What Can Cells Teach Us About Computing?

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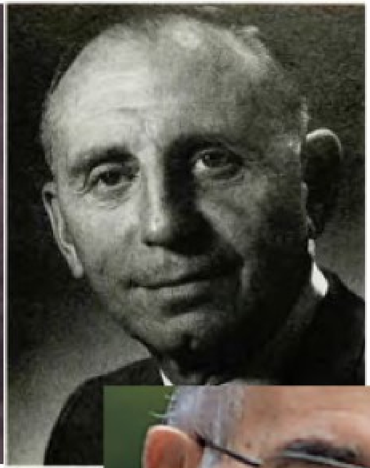
Honoring Those Who Came Before

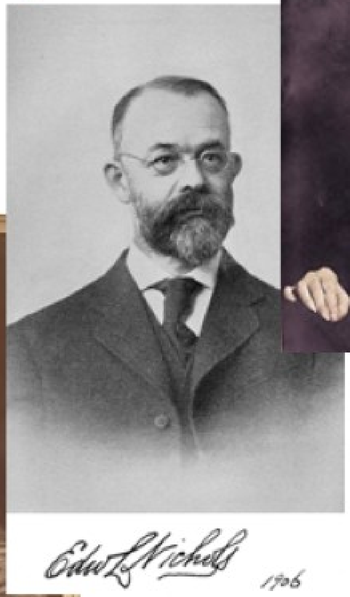
Academic Genealogy

Roswell Clifton Gibbs

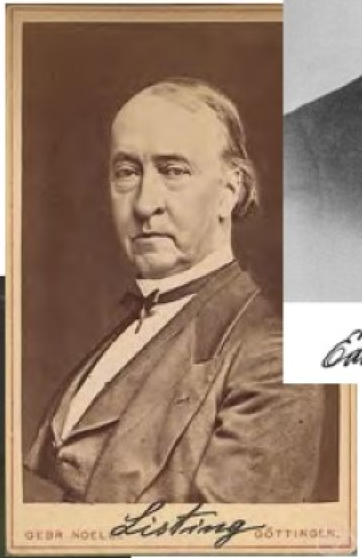
Lloyd Preston Smith



Edward Leamington Nichols



Johann Benedikt Listing



George Warfield

Charles Roger Westgate

Carl Freidrich Gauss

Andreas Gregory Andreou

Cogito, ergo sum
– René Descartes, 1641

August Rodin, photo by Jean-Pierre Dalbéra

What is computing?

- ***goal-oriented activity requiring, benefiting from, or associated with the creation and use of computers***
  – Computing Curricula 2020 (ACM & IEEE)
- designing and constructing hardware and software systems for a wide range of purposes:
  - processing, structuring, and managing various kinds of information
  - problem solving by finding solutions to problems or by proving a solution does not exist
  - making computer systems behave intelligently
  - creating and using communications and entertainment media
  - finding and gathering information relevant to any particular purpose

~~What is computing?~~ Do cells compute?

- ***goal-oriented activity requiring, benefiting from, or associated with the creation and use of computers***
  – Computing Curricula 2020 (ACM & IEEE)
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  - processing, structuring, and managing various kinds of information
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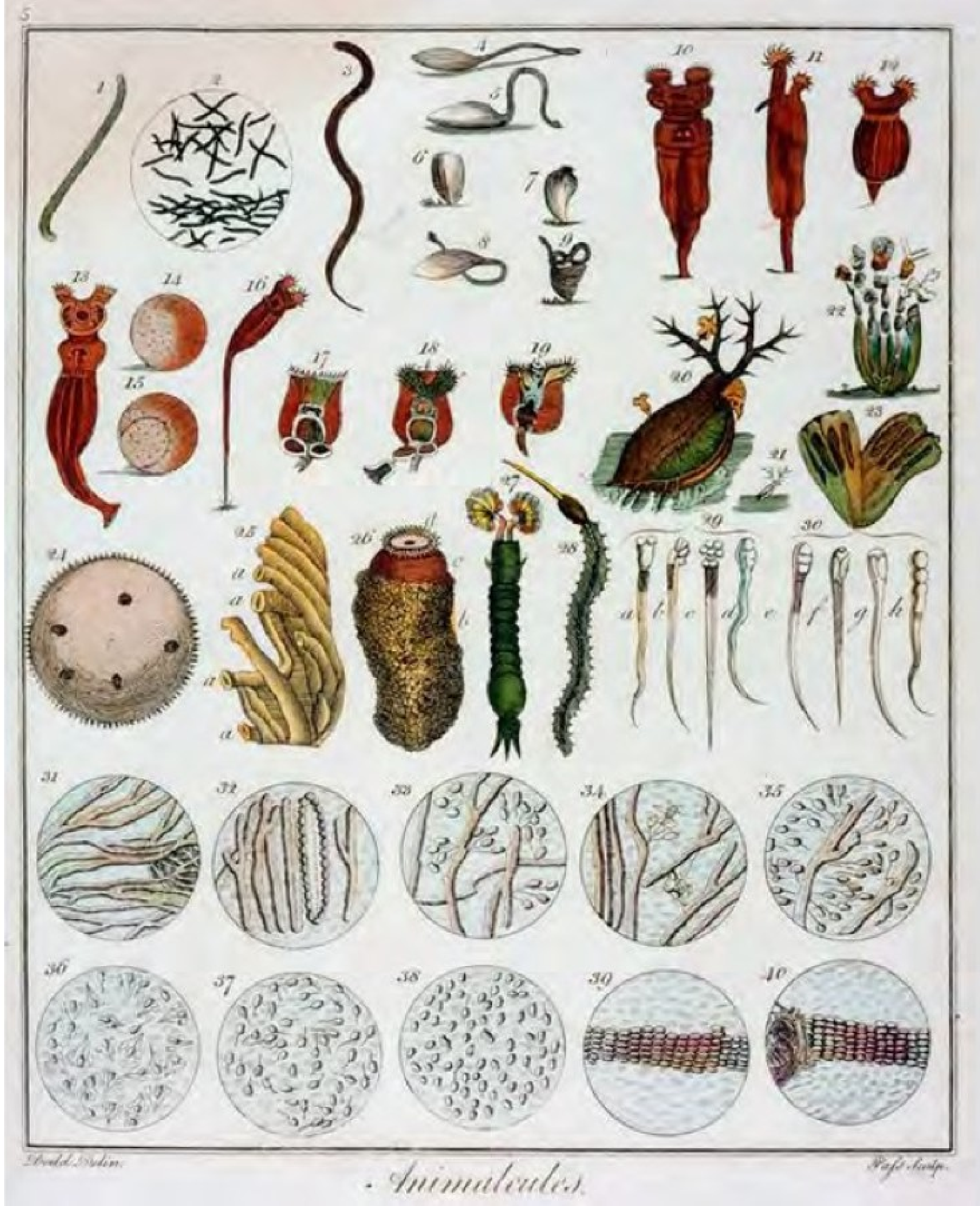
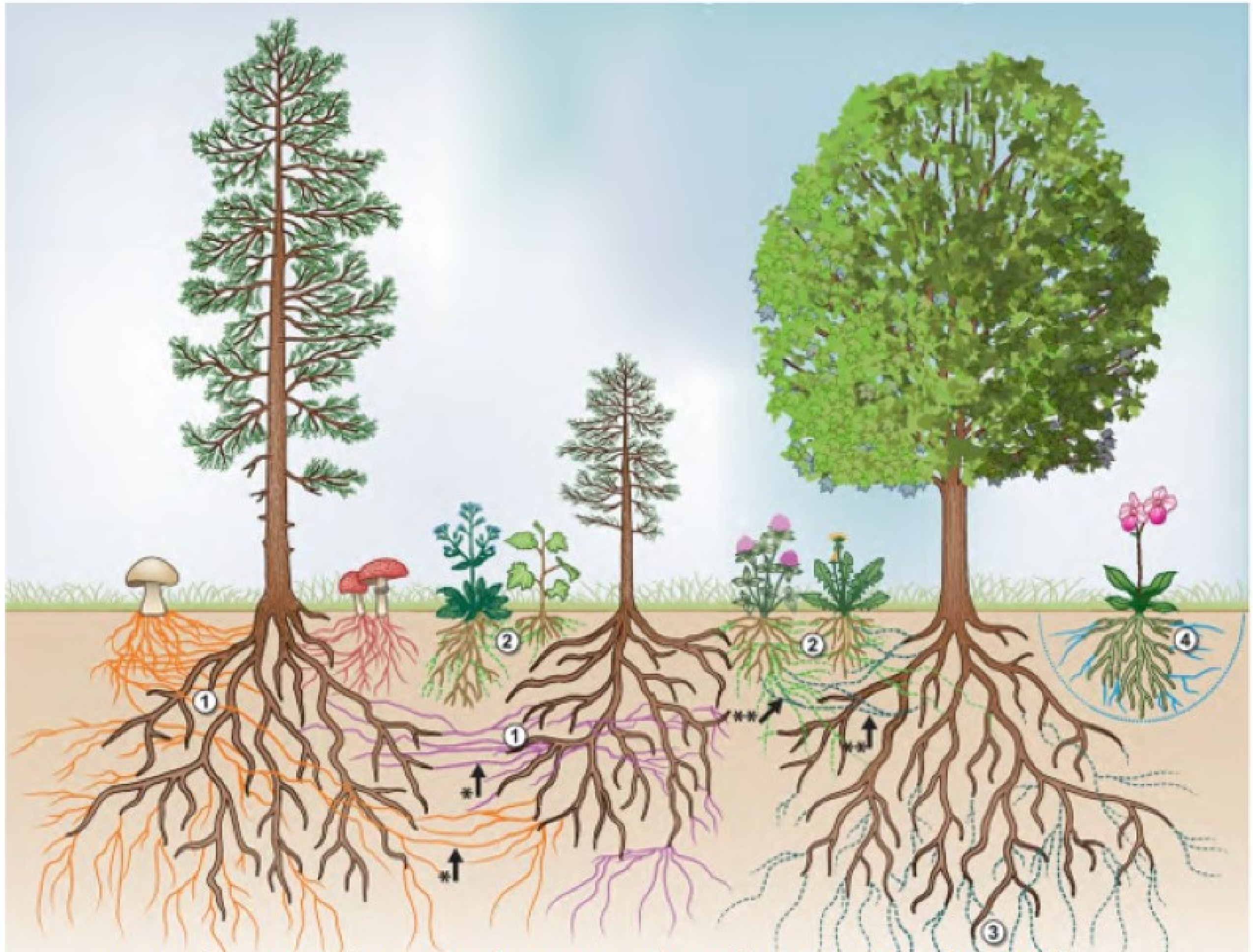
Animalcules

- Microscopic organisms observed by 17th-century Dutch scientist Antonie van Leeuwenhoek in rainwater
  - Single lens 300X microscope
- Directed movements and capabilities were a great source of fascination



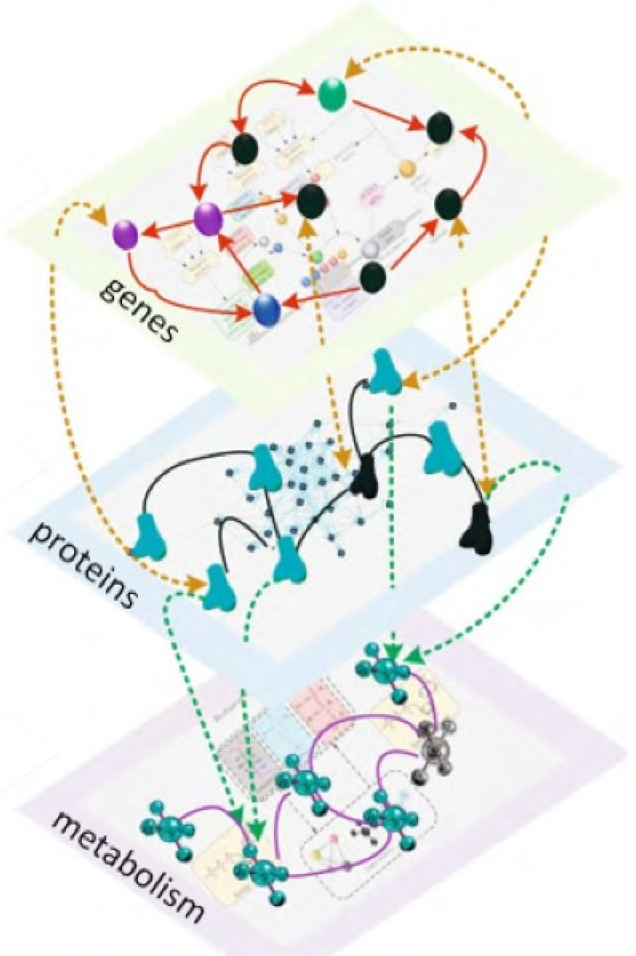
Complex Networks in Biology

Mycorrhizal networks -- *the wood wide web*



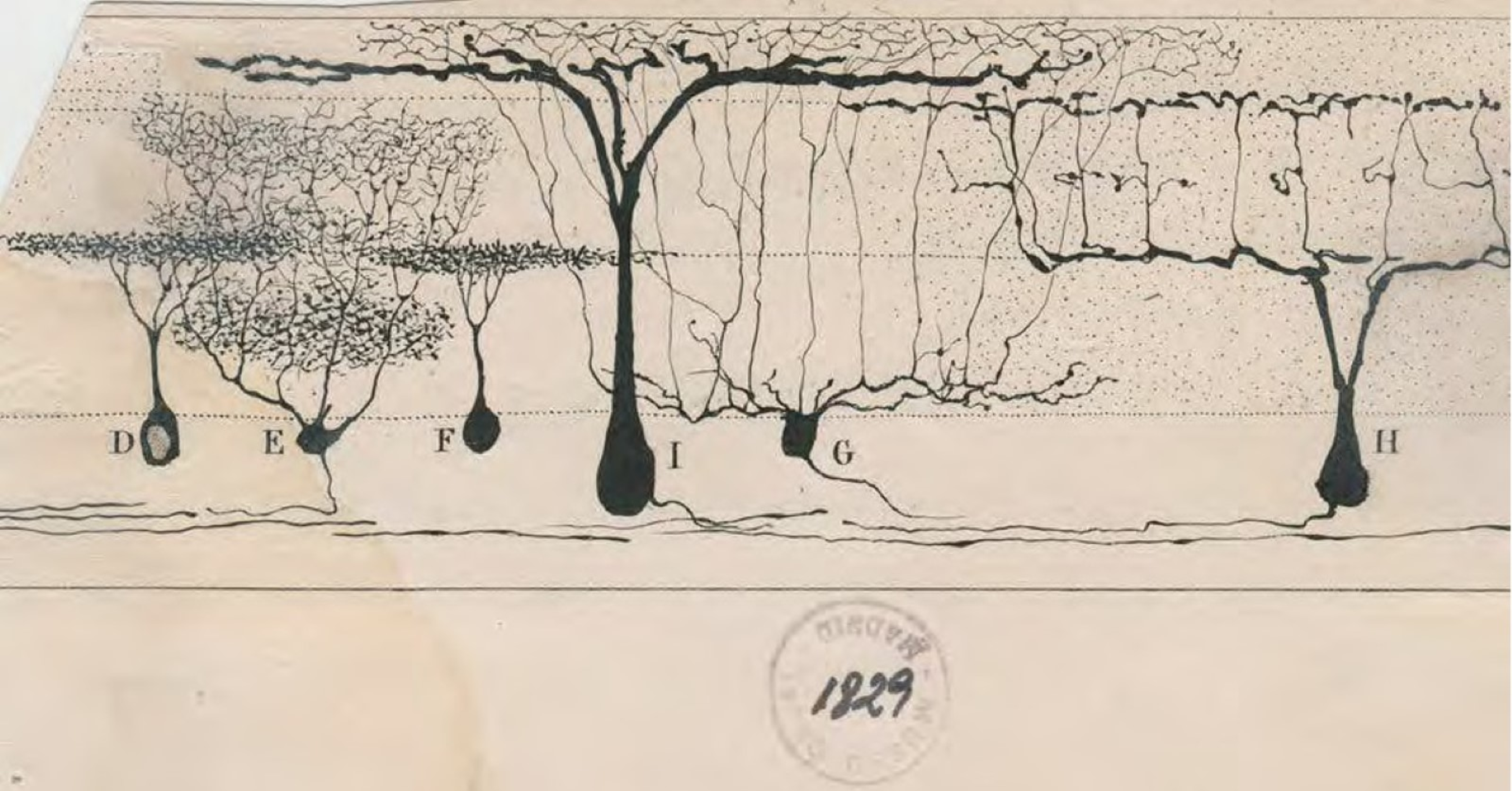
van der Heijden et al., New Phytologist, 205 (2015)

Macromolecule networks



Adapted from Liu et al. Nat Commun ***11,*** *6043 (2020)*

86 billion neurons
85 billion glia
125 trillion synapses



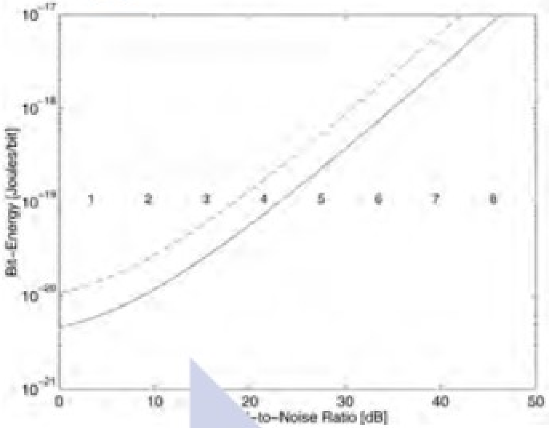
Ramón y Cajal, *Estructura de los centros nerviosos de las aves*, 1905

Nature's nearly optimal:
Information-Power efficiency in wetware & Si

Quick history of energy cost of computing

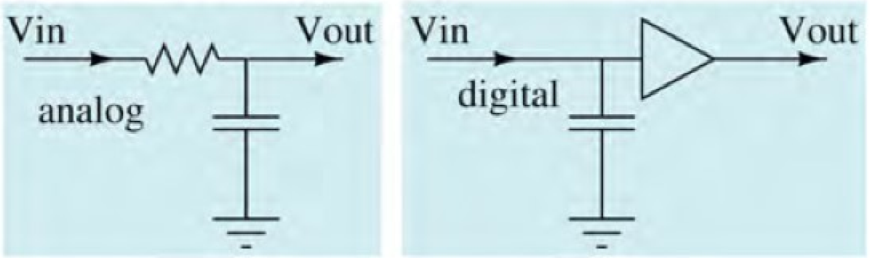
Maxwell 1871
Maxwell's
demon

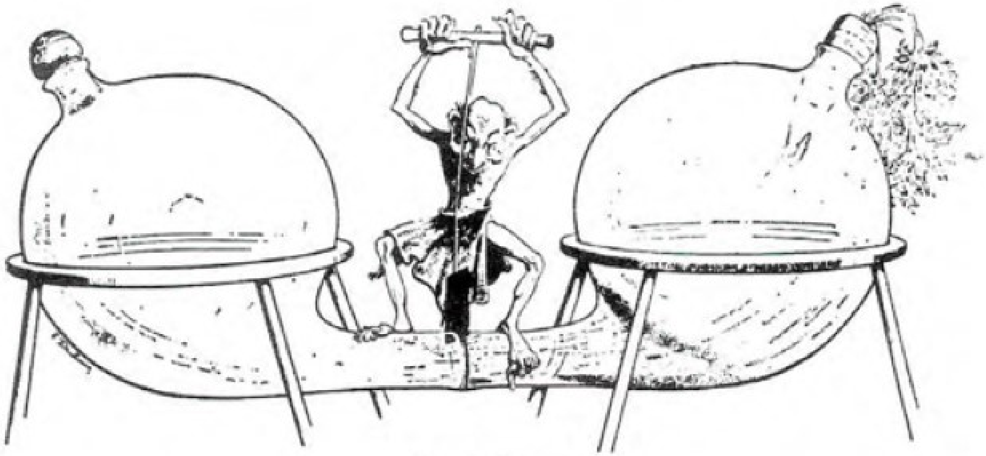
Bennett 1973
No min energy!
Only for speed
& output



Landauer 1961
Min energy
kT (ln2) per bit

Hosticka 1985
comparison of
delay function

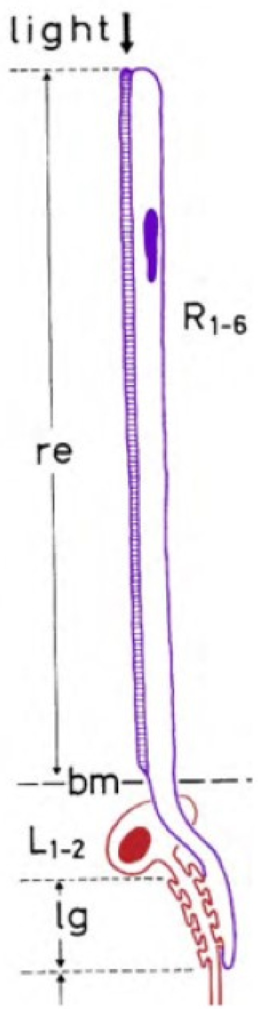


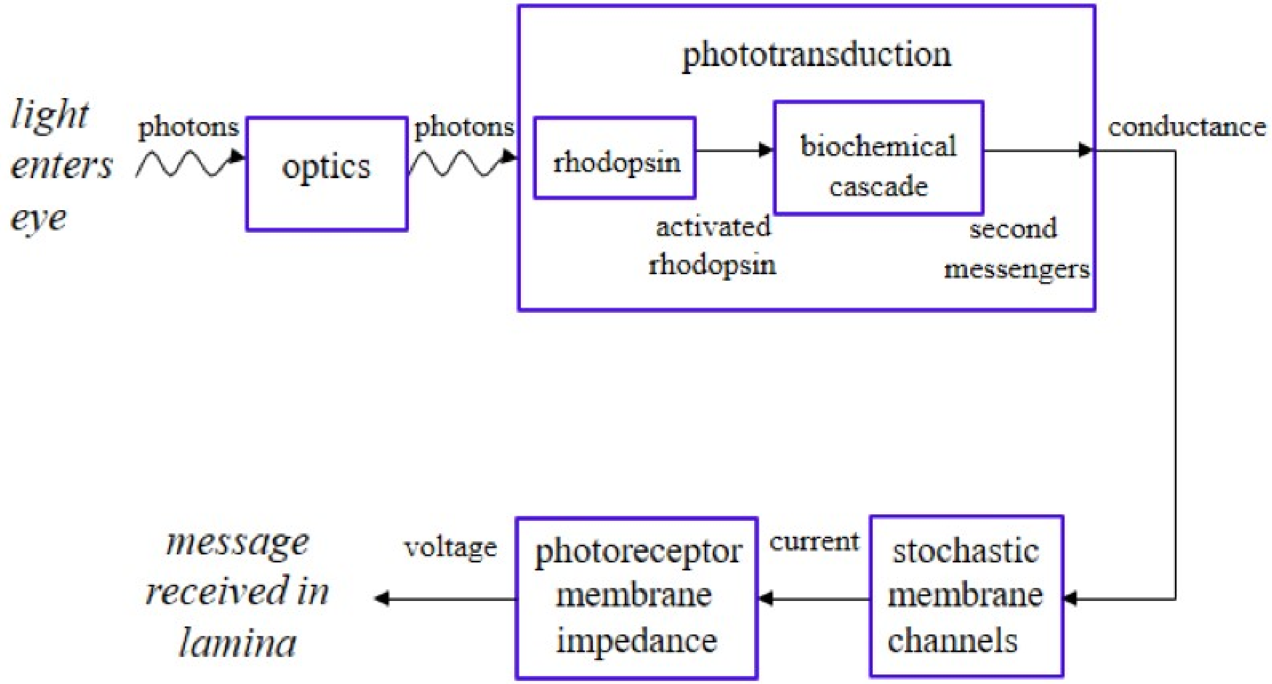


Maxwell's demon at work

Darling & Hulbert, Am. J. Phys., 23:470 (1955)

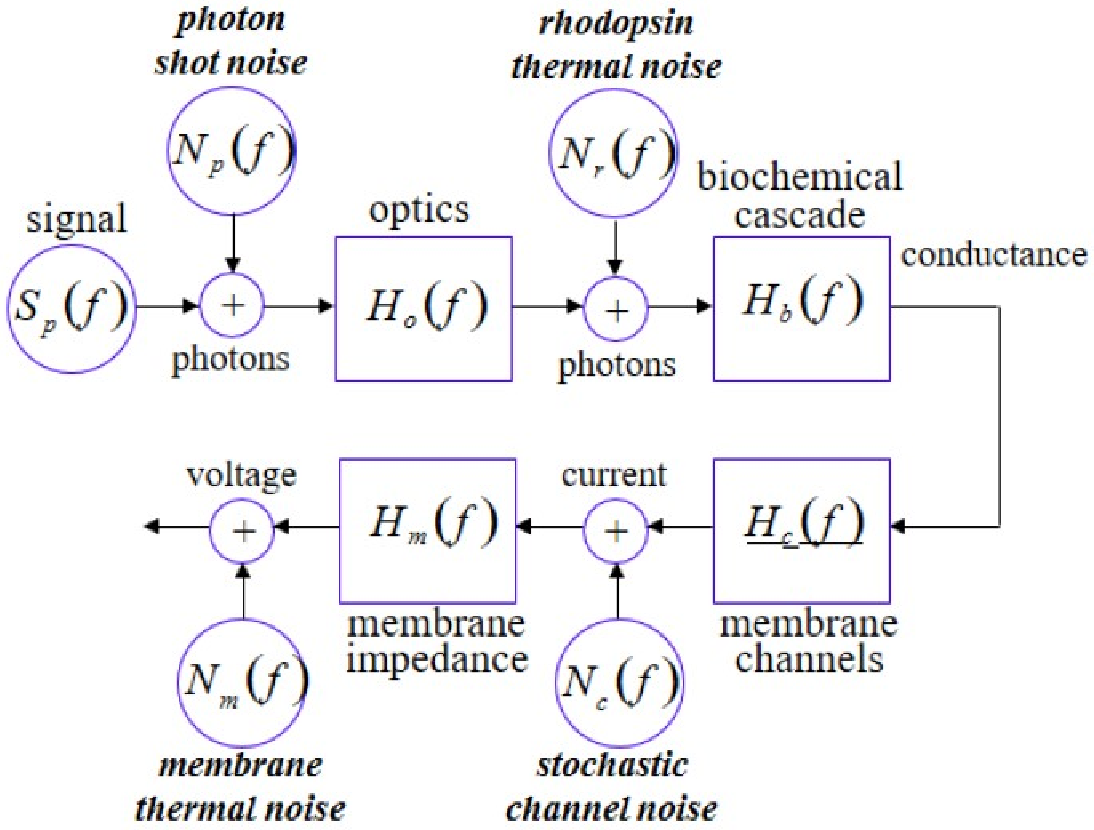
Transduction pathway of blowfly photoreceptor





with Andreas Andreou (JHU)

Linearized system model of blowfly photoreceptor

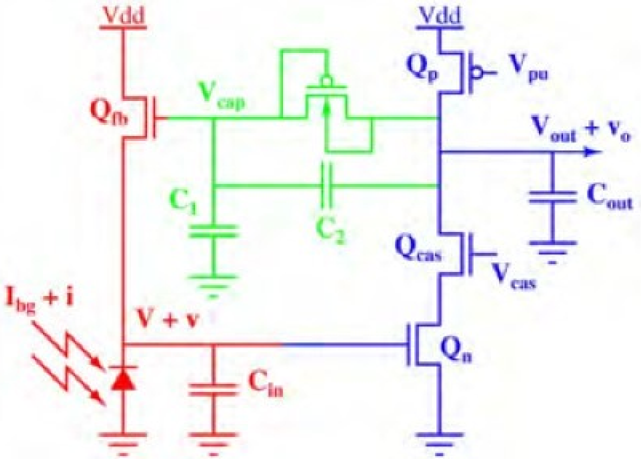


$$S_n(f) = \prod_i |H_i(f)|^2 S_p(f) \qquad N_n(f) = \sum_j \prod_i |H_i(f)|^2 N_j(f)$$

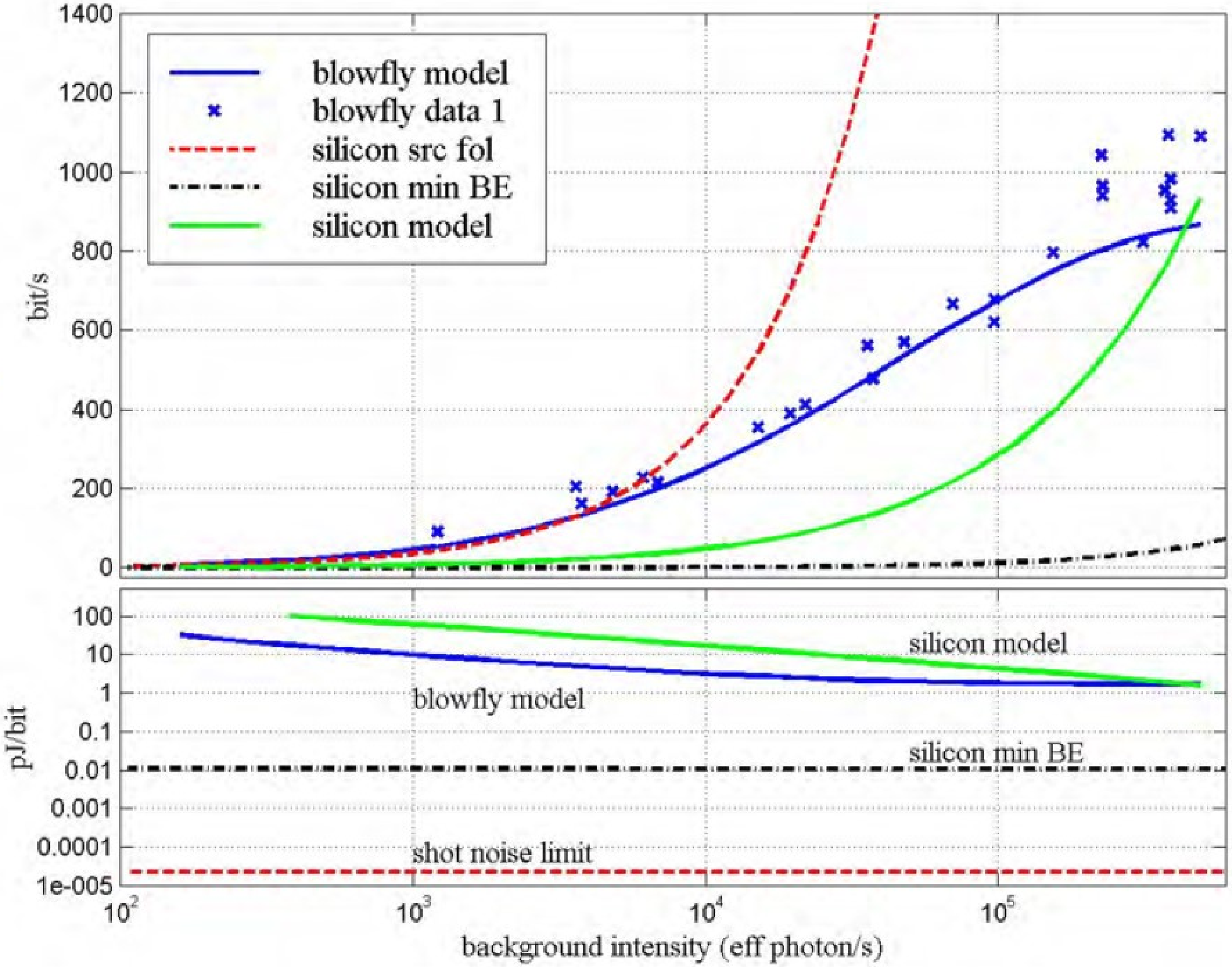
with Andreas Andreou (JHU)

Compare biological & silicon photoreceptors

Biology more efficient at low intensities

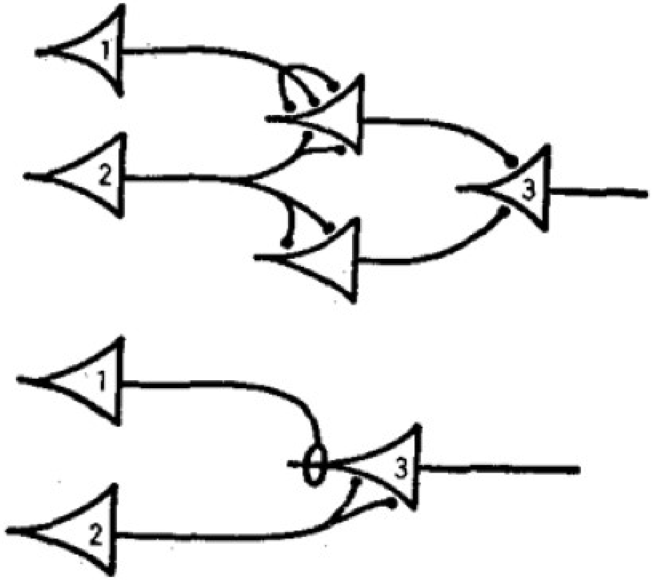


although silicon can be more efficient at high intensities



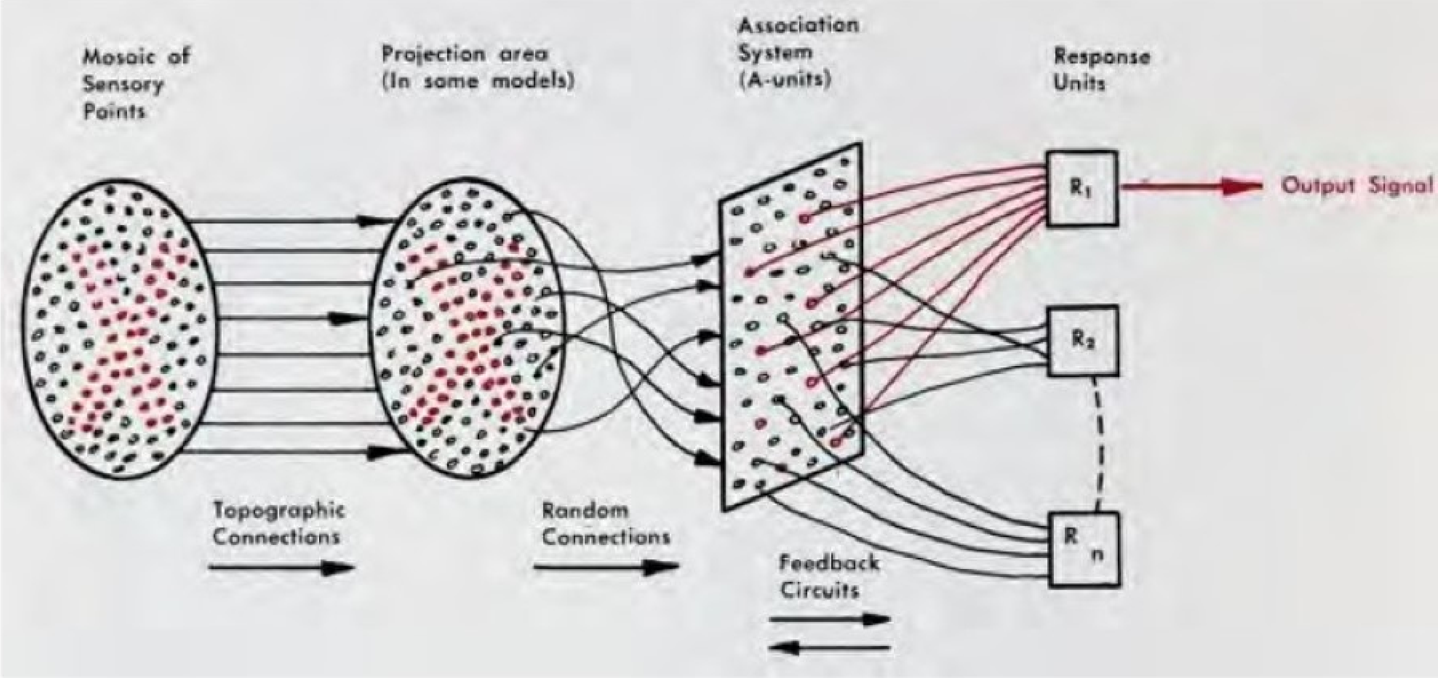
Artificial Neural Networks

McCulloch and Pitts 1943
- First mathematical model of a neuron
- Nonlinearity modeled with threshold
- Model any logical function
- No learning



McCulloch & Pitts, Bulletin of Math. Biophysics, 5 (1943)

Perceptron (Rosenblatt) 1958
- Introduces learning

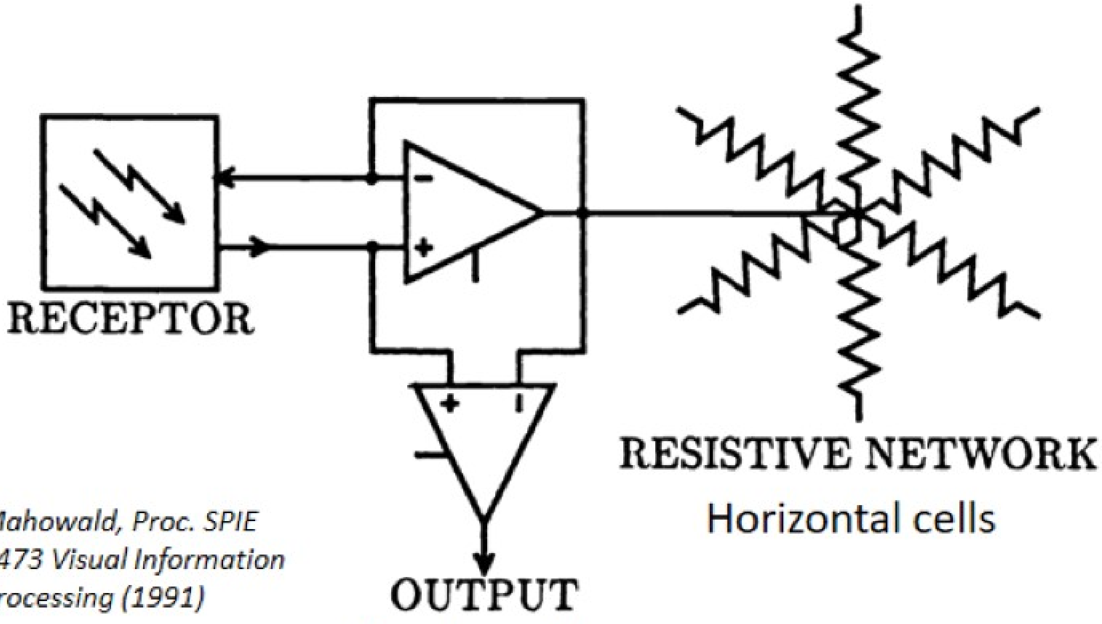


Rosenblatt, Psychological Review 65(6): 386-408 (1958)

What computations do real neurons perform?

- Normalization
- Averaging
- Logical functions
- Thresholding
- Synaptic adaptation
  - Long term potentiation and depression
    - Spike time dependent plasticity
  - Short term facilitation and depression
  - Homeostatic synaptic plasticity

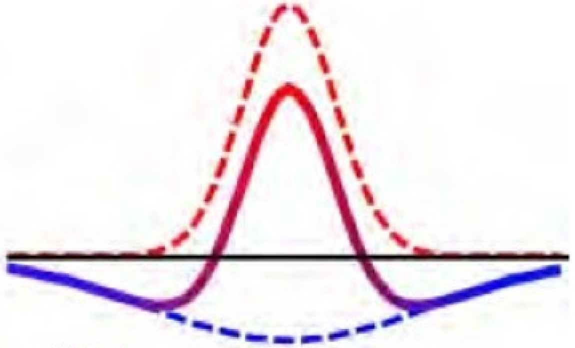
Contrast normalization in vertebrate retina



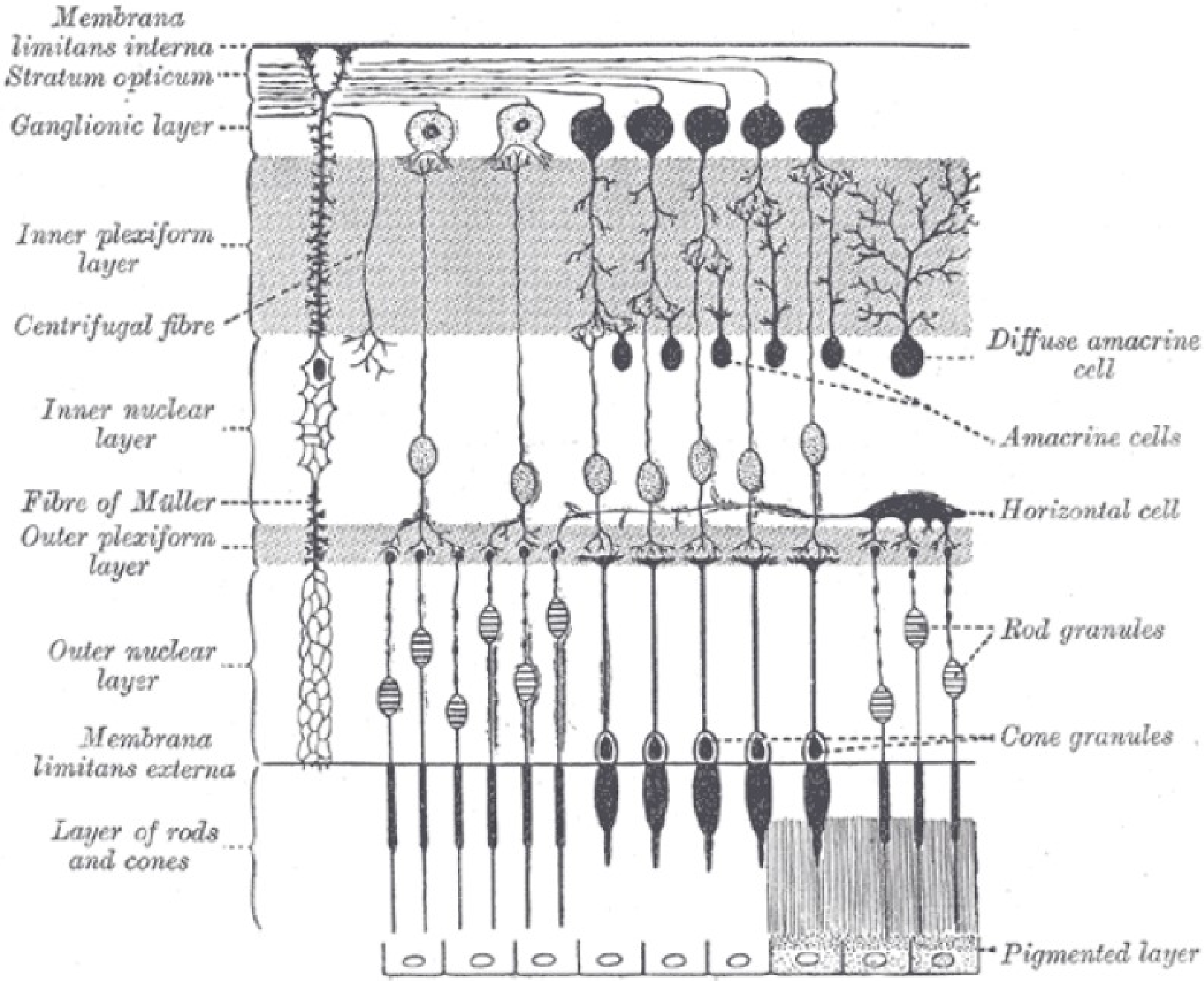
Horizontal cells

Bipolar cells

Mahowald, Proc. SPIE 1473 Visual Information Processing (1991)



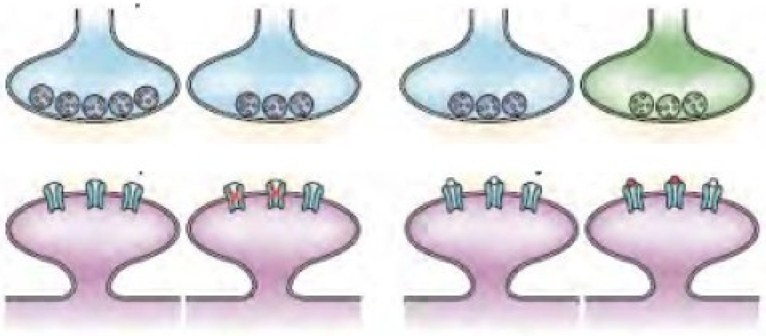
Biology of Preception. (2020).
https://med.libretexts.org/@go/page/12597



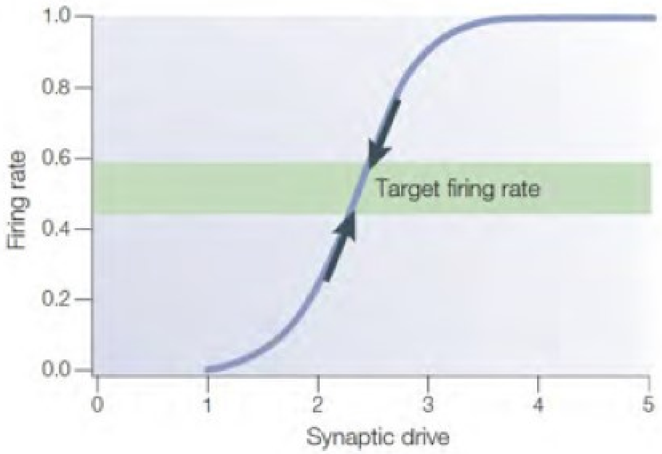
Gray, *Anatomy of the Human Body* (1918)

Synaptic plasticity: changes in strength over time

Short term plasticity



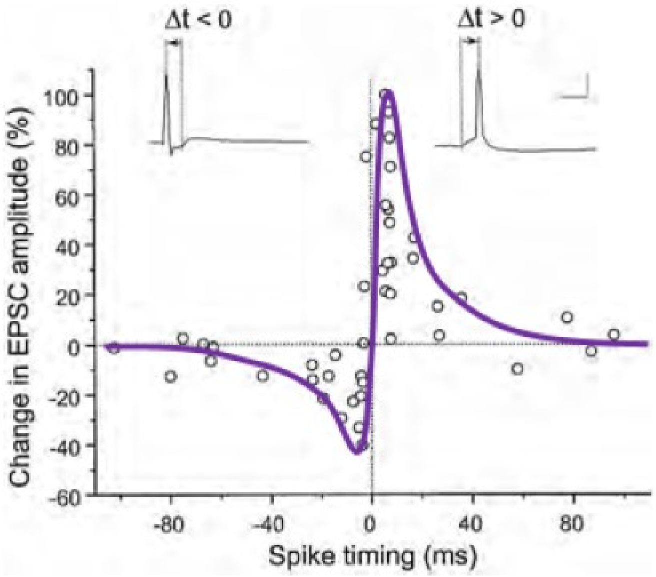
*Blitz et al. Nat Rev Neurosci **5**, 630–640 (2004)*



Turrigiano & Nelson, Nat Rev Neurosci. 5(2):97 (2004)

Homeostatic plasticity

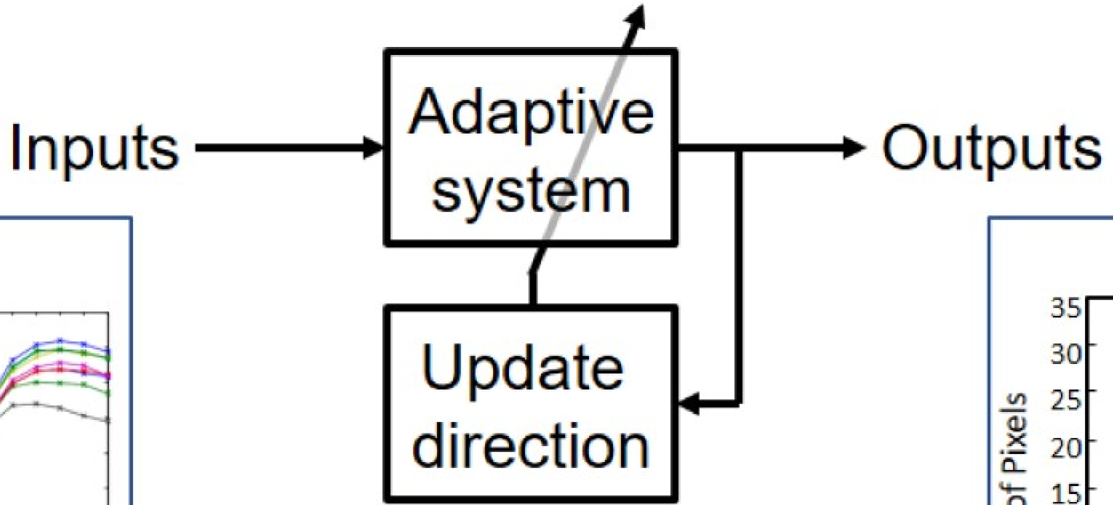
Long term plasticity



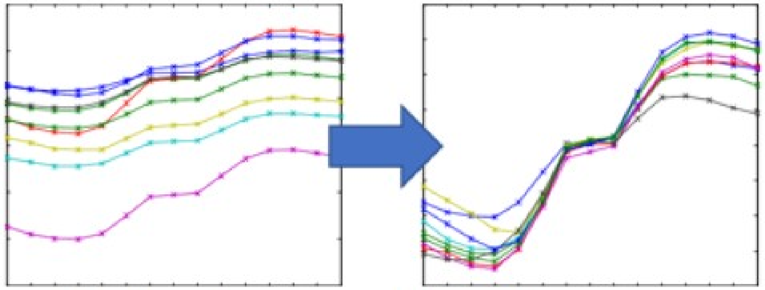
Bi & Poo, J Neurosci. 18(24):10464 (1998)

How can we learn to make better circuits?

- Engineering ***is*** efficient use of resources
- Conventional electronics: analog sensor readings converted to digital, then calibrated digitally
  - High price (size, complexity, power) for high precision
- Biology uses cheap, inaccurate components with adaptation (lots of it)
- SWaP matters!
  What if you could automatically "fix" analog computers?
- Integrated circuits with local storage and autonomous feedback to:
  - Cancel fabrication errors
  - Adjust to changing conditions / task demands

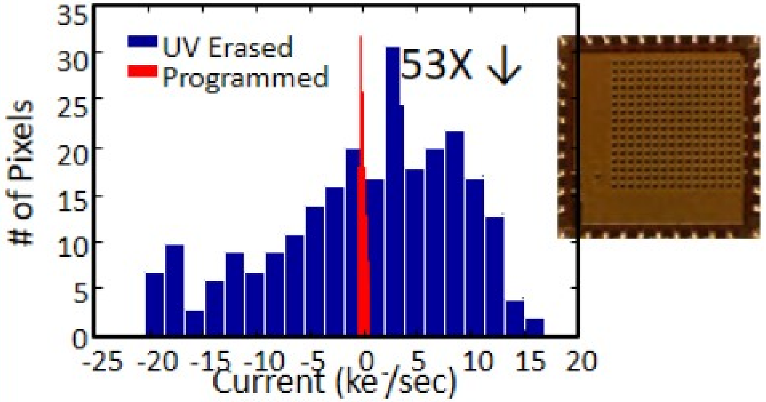


Dr. Peng Xu, now at TI



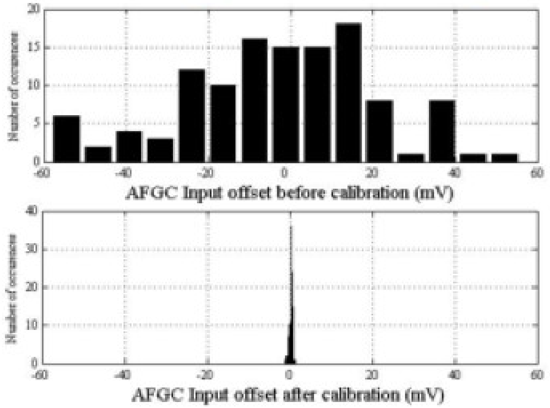
Motion imager w/ kernel programming & offset cancellation

Dr. David Sander, now at APL



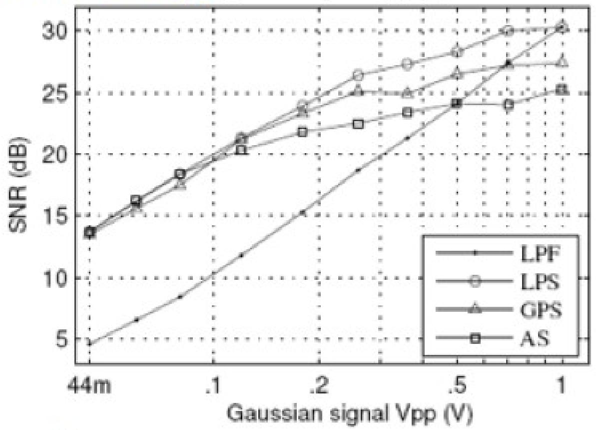
CTIA imager w/ offset cancellation

Dr. YanYi Wong, now at Virage Logic



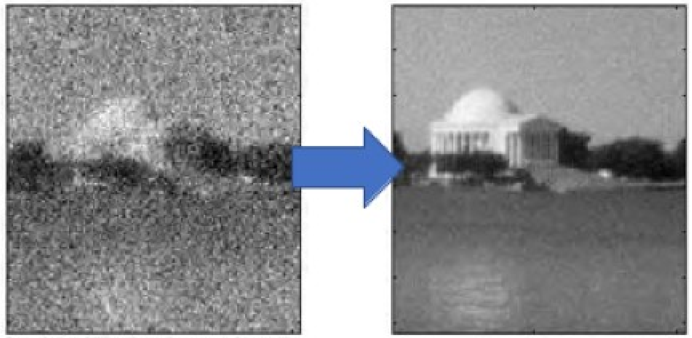
Comparator w/ offset cancellation

Dr. YanYi Wong



ADC w/ Online Histogram Equalization

Dr. YanYi Wong



Imager w/ offset cancellation

My “fearless” idea

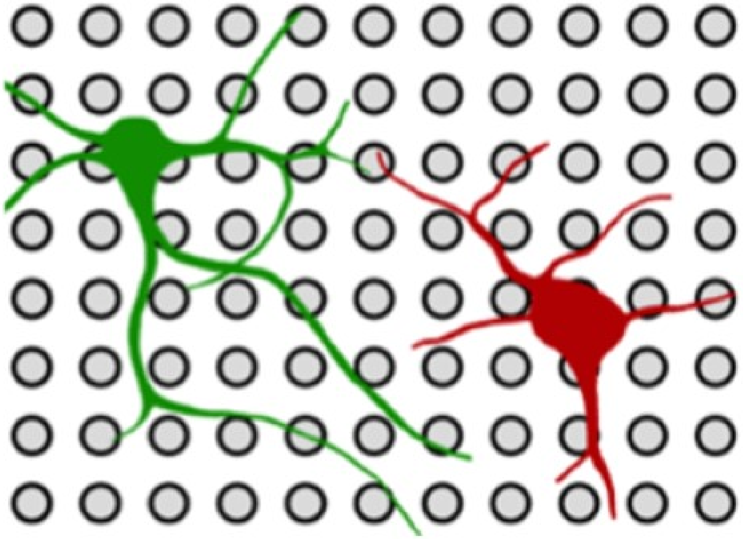
- Why can’t we do this for neurons too???

Opportunity for Technology Convergence

Let's use synaptic plasticity as an engineering tool!

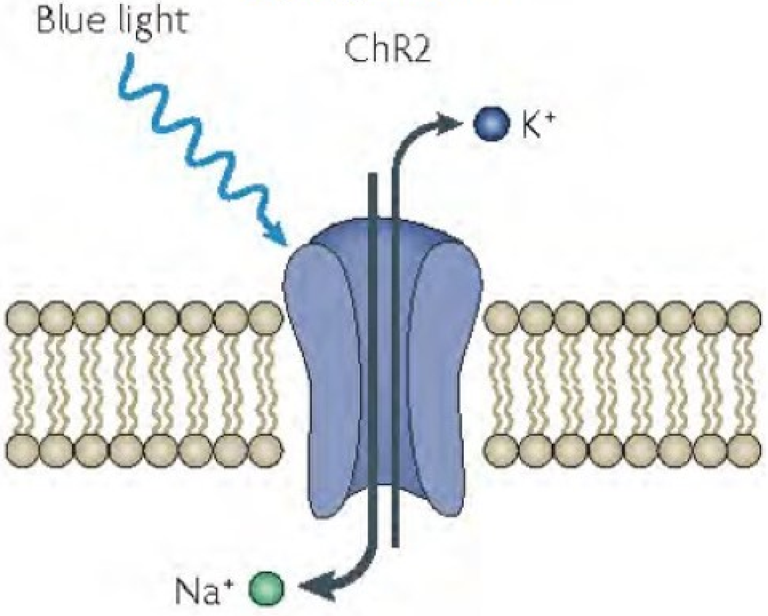
Technology elements demonstrated separately but not integrated:

High density microelectrode arrays



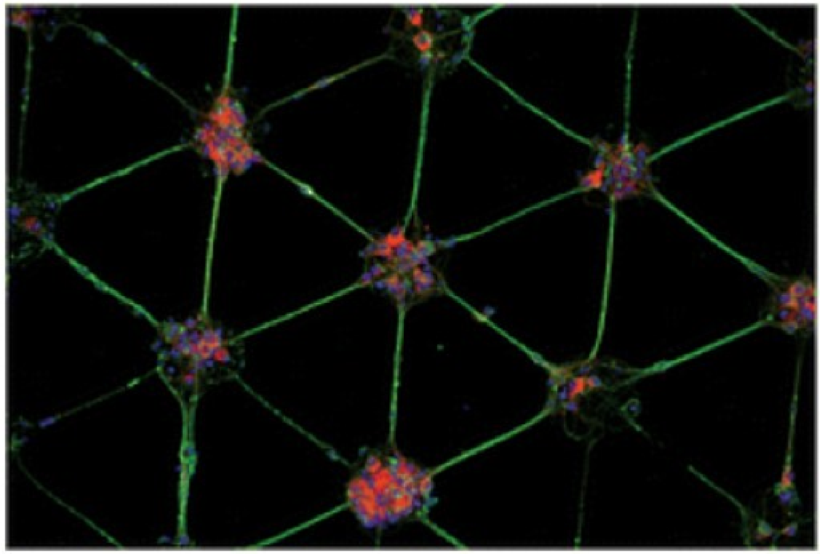
MaxWell Biosystems https://www.mxwbio.com/

Optogenetics



Zhang et al., Nat Rev Neurosci. 8(8): 577 (2007)

MEMS surface patterning

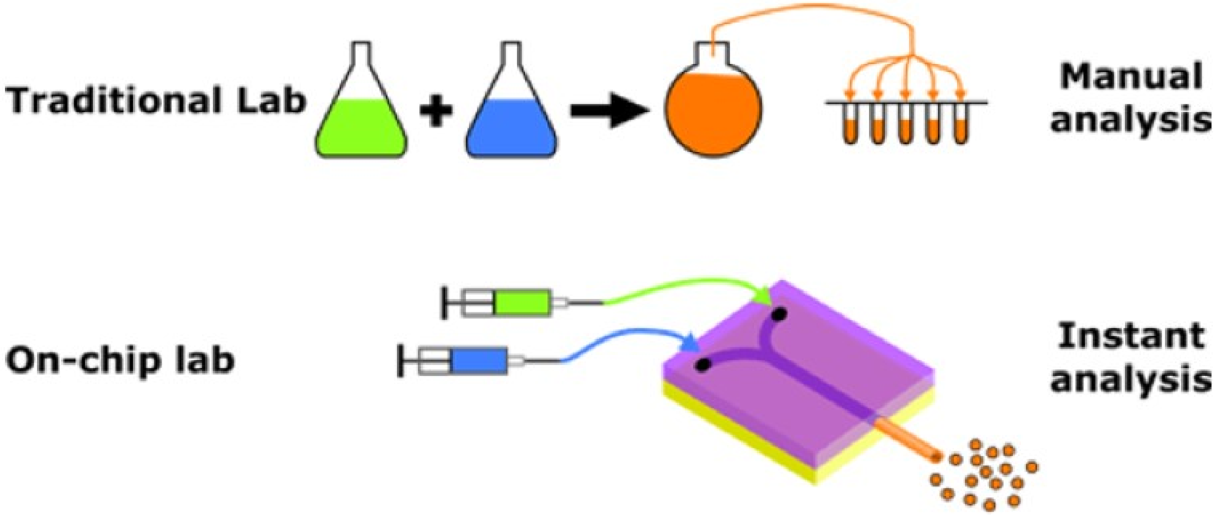


Neurons patterned w/ PolyLysine on PLL-g-PEG
Hardelauf et al. Analyst 139(13): 3256 (2014)

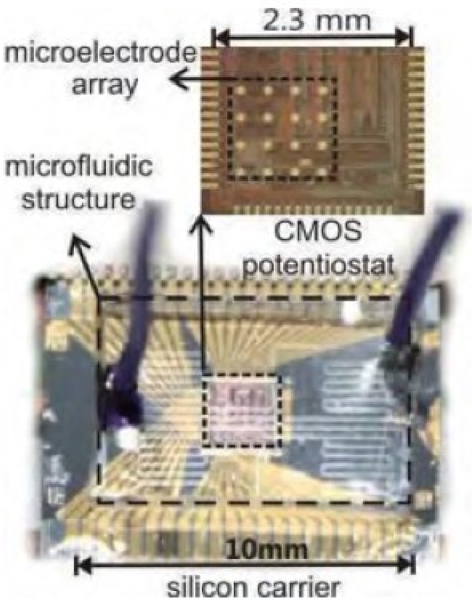
Lab-on-chip vs Lab-on-CMOS

- Integrate multiple laboratory functions onto a "chip"
- Miniaturization, speed, cost, automation

- Reality: Most LoCs are chips in labs
- Reality 2: Most LoCs are labs-on-slides
- Leverage Moore's law for biosensing!
- Significant integration challenges

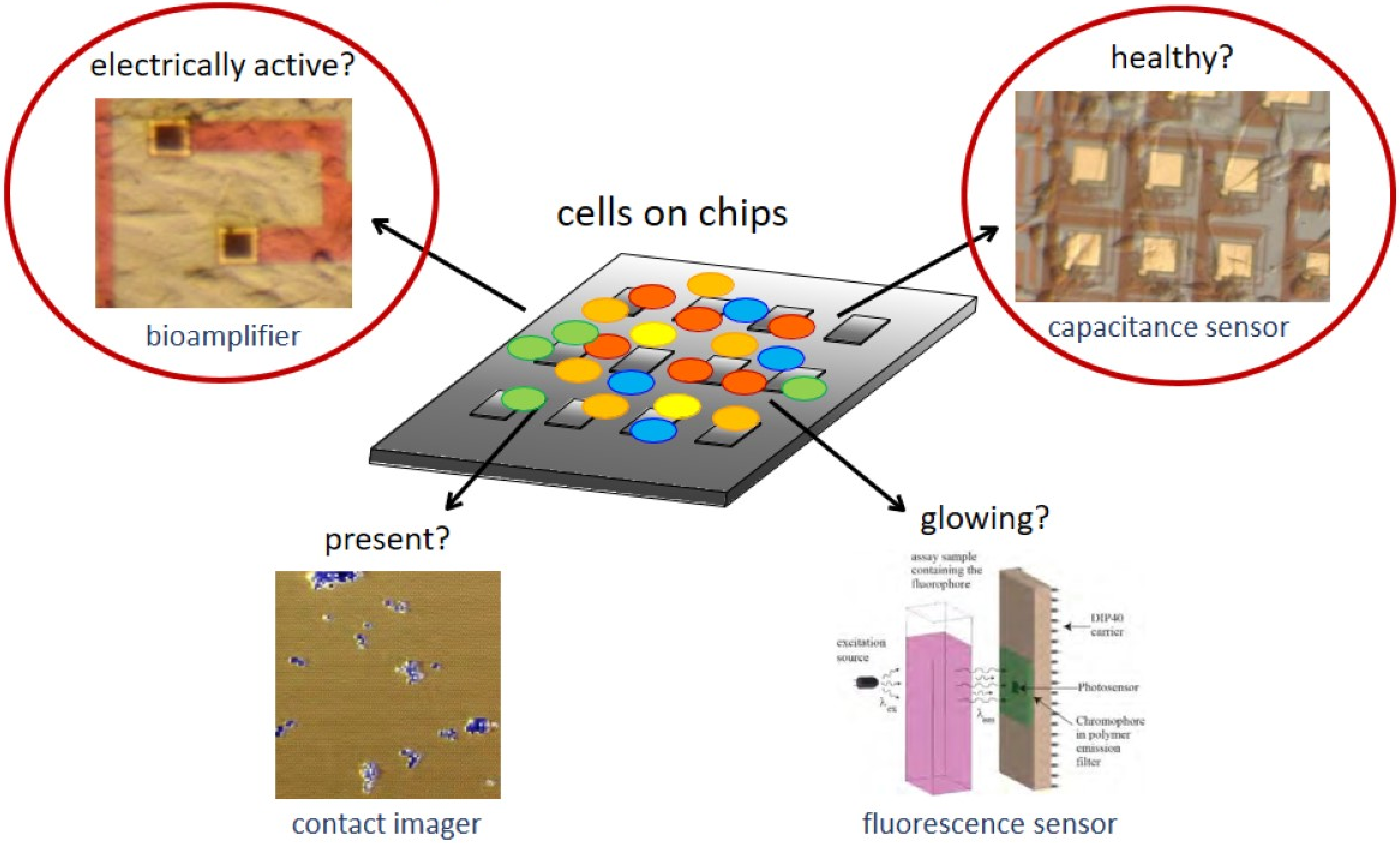


Redrawn from: Brivio, M., Verboom, W., & Reinhoudt, D. N. (2006). Miniaturized continuous flow reaction vessels: influence on chemical reactions. *Lab on a Chip*, 6, p. 329.

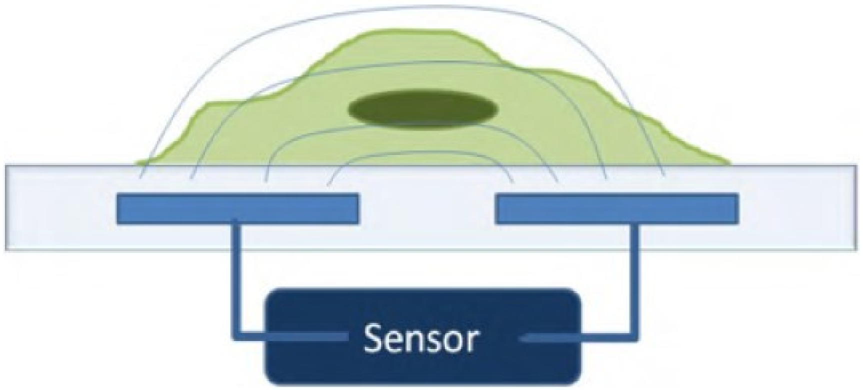


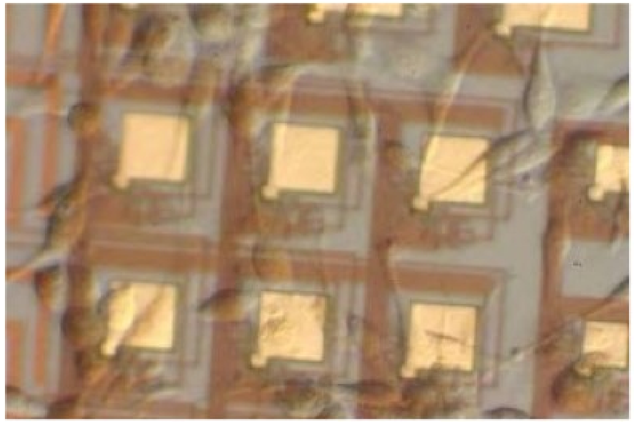
Huang & Mason, *6th IEEE Int'l Conf on Nano/Micro Engineered & Molecular Systems* (2011)

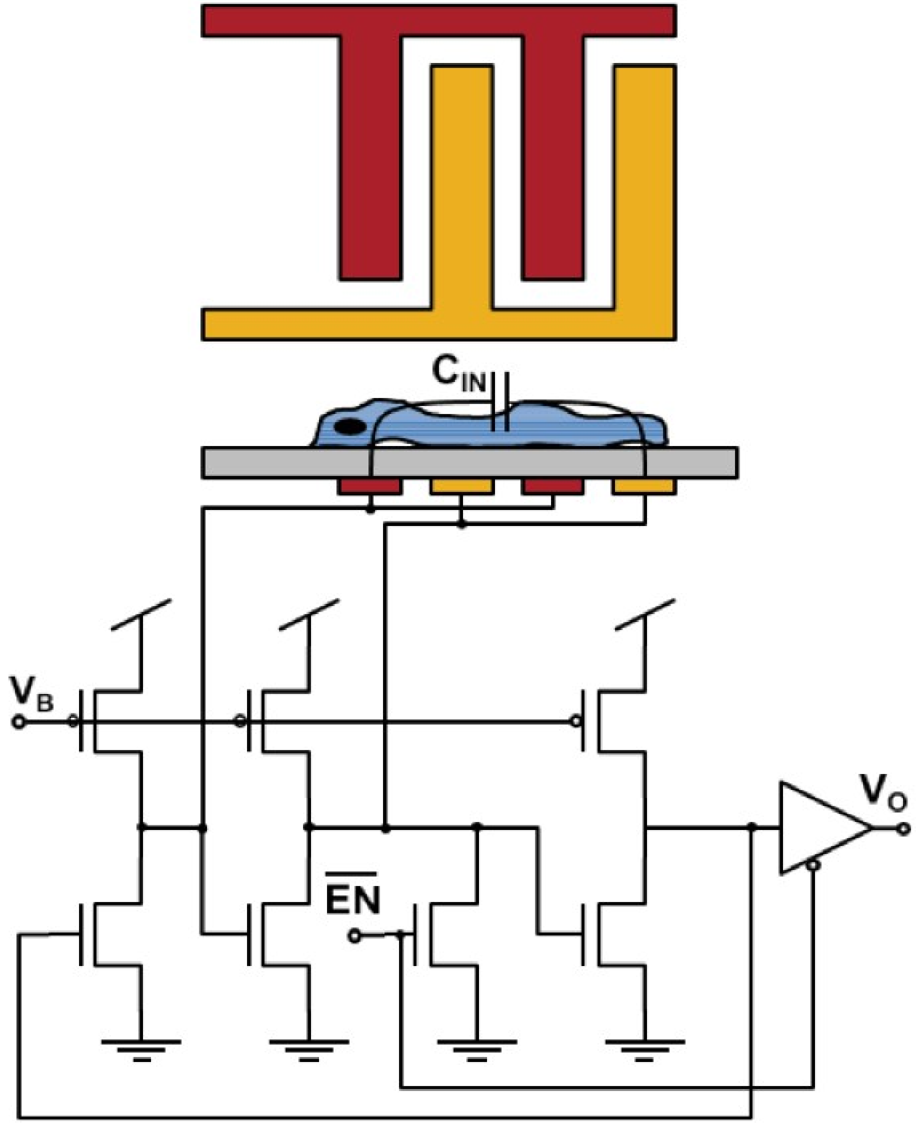
Lab-on-CMOS systems for monitoring cells



Cell capacitance sensor

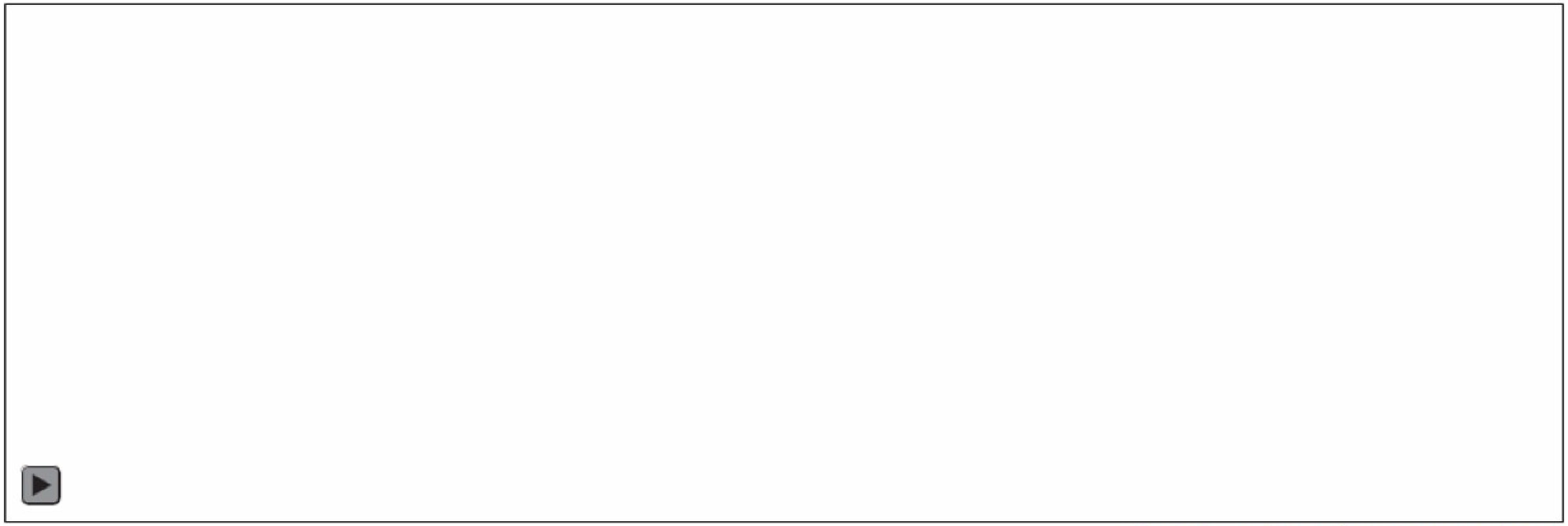



Heart cells on capacitance sensors



Dr. Somashekar Prakash, now at Intel
Dr. Timir Datta, now at Feinstein Institute for Medical Research
Ms. Emily Naviasky, now a PhD candidate at UC Berkeley

Simultaneous *in vitro* capacitance + microscopy



Dr. Marc Dandin, now at Carnegie Mellon
Dr. Bathiya Senevirathna, now at Intel
Mr. Sheung Lu, PhD candidate at UMCP

Open Access Dataset

"Measurements of cancer cell proliferation using a Lab-on-CMOS capacitance sensor with time-lapse imaging", IEEE Dataport, 2019. http://dx.doi.org/10.21227/9zzd-w936.

with Elisabeth Smela (UMCP) & John Basile (UMB)

What can we see?

Cell motility

Cell mitosis

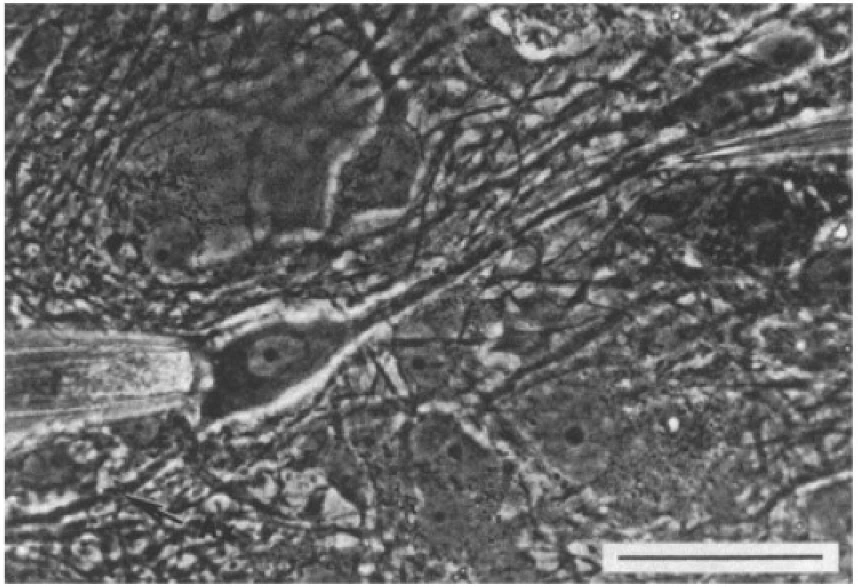
Cell death

Mr. Nathan Renegar, UMCP undergraduate
Mr. Utku Noyan, PhD candidate at UMCP

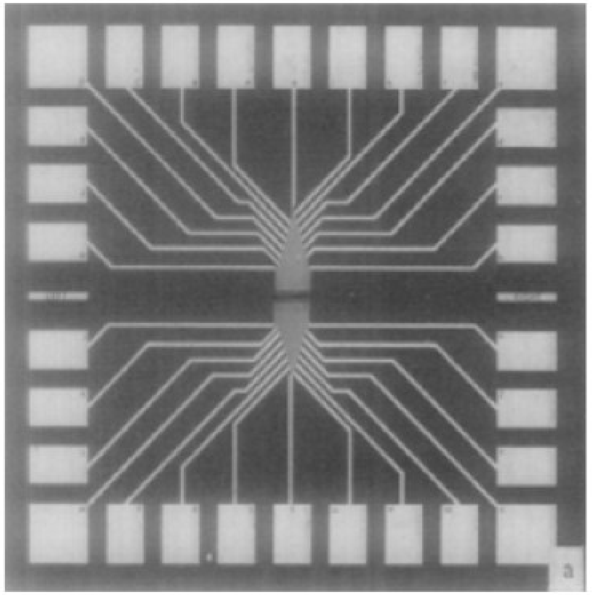
with Elisabeth Smela (UMCP) & John Basile (UMB)

Long history of neuronal culture & recording

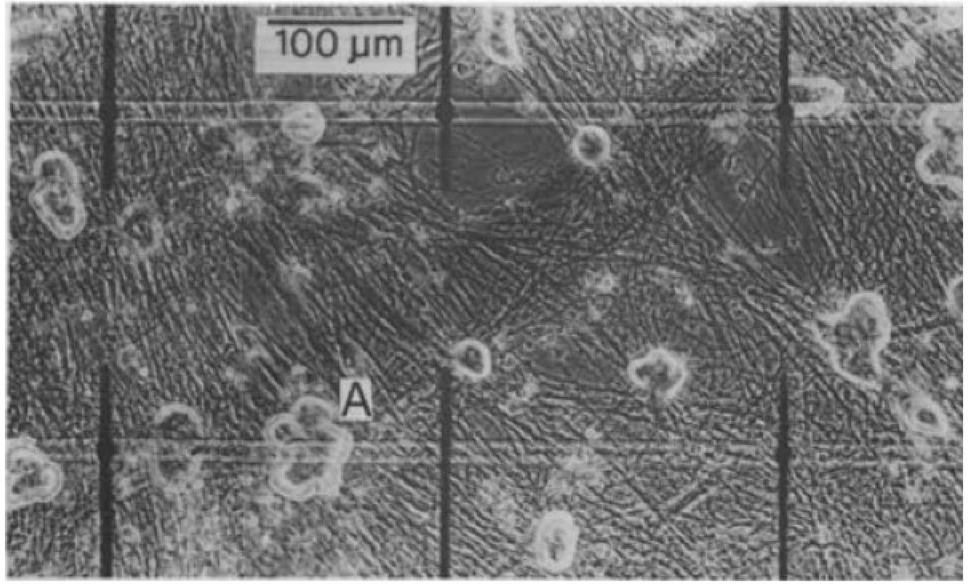
- 60 years … culturing neurons and glial cells on chips
- 40-50 years … microelectrode arrays (MEAs) for recording from neurons



Cerebellar neurons & glia,
Hild & Tasaki 1962



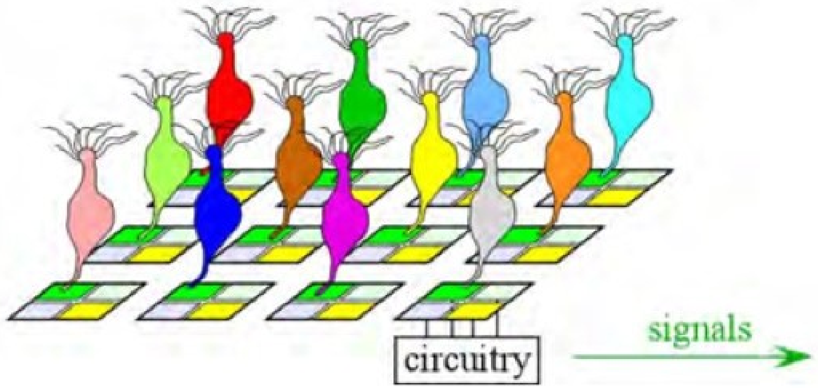
Microelectrode array recordings,
Thomas et al 1972



Microelectrode array recordings of
dissociated neurons, Pine 1980

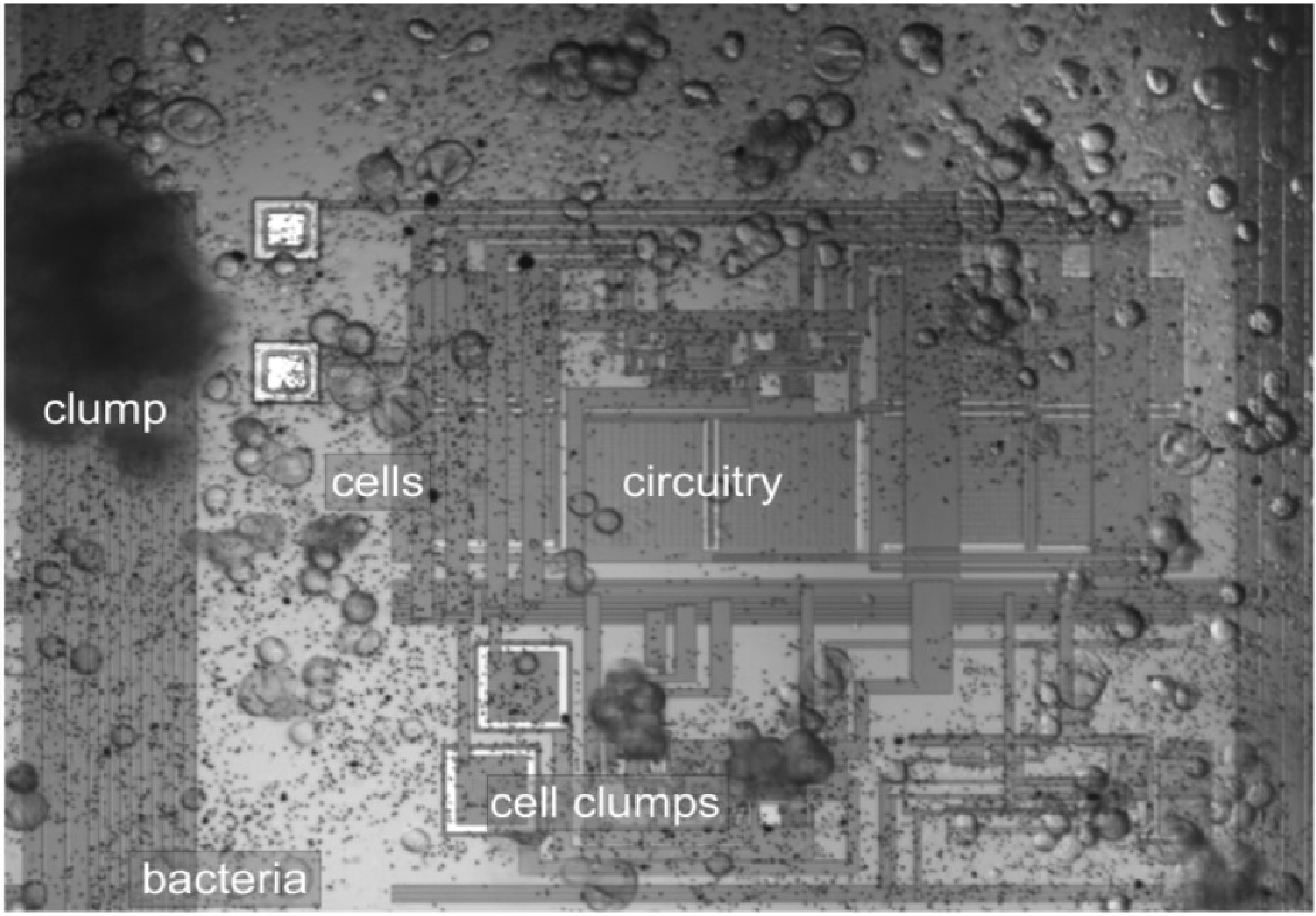
Nose on a chip

- Dogs are *still* the gold standard …
  - Expensive, troublesome
- Why not use the same sensors as dogs? (olfactory sensory neurons)



- Proof of concept ✓
- Currently working towards more robust cells

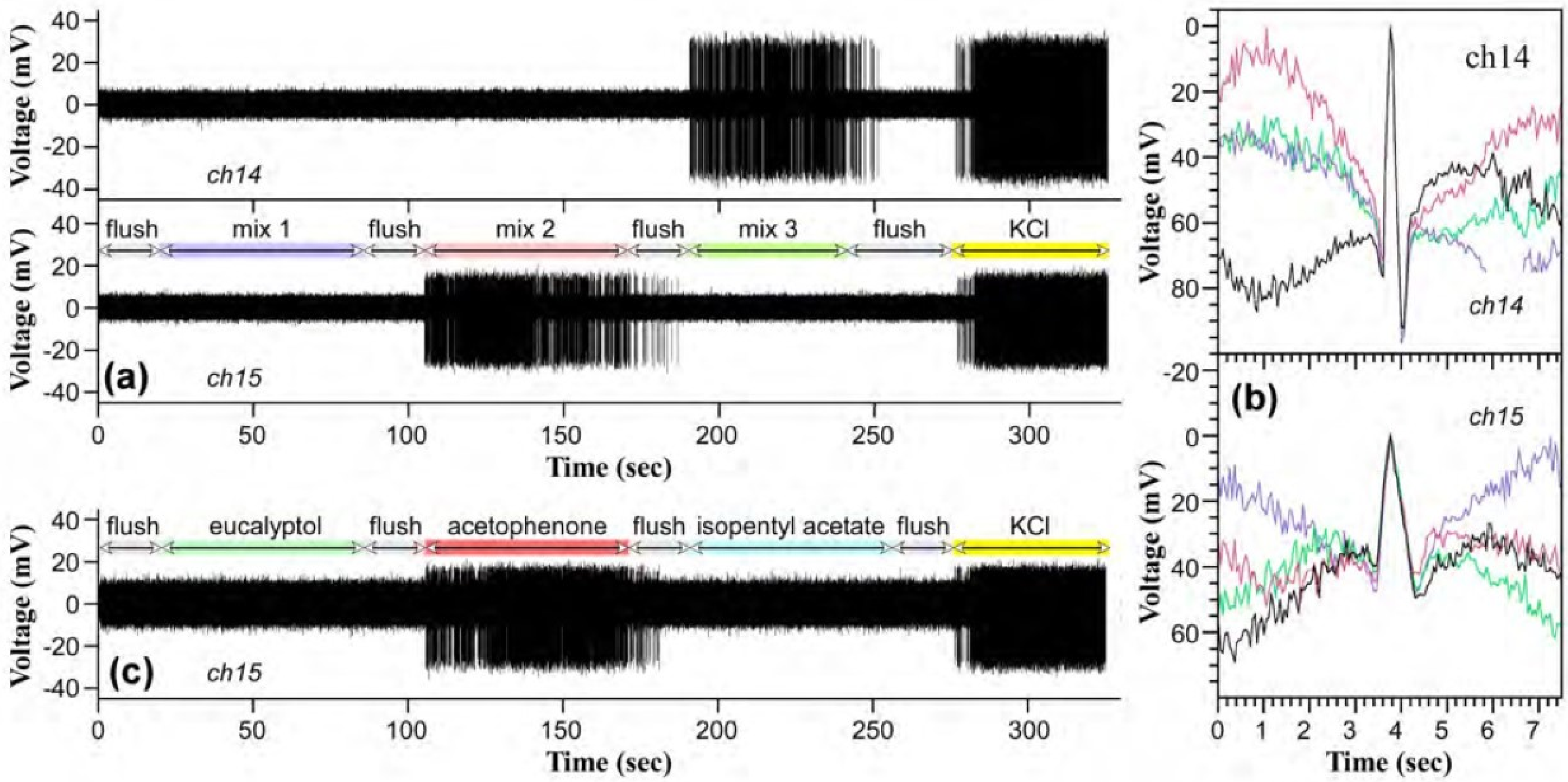
Dr. Timir Datta, now at Feinstein Institute for Medical Research



with Elisabeth Smela & Ricardo Araneda (UMCP)

Consistent, reproducible responses

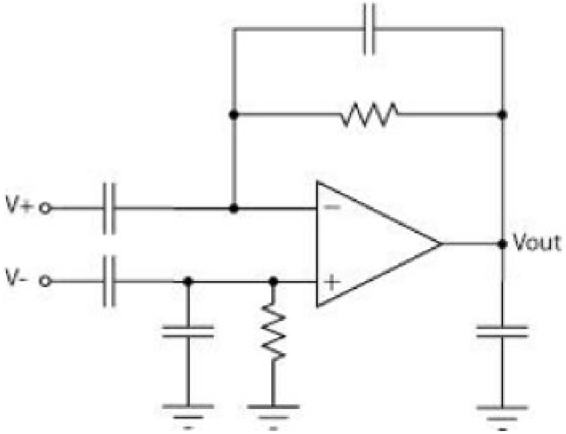
Dr. Timir Datta



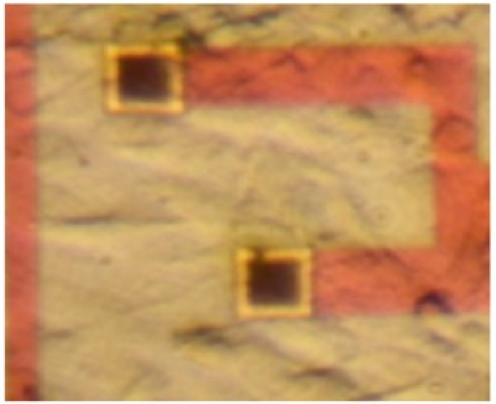
with Elisabeth Smela & Ricardo Araneda (UMCP)

Bioamplifier

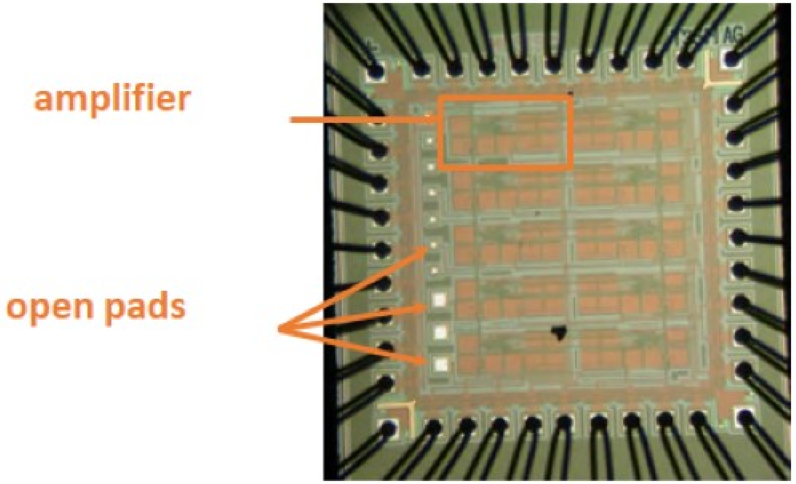
Dr. Jean-Marie Lauenstein, now at NASA Goddard
Dr. Nicole MacFarlane, now at Univ. of TN Knoxville
Dr. Somashekar Prakash, now at Intel

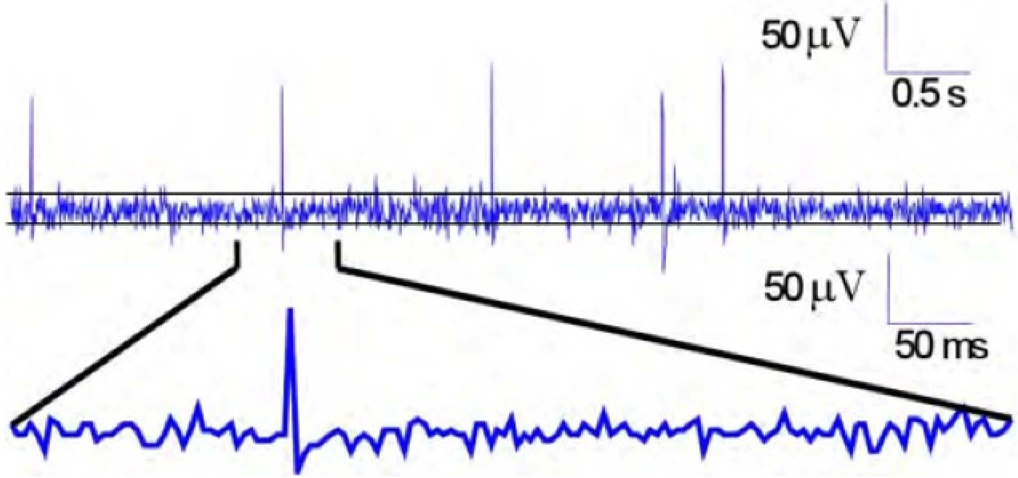


Harrison & Charles, IEEE JSSC 38: 958 (2003)

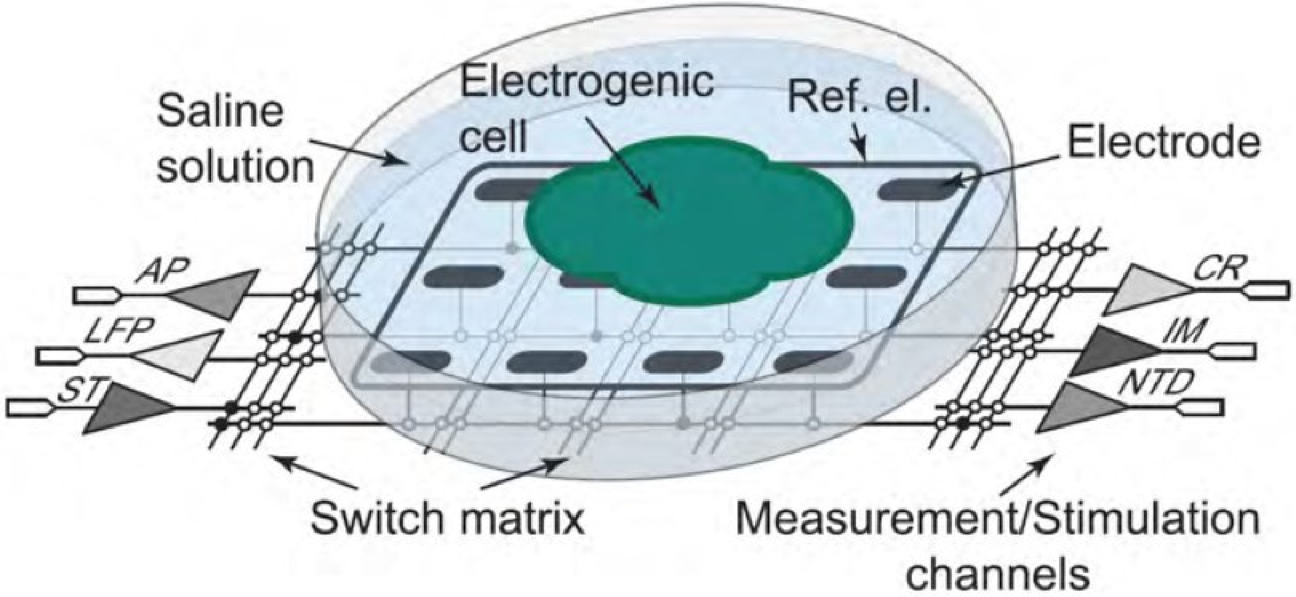


BAOSMC on electrodes

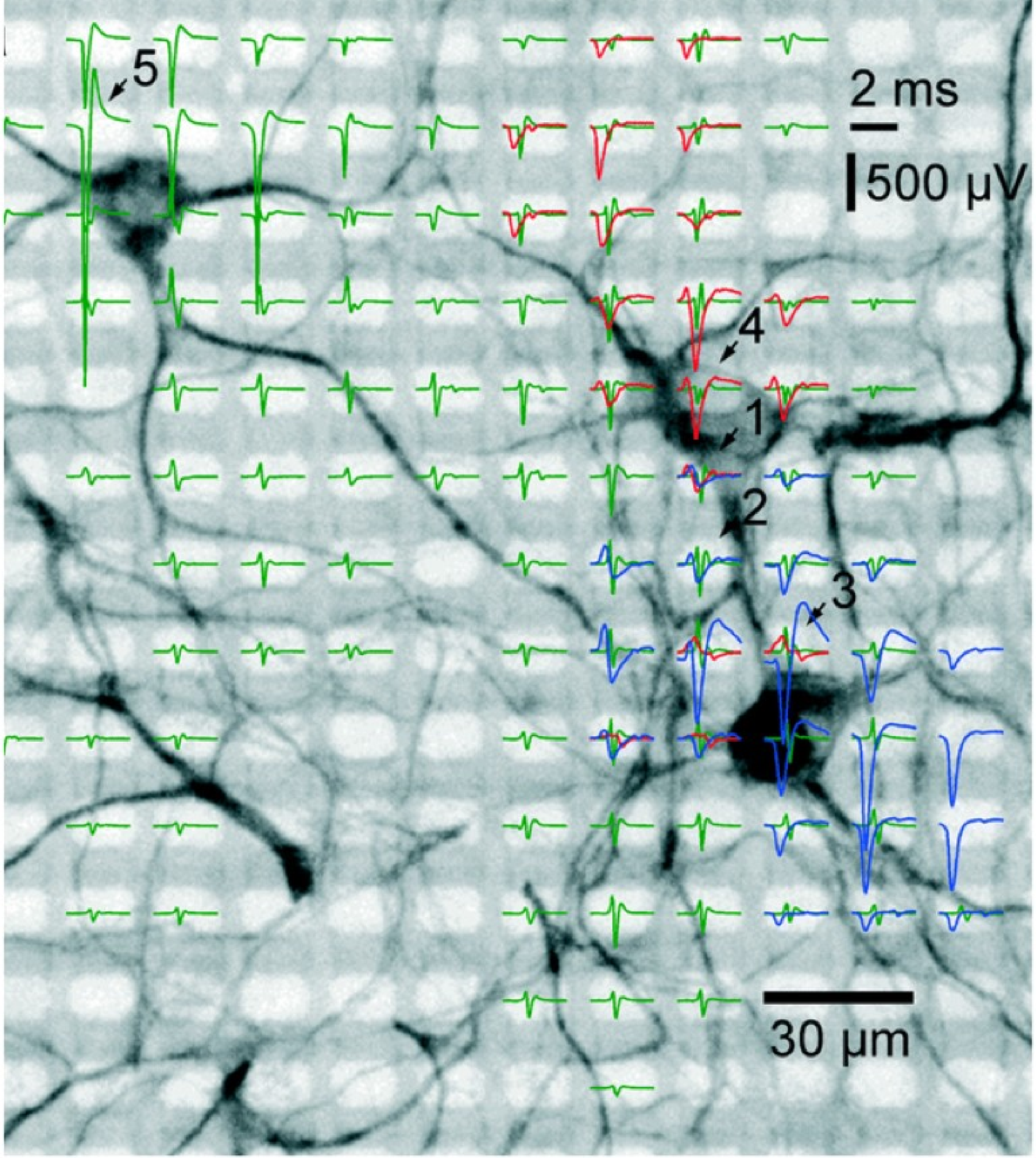




High density microelectrode arrays

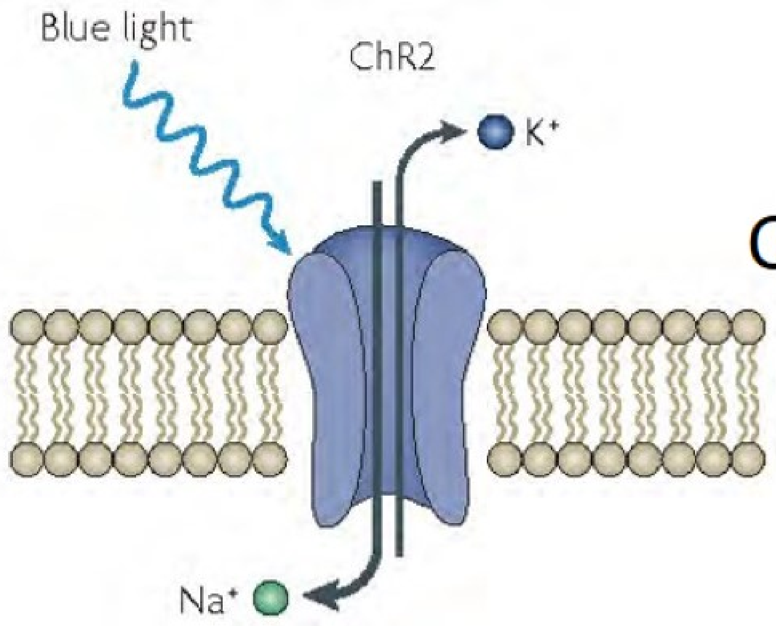


Dragas et al. IEEE J Solid-State Circuits 52(6): 1576 (2017)

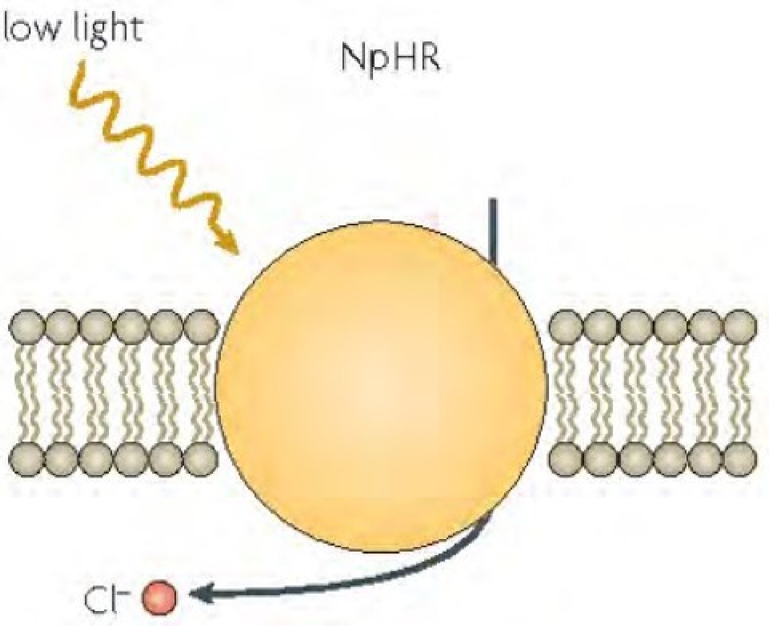


Müller et al. Lab Chip 15: 2767 (2015)

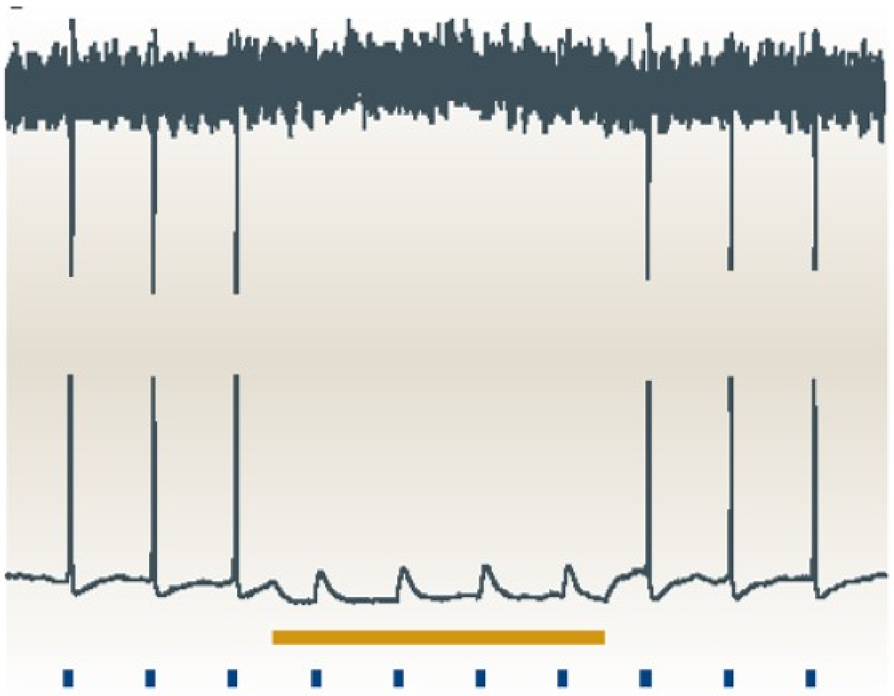
Optogenetics: optical stimulation



Channelrhodopsin-2 (ChR2)



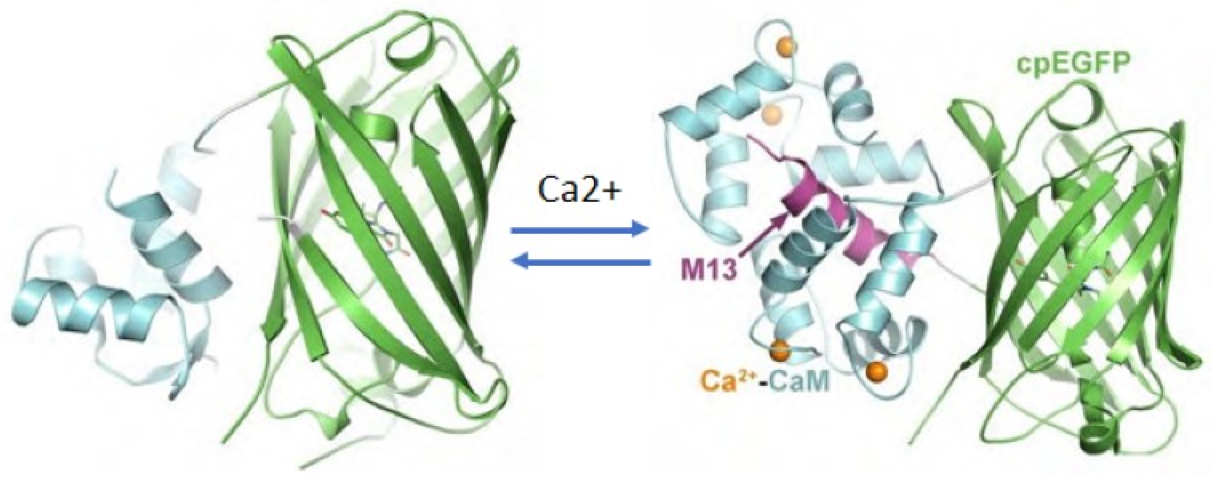
Halorhodopsin (NpHR)



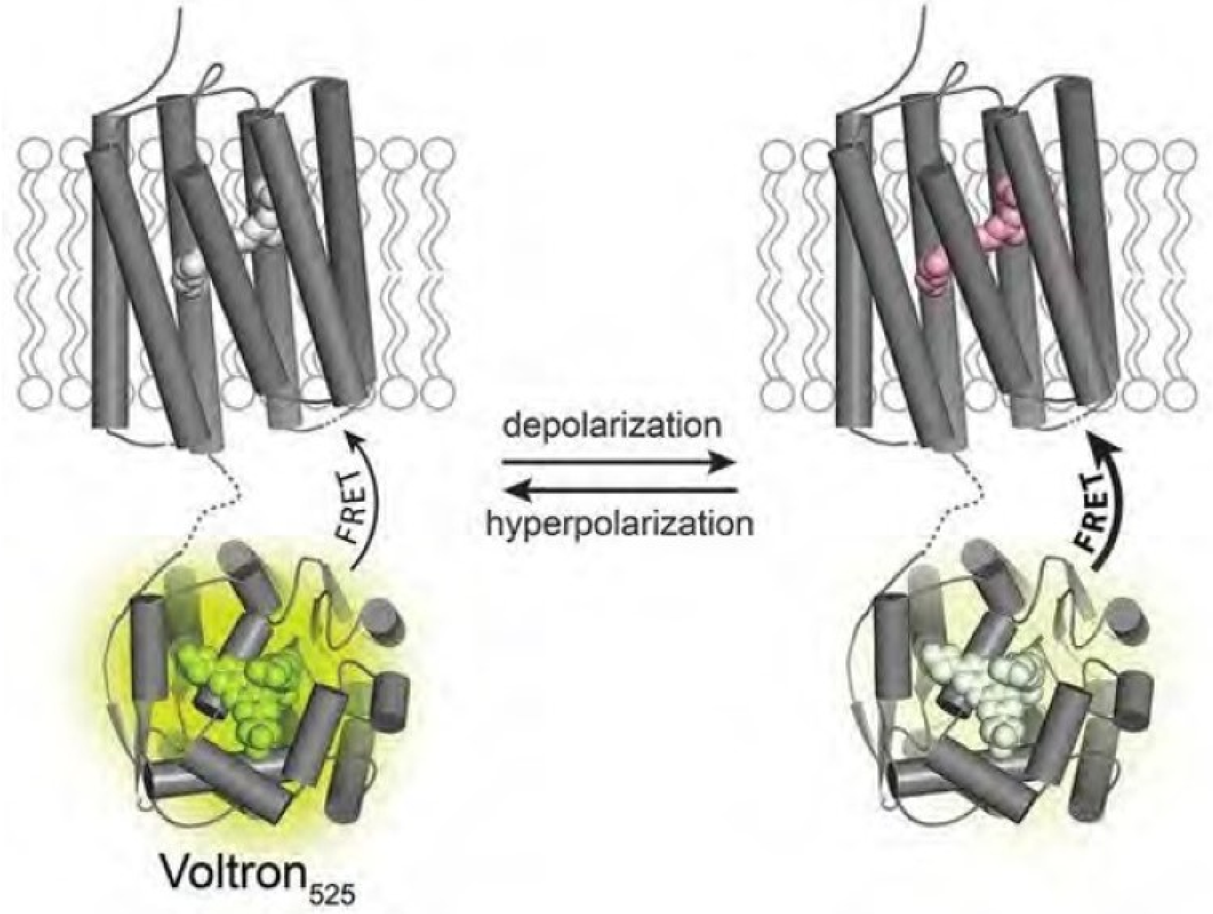
Blue light stimulates, yellow light suppresses

Zhang et al. Nat Rev Neurosci. 8(8): 577 (2007)

Genetically encoded calcium & voltage indicators: optical recording



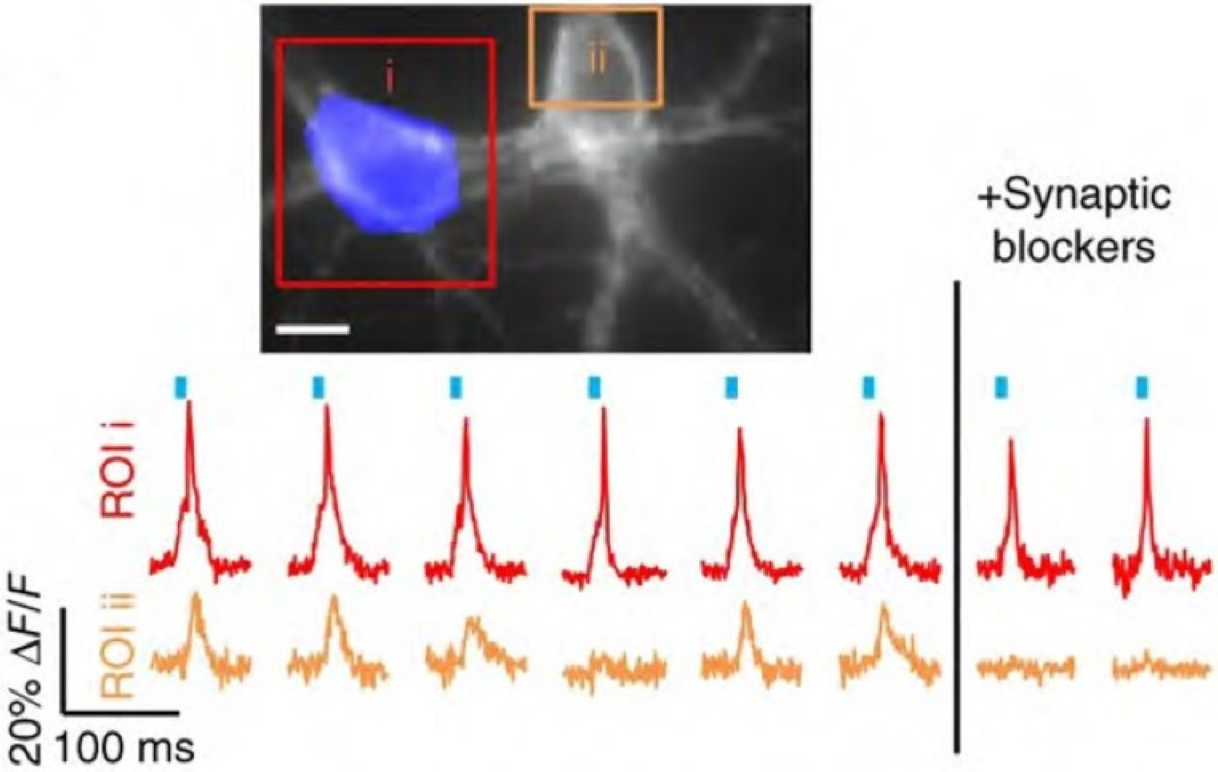
Akerboom, Rivera, Guilbe, Malavé, Hernandez, Tian, Hires, Marvin, Looger, Schreiter ER - http://www.jbc.org/content/284/10/6455/F1.large.jpg, https://commons.wikimedia.org/w/index.php?curid=15140508



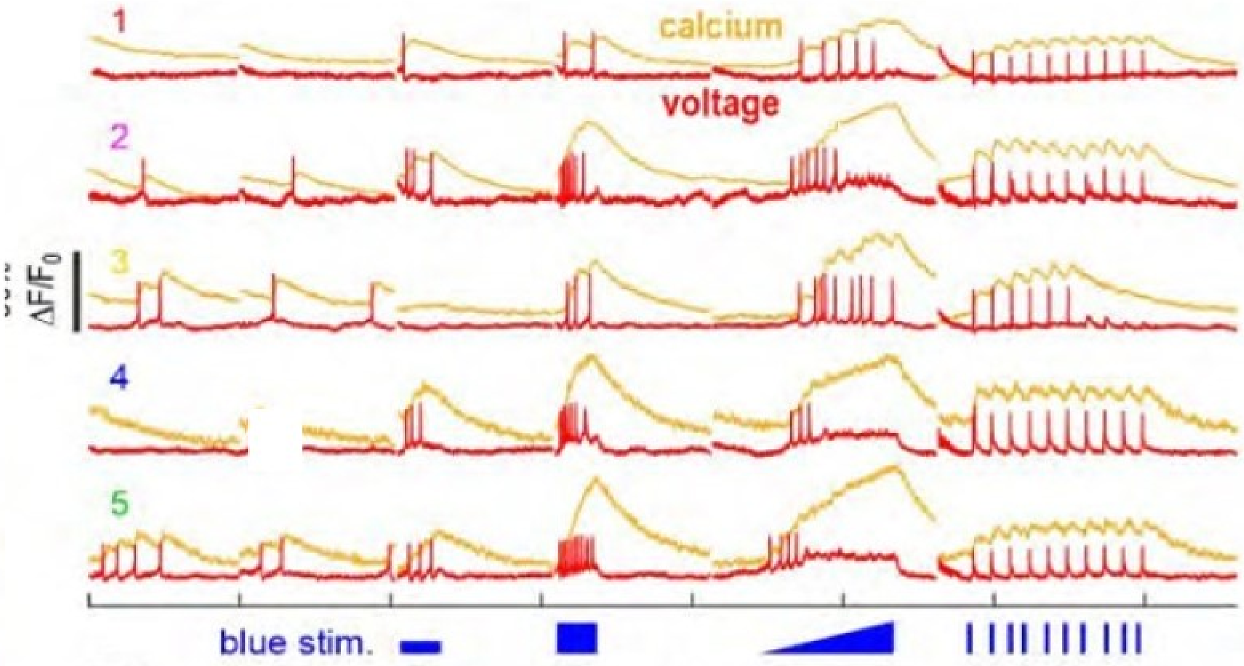
Abdelfattah et al., Science 364: 699 (2019)

All-optical electrophysiology

- Genetically encoded channels stimulate AND measure responses

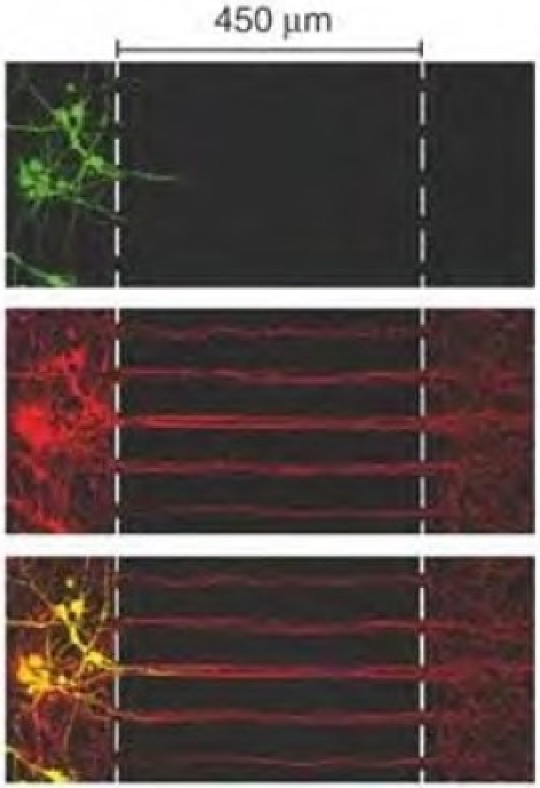


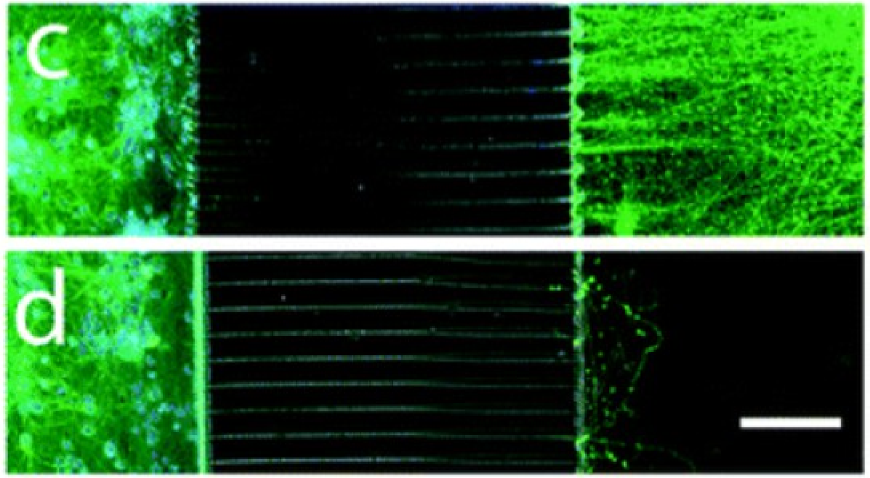
Synaptic transmission confirmed via optical stimulation (blue) & recording w/ & w/out synaptic blockers. *Hochbaum et al. Nat Methods. 11(8): 825 (2014)*

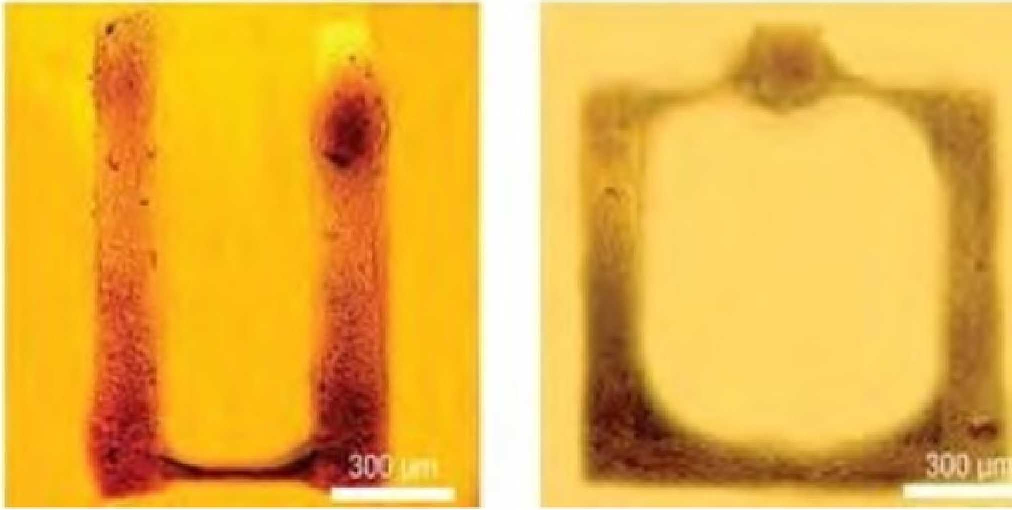


Synchronized voltage & calcium recordings.
Nguyen et al. Biomed Opt Express. 10(2): 789 (2019)

MEMS surface patterning for co-culture & topology





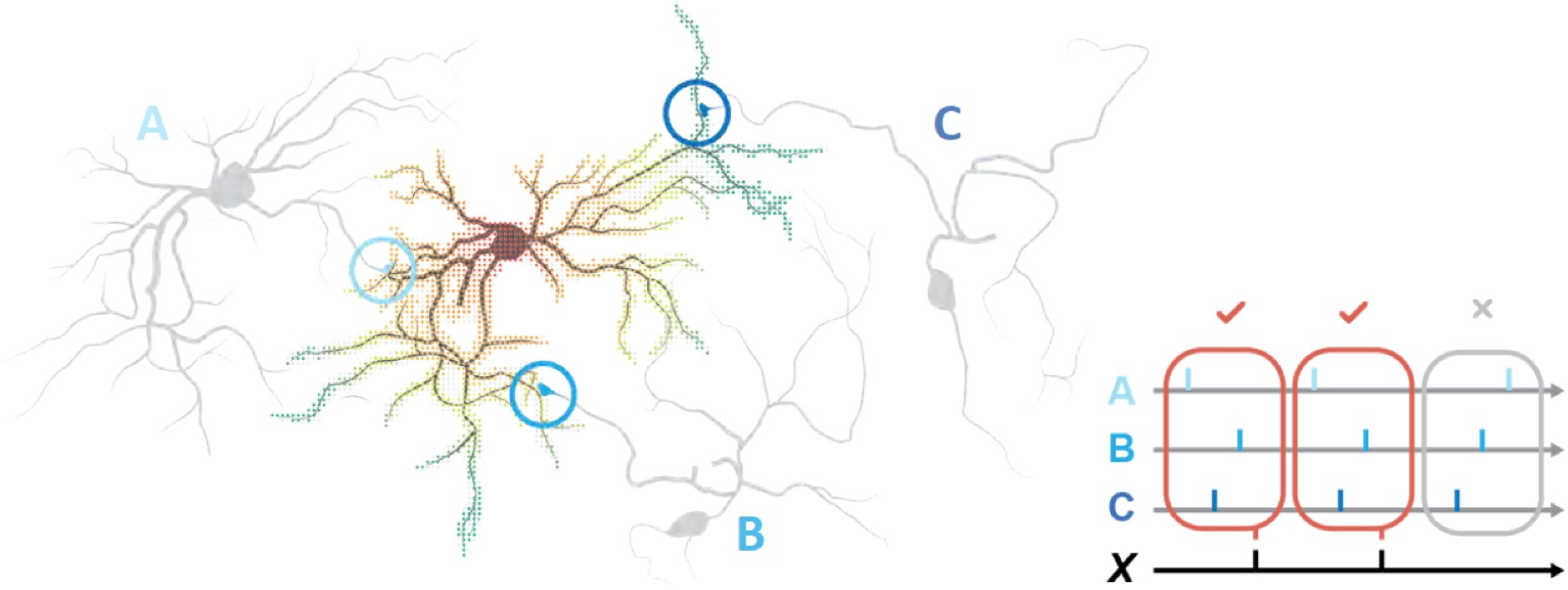


Only axons and not dendrites get through appropriately sized channels.
Taylor et al. Nat Methods 2(8): 599 (2005)

Tapered channels (15 um 3 um) produce directional axonal projections.
Peyrin et al. Lab Chip. 11(21): 3663 (2011)

Microfluidic devices for logic devices.
Feinerman et al. Nature Phys 4: 967 (2008)

Can we *program* a single neuron to respond selectively to one pattern out of many?



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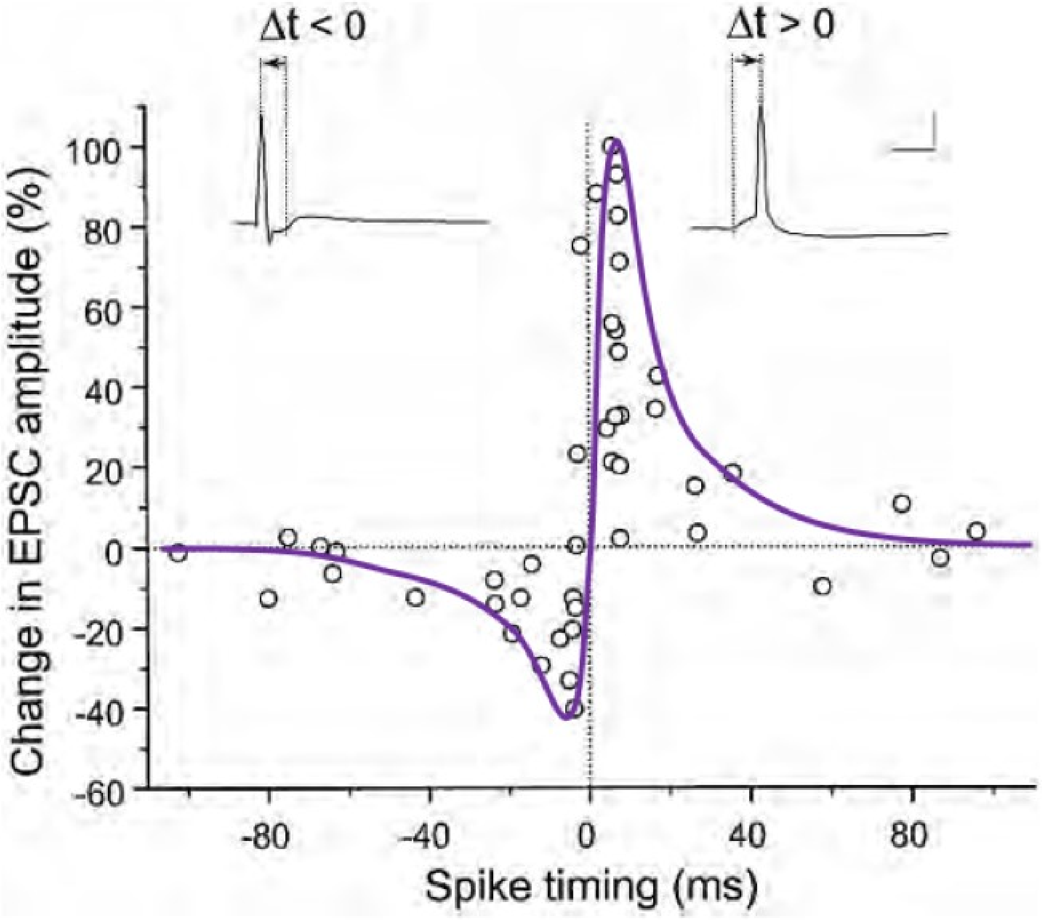
Synaptic plasticity depends on timing

- Depends on relative timing of pre- & post-synaptic spikes
- Interactions with other neurons may become complicated



Bi & Poo, J Neurosci. 18(24):10464 (1998)

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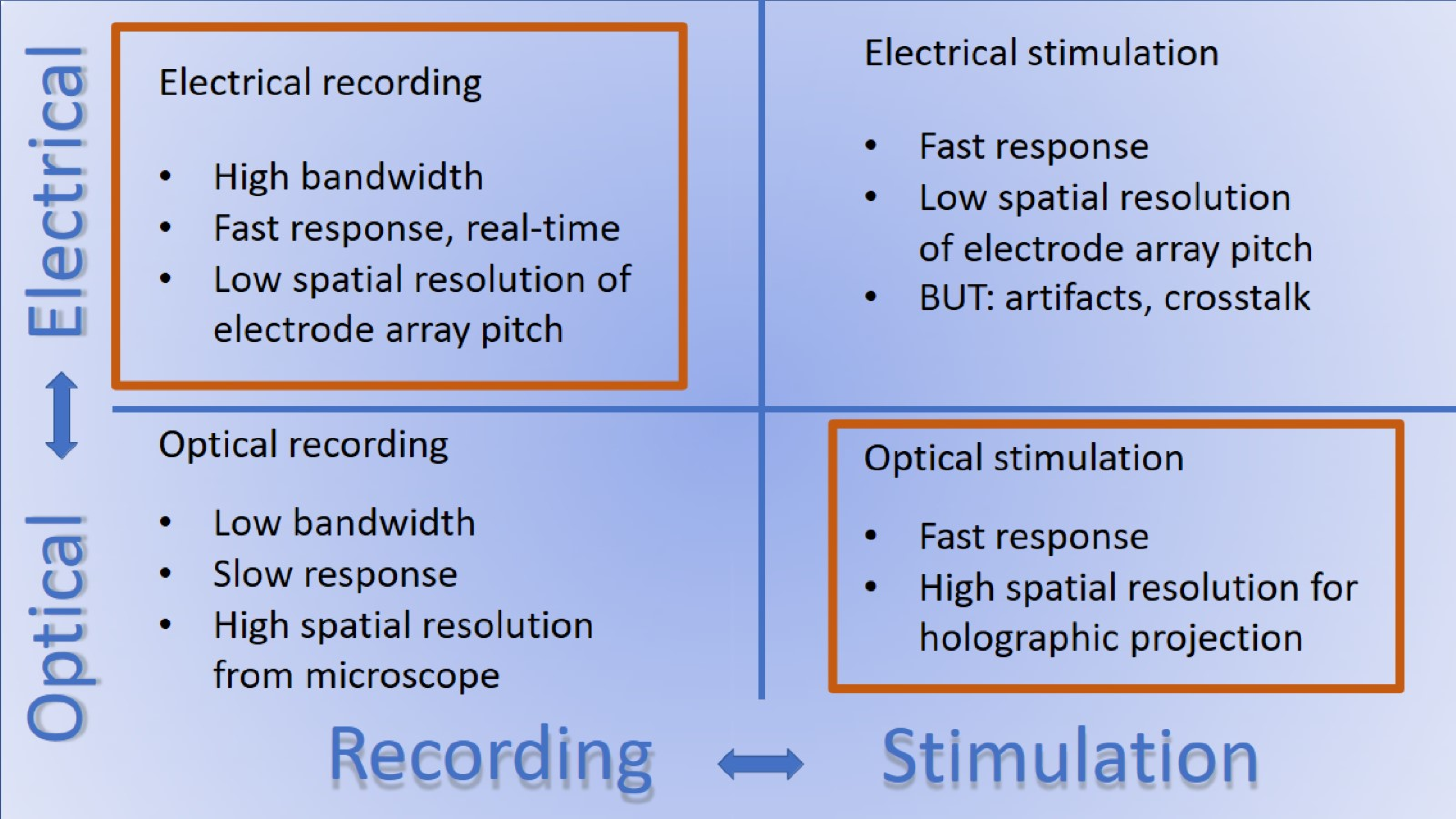
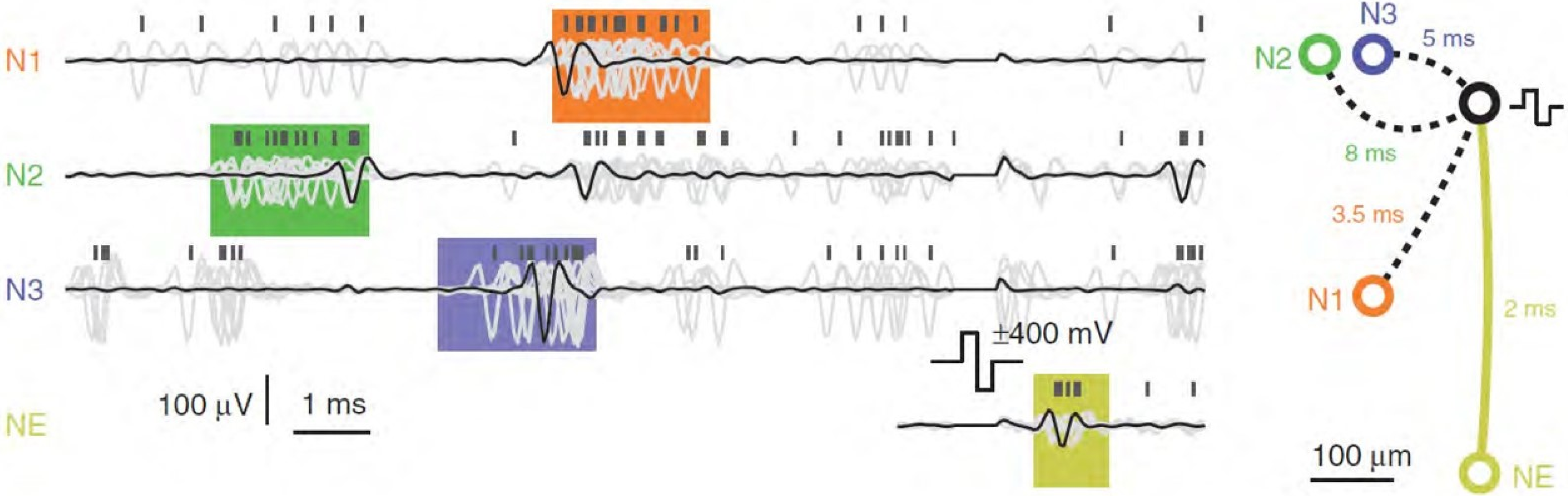

Electrical recording
• High bandwidth
• Fast response, real-time
• Low spatial resolution of electrode array pitch
Electrical stimulation
• Fast response
• Low spatial resolution of electrode array pitch
• BUT: artifacts, crosstalk
Optical recording
• Low bandwidth
• Slow response
• High spatial resolution from microscope
Optical stimulation
• Fast response
• High spatial resolution for holographic projection
Electrical
Optical
Recording
Stimulation

Spatiotemporal pattern detection

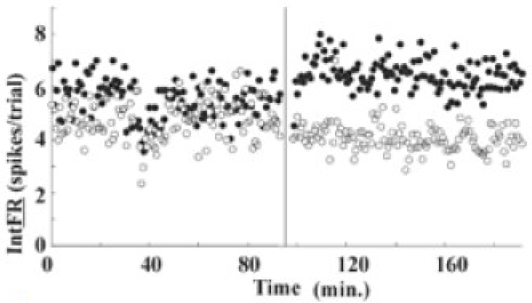


- Feedback stimulation after detected activity pattern

Müller et al. Front Neural Circuits 6: 121 (2013)

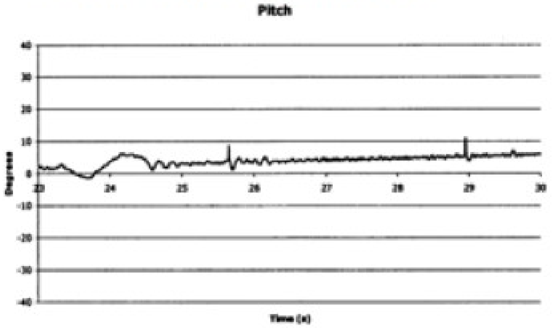
What capabilities have been shown?

- Simple pattern classification & training

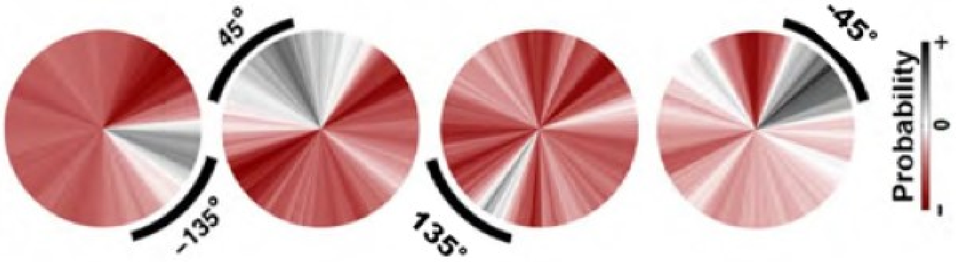


Firing rate after 2 tetanic stimulation patterns
Ruaro et al IEEE Trans Biomed Eng. 52(3): 371 (2005)

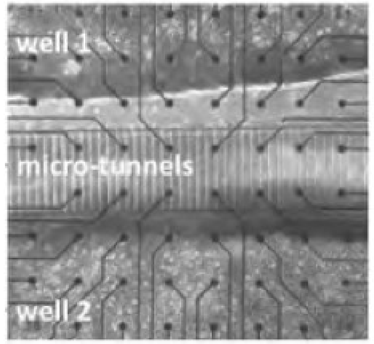
Error in aircraft pitch control, *DeMarse & Dockendorf, IEEE IJCNN, 2005*



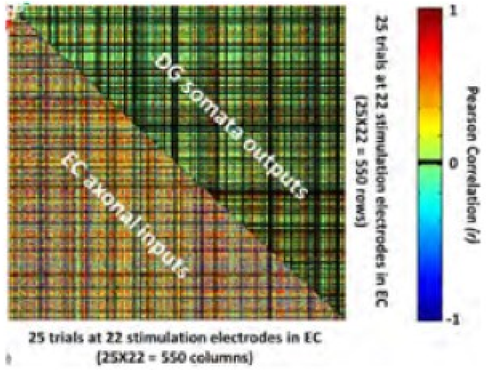
- Model-free closed loop "black box" training
  - Neural culture activity trained to persist in specific quadrant



Bakkum et al., J Neural Eng. 5(3): 310 (2008)



- Pattern separation and completion in hippocampal cultures
  - Pairwise interactions btw hippocampal subregions
  - Pattern separation vs completion are enhanced for specific pairs



Poli et al., J Neural Eng. 15(4): 046009 (2018)

A Tale of Persistence

1. *Wet Computers Based on Trainable Neural Cultures*, NSF Semiconductor Synthetic Biology for Information Processing and Storage Technologies, October 2017, declined
2. *Wetware Computers*, BBI Seed Grant Proposal, Feb 2018, declined
3. *Wetware Computers Based on Patterned Neural Cultures*, NSF Integrative Strategies for Understanding Neural and Cognitive Systems, April 2018, declined
4. *ENS Neural Interface*, BBI Seed Grant Proposal, April 2019, declined
5. *Harnessing Synaptic Plasticity in Living Neuronal Networks*, NSF Science of Learning, July 2020, declined

Shift from technology development to science

6. *Computer in a Petri Dish*, Keck Foundation, April 2021, declined
7. *Learning the Rules of Neuronal Learning*, NSF Understanding the Rules of Life, May 2021

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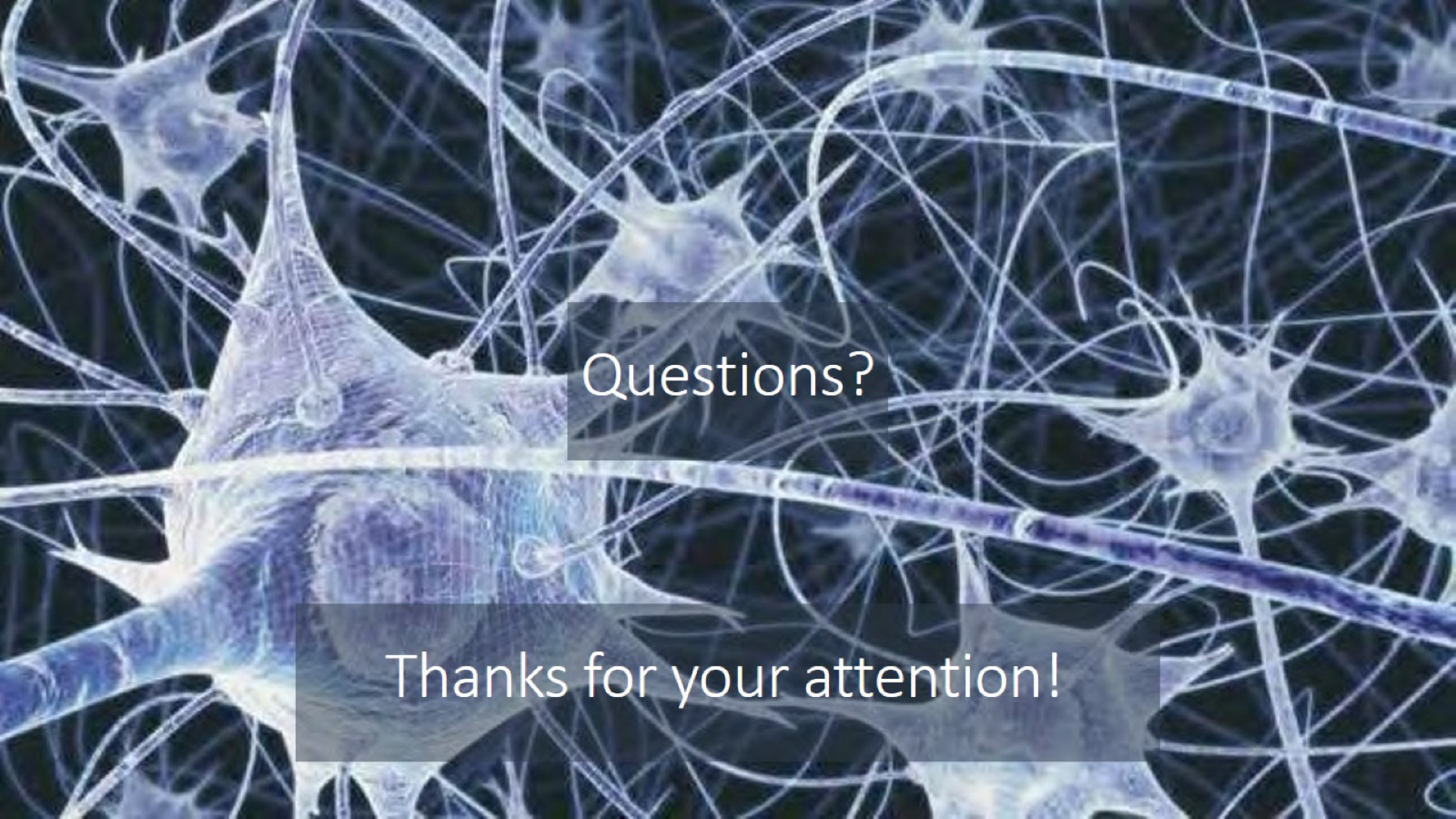
Questions?
Thanks for your attention!