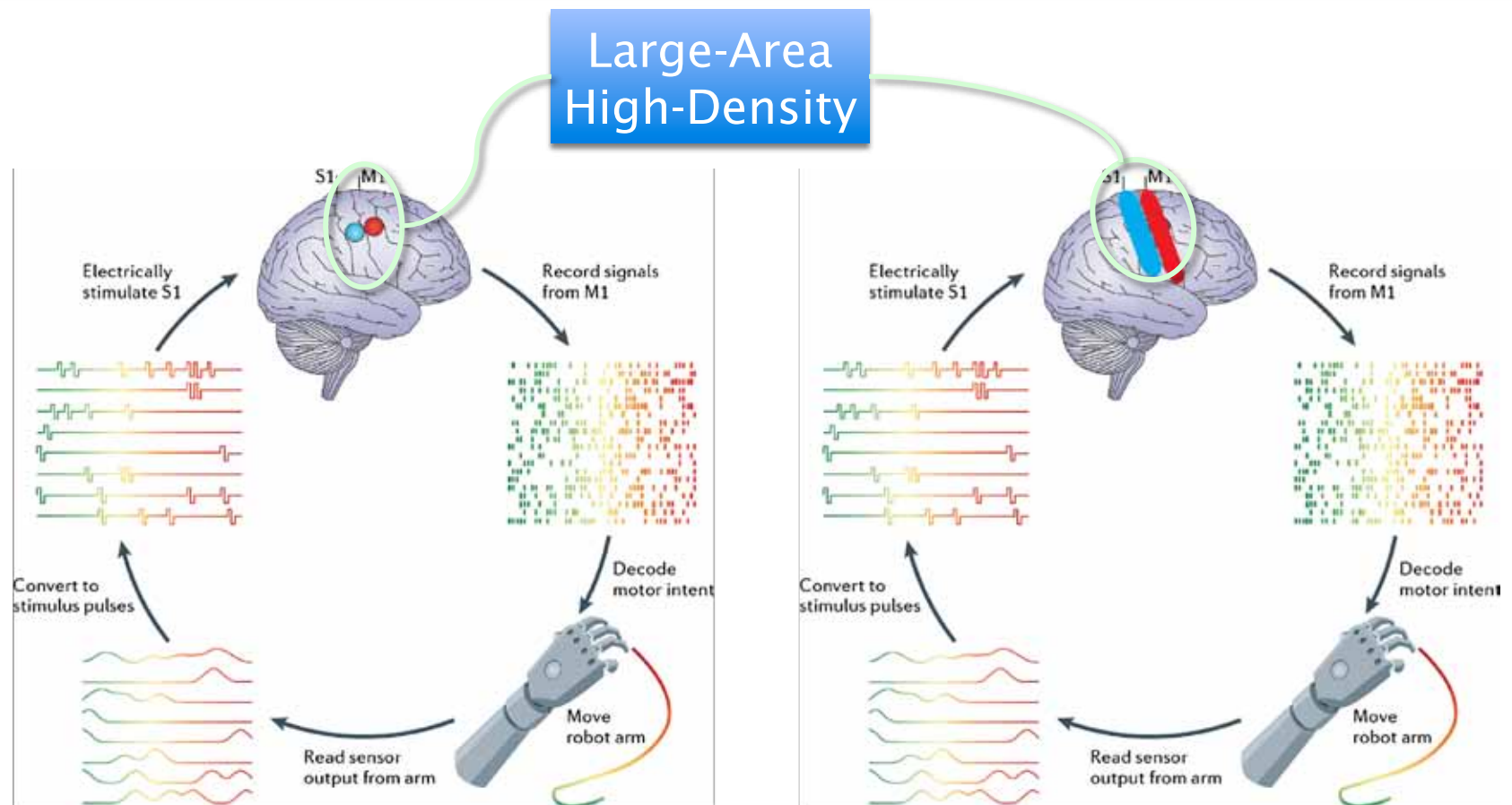


How can you talk if you  
haven't a brain?

Oh some people without  
brains do an awful lot  
of talking.



# Closed-loop Brain Machine Interfaces



Journal of Neuroscience Methods

journal homepage: [www.elsevier.com/locate/jneumeth](http://www.elsevier.com/locate/jneumeth)



DARPA-funded efforts in the development of novel brain-computer interface technologies

Robbin A. Miranda <sup>a,\*,</sup> William D. Casebeer <sup>b,</sup> Amy M. Hein <sup>c,</sup> Jack W. Judy <sup>d,</sup>  
Eric P. Krotkov <sup>e,</sup> Tracy L. Laabs <sup>c,</sup> Justin E. Manzo <sup>f,</sup> Kent G. Pankratz <sup>f,</sup> Gill A. Pratt <sup>g,</sup>  
Justin C. Sanchez <sup>b,</sup> Douglas J. Weber <sup>b,</sup> Tracey L. Wheeler <sup>h,</sup> Geoffrey S.F. Ling <sup>b</sup>

# Advancing BMI will benefit from:



- 1) instrumentation for high spatio-temporal resolution recording of neural activity from many sites

(*Today*:  $\sim 10^2$  electrodes, *Goal*:  $10^4 - 10^5$  electrodes,  $100 \mu\text{m}$  pitch)

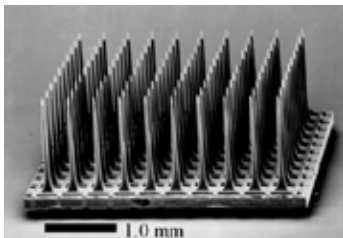
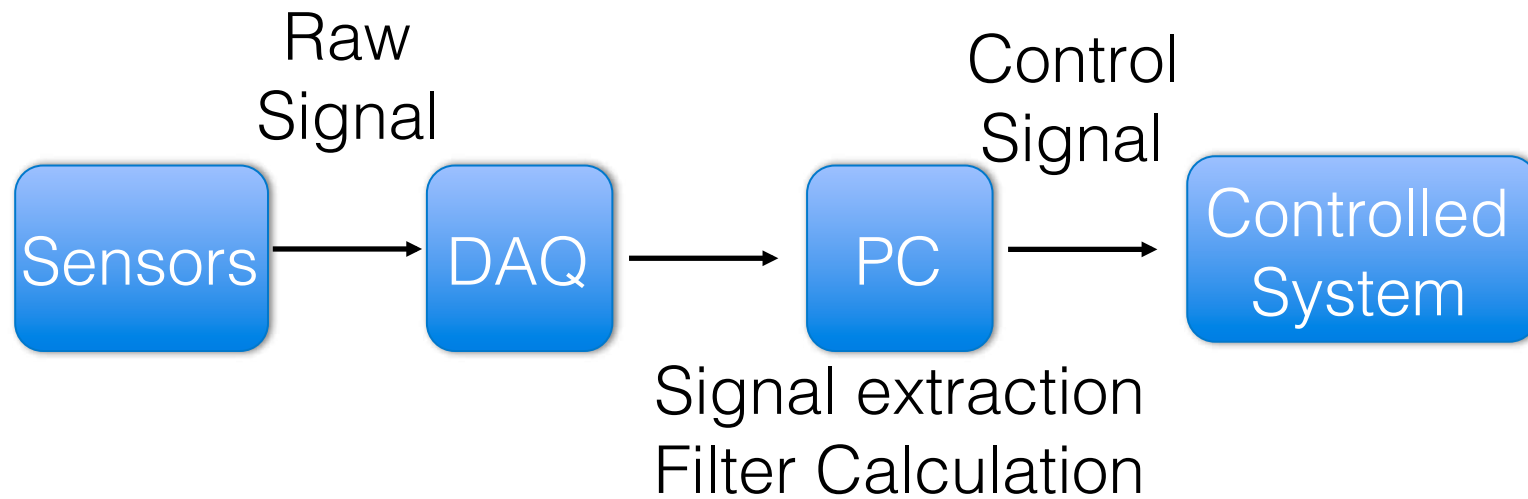
- 2) computational methods for extracting structure from the resulting massive amounts of data in real-time

(*Goal*:  $10^4 - 10^5 \times 16\text{B} \times 20\text{kHz} \leq 4 \text{ Gb/s} \sim 350\text{Tb} / \text{day}$ )

[*Neuro*:  $\infty$  / *Light Source*: Lots! / *HEP*: That's It?]

- 3) high-throughput experimental preparations that engage multiple neural circuits during complex behaviors  
(rapid turn-over of tech to testing)

# Hardware/Computing in Current BMI pipeline

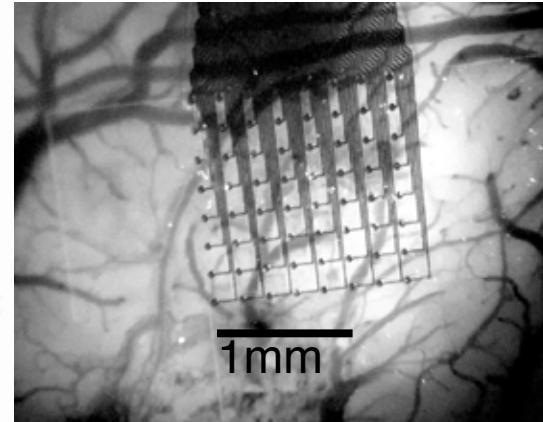
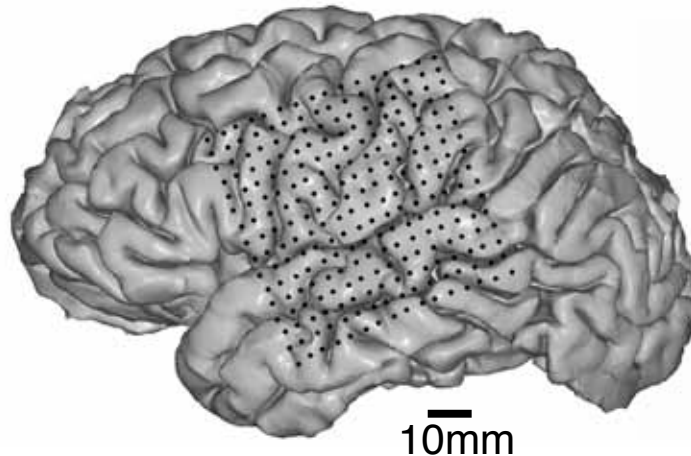


Today: R&D

Off-the-shelf

Today: R&D

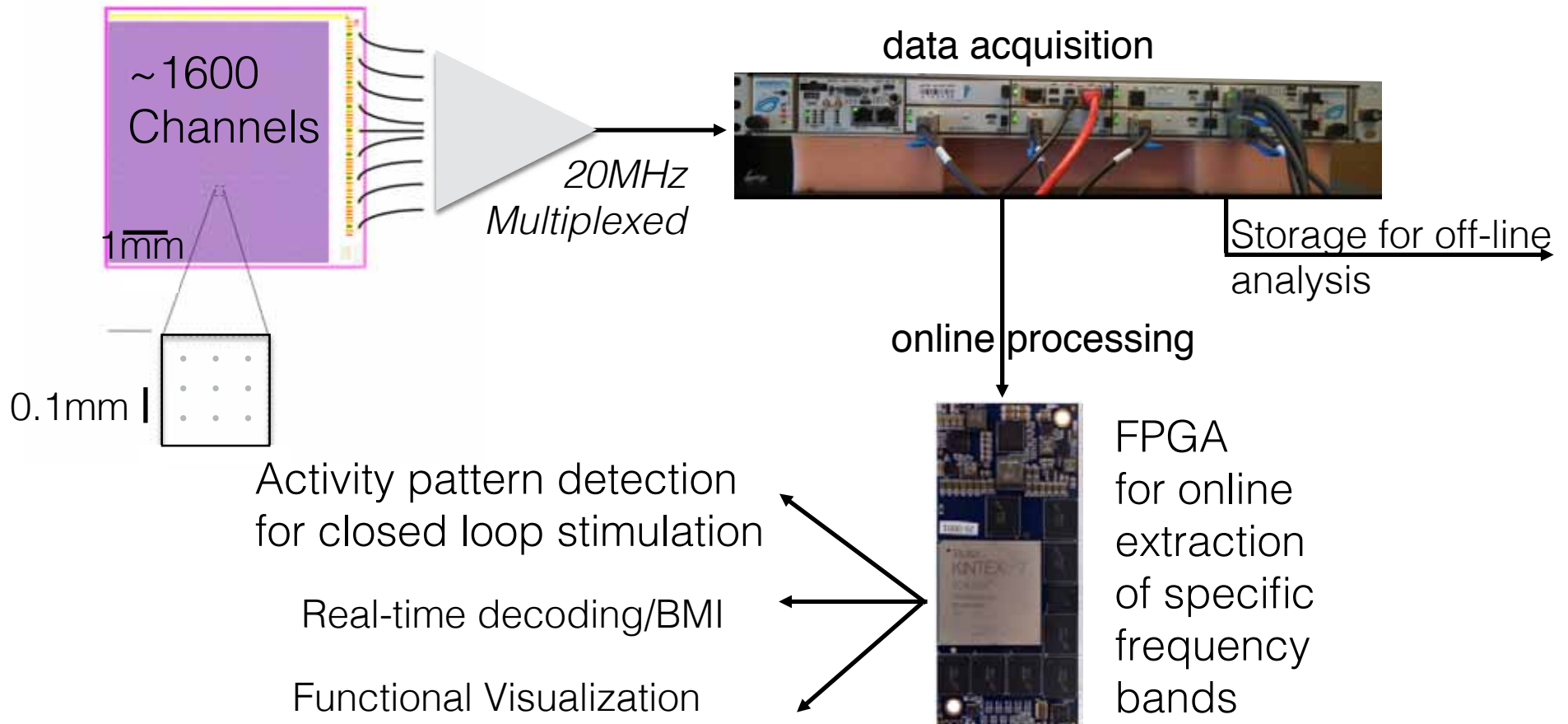
# Advancing BMI through ultra-high density ECoG



- 1) large area for diversity of independently controllable sites
- 2) technologically scalable to high spatial resolution
- 3) high-temporal resolution
- 4) long-term stability
- 5) large magnitude, robust, meaningful field potential signals
- 6) able to detect action potentials with uECoG
- 7) rapid translation to humans

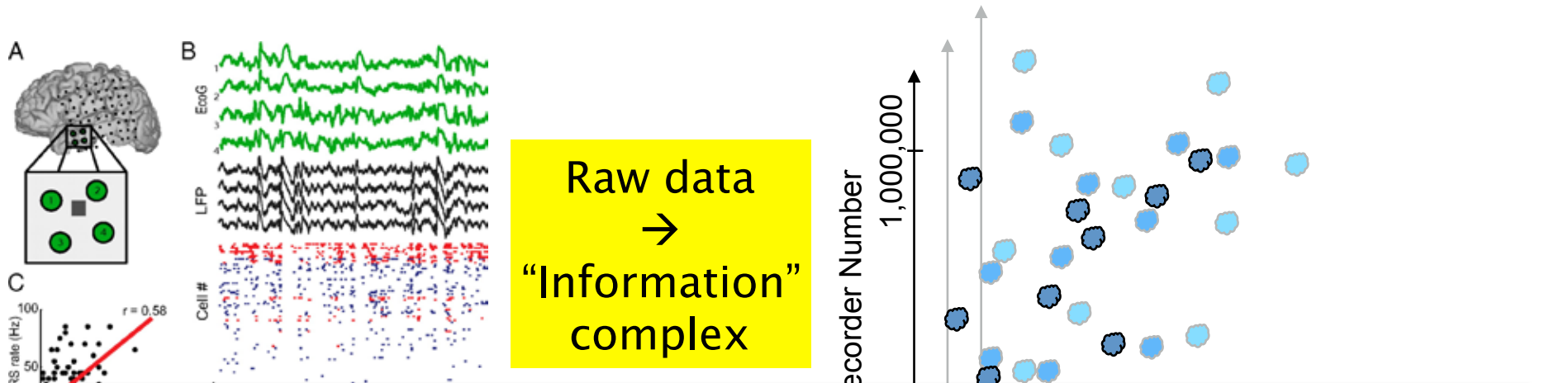
# Massive Channel Count, High-density Electrophysiology

e-Chip



# Massive Channel Count & Computational Challenges

- $10^6$  recorders at 1 kHz
- Look for correlations (in a  $10^6 \times 10^6$  recorder x ms x N space)

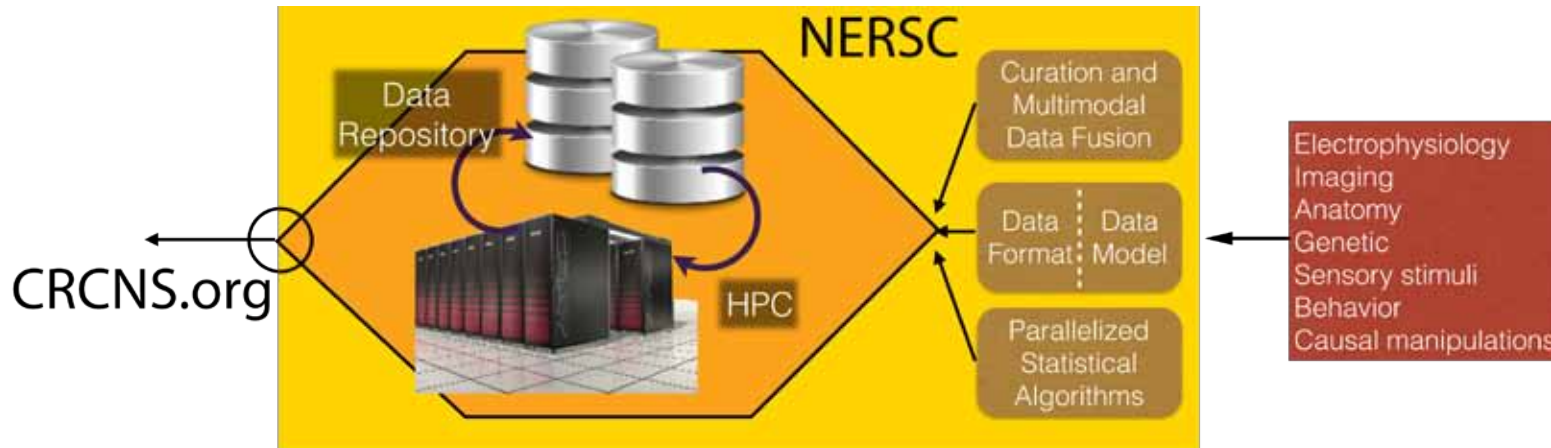


$10^6 \times 1$  kHz  $\neq$  1,000 Megapixel/s

- Consecutive Measurements are not Independent
- Long-distance/time correlations

- Dimensionality reduction
- Coding schemes
- Visualization

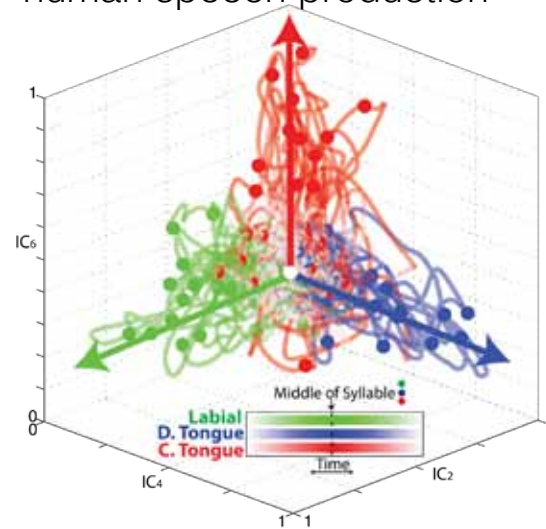
# Advances in HPC for Neuroscience



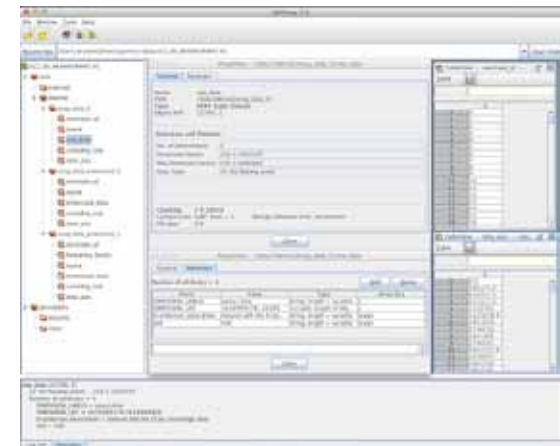
CRCNS portal and repository for community access to data



Sparse neural activity for human speech production



HDF5 format and data model for high-performance computing



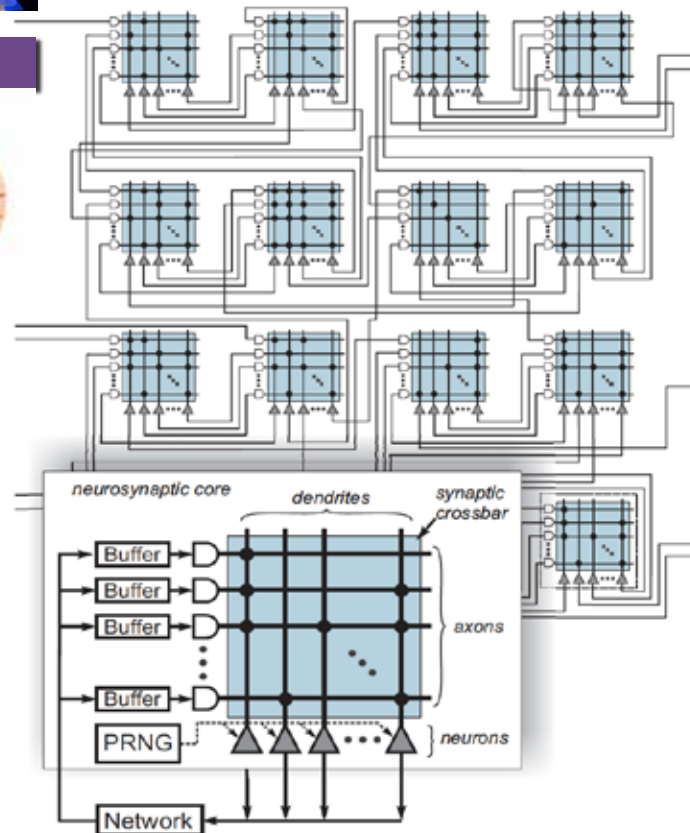
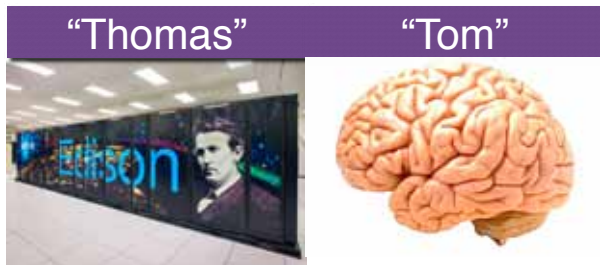


# Neuromorphic Computing



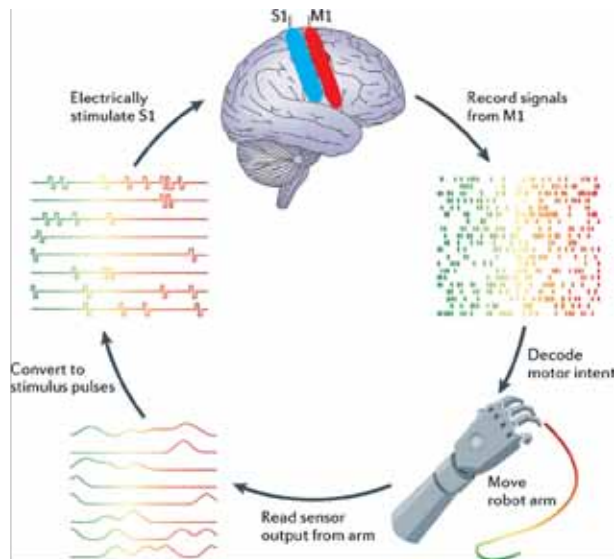
- The brain is pretty good at certain tasks
- Brain-inspired computing?

- Neural networks
- IBM TrueNorth

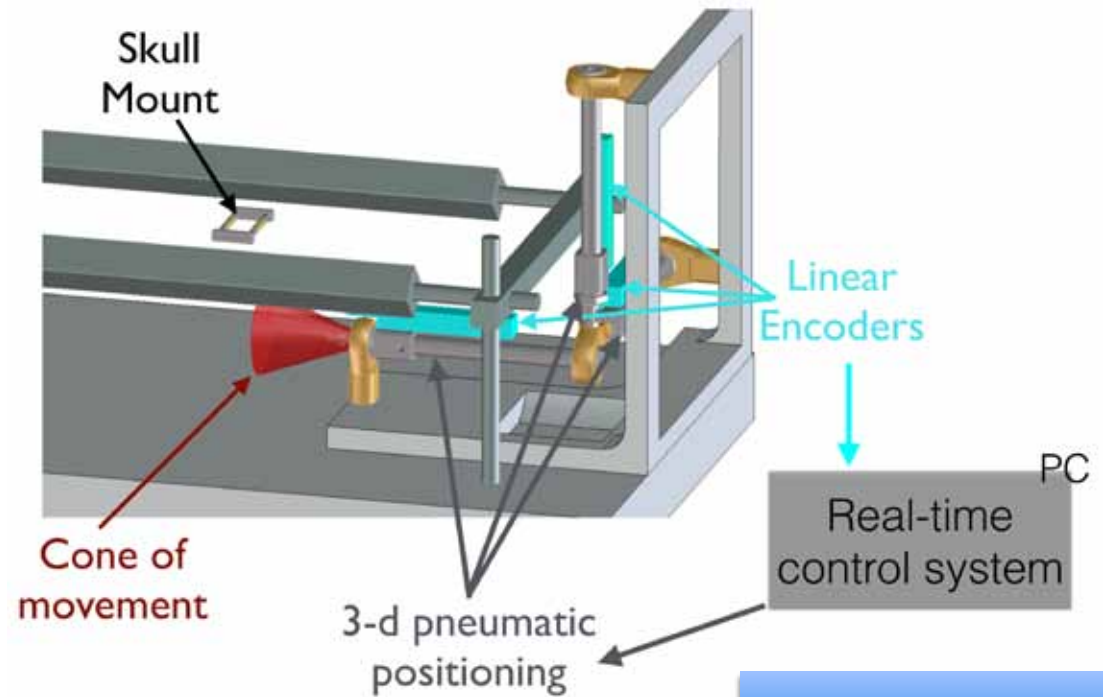
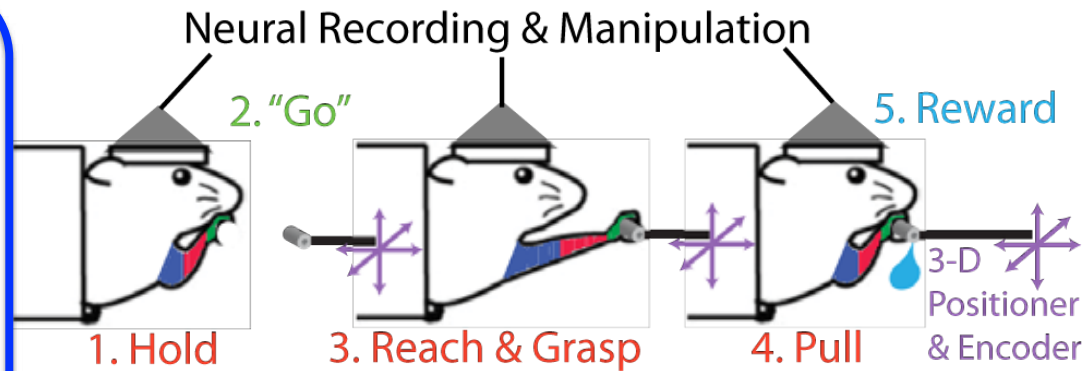


# Complex Tasks for Rodent Experiments

## Not Plug-N-Play



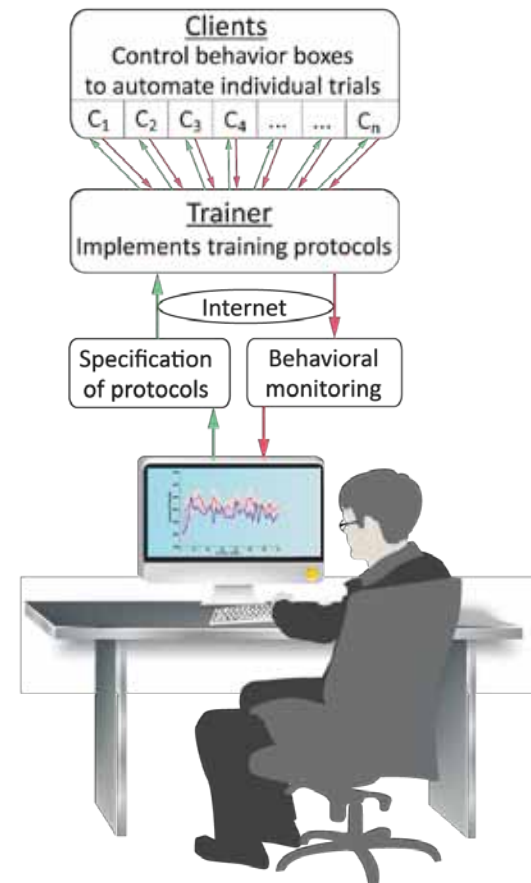
Develop in Model Systems



“Instrumentation”

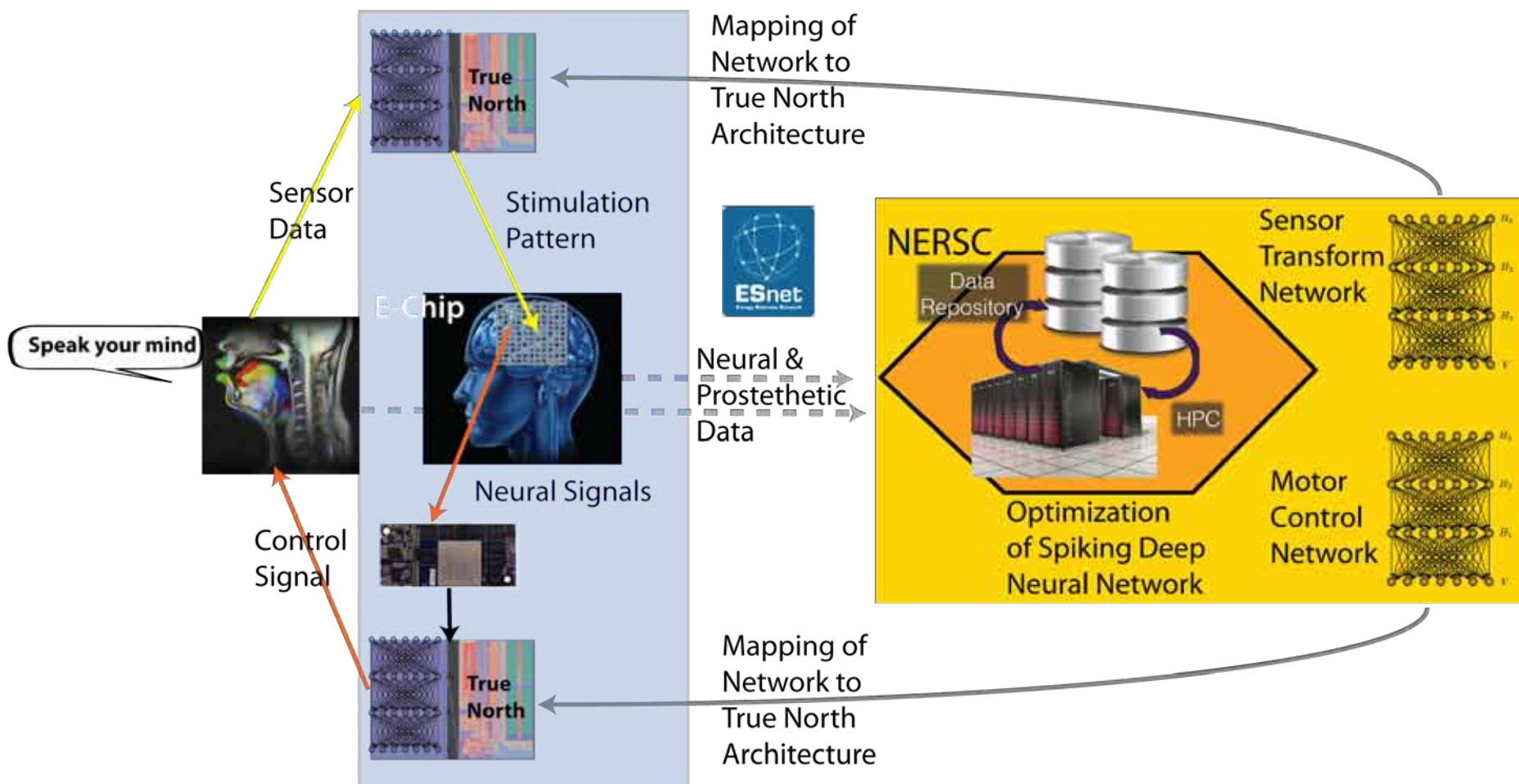
**BRAINseed**

# High-throughput Rodent Experiments



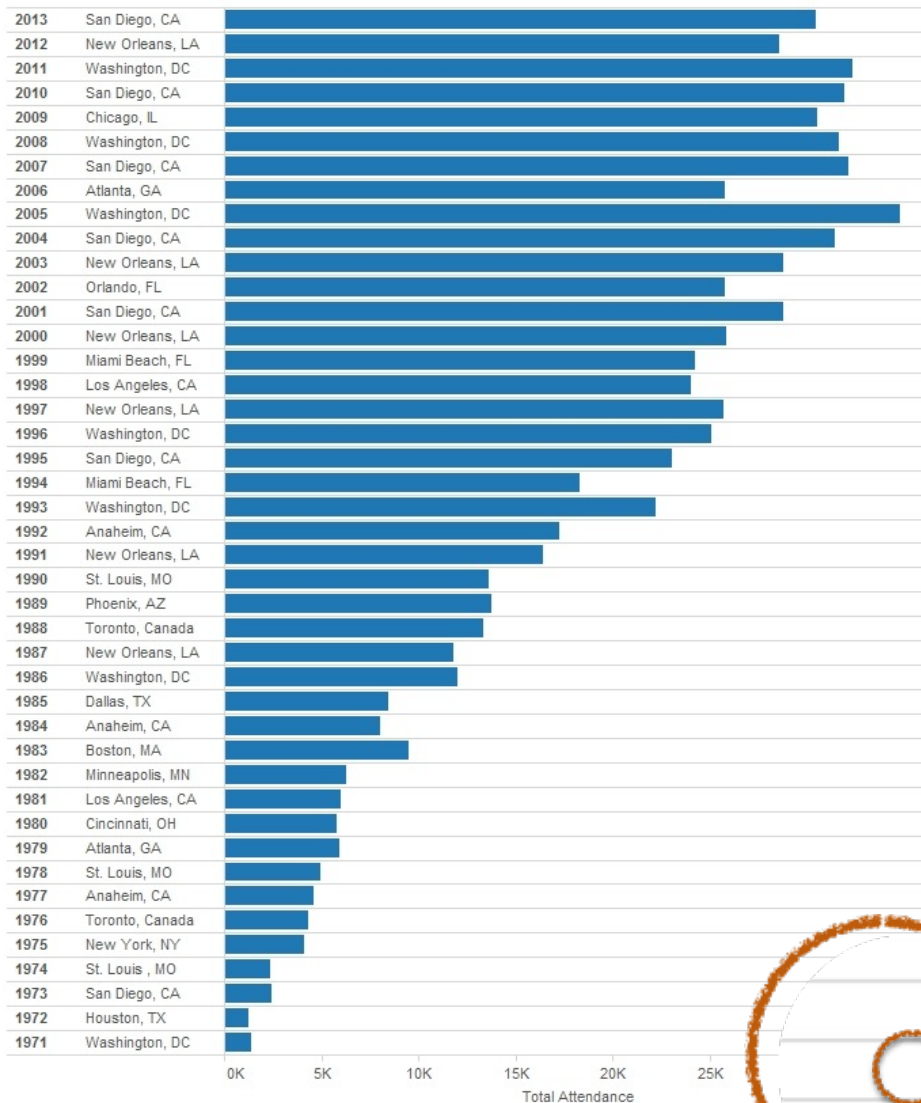
“Instrumentation”

# “Speak your Mind” speech prosthetic



# Neuroscience is a Large and Diverse Field

Annual Meeting Attendance (1971-2013)



- Lots of practitioners
- Lots of directions
- (largely single-PI)
  
- **What are the questions?**
  
- Much known at the single neuron level
- Can now observe ~100 neurons
- To understand circuits, need to observe much larger numbers
  
- Better tools can point to the right questions
  
- Described above is only a fraction of what we are doing
  - and a small fraction of what is being done





# Opportunities - Federal Agencies

**POLICYFORUM**

**RESEARCH PRIORITIES**

## The NIH BRAIN Initiative

Thomas R. Insel • Stacy C. Landis • Francis S. Collins\*

On 2 April 2013, President Barack Obama announced the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. In front of some 200 scientists in the East Room of the White House, the President declared, "...there is this enormous mystery waiting to be unlocked and the BRAIN Initiative will change that by giving scientists the tools they need to get a dynamic picture of the brain in action and better understand how we think and how we learn and how we remember. And that knowledge could be transformative" (1).

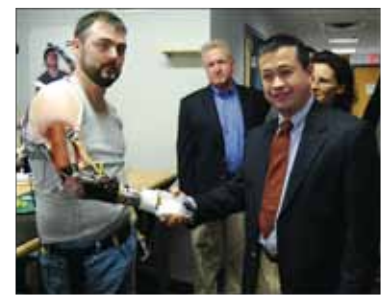
Many scientists have been skeptical of an ambitious new project when support of cutting-edge science is waning. Others have been excited about how this project will accomplish its goals, because mapping the brain is far more complex and open-ended than mapping the genome. Still others have speculated about whether this is really a new initiative, with new funding, or if it simply reflects rebranding of current research. Here, we will try to address these concerns and explain in more detail the NIH vision for the BRAIN Initiative.

The BRAIN Initiative is being launched with a proposal for federal funding of just over \$100 million in the first fiscal year and will be led by the National Institutes of Health, the Defense Advanced Research Projects Agency (DARPA), Private Partners—such as the National Science Foundation, the Defense Science and Engineering Graduate Fellowship, the Kavli Foundation, and the Salk Institute for Biological Studies—and also committed to ensuring that a preliminary vision, called the "Brain Activity Map," was initially developed as a series of meetings sponsored by the Kavli Foundation, the Gatsby Charitable Foundation, and the Allen Institute for Brain Science (2, 3). BRAIN seeks to significantly extend and shape the vision, expanding the research plan to represent neuroscience community-wide and to include basic and applied research in brain structure and function. It is already an exciting field of science. New areas of research are being discovered. We argue that current technological advances render of individual cognitive traits (4).

Do current technological advances render of individual cognitive traits (4). We argue that current technological advances render of individual cognitive traits (4).

\*Corresponding author. E-mail: fscollins@nih.gov (F.S.C.)  
E-mail: stacy@nihs.nih.gov (S.L.L.)  
E-mail: tinsel@nih.gov (T.R.I.)

www.sciencemag.org SCIENCE VOL. 340 10 MAY 2013



NEWSMAKER INTERVIEW: GEOFFERY LING

## DARPA Aims to Rebuild Brains

On 11 November, a monetary slip set the rumor mill spinning at the Society for Neuroscience meeting in San Diego, California. At a press conference for the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, a National Institutes of Health (NIH) official suggested that the Defense Advanced Research Projects Agency (DARPA) planned to develop technology that transfers memory from one brain to another.

Geoffery Ling, deputy director of the Defense Science Office and program manager for one of DARPA's new BRAIN projects, was horrified. "I said, 'What? No, we're restoring memory, and she says, 'Oh yeah, that's what I meant to say.'" But the gene was out of the bottle—by the end of the day even Tom Insel, director of the National Institute of Mental Health, was spreading the word about Vulcan mind meld-style memory transfer. "It's wild," he told Science.

The confusion was understandable: in contrast to NIH, which held a series of open meetings over the summer to discuss its BRAIN research goals, DARPA has until recently kept plans for its \$70 million portion of the project under wraps. And although brain-to-brain memory transfer isn't on the agency's to-do list, its actual goals are still wildly ambitious. So far, DARPA has released two calls for grant applications, with at least one more likely: The first, called SUBNETS (Systems-Based Neurotechnology for Emerging Therapies), asks researchers to develop novel, wireless devices, such as deep brain stimulators, that can cure neurological disorders such as posttraumatic stress (PTS), major depression, and chronic pain. The second, RAM (Restoring Active Memory), calls for a separate wireless device that repairs brain damage and restores memory loss.

In San Diego, Science sat down with Ling, a neuroscientist and former Army colonel who specialized in traumatic brain injuries while in the military, to talk about the project. The following has been edited for brevity and clarity; an extended version is online at <http://sciencemag.org/darpa/brain>.

—EMILY UNDERWOOD

**NEWS&ANALYSIS**

**Restore.** After guiding a DARPA effort to create a brain-science genetic arm, Geoffery Ling wants to entice scientists to his injured brain.

light, but it has a use for civilians who have stress disorders and civilians who also have memory disorders from dementia and the like. But at the end of the day, it is still meeting President Barack Obama's directive. Of all the things he could have chosen—global warming, alternative fuels—he chose this, so in my mind the neuroscience community should be as excited as all get-up.

**Q: Why does SUBNETS focus on deep brain stimulation (DBS)?**  
**GL:** We've opened the possibility of using DBS, but we haven't exclusively said that. We're challenging people to go after neuroscientists' disease like PTSD [and] depression. We're challenging the community to come up with something in 2 years that's clinically feasible. DBS is an area that has really been traditionally underfunded, so we thought what the heck, let's give it a go—in this new BRAIN initiative the whole idea is to go after the things that there aren't 400 R01 grants for—and let's be bold, and boy, if it works, fabulous.

**Q: For RAM, why did DARPA choose to focus on memory, and what kinds of memory do you hope to restore?**  
**GL:** All these [injured] guys and gals want to go back into the service. A lot of them can't go back because we've got prosthetic legs, and now we've got the prosthetic arm that really close to being FDA [Food and Drug Administration] approved. But the thing with brain-injured guys—the thing that really keeps them out—is they can't remember how to do certain motor tasks like drive a car or operate machinery. Now I don't know if we are at that point that we can fix hearts, and we can fix body broken bones, why can't we fix part of the brain? If you had to pick an area of the brain that you can fix, the memory area is the most obvious because motor-task memory is really pretty well-worked out in preclinical models. Declarative memory is very different than associative memory and emotional memory—that stuff, nobody even knows

**UNDERSTANDING THE BRAIN**  
The National Science Foundation's role in the BRAIN Initiative

What is the BRAIN Initiative?  
The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is a multi-agency effort to advance neuroscience research and develop new technologies to understand the brain and its functions. The initiative is led by the National Institutes of Health (NIH), the Defense Advanced Research Projects Agency (DARPA), and other federal agencies, as well as private partners. The goal is to create a dynamic picture of the brain in action and better understand how we think and how we learn and how we remember.

Why is the BRAIN Initiative important?  
The brain is the most complex organ in the human body, and it is the seat of our thoughts, emotions, and behaviors. Understanding the brain is one of the most important challenges facing humanity today. The BRAIN Initiative is a major effort to advance our understanding of the brain and its functions, and to develop new technologies to study the brain and its functions.

What are the goals of the BRAIN Initiative?  
The goals of the BRAIN Initiative are to create a dynamic picture of the brain in action and better understand how we think and how we learn and how we remember. The initiative is focused on three main areas: understanding the brain's structure and function, understanding the brain's activity and its role in behavior, and developing new technologies to study the brain and its functions.

How is the BRAIN Initiative being funded?  
The BRAIN Initiative is being funded by a combination of federal agencies, including the NIH, DARPA, and the Department of Energy (DOE), as well as private partners. The total funding for the initiative is estimated to be over \$1 billion over the next several years.

What are the challenges facing the BRAIN Initiative?  
The BRAIN Initiative faces several challenges, including the need for increased funding, the need for increased collaboration between agencies and private partners, and the need for increased public awareness of the importance of brain research.

What are the opportunities facing the BRAIN Initiative?  
The BRAIN Initiative offers several opportunities, including the potential to develop new treatments for neurological disorders, the potential to develop new technologies for brain research, and the potential to advance our understanding of the brain and its functions.

- NIH
- DARPA (IARPA)
- NSF
- FDA
- (DOE) ?



NEUROSCIENCE  
**Brain Project Draws Presidential Interest, but Mixed Reactions**

Even some in the neuroscience community expressed concern. "If this takes away from any of the R01s [individual investigator grants] that would normally be funded by the NIH, it would be bad," says Eve Marder of Brandeis University in Waltham, Massachusetts, a former president of the Society for Neuroscience, who had attended one of the early planning workshops for BAM. "Right now the community is already so strapped we're at a breaking point."

Whatever one's initial reaction to the new initiative, there is little doubt that researchers, and potentially physicians, would benefit from better ways of observing the brain

THE BRAIN INITIATIVE and BRAIN RESEARCH THROUGH ADVANCING INNOVATIVE NEUROTECHNOLOGIES are service marks of the U.S. Department of Health & Human Services (HHS).

# Cal-BRAIN



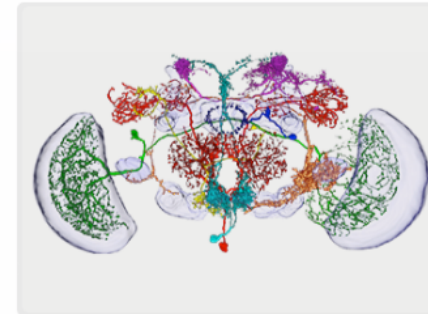
## Eligible Areas

### Examples\* of Research Areas Eligible for Support

In model systems and humans, with the potential to scale to highly parallel measurements.

Projects supported by this seed grant program may include, but are not restricted to, those that develop:

- sensors of nerve cell electrical or chemical activity, either biologically or nano-material based
- micro- and nano-scale, biocompatible devices for transmitting sensor signals or for targeted therapeutic stimulation
- new modalities for brain activity imaging
- tracers to enhance current brain activity imaging technologies
- new technologies for neural prosthetics (e.g., motor control, memory, addiction control)



\*Since a goal of Cal-BRAIN is to determine the most promising neurotechnologies, this list is illustrative, and not exhaustive.



### Seed Grant Program 2014-15 Application Guidelines

October 20, 2014

Mandatory Letter of Intent (LOI) Deadline	November 24, 2014 5:00 PM PT
Full Application Submission Deadline	December 15, 2014 5:00 PM PT
Notification of Awards	January 26, 2015
Award Start Date	February 1, 2015 or soon thereafter
Maximum Award Size	\$120,000 total, including IDC
Maximum Award Period	12 months

### Cal-BRAIN:

Ralph J. Greenspan, I

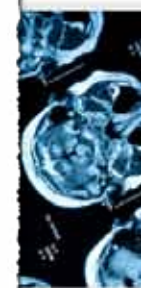
Cal-BRAIN (the Califor statewide program to capable of monitoring

Goal: Develop new te ability to monitor and

Impacts: Advances fo prosthetic devices. At intelligent systems ca enhance the capabiliti generation of interdisc Neurotechnology, w

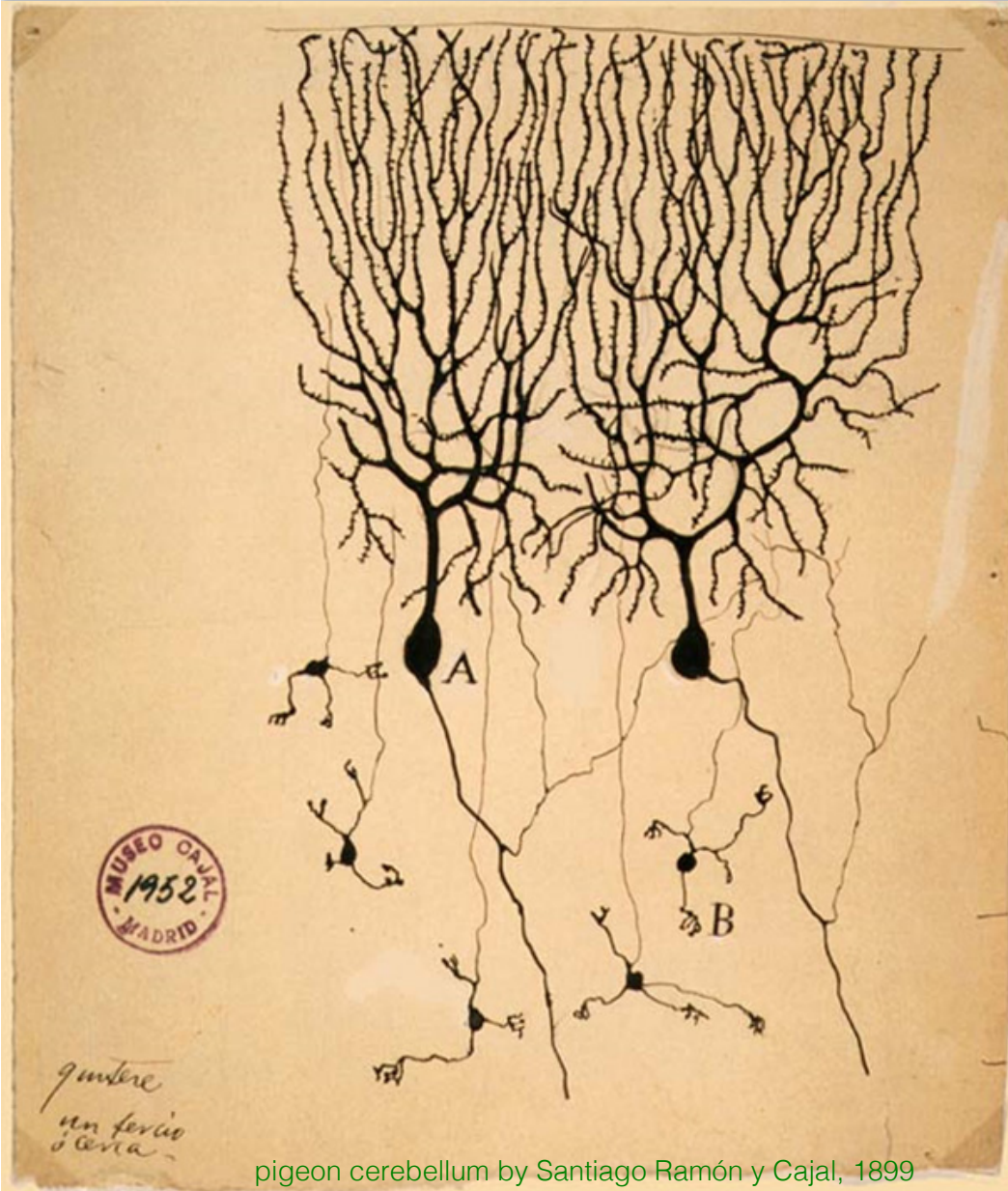
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# Interdisciplinary Instrumentation



- Hard problem!
  - $10^6$ , kHz,  $\mu\text{m}$ , 3D, ...
- Requires all of our skills\*
  - Biology
  - Computing
  - Engineering
  - Physical Sciences
  - ...
- *Plus*
  - Clinical / Medical
  - Neuroscience
  - ...
- DOE has unique ability to systems-engineer science-based technology
- LBNL has unique ability to collaborate, interdisciplinate (and execute)
  - Now have a group of \*these people working together