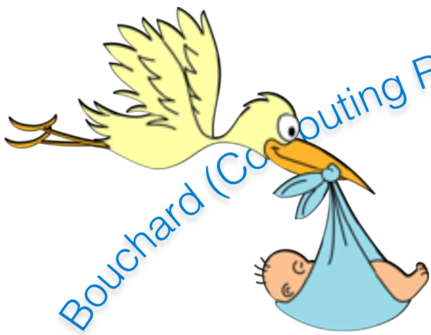
BRAIN

ultimate Interdisciplinary Instrumentation

Kris Bouchard (Computing Research) – Bruce Cohen (Molecular Foundry) – Peter Denes (Physical Sciences)

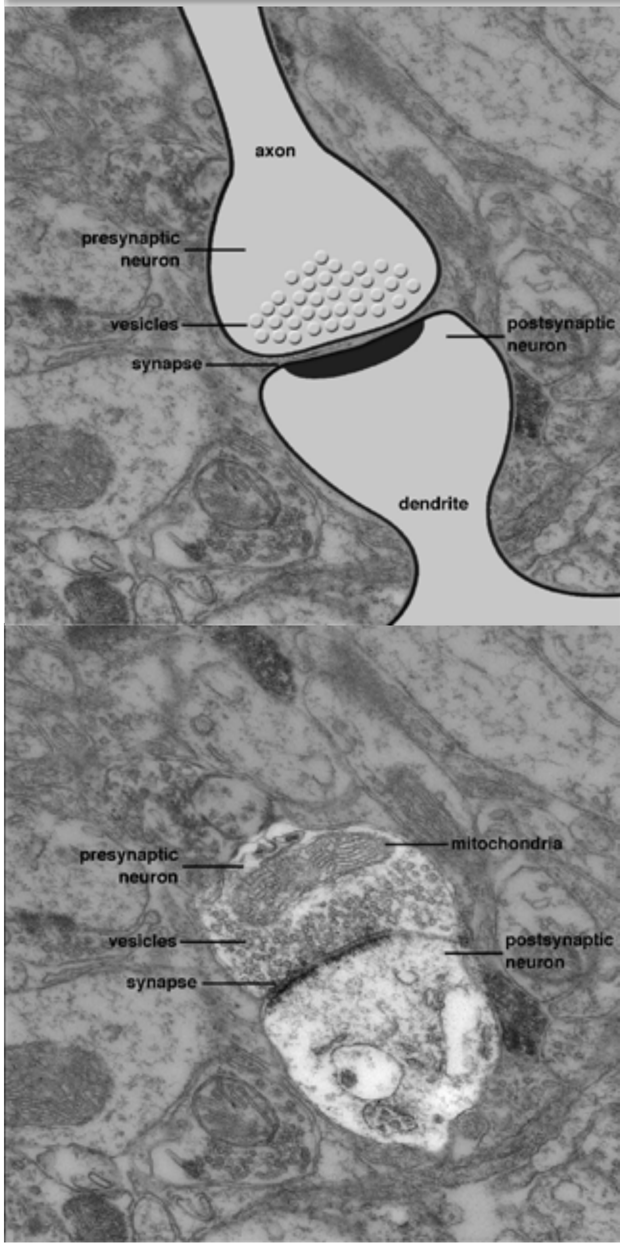


A FLOP?

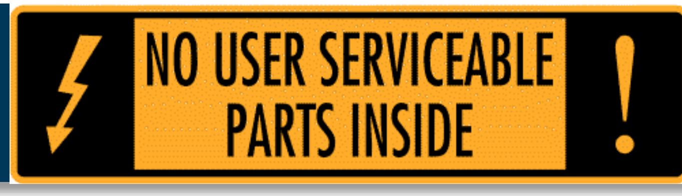
“Thomas”	“Tom”

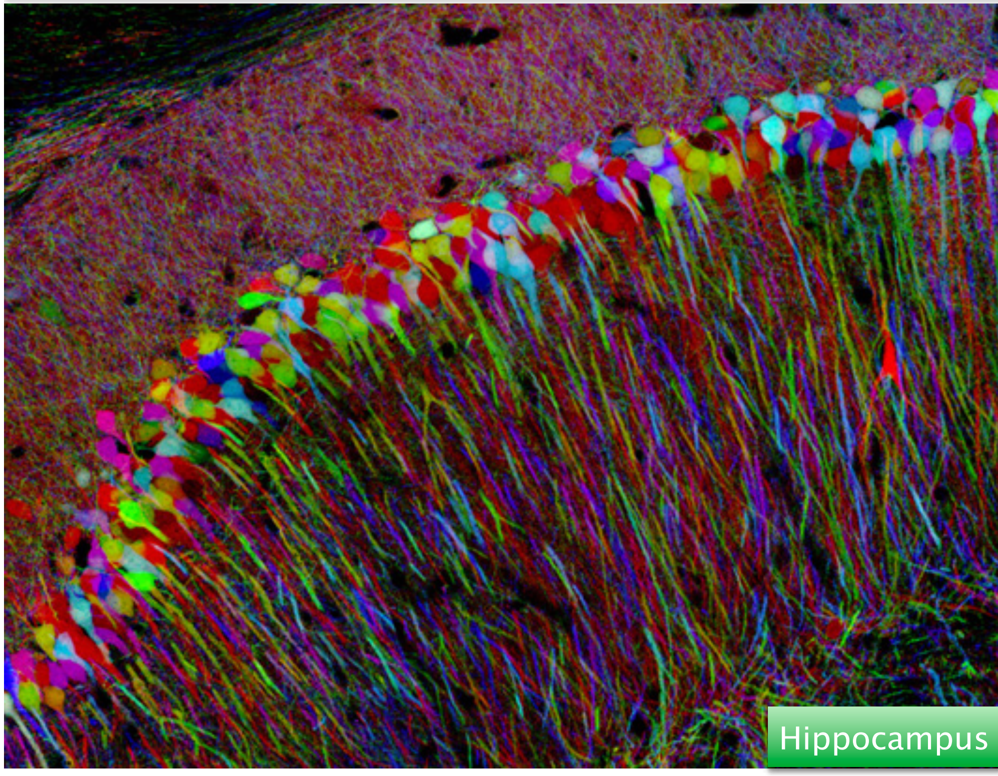
Processors		~1	10^{11}	Neurons
	10^5			
	10^{14}		stors	
Connections			10^{15}	Synaptic
	10^{15}		AM	
Clock Speed	2	10^{-LOTS}	10^{-9} — 10^{-5}	
Volume	10^8		2	
Weight	10^5		3	
Power	$1.6x10^6$		~20	

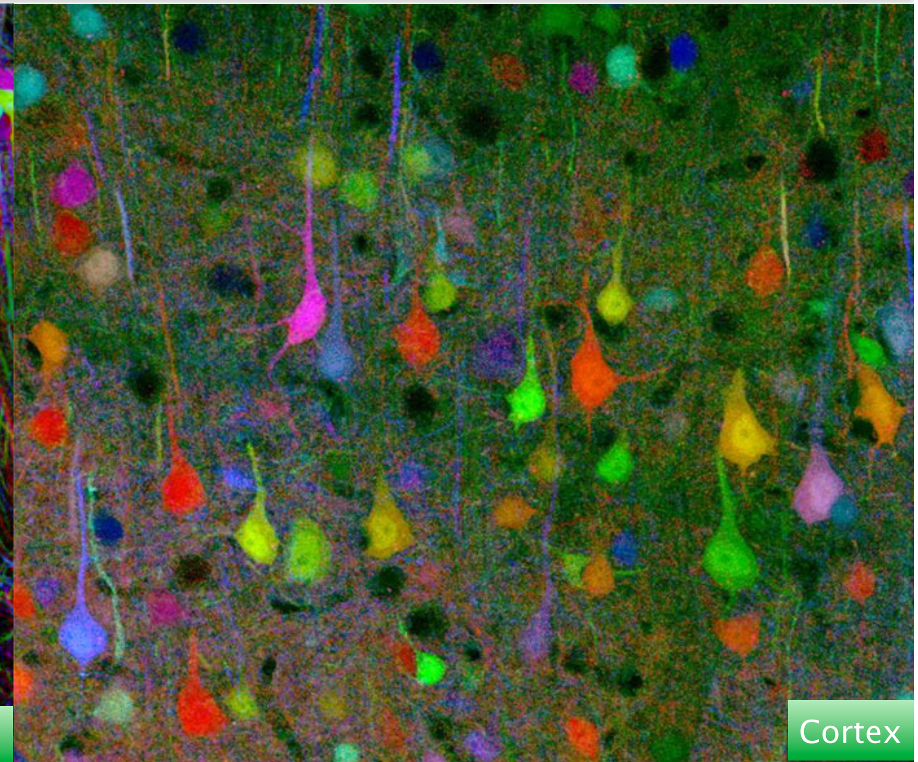
A “Multiscale” Problem



Human Brain Project 2012

Daunting  but…





- Length scale μm (s)
- Micro / Nano technology to the rescue?

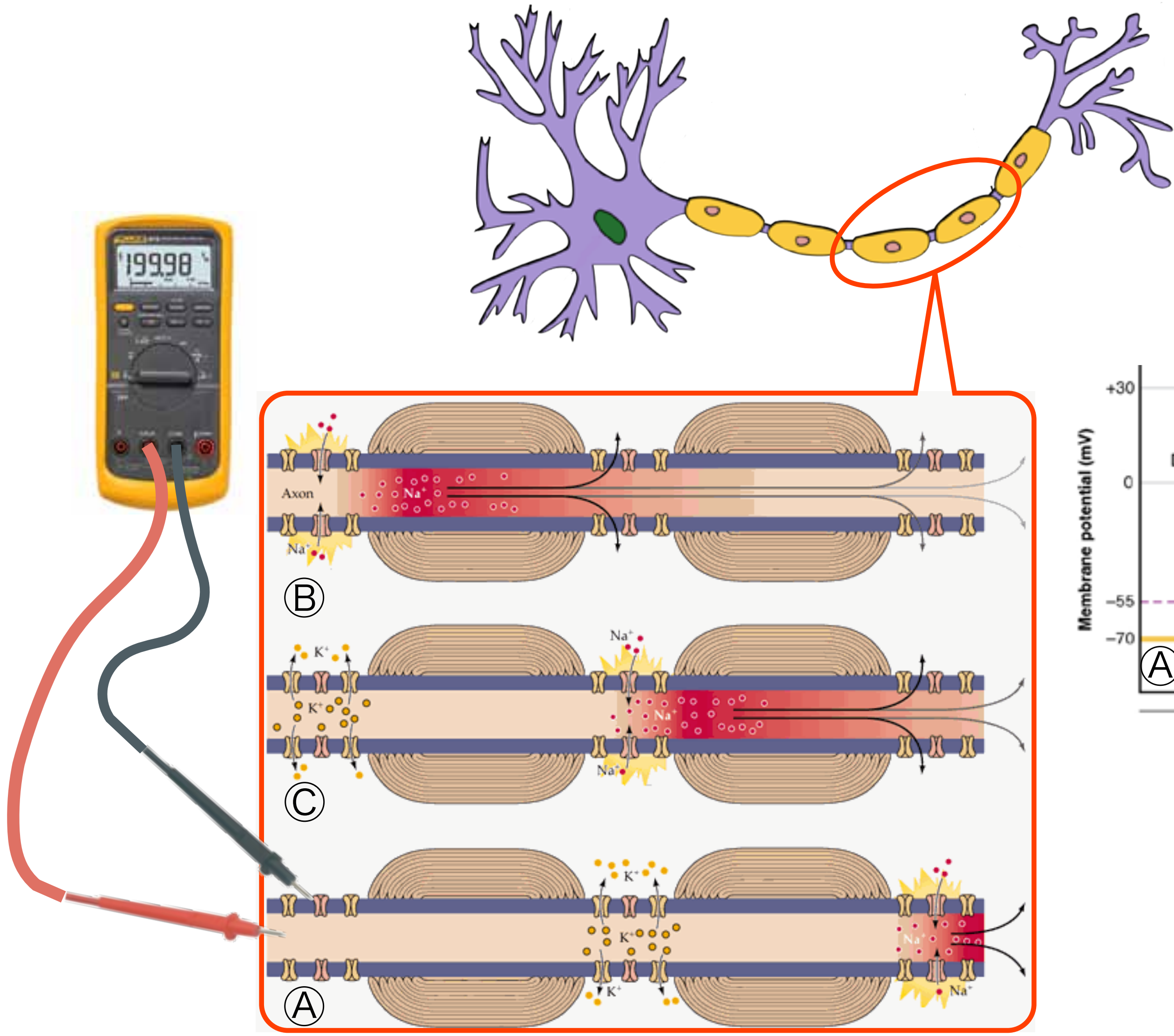
BRAINBOW: http://cbs.fas.harvard.edu/science/connectome-project/brainbow

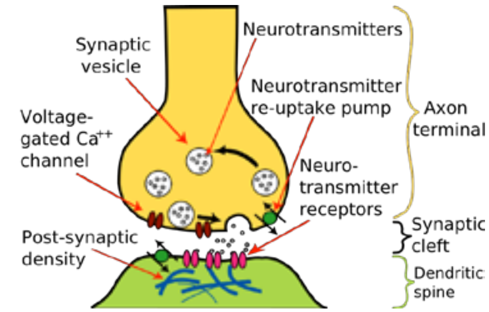
BRAIN Initiative

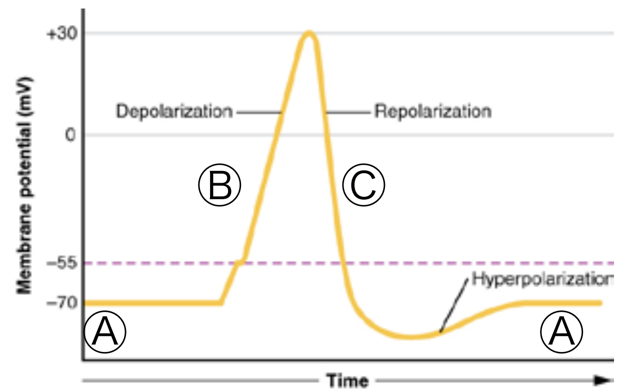
- Presidential Initiative
  - April 2013
  - "The BRAIN Initiative will accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact at the speed of thought."

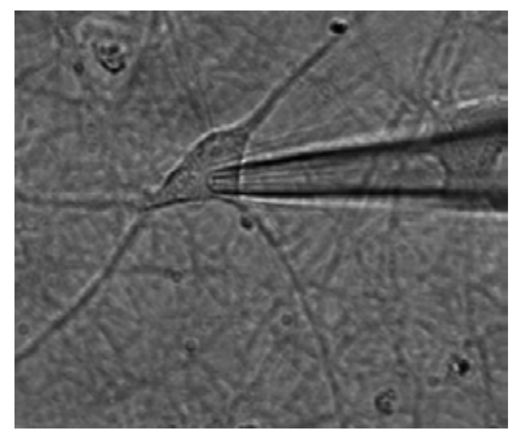
"Grand Challenge" – observe 1 million neurons, on ms timescale with "markedly reduced invasiveness"

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

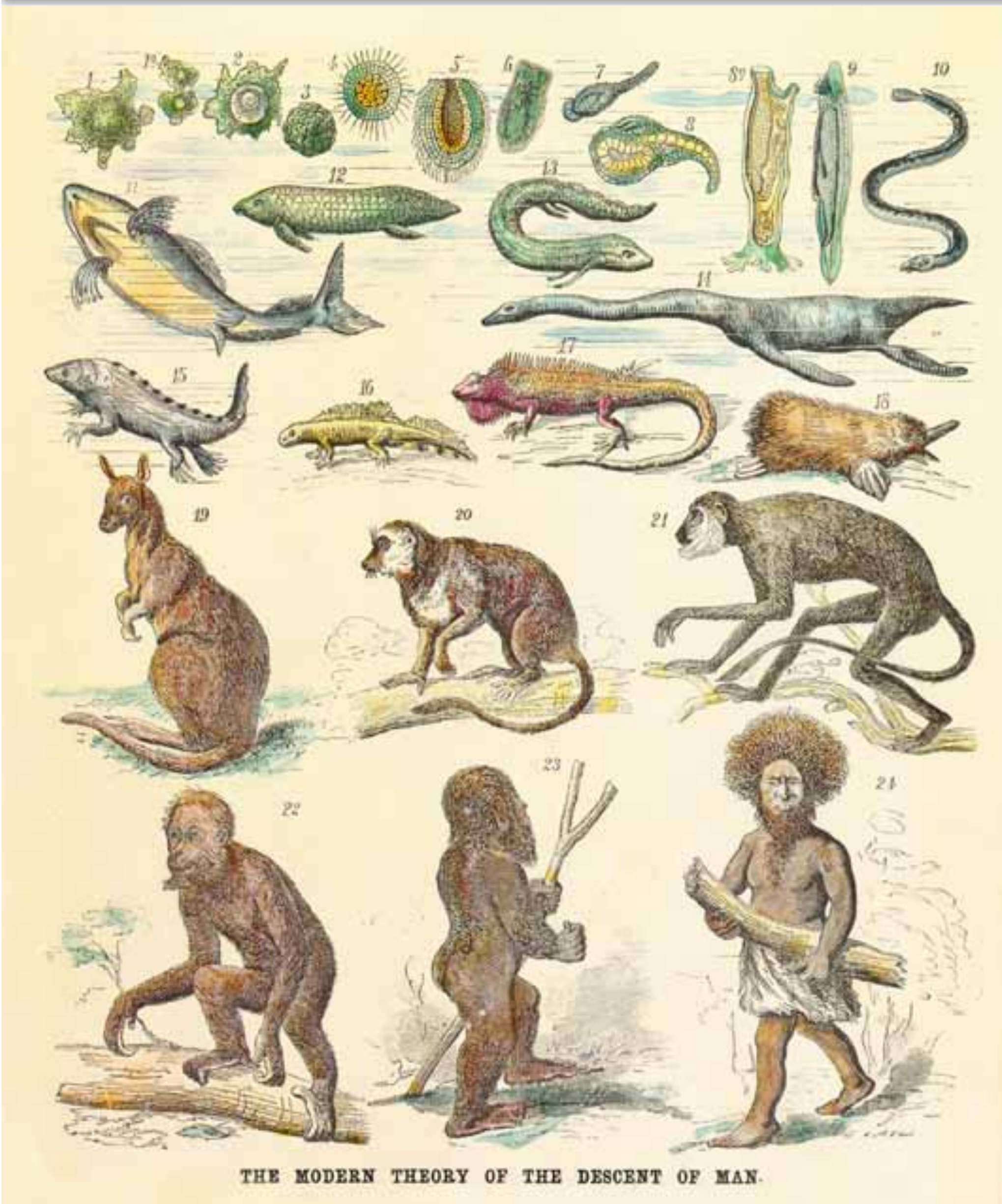






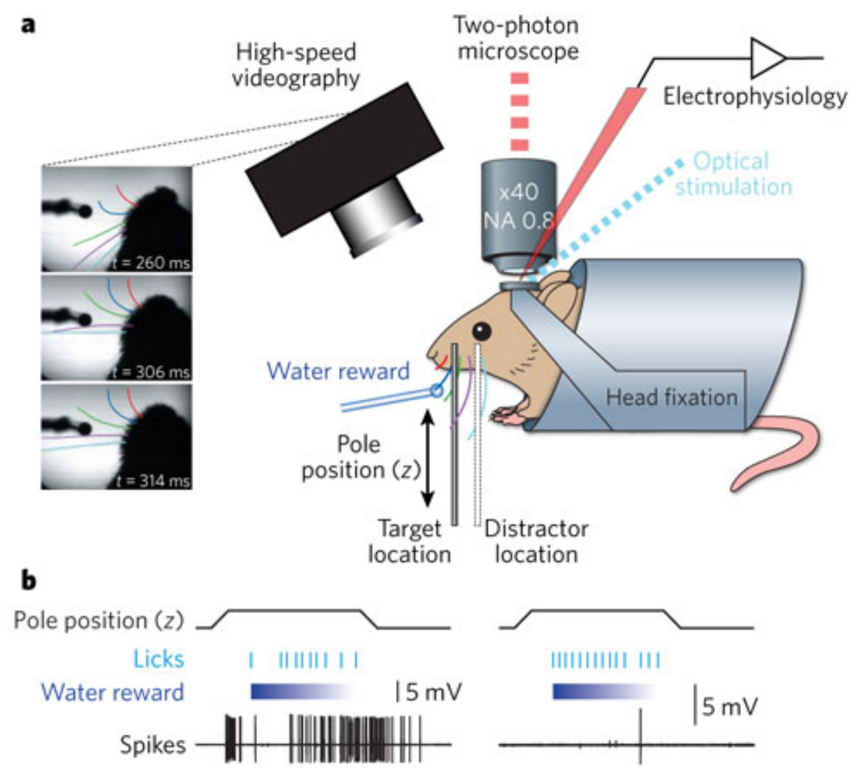


"Non-Invasive"

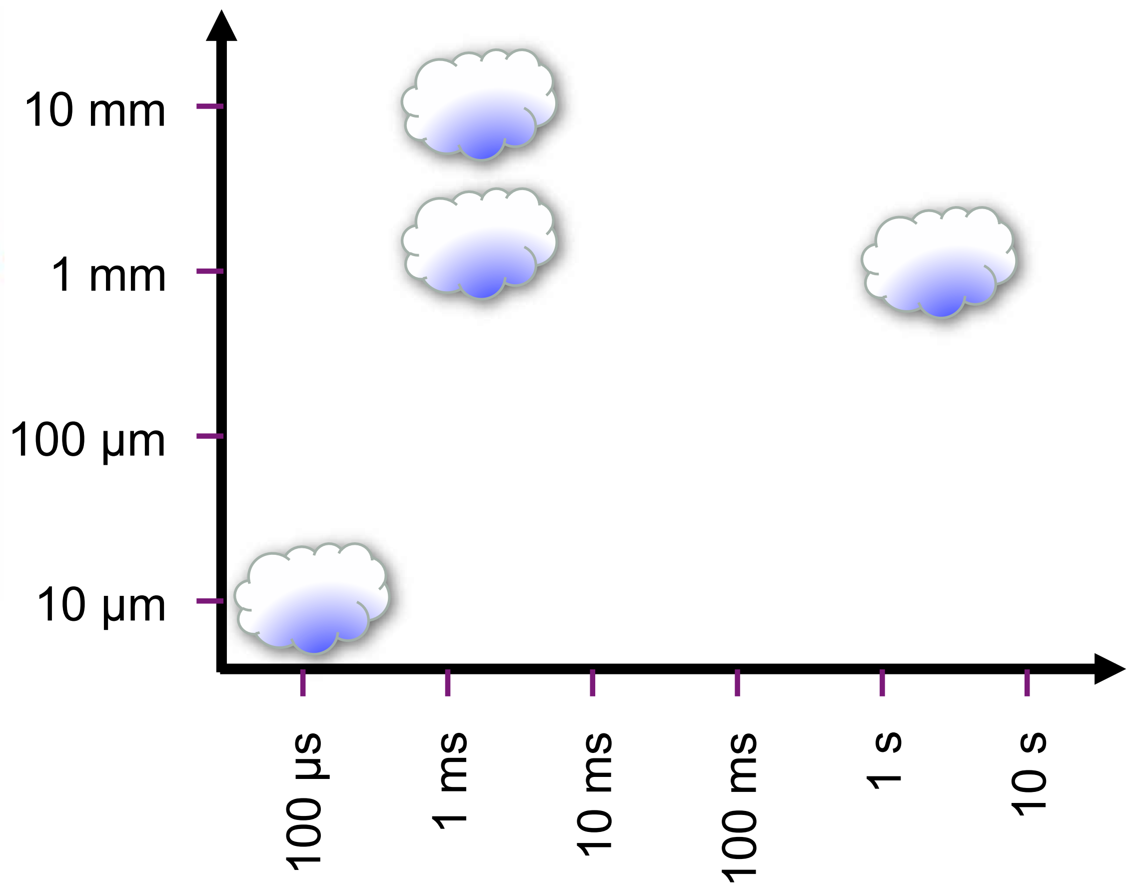


"Grand Challenge" – observe 1 million neurons, on ms timescale with "markedly reduced invasiveness"

- Not for you?
- Study model systems.



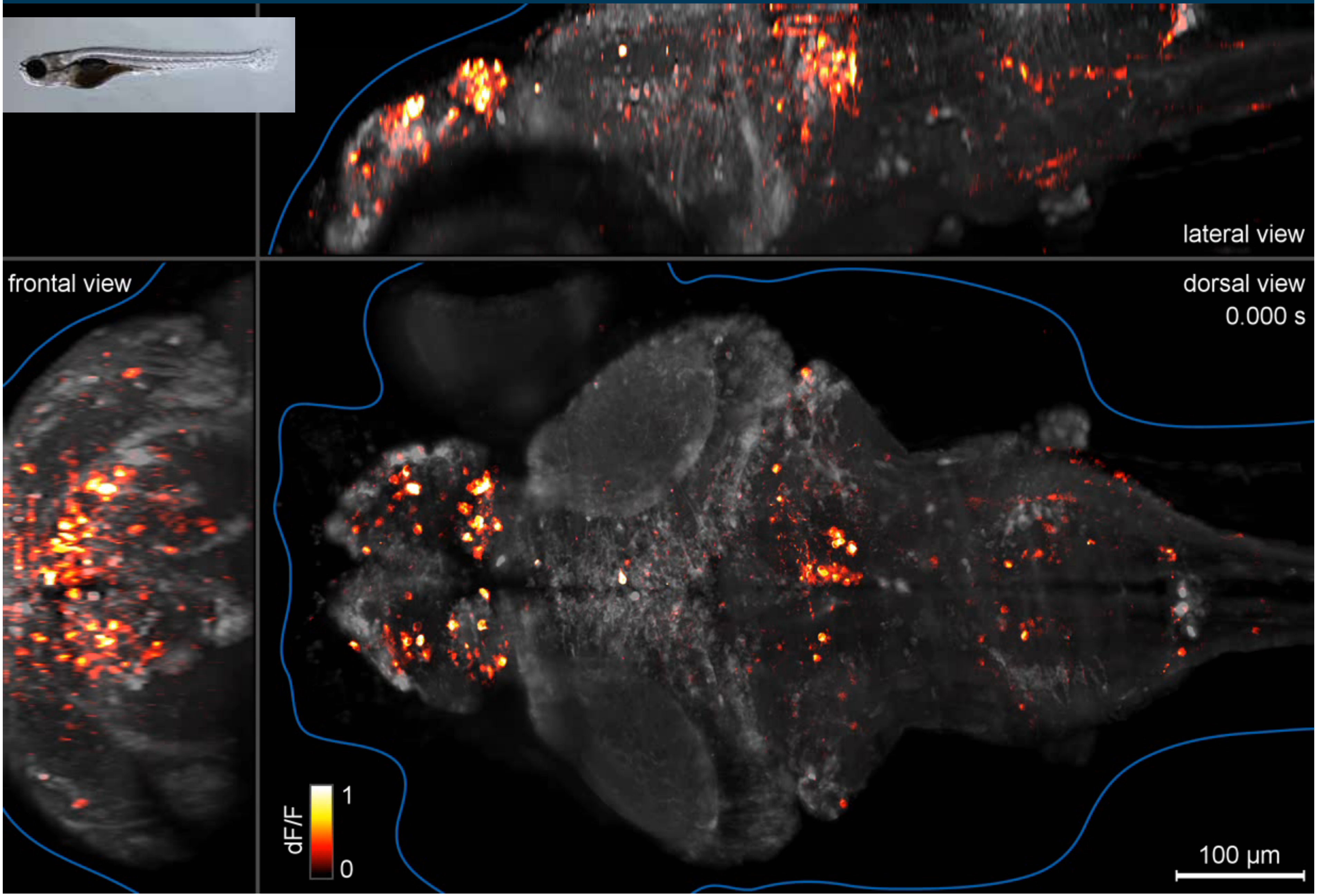
(some) Current Human Neuroscience Tools



- and in 3D
- and non-invasive
- and and and

- +other current methods (PET, MEG, …)

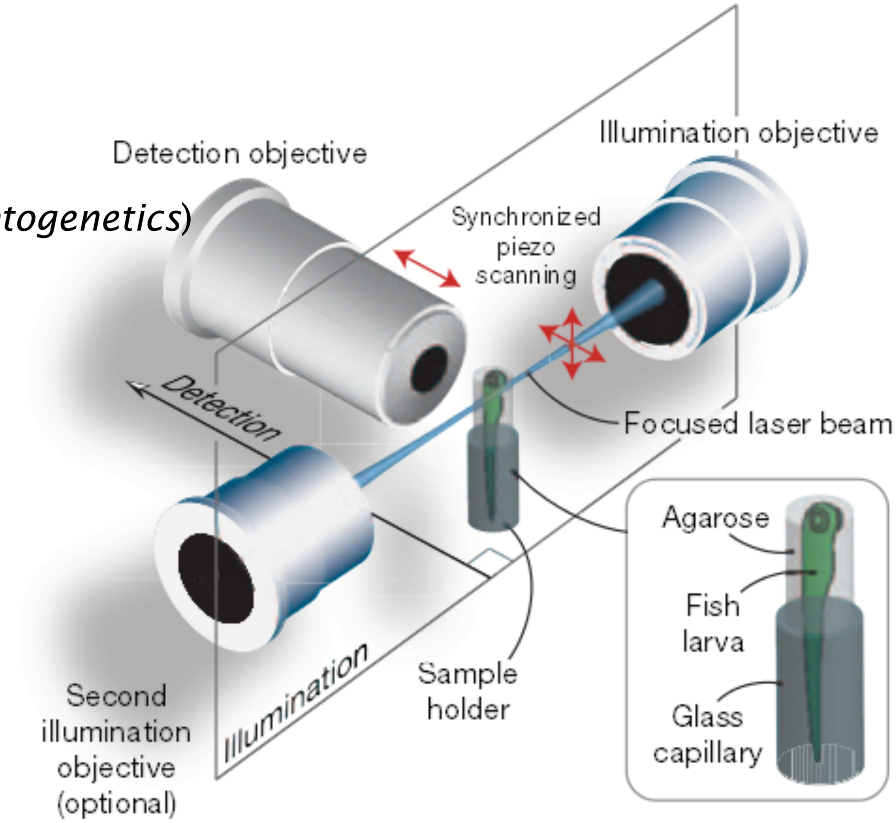
Optical Sensors of Neuronal Activity



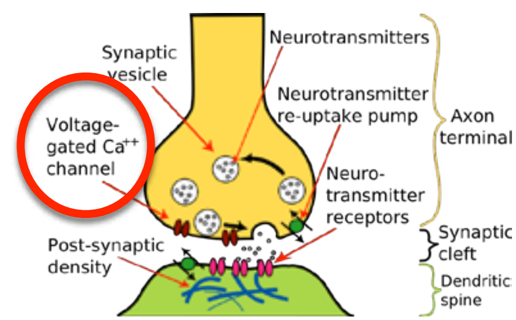
Technique (and Needs)

Stunning successes

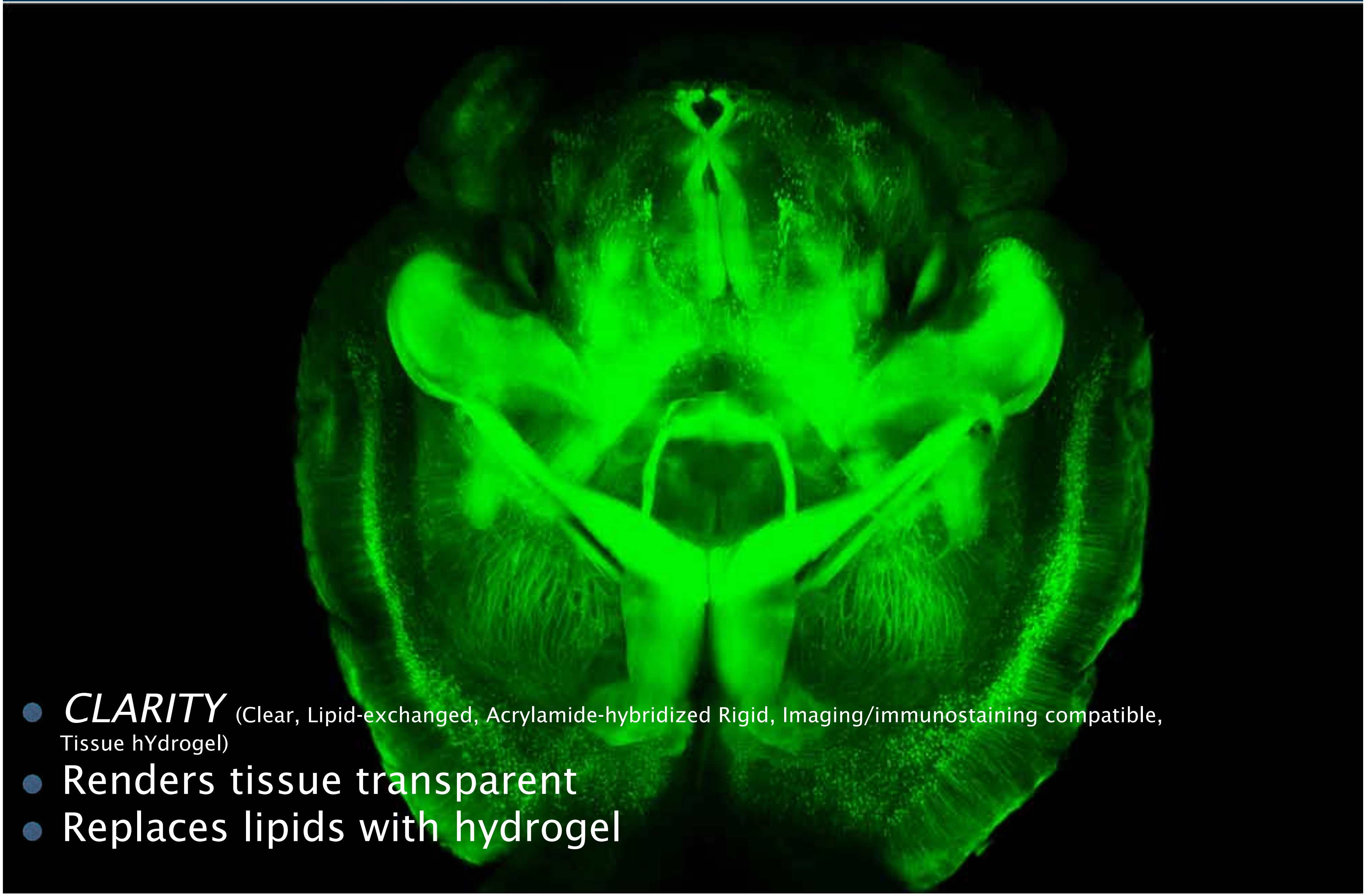
- Optically active:
  - Sensors (report activity)
  - Actuators (stimulate or silence neurons: *Optogenetics*)
- Many techniques



- 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 (Na^+, K^+)
  - Neurotransmitters
  - Improved voltage sensors

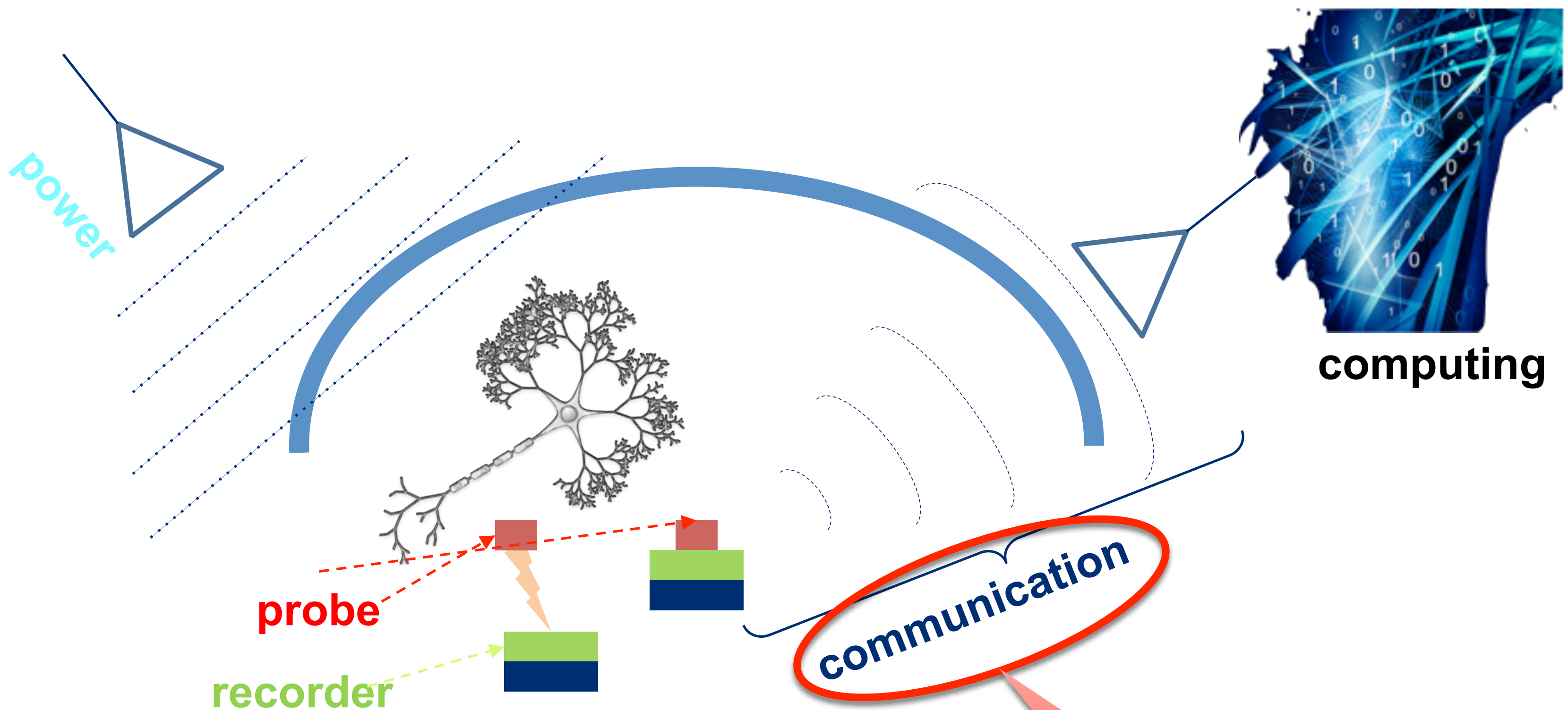


Many Ways to use Light



- *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?

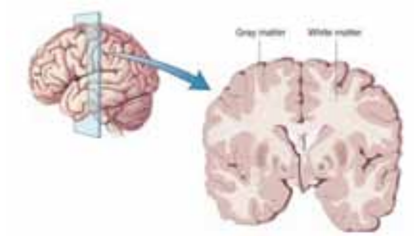


"**probe**" – detector or transducer of neuronal activity (electrical, optica… …emical …)
"**recorder**" – receives information from "probe", "communicates" the inf… …rhaps, position …) to outside world; harvests energy
"**communication and data acquisition system**" – means for tran… …ne outside world, and capturing it; potential power source
"**computing**" – processing the acquired data

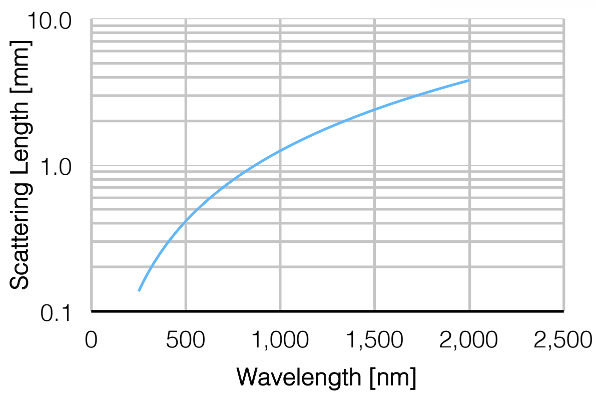
This is the problem

Communication

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

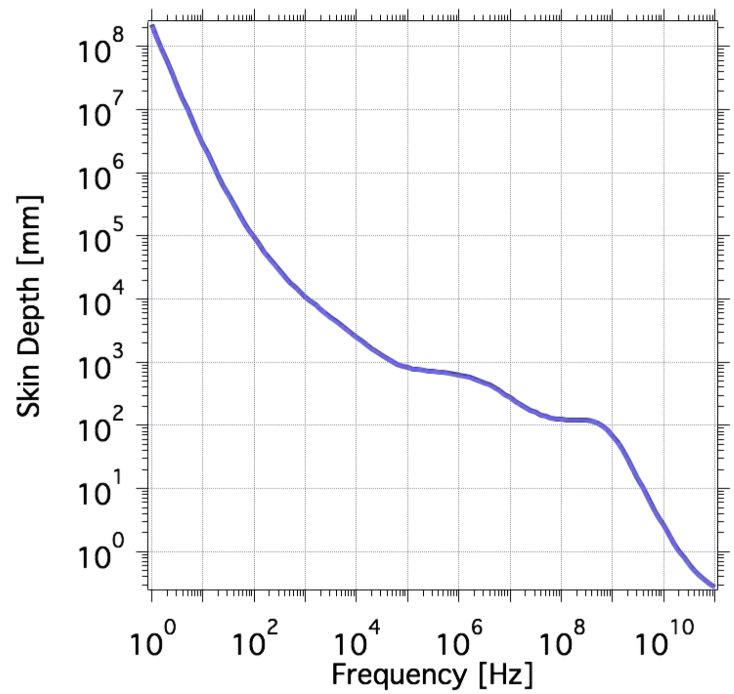


  - Scattering*



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

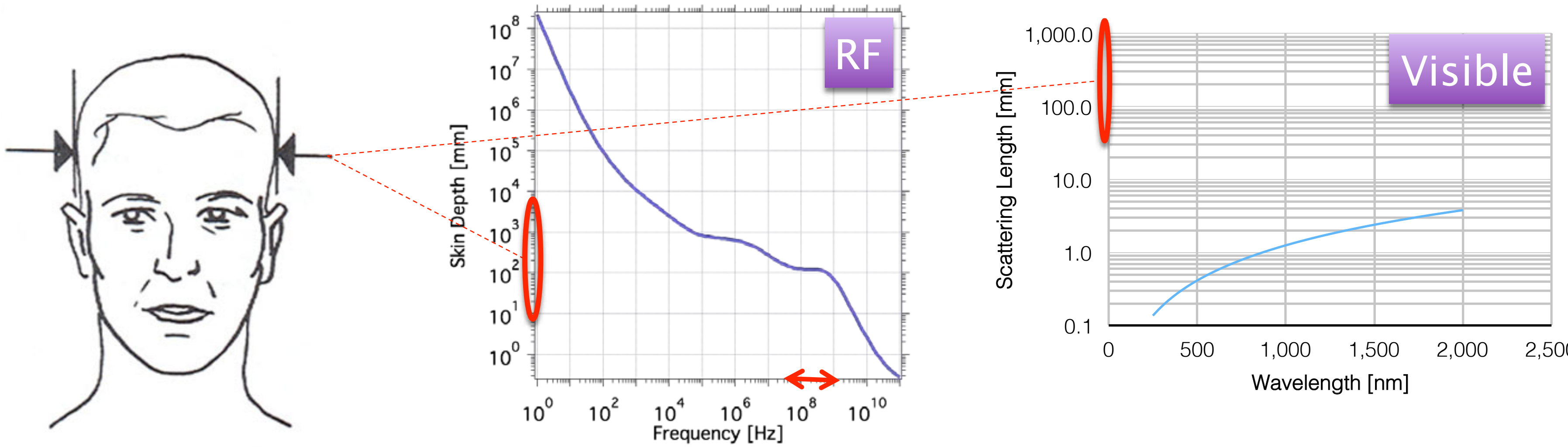
- **Electrical**
  - Skin depth*



- **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 x 10^3 Hz (→ > 10^3 Hz) x _ bits = (*many*) GHz BW
  - Not light, sound or RF

How to

- Goals: 3D, $N = 10^6$, t = 1 ms, (x = _ μm)
- **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 = _ µm)
- **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: $\Delta T \sim 1^\circ C$

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 LAB | 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 turn out 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."

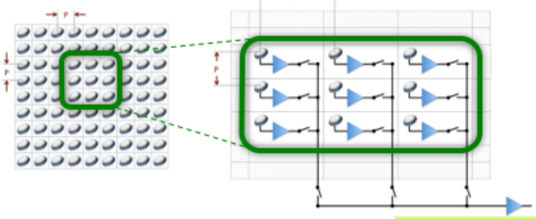
Successful "seeds" of the regional program will be calibrated on technical excellence, innovation, and the substantive involvement of the collaborative partners across multiple disciplines. To ensure impact, each project must have a clear path from concept to the development of a competitive proposal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

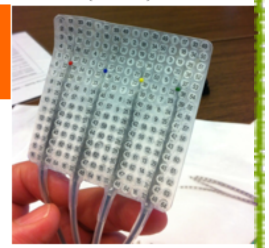
Go here to learn more about the Tri-Institutional Partnership and the BRAIN R&D seed-funding project to support innovative neurotechnology.

Very High Density Electrocorticography

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

State of the art - 256 electrodes
<10 electrodes / cm^2
Improve to 10^4 electrodes / cm^2



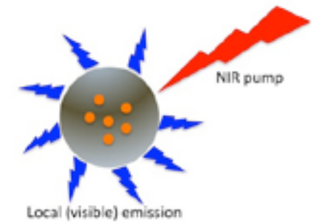


- Analysis *already* complex
- **If successful, data ⬆10^3**
- HPC
- Format, portal, …

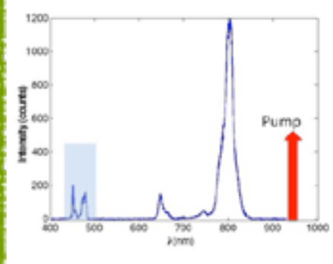
Nanocrystal Light Bulbs

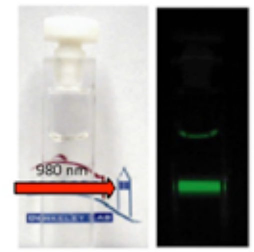
Bruce Cohen (LBNL), Chris Chang (UCB), Charles Craik (UCSF), Robert Edwards (UCSF), Ehud Isacoff (UCB)

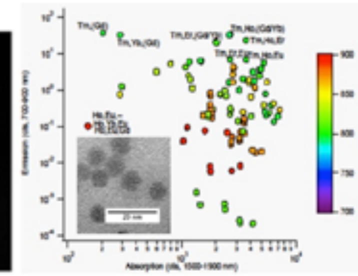
- Tether-less light bulbs (injectable)
- Synthesis of nanocrystals that convert NIR light to visible, to activate nearby sensors and photoswitches
- NIR pump provides
  - Deep-tissue penetration
- UNCPs:



Emission wavelength…

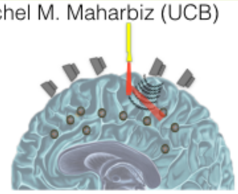




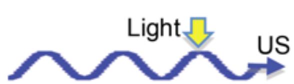


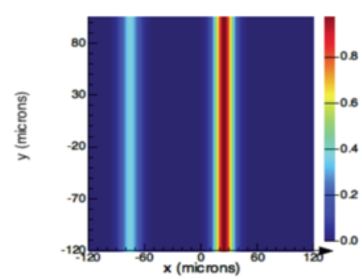
Acousto-optic 'Virtual' Waveguides

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



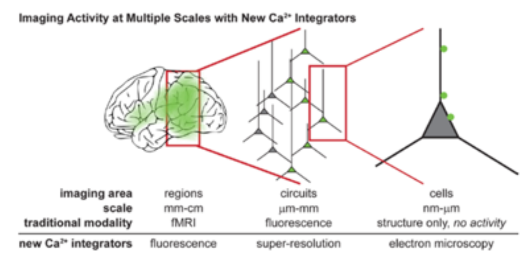


Confined optical mode in a US peak

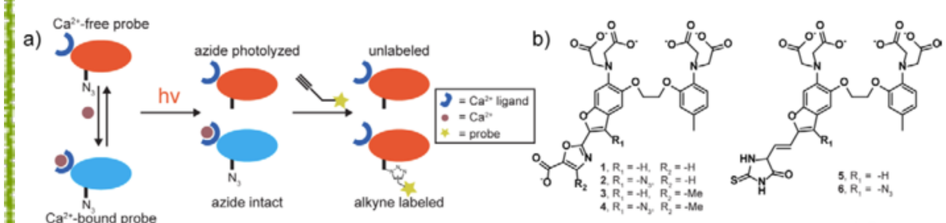
Ca^{2+} Dosimeters

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

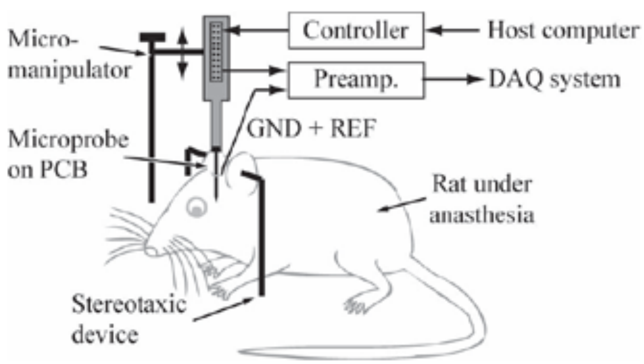
- Probes which remember Ca^{2+} concentration
- Cover multiple length scales
- (post hoc)

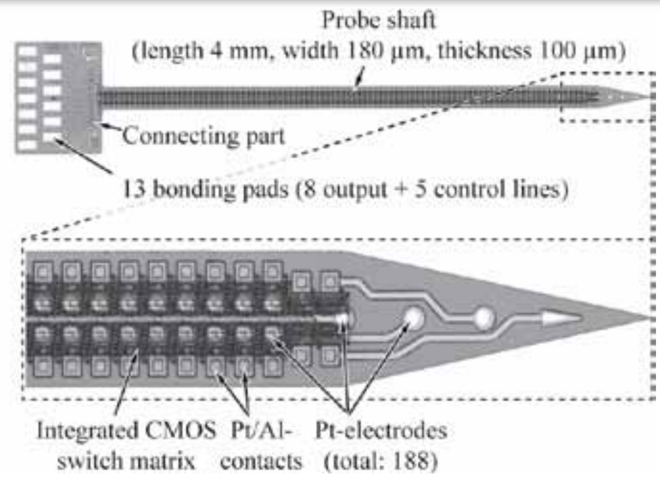


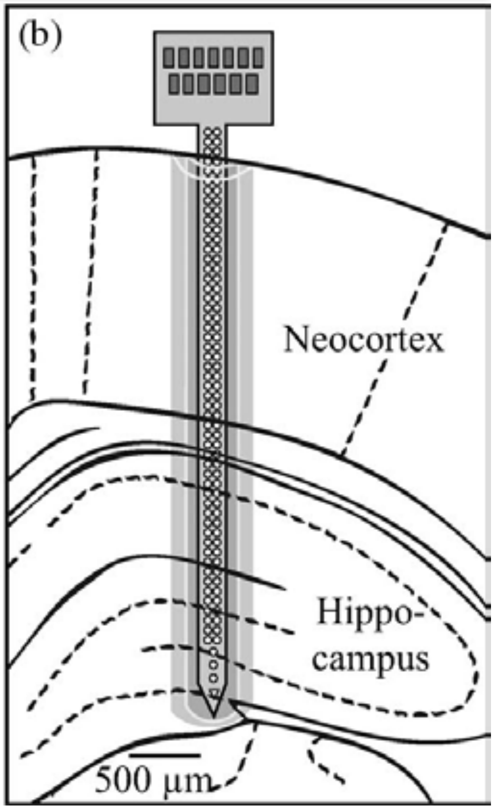
- 3D reconstruction of activity across entire brain regions with cellular resolution



Electrical Recording

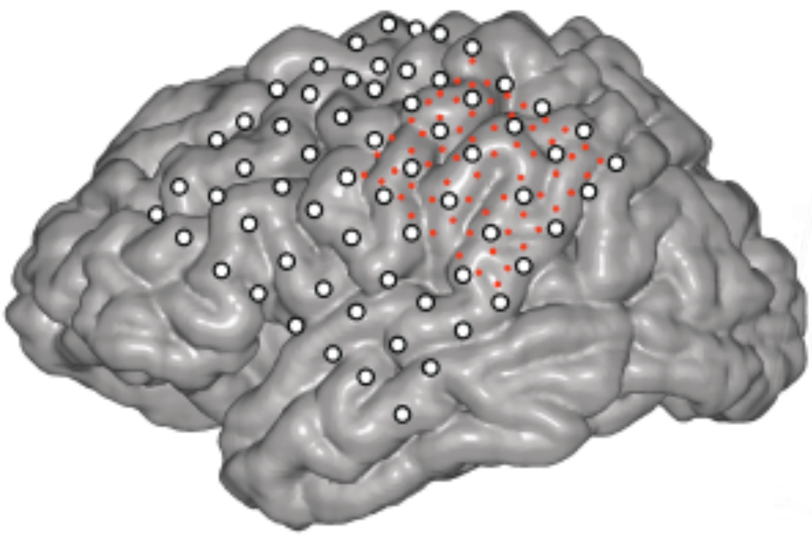




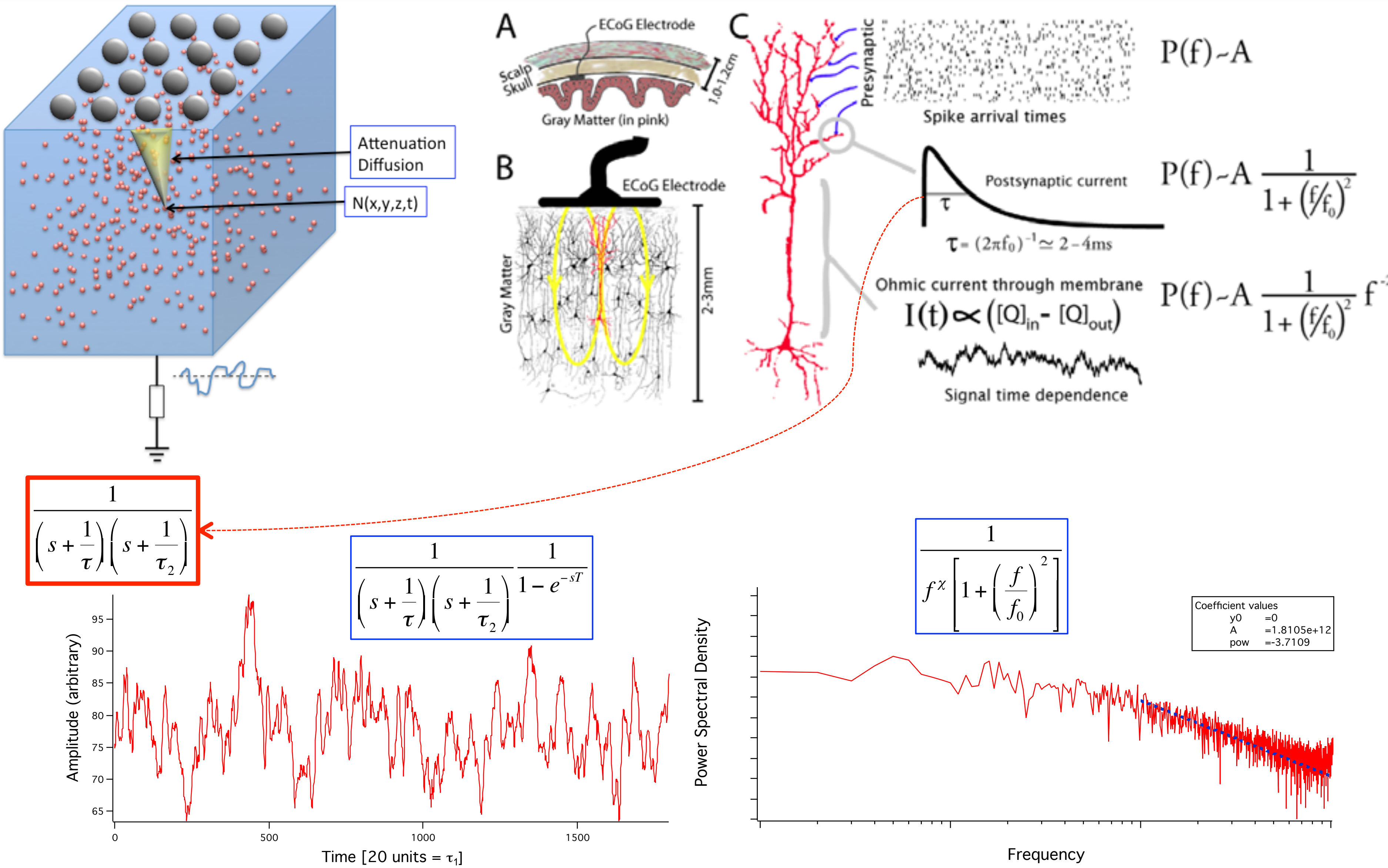


Somewhat invasive

Somewhat less invasive

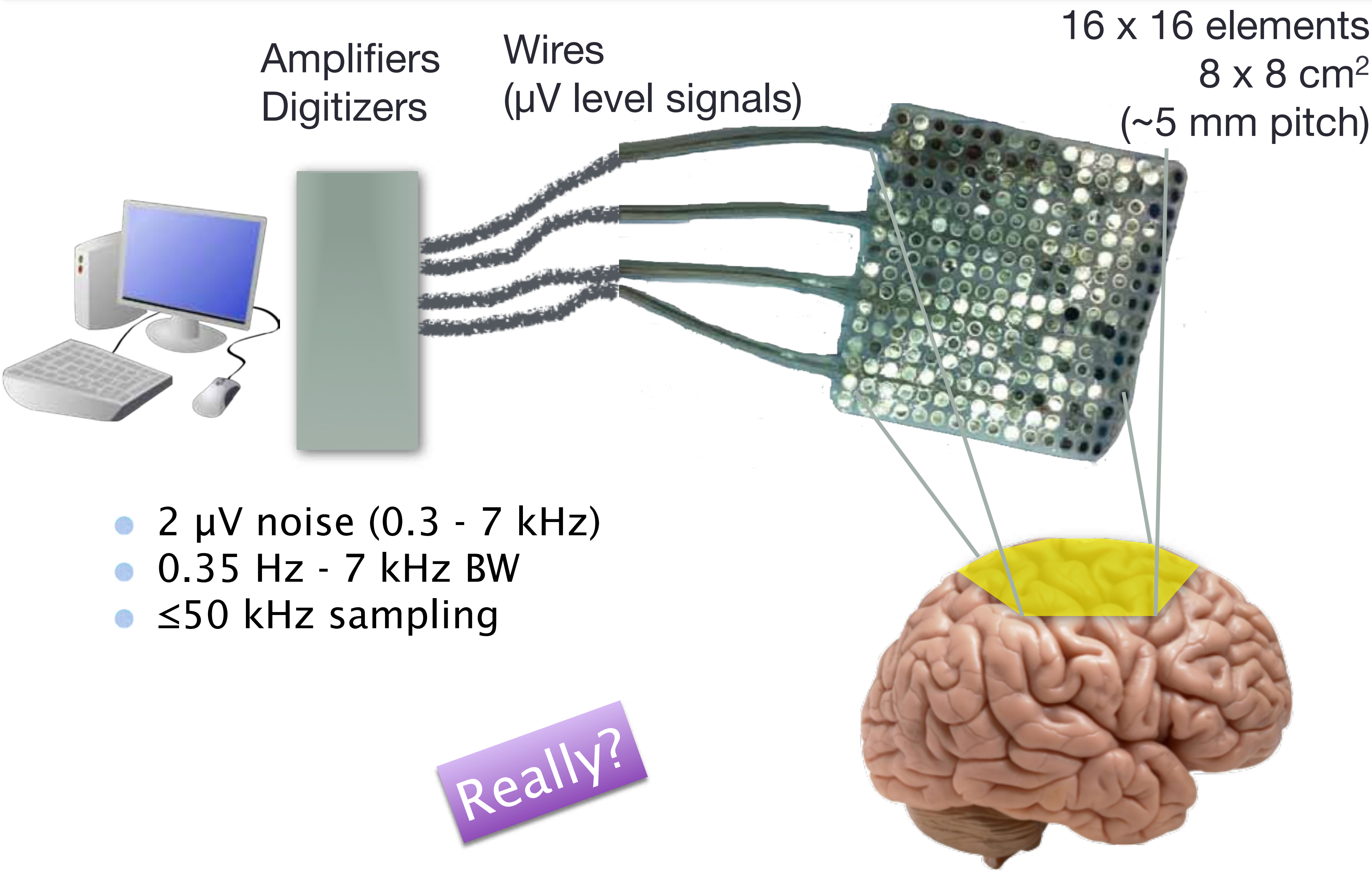


Problem Statement



Under 1 electrode: 10^N (N=4+) neurons with ~10^4 synapses

State-of-the-Art (Human)

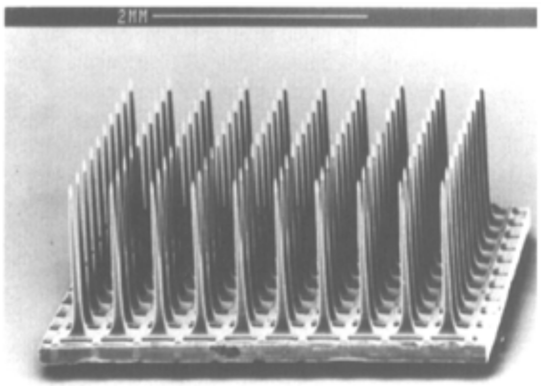


- 2 µV noise (0.3 - 7 kHz)
- 0.35 Hz - 7 kHz BW
- ≤50 kHz sampling

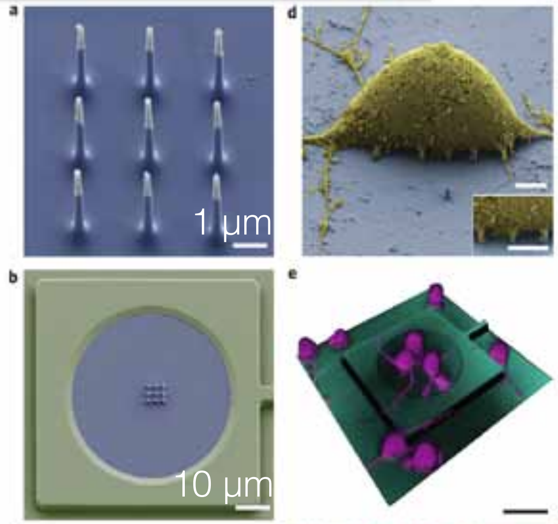
Really?

Sophisticated Electrodes

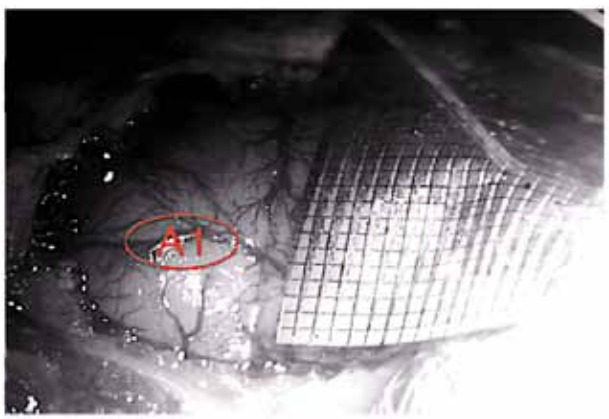
Passive – 1 wire/electrode



Utah Array (Si - 1990s)



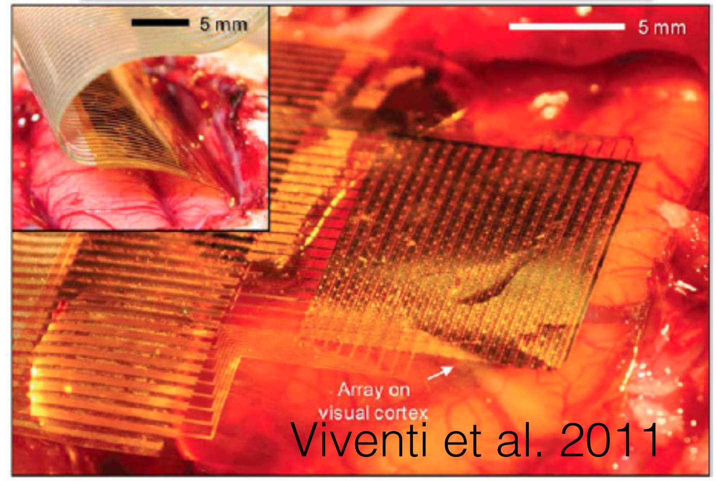
Robinson et al. 2012



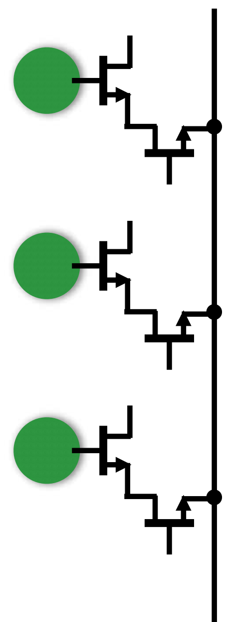
Berkeley Array (paralyne)
semi-transparent

+ ...

Multiplexed - SNR



Viventi et al. 2011



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 µm “pixel”
- 4 mW/cm² → 400 nW/pixel (“very hard”)

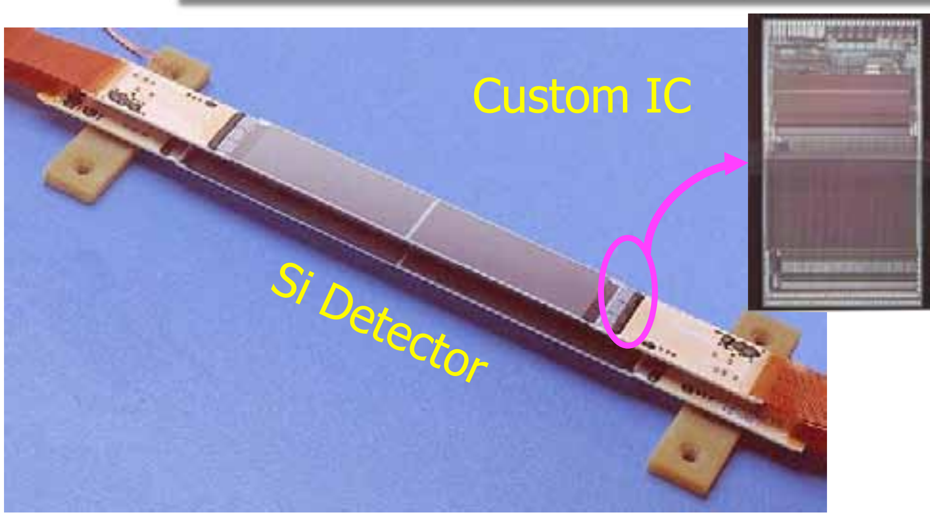
$$V_n \approx \sqrt{\frac{4kT}{g_m} \times BW}$$

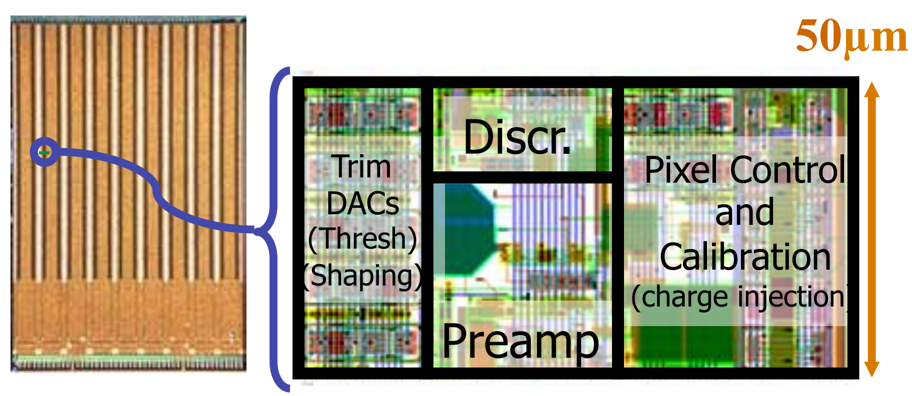
$$g_m \xrightarrow[WI]{} \frac{I_D}{nU_T}$$

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

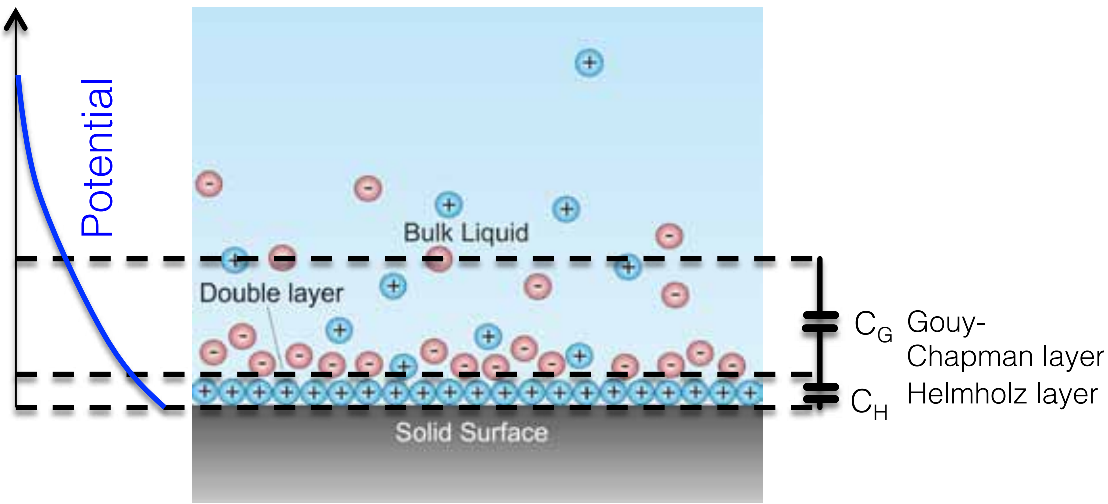
µV noise → µW(s) power

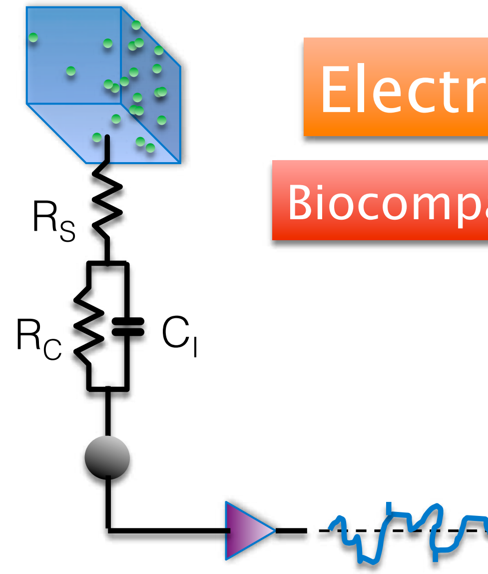
HEP analogy: “strip” (1D) and “pixel” (2D) detectors





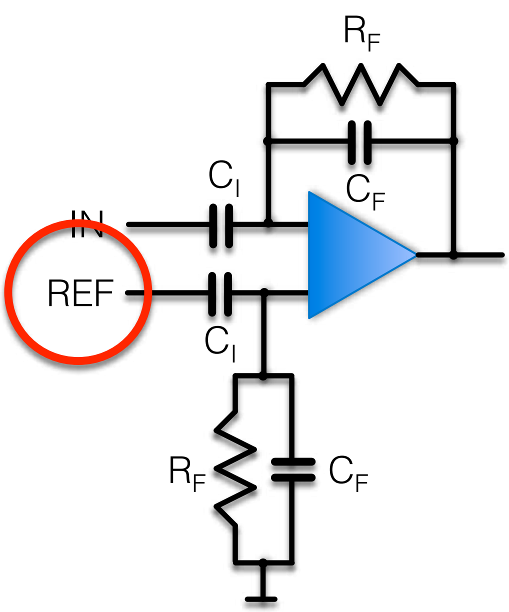
Getting the Signal





Electrodes

Biocompatibility

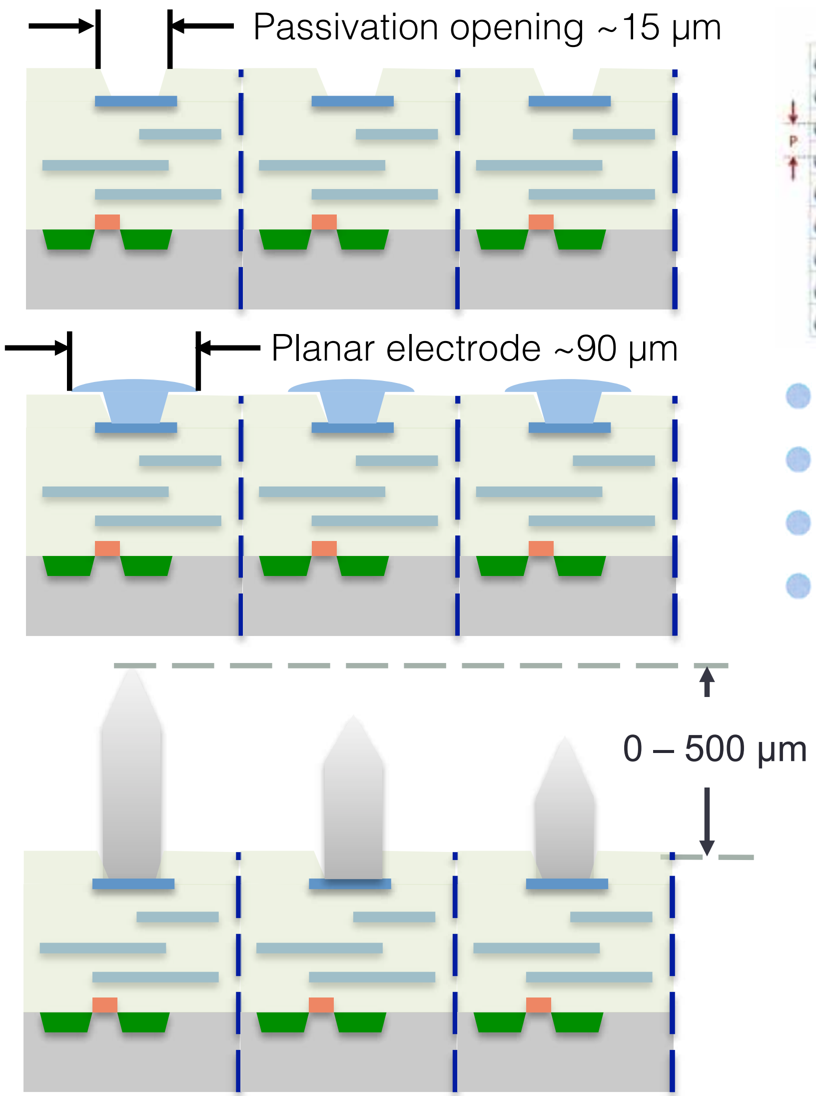


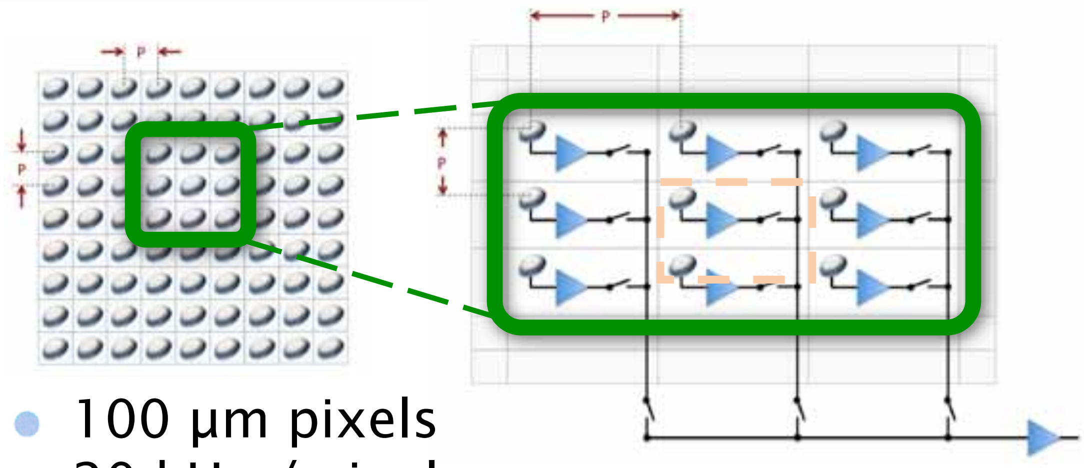
Most typical:

- AC-coupled
- Gain = C_I/C_F
- $\tau_{LF} = R_F C_F$
- e.g. C_I = 10 pF, Gain = 100 → C_F = 100 fF
- τ_{LF} ~ Hz → R_F = 1 TΩ
- (and, CMOS generally ~1 fF/µm²)

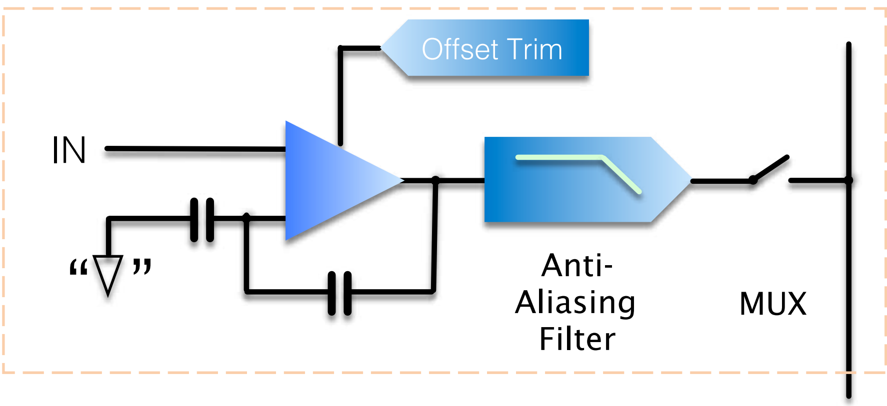
100 µm²

e-chip





- 100 µm pixels
- 20 kHz / pixel
- 1 wire / 1,000 pixels
- Grow electrodes on chip
  - (or bump bond chip to array)

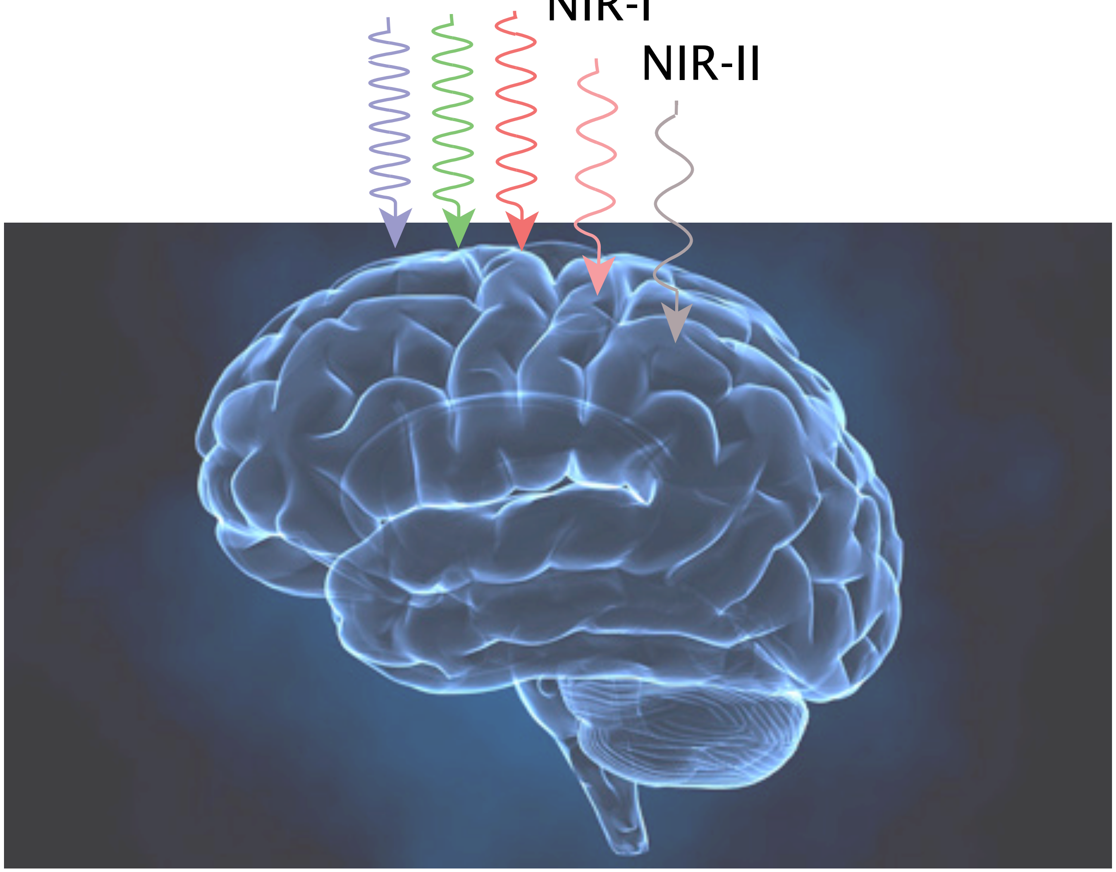


Later – an app for this

BRAINseed

Interrogating the Brain with Light

How deep can we go?

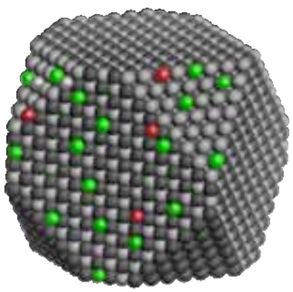


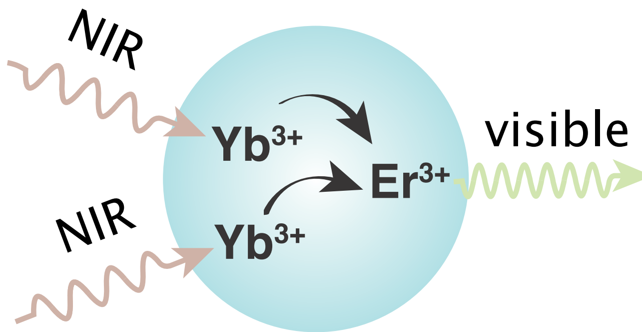
mouse optogenetics

BRAINseed

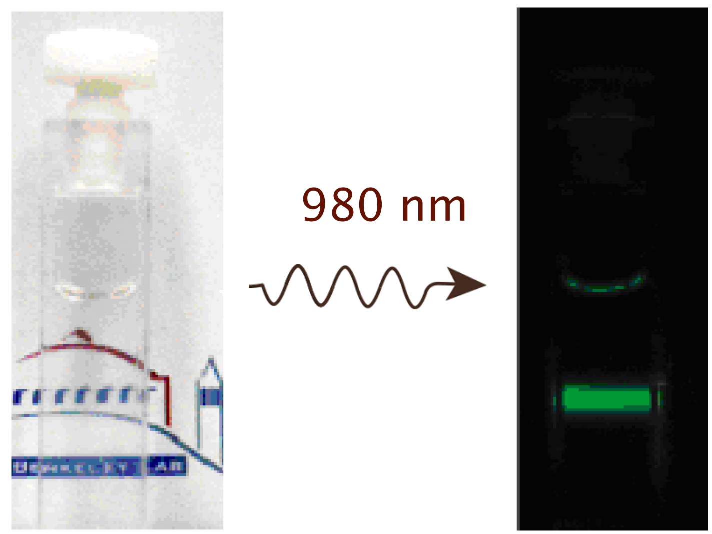
Nanocrystals as Optical Transducers

UCNP





- 20% Yb^{+3} - *sensitizer*
- 2% Er^{+3} - *emitter*
- $NaYF_4$ – *host matrix*

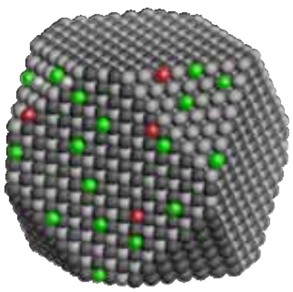


...require new light sources and detectors

BRAINseed

Nanocrystals as Optical Transducers

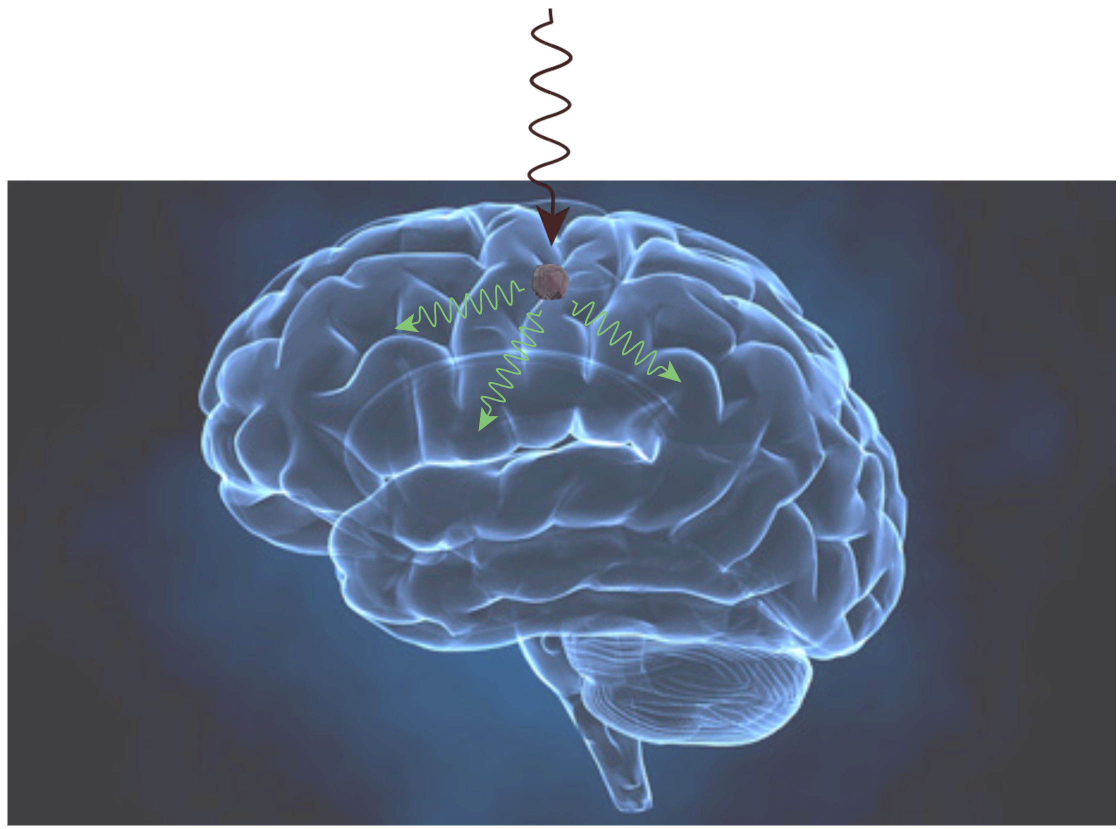
UCNP



Wish list

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

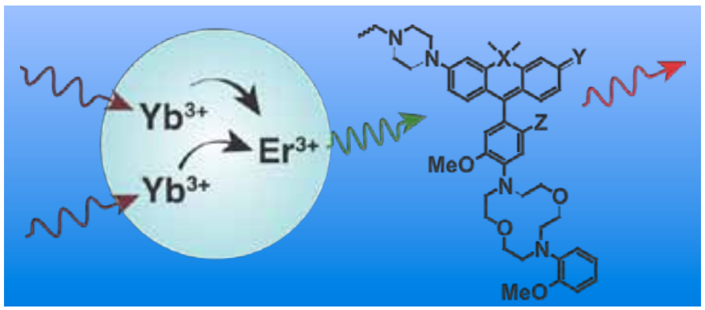
NIR-I (700 – 1200 nm)

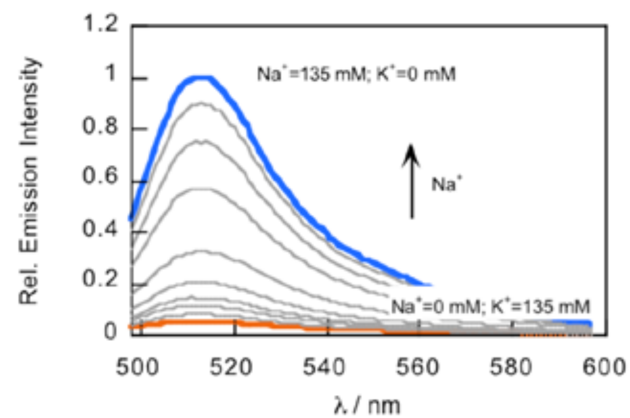


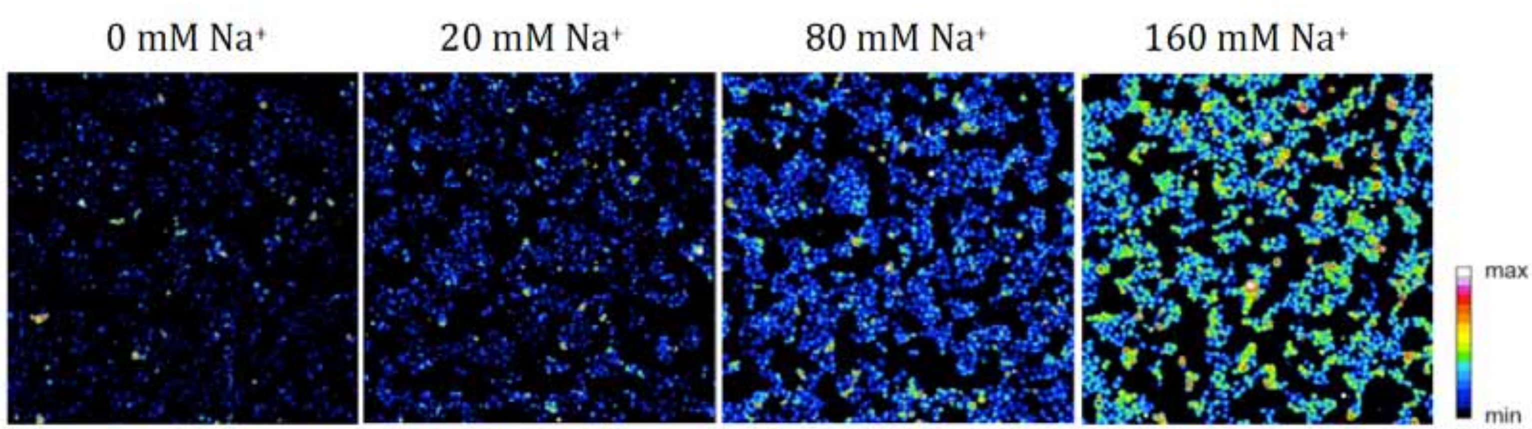
BRAINseed

Sensing Na^+ ions with NIR light

with Chris Chang, UCB/LBNL







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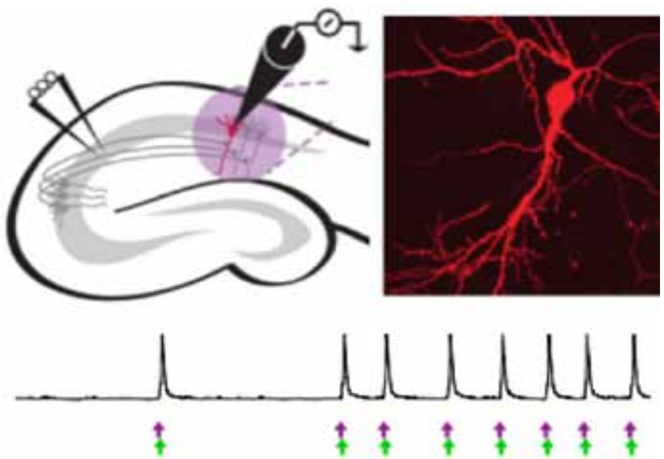
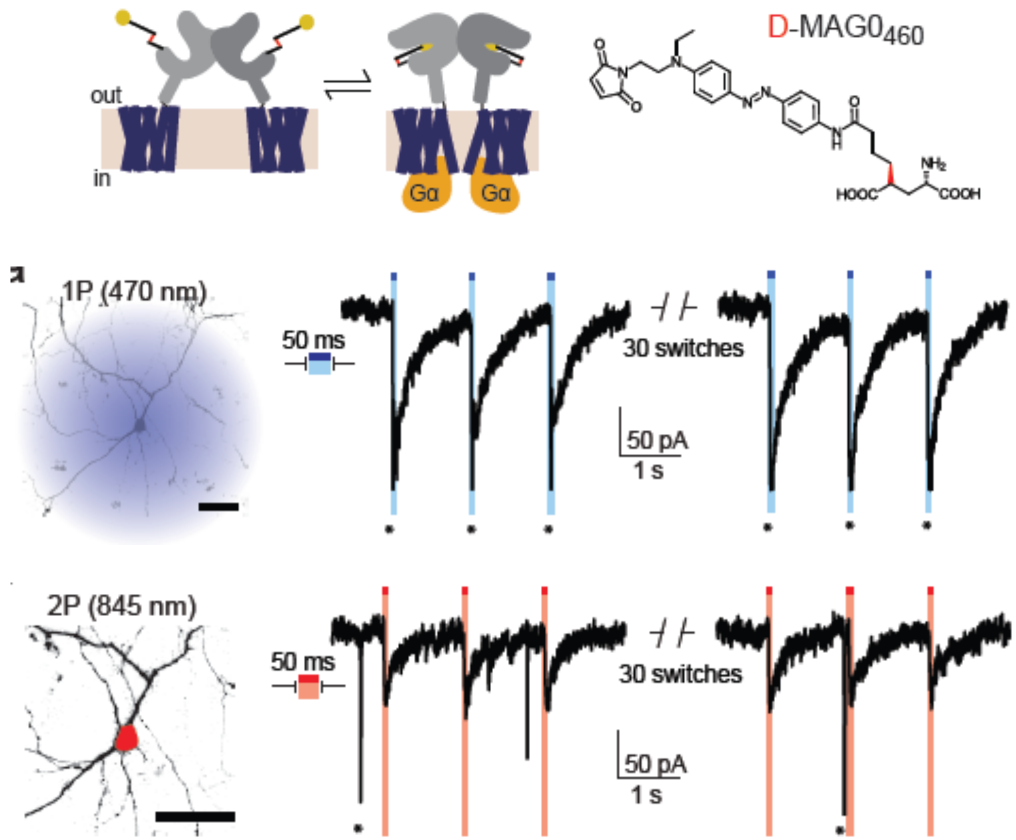
Activating neurons with NIR light

with Udi Isacoff, UCB/LBNL

Light-activated neuronal firing:



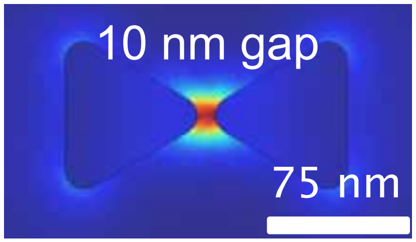
Shifting to NIR wavelengths:

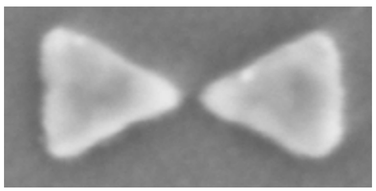


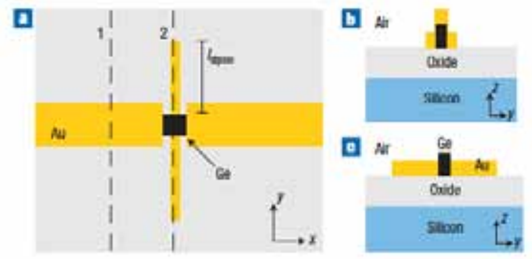
BRAINseed

Nanotech-inspired Approaches

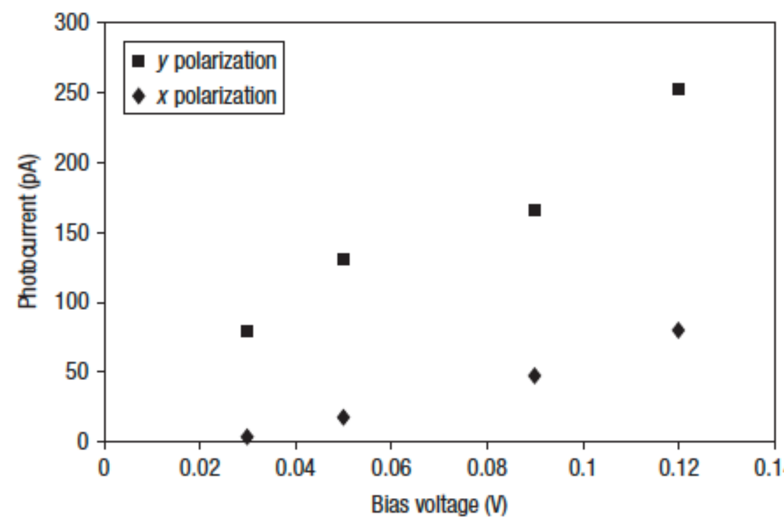
Plasmonic optical antennas - as single photon detectors (or re-radiators)





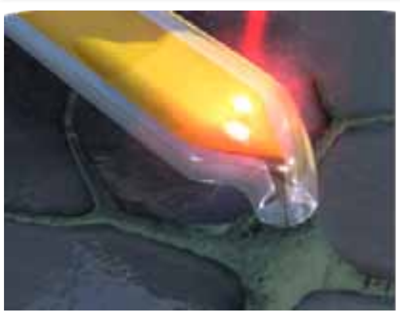


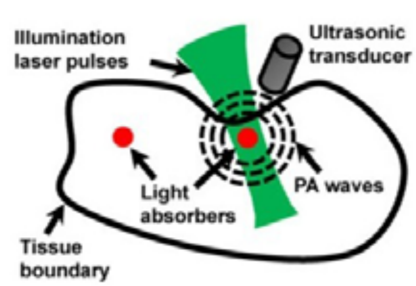
- µm-scale device
- est. 5 *aF* capacitance
  - 1 e⁻/5 aF = 160 mV



A few technical details remain

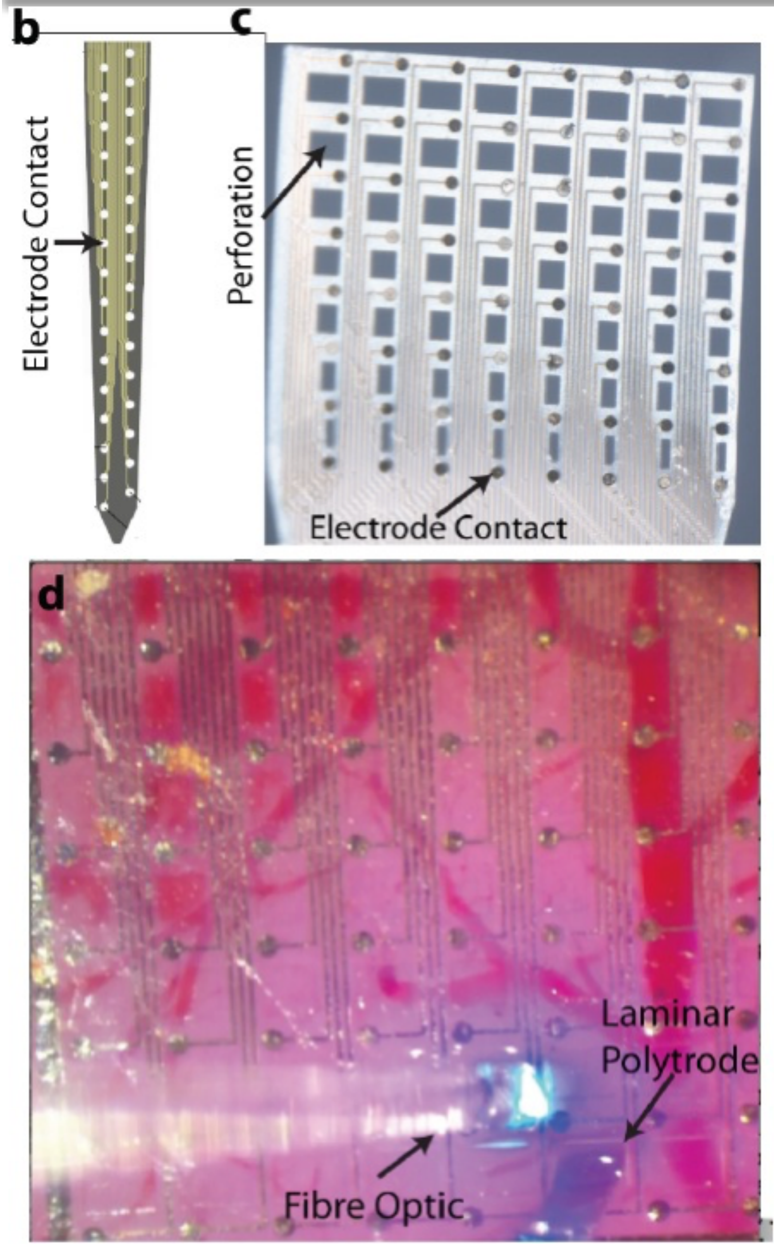
Micro-cantilevers as (photo) acoustic (ultrasound) sensors



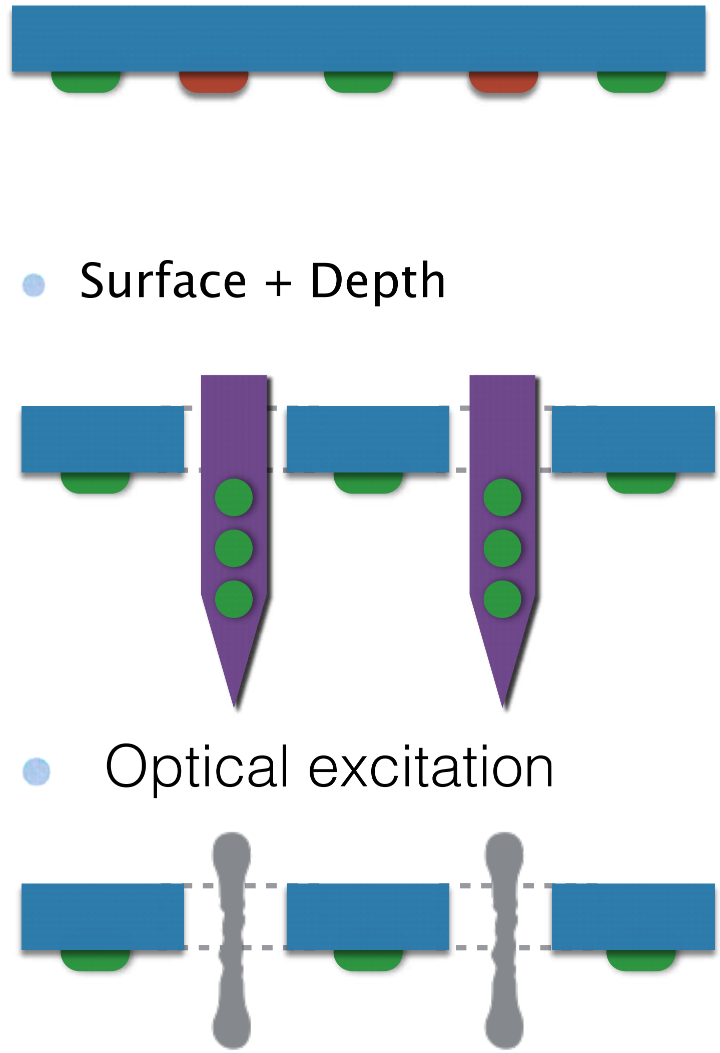


Tang, L. et al. Nanometre-scale germanium photodetector enhanced by a near-infrared dipole antenna. Nature Photon 2, 226–229 (2008).

Excitation and Sensing



- Electrical Excitation
- Surface + Depth
- Optical excitation



An App

~~Available~~ on the App Store

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Closed-loop Brain Machine Interfaces

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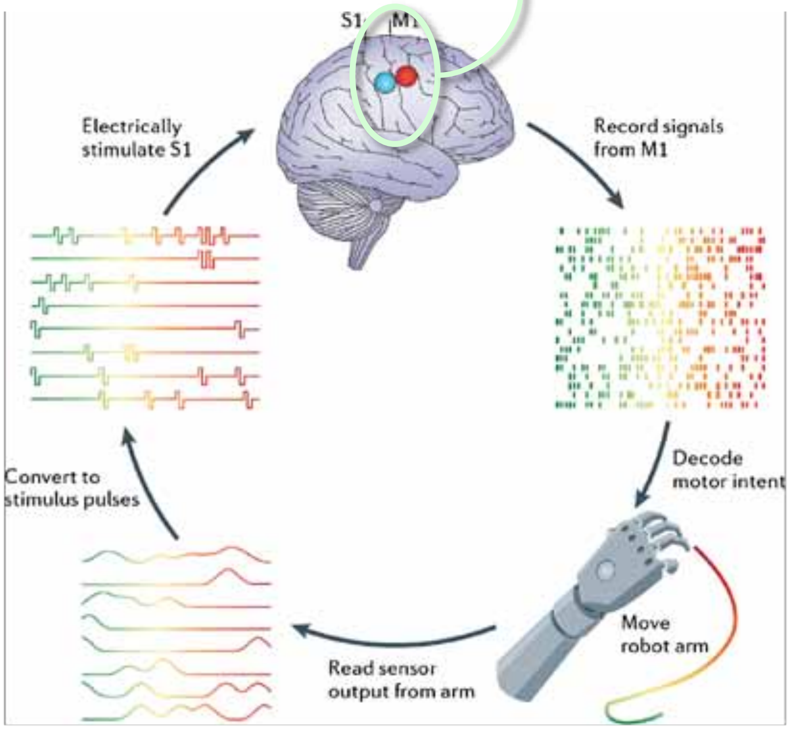
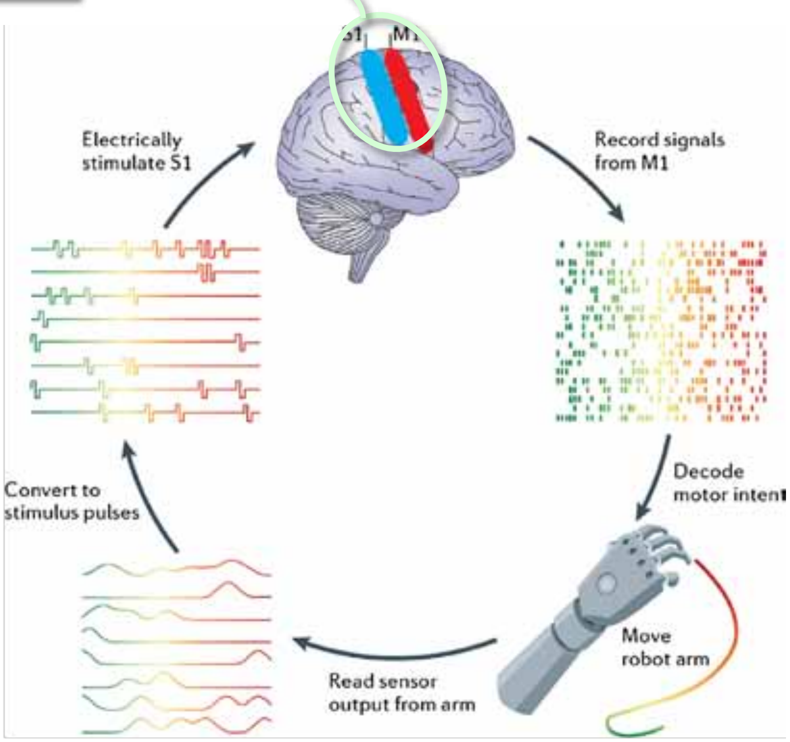
Large-Area High-Density





Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

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

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

Advancing BMI will benefit from:

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

(*Today:* ~10^2 electrodes, *Goal*:10^4 -10^5 electrodes,100 μm pitch)

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

(*Goal*:10^4 -10^5 x16B x 20kHz ≤ 4 Gb/s ~ 350Tb / day)

[Neuro: ∞ / 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)

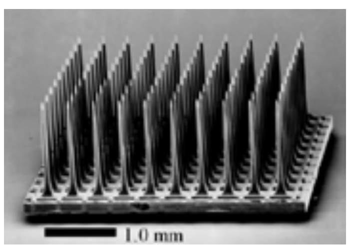
Hardware/Computing in Current BMI pipeline

Raw Signal

Control Signal

Sensors → DAQ → PC → Controlled System

Signal extraction
Filter Calculation

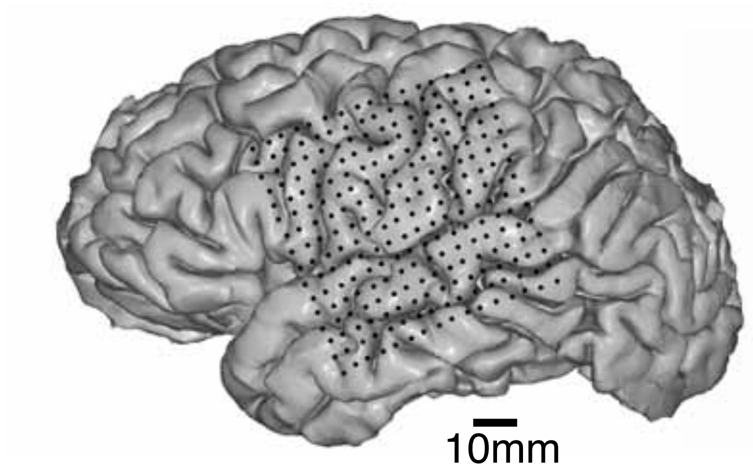


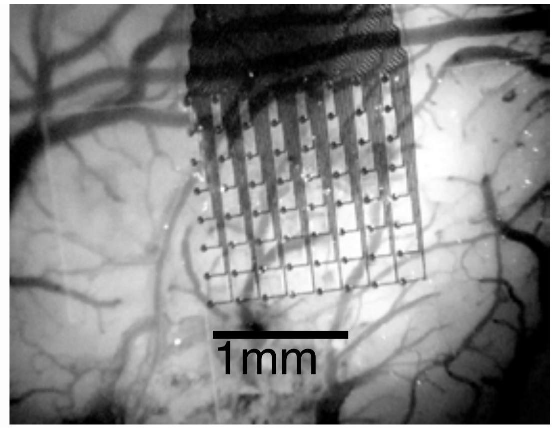
Today: R&D

Off-the-shelf

Today: R&D

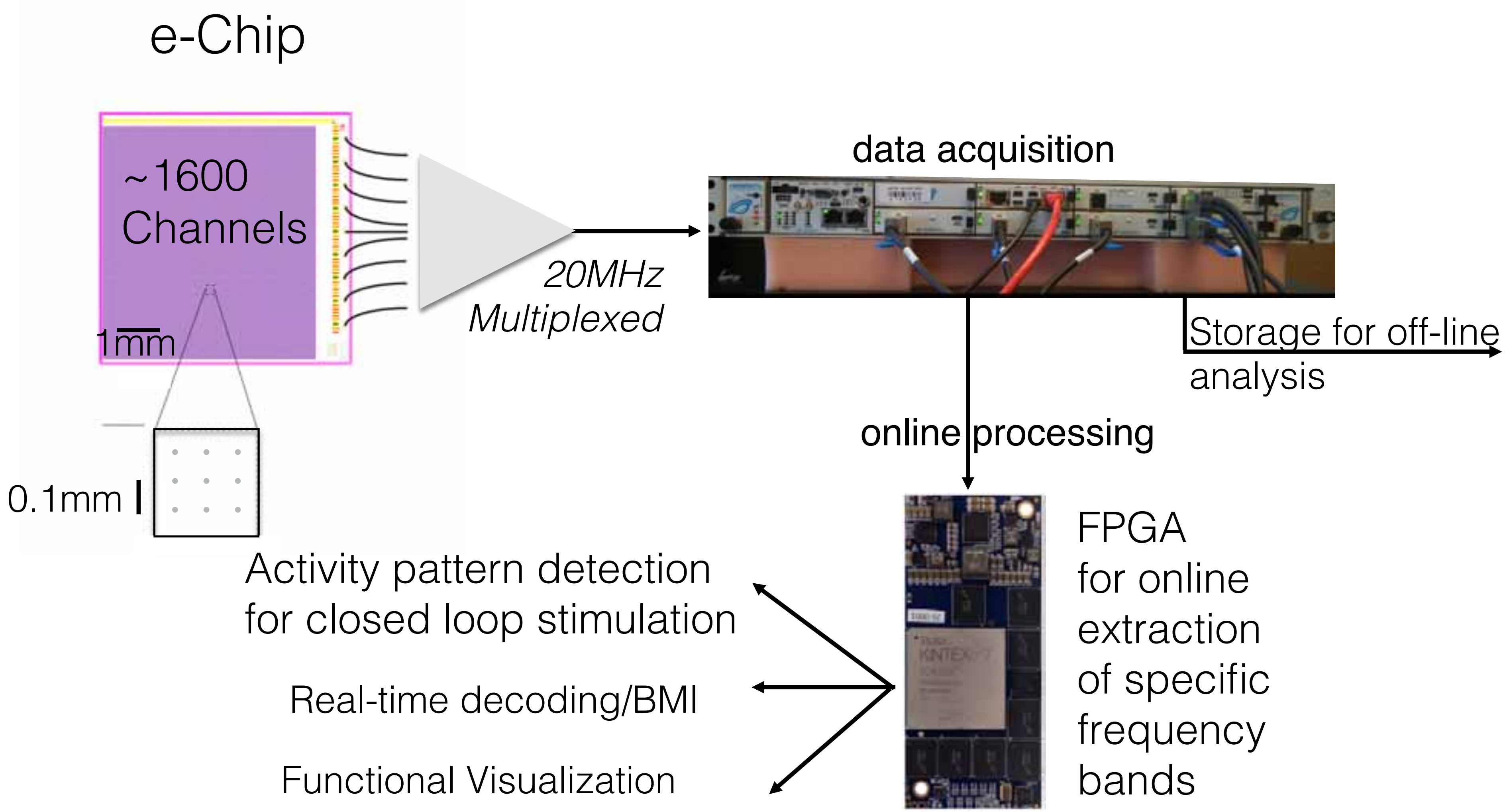
Advancing BMI through ultra-high density ECoG





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



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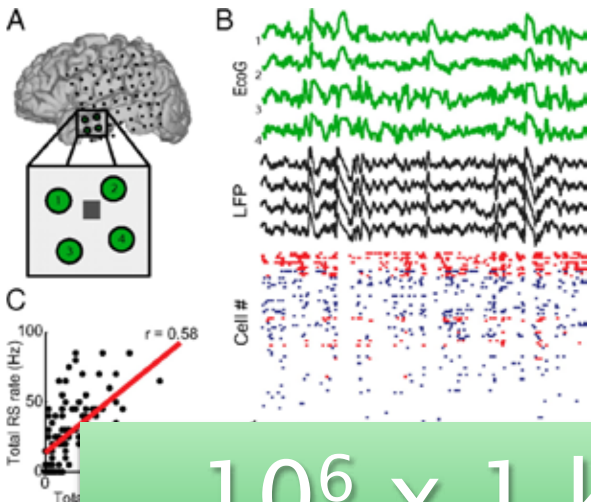
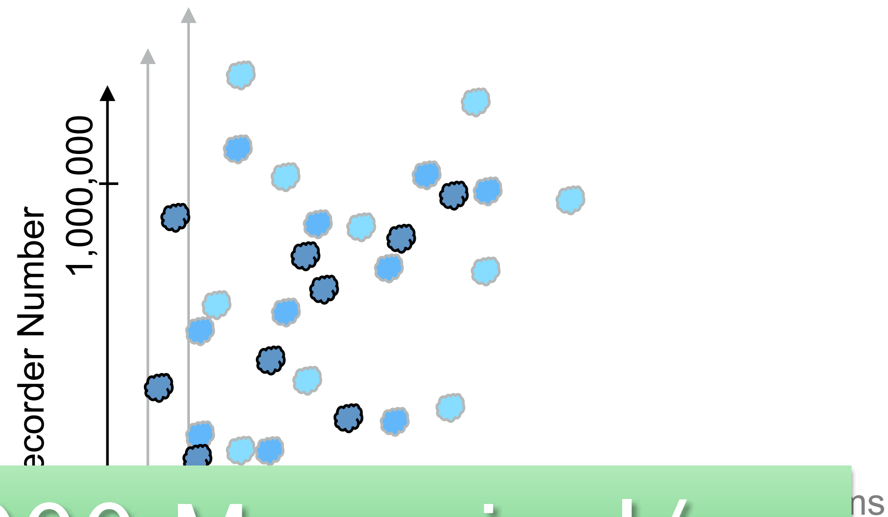
Massive Channel Count & Computational Challenges

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



Raw data
→
"Information" complex



10^6 x 1 kHz ≠ 1,000 Megapixel/s

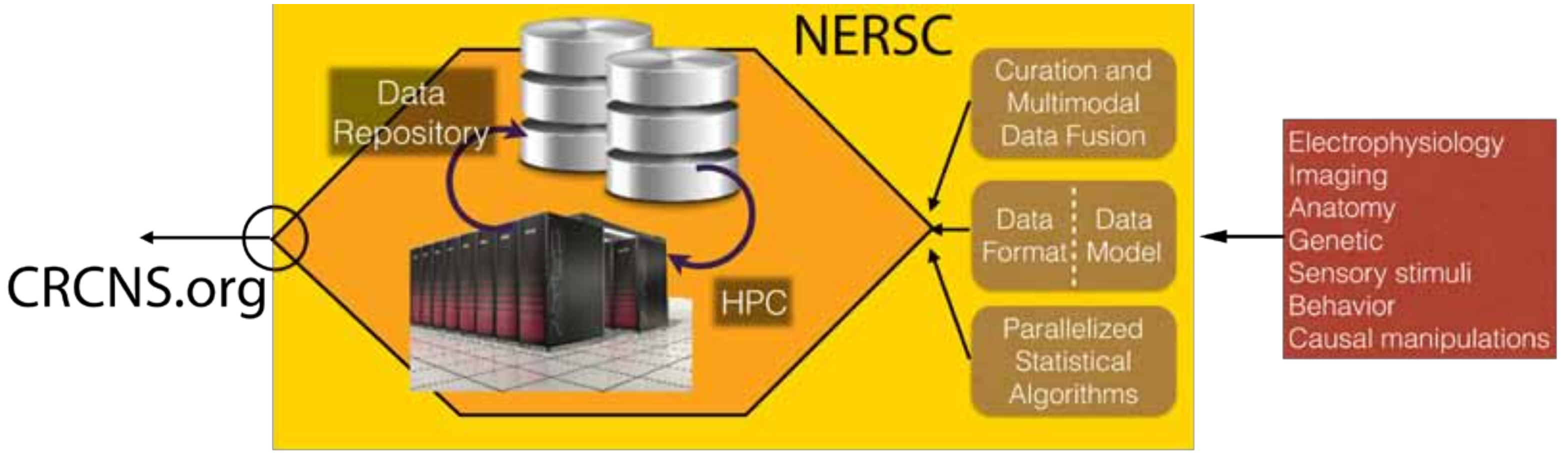
Consecutive Measurements are not Independent

Long-distance/time correlations

temporal domain

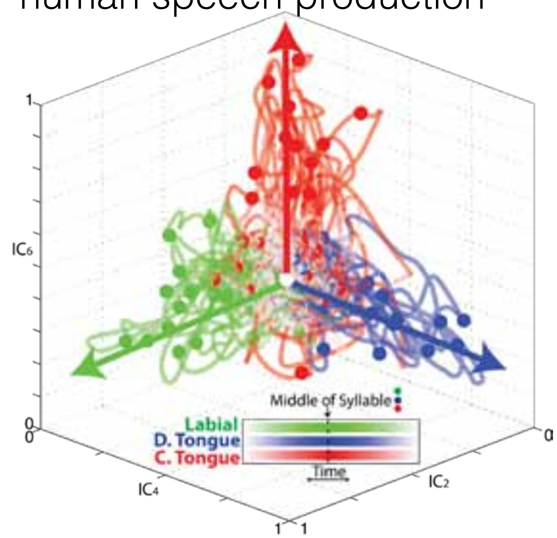
- **Dimensionality reduction**
- Coding schemes
- Visualization

Advances in HPC for Neuroscience

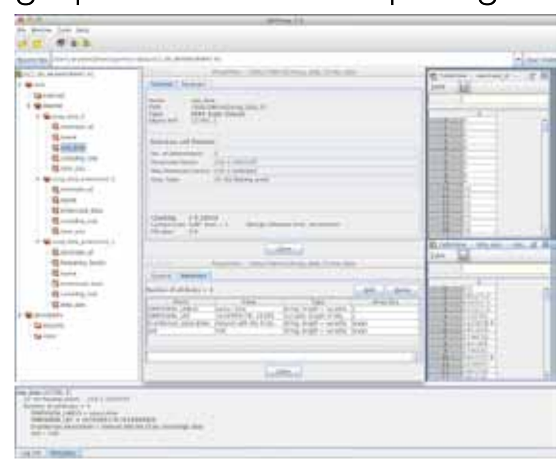


CRCNS portal and repository for community access to data

Sparse neural activity for human speech production



HDF5 format and data model for high-performance computing



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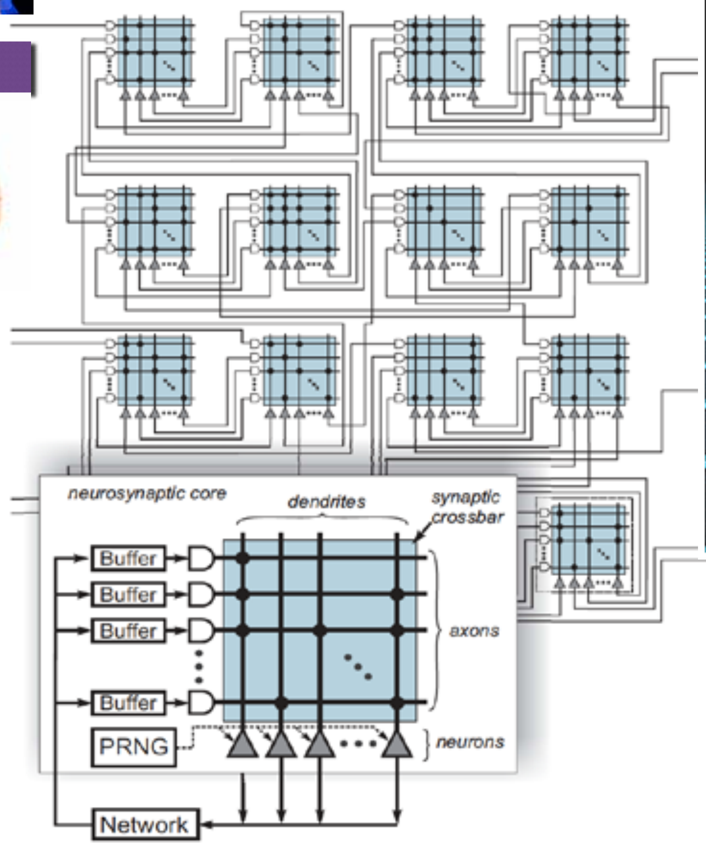
Neuromorphic Computing

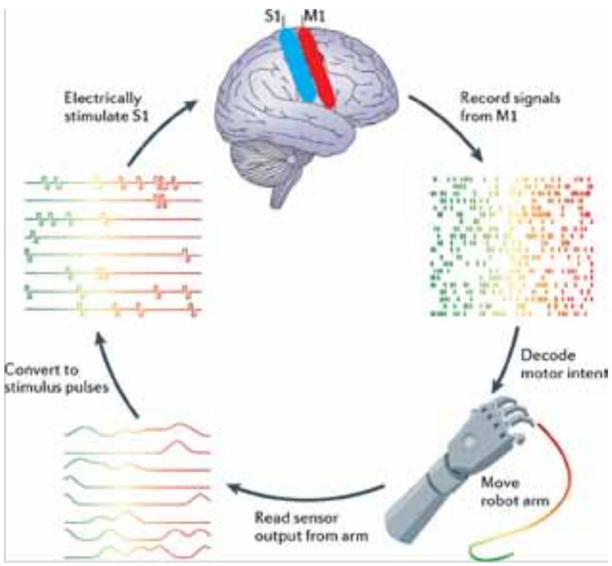
- The brain is pretty good at certain tasks
- Brain-inspired computing?

- Neural networks
- IBM TrueNorth

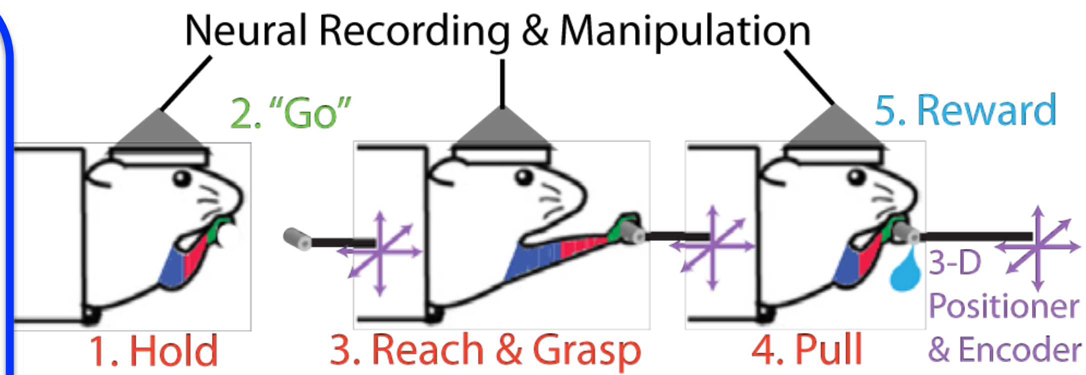


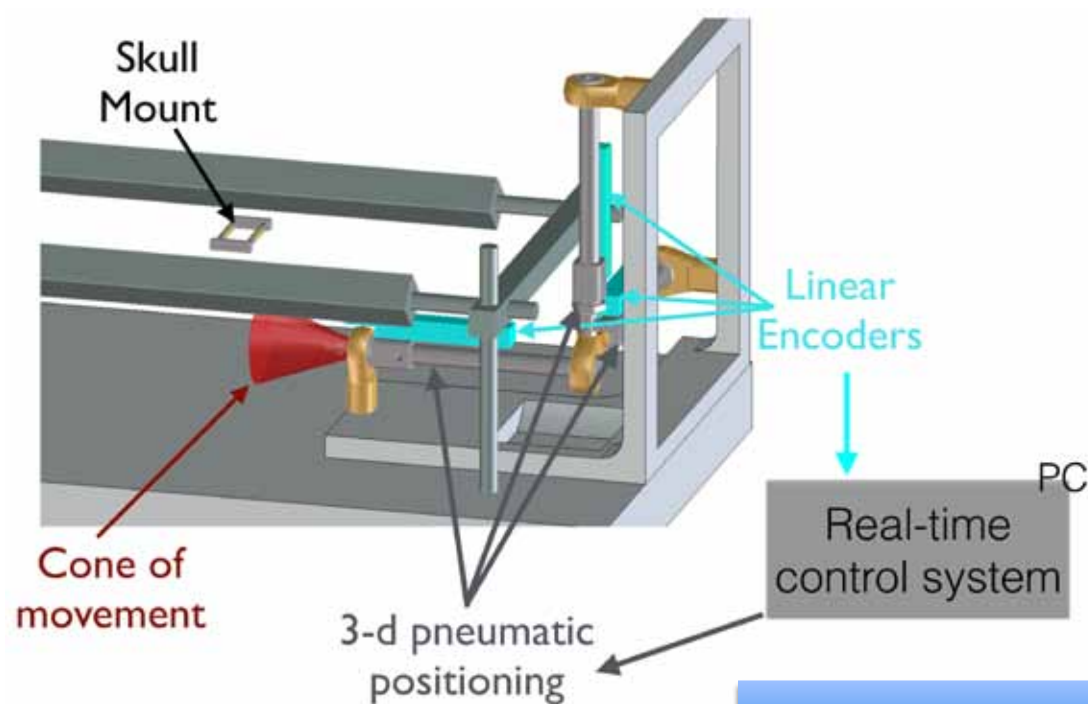
Complex Tasks for Rodent Experiments

Not Plug-N-Play



Develop in Model Systems

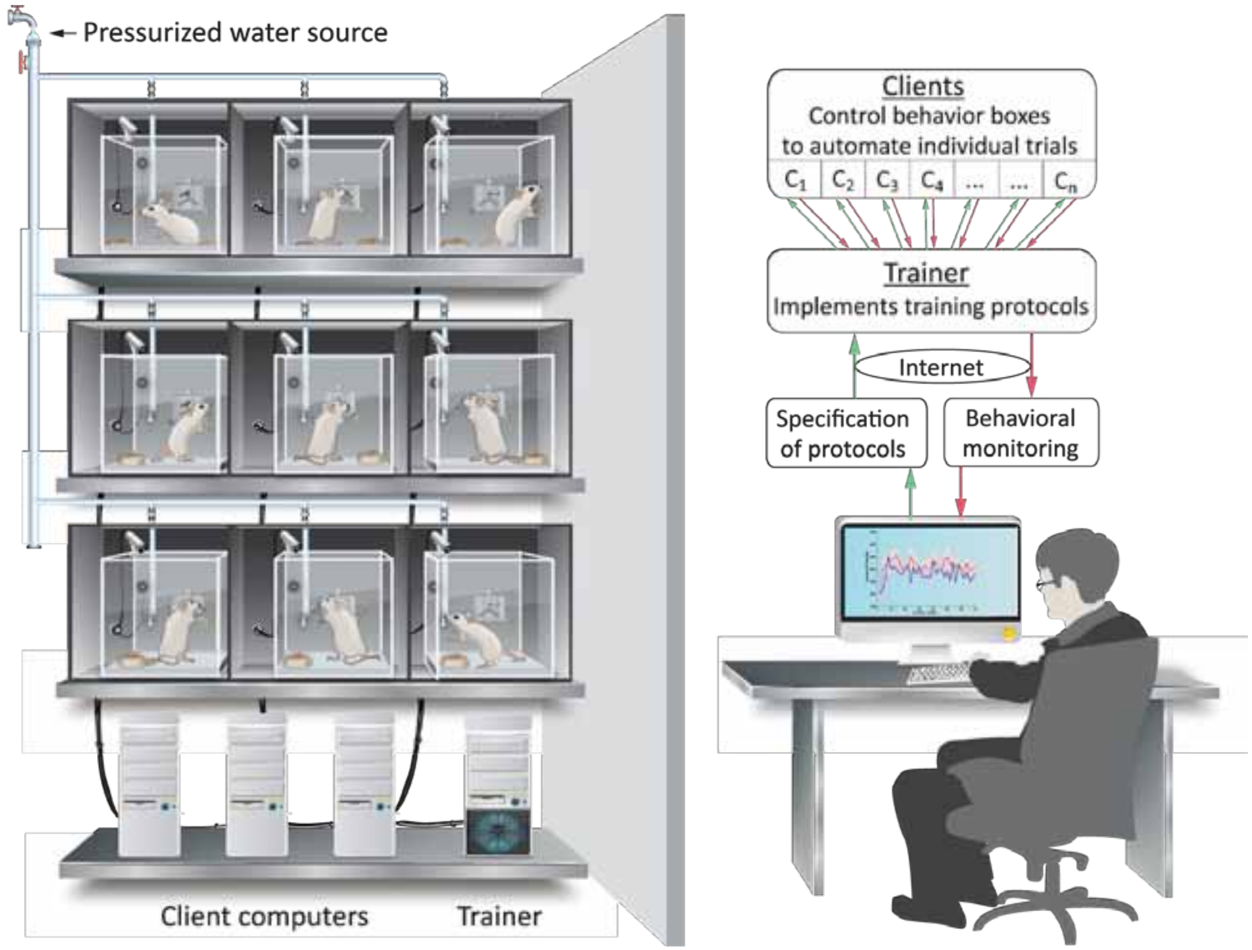




"Instrumentation"

BRAINseed

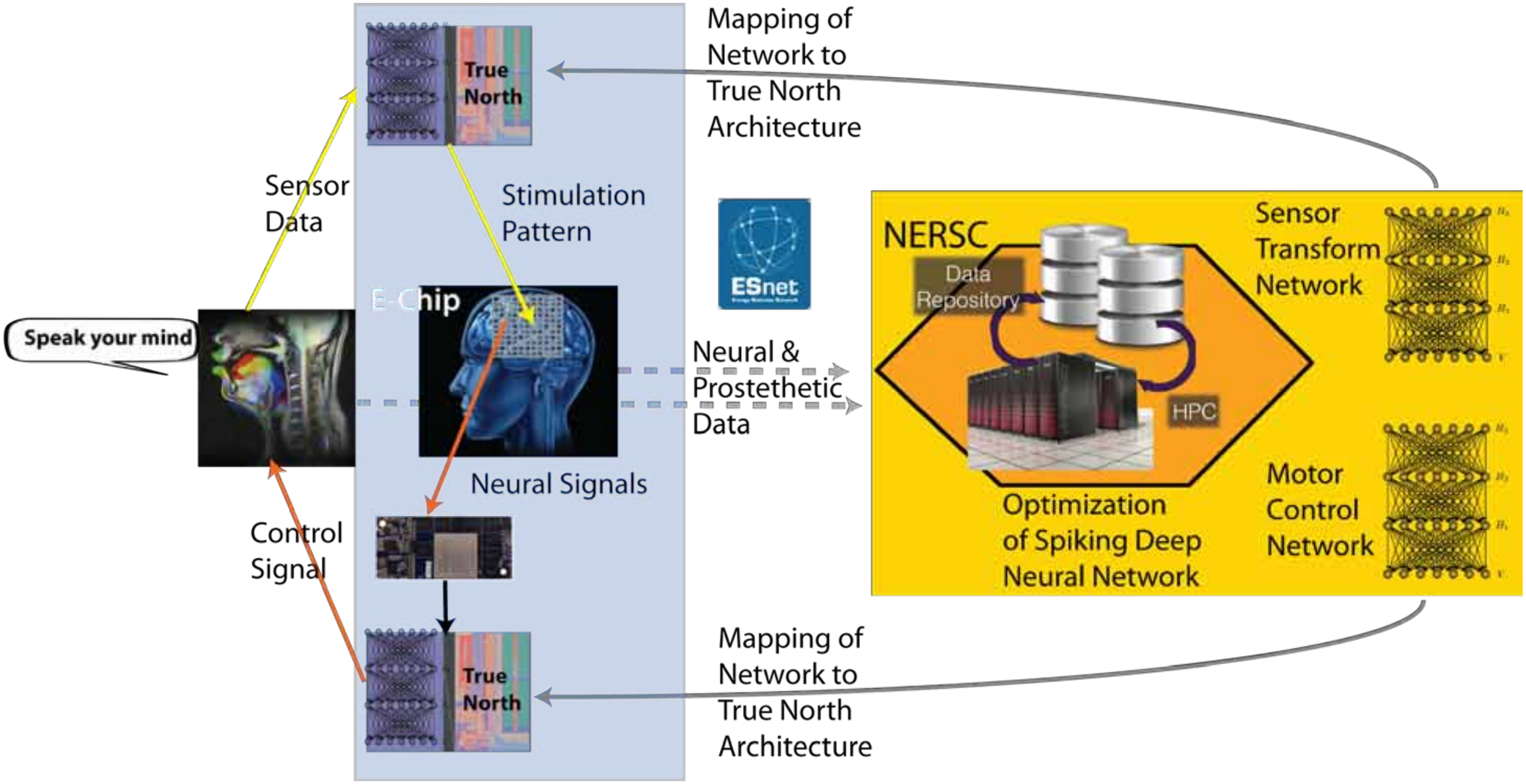
High-throughput Rodent Experiments



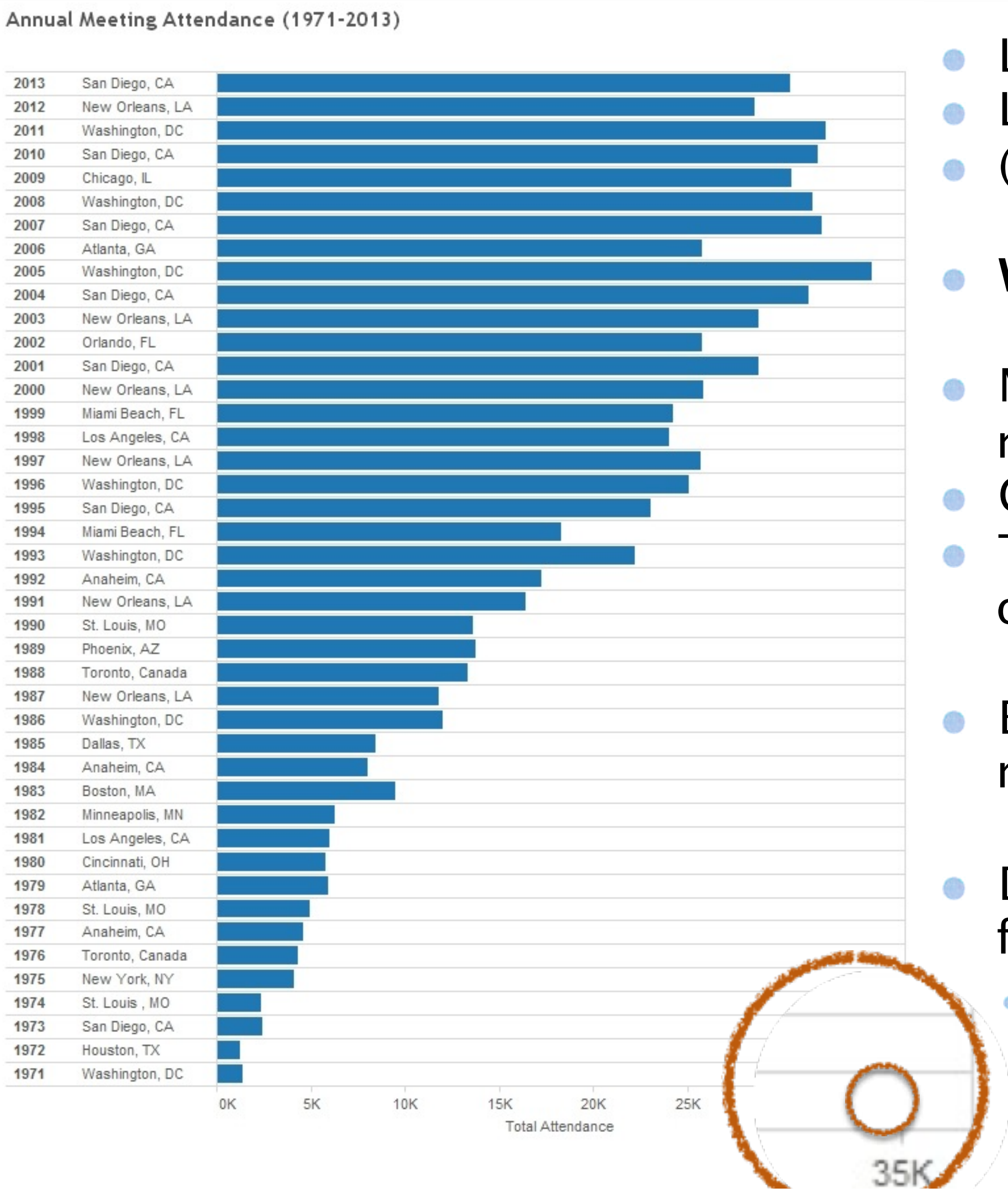
"Instrumentation"

B. Olveczky - Harvard

"Speak your Mind" speech prosthetic



Neuroscience is a Large and Diverse Field



- 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

Cusp

- Micro / Nano technology is now within reach (10 – 50 years) of providing fundamental understanding

View 1

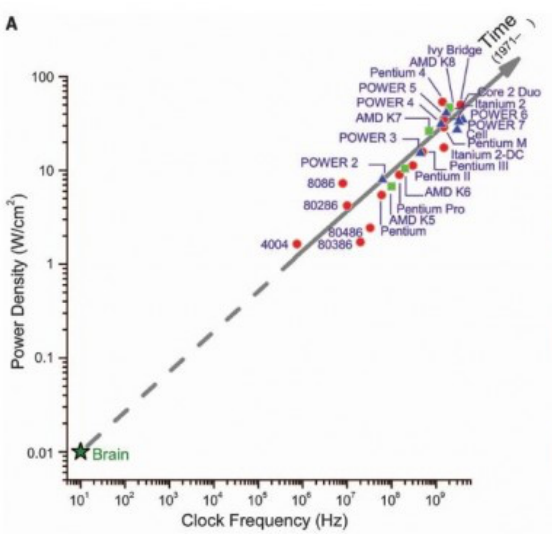
← BRAIN / TECH →

View 2

BRAIN / TECH →

View 3

BRAIN \ TECH →



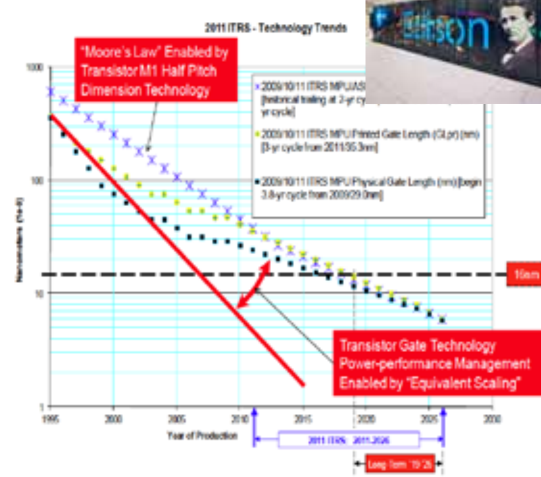
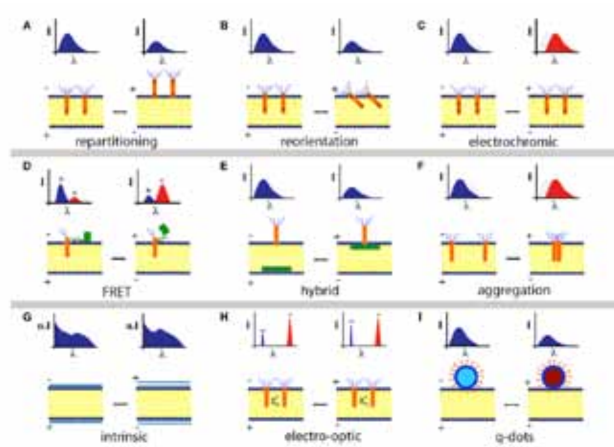
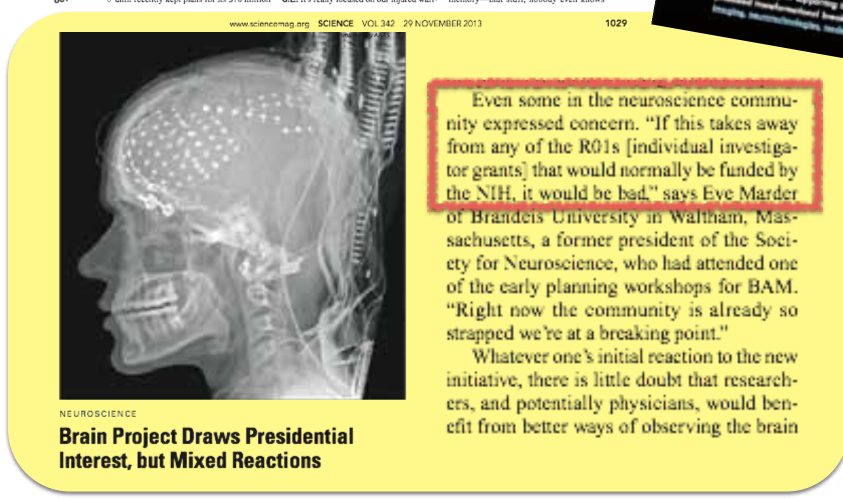


Figure 11 2011 ITRS—MPU/High-performance ASIC Half Pitch and Gate Length Trends



Opportunities - Federal Agencies

BERKELEY LAB



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

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

BERKELEY LAB

Eligible Areas

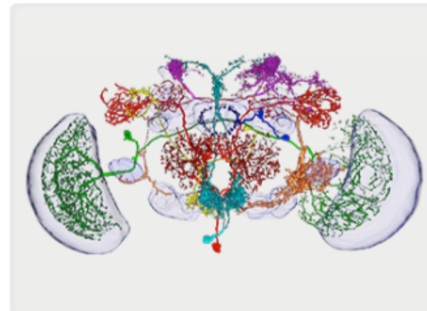
Examples* of Research Areas Eligible for Support

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.



Cal-BRAIN:

Ralph J. Greenspan, I

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

Goal: Develop new te
ability to monitor and

Impacts: Advances fo
prosthetic devices. A t
intelligent systems ca
enhance the capabiliti
generation of interdisc
Neurotechnology, wi

Cal-BRAIN

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

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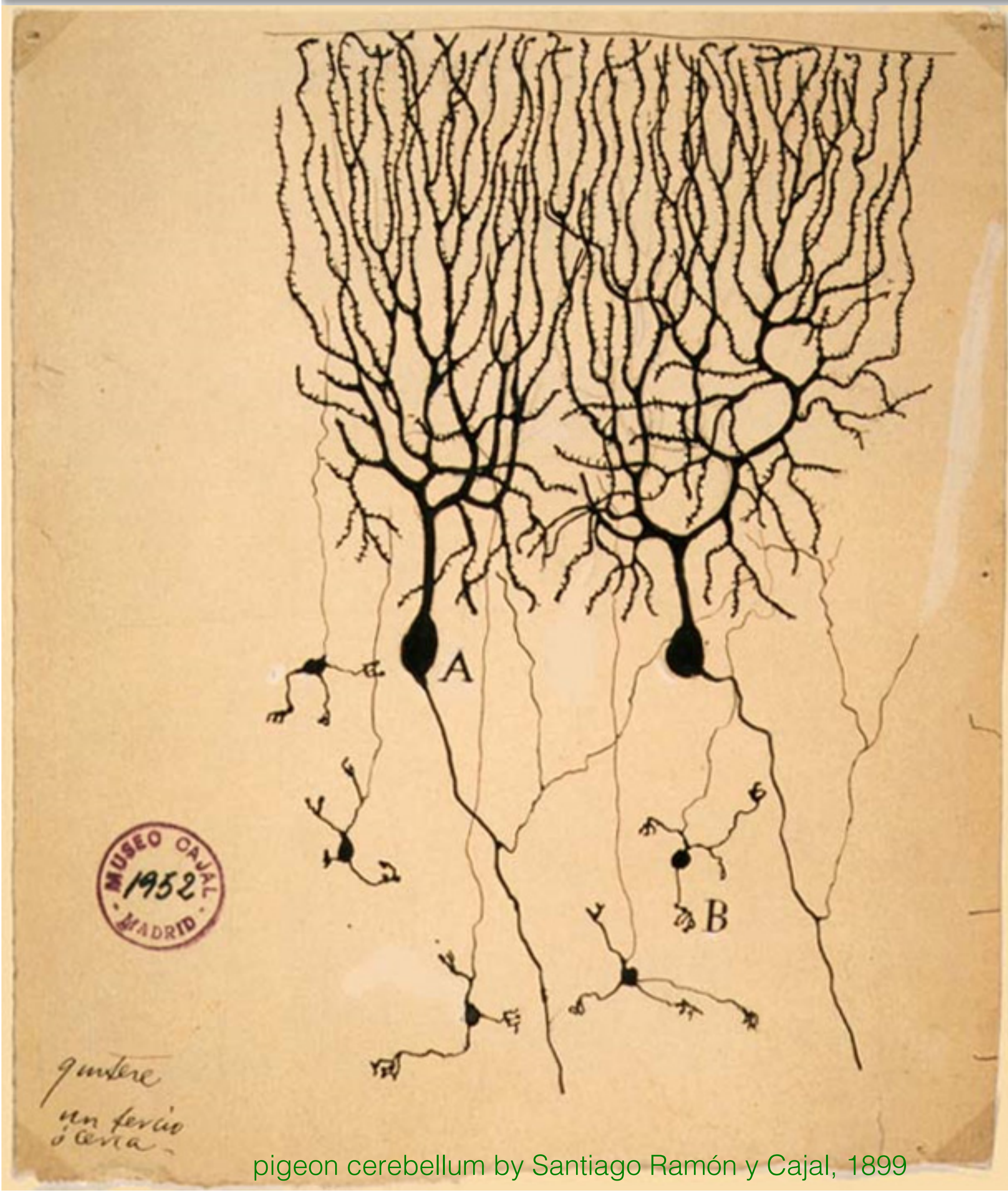
Interdisciplinary Instrumentation



pigeon cerebellum by Santiago Ramón y Cajal, 1899

- Hard problem!
  - 10^6, kHz, μm, 3D, …
- Requires <u>all</u> 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