Advanced Optical Microscopes and their Applications to Neuroscience

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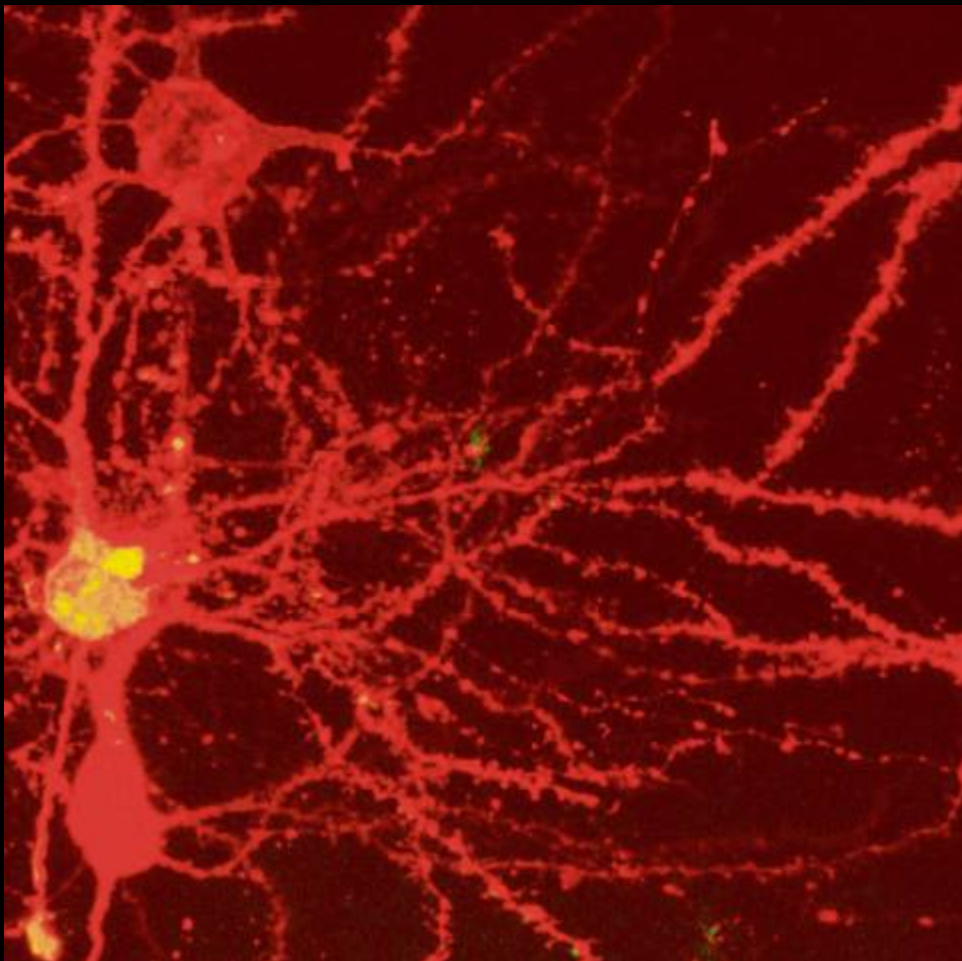
Outline

- Introduction
  - Observations of Nature
  - Principle of Microscopes (Laurent Bentolila)
- Advanced Microscopes
  - Super resolution (Laurent Bentolila)
  - High-speed
- Applications to Neuroscience
  - High-speed motion and action potentials
  - Neural networks
- Future directions
  - Voltage sensing dyes
  - Optical Excitation

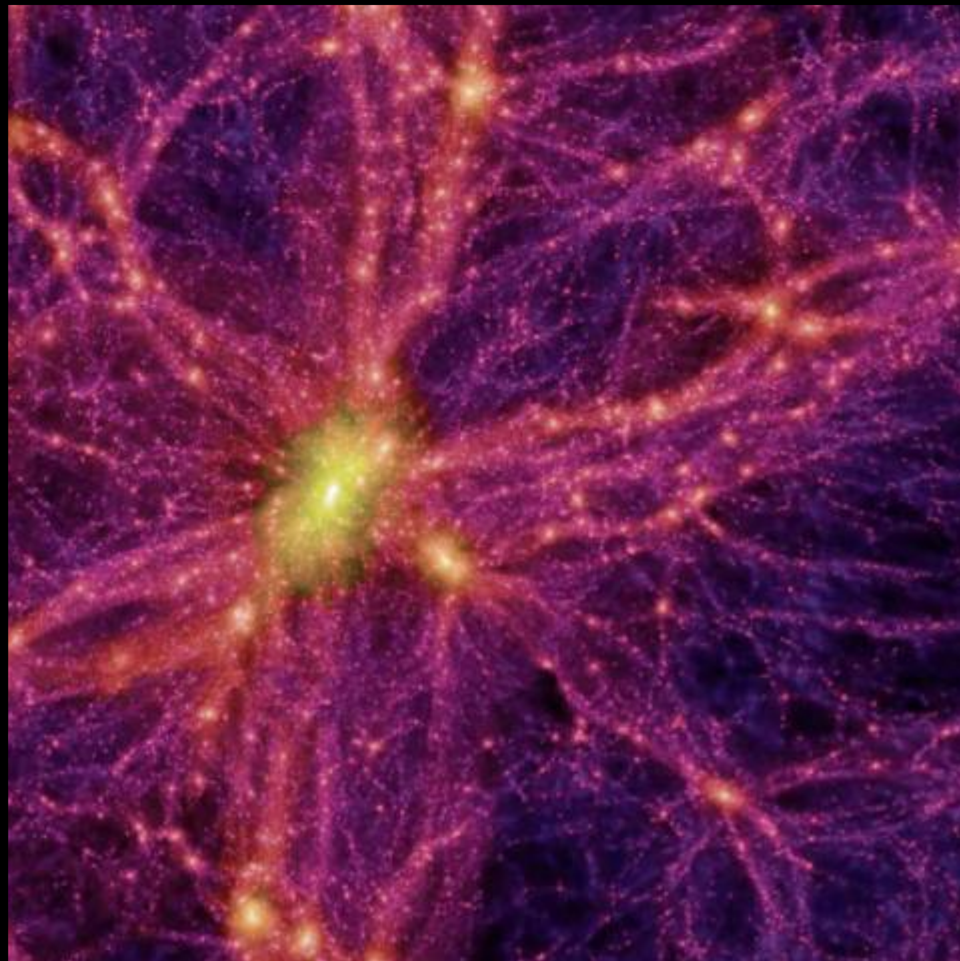
Introduction

Brain



100 Billions Neurons

Universe

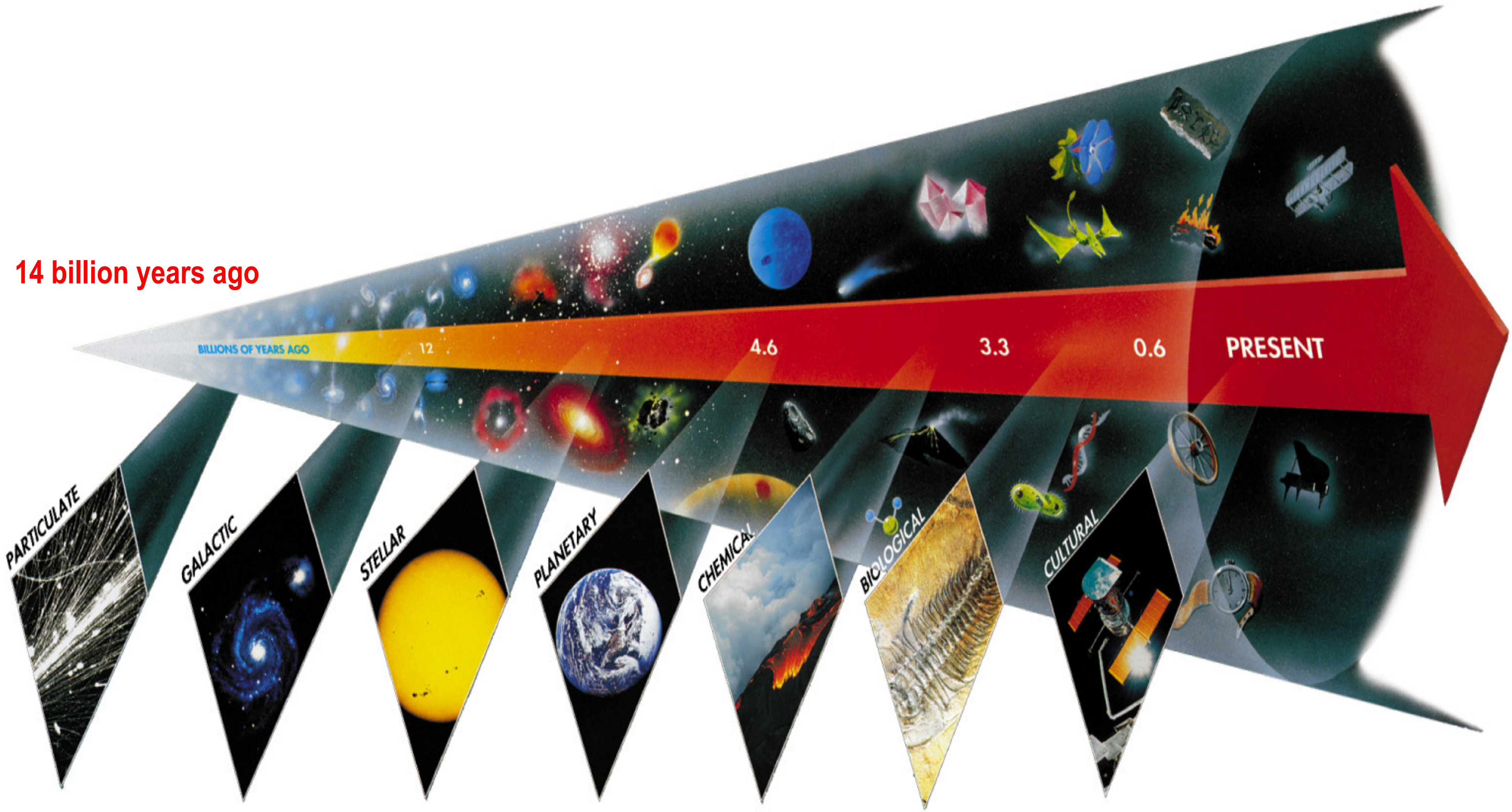


100 Billions Galaxies

New York Times 8/21/2006

Observation of Natures

Seven Phases of Cosmic Evolution



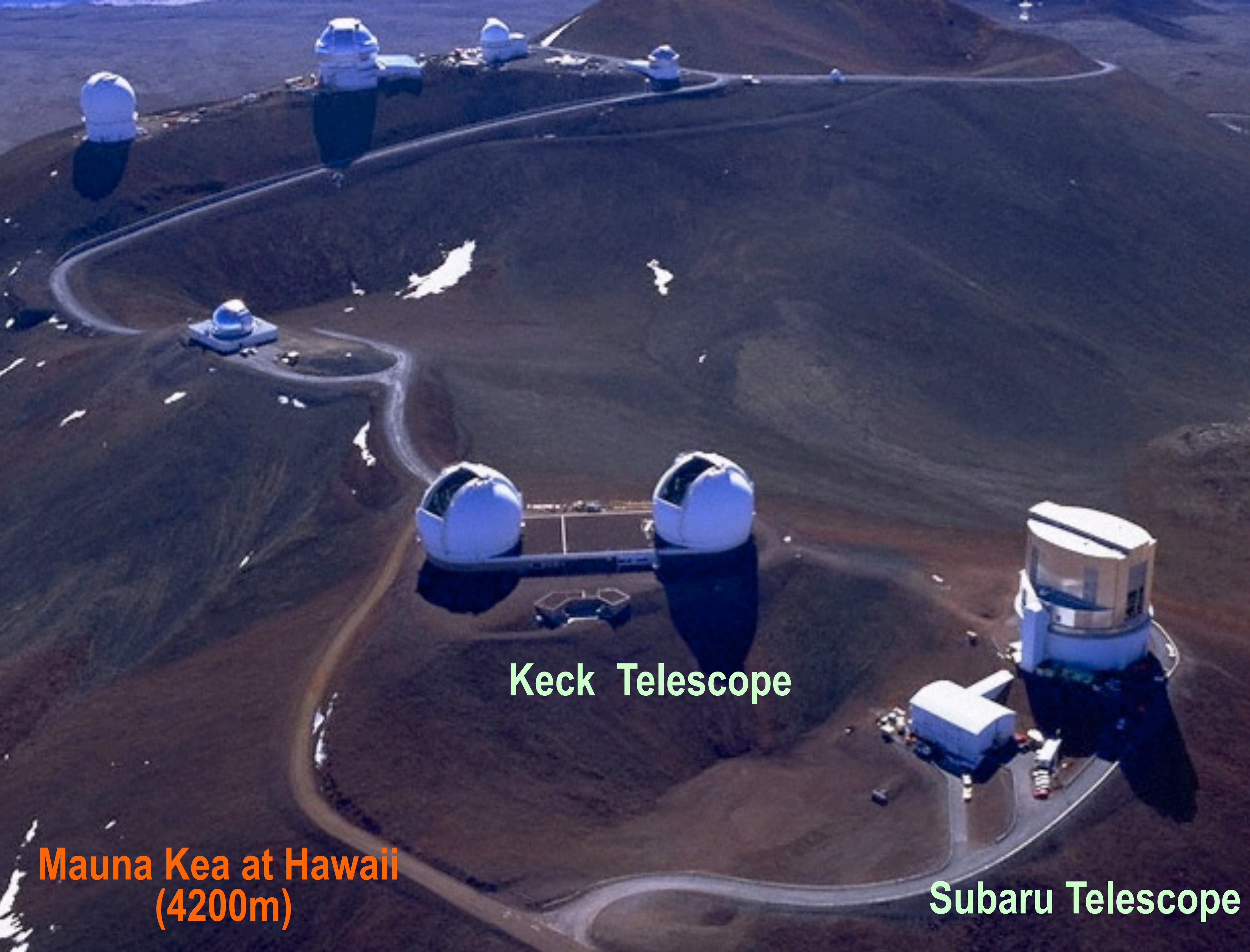
Origin of Particles

Origin of Structure

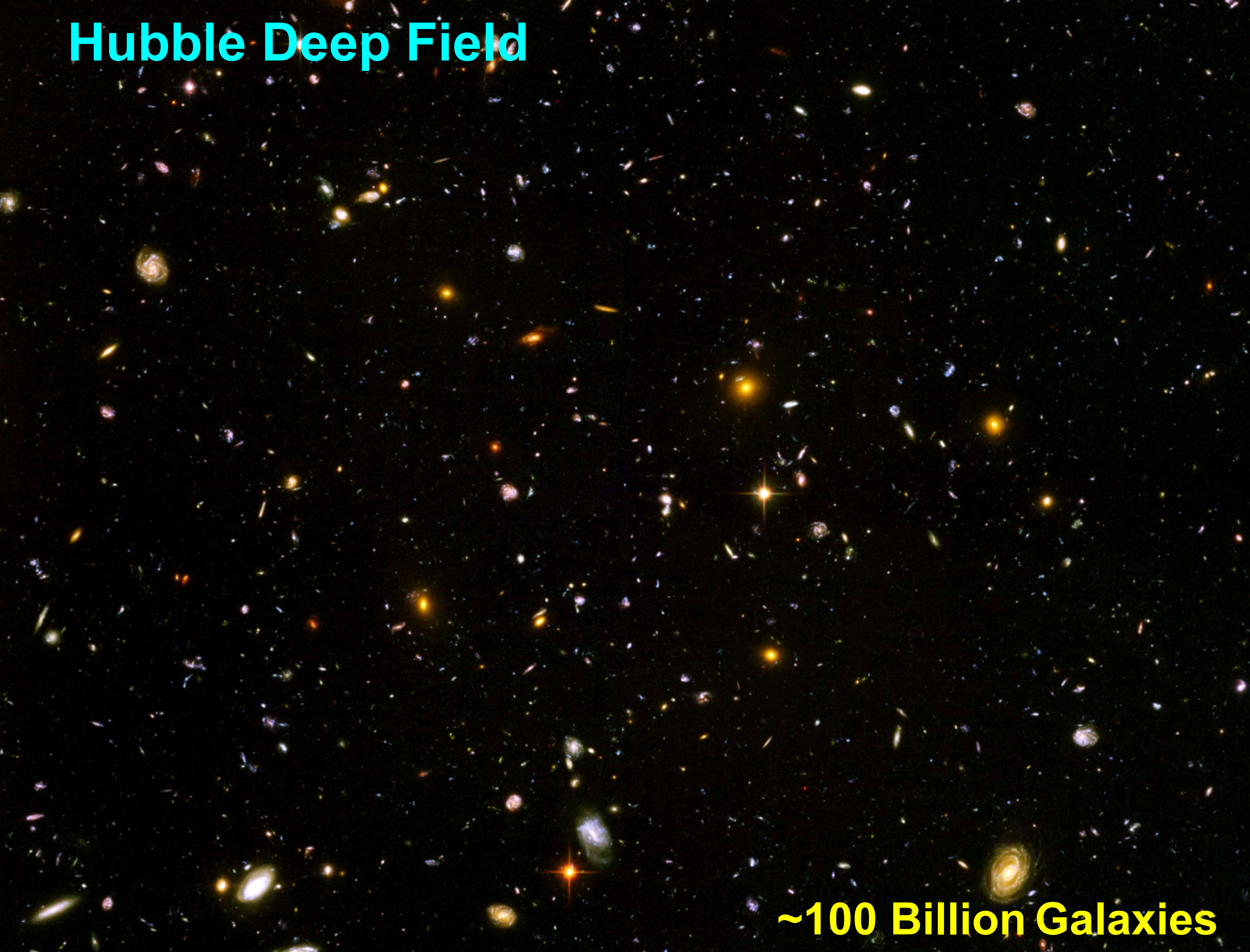
Origin of Life

Origin of Consciousness

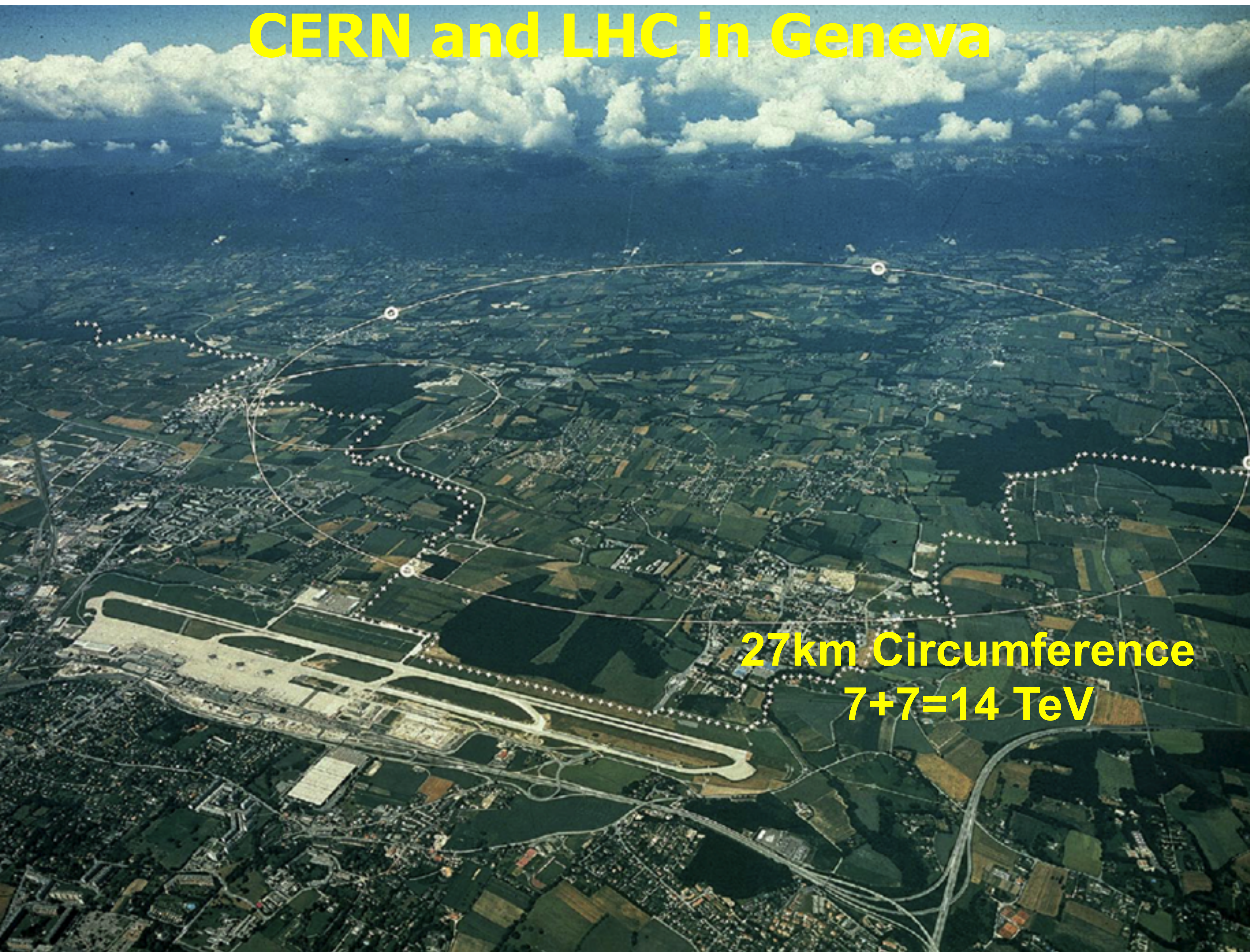

Andromeda
~100 Billions Stars in a Galaxy


Keck Telescope
Subaru Telescope
Mauna Kea at Hawaii
(4200m)

Hubble Telescope

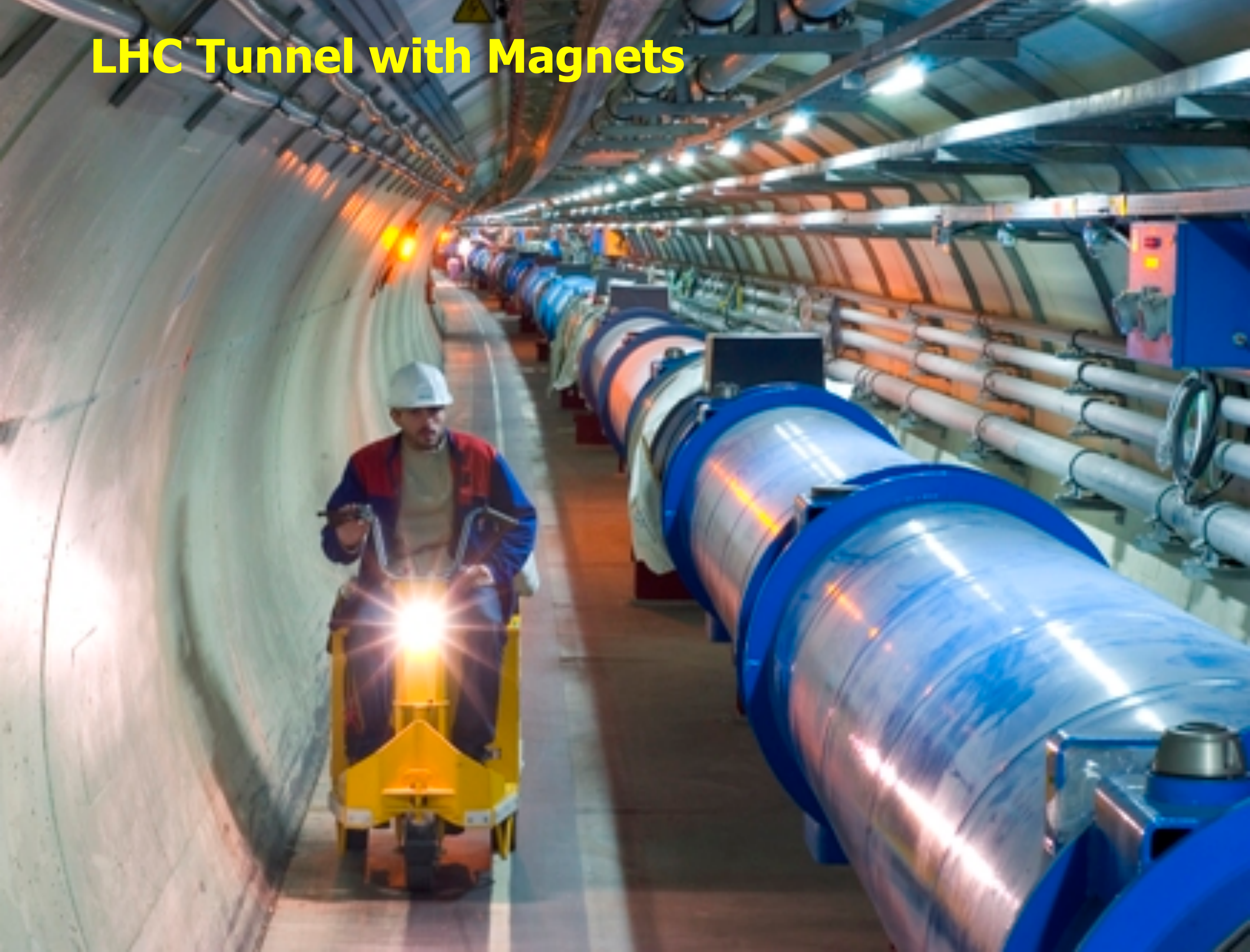

Hubble Deep Field
~100 Billion Galaxies

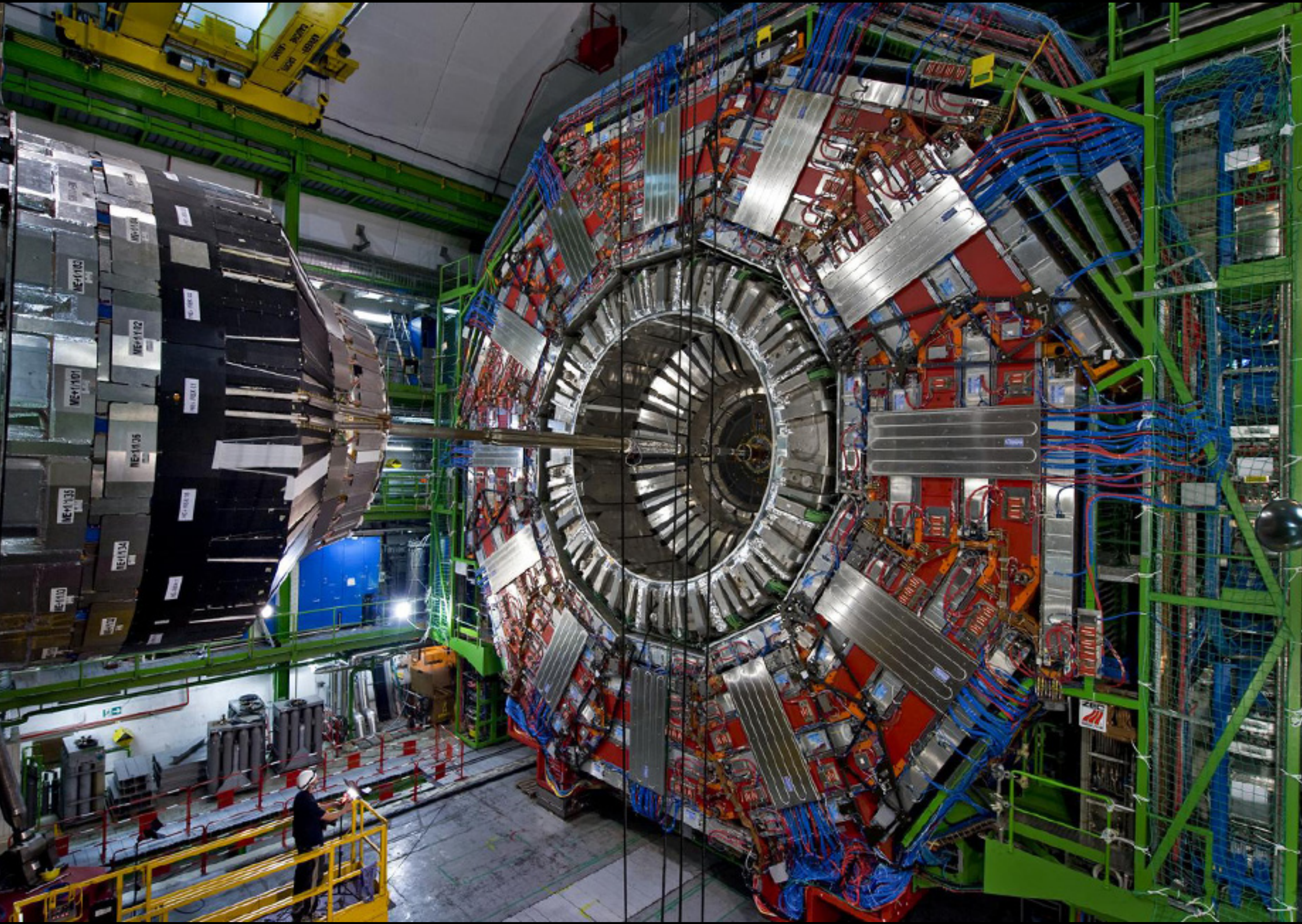
CERN and LHC in Geneva



27km Circumference
7+7=14 TeV

LHC Tunnel with Magnets

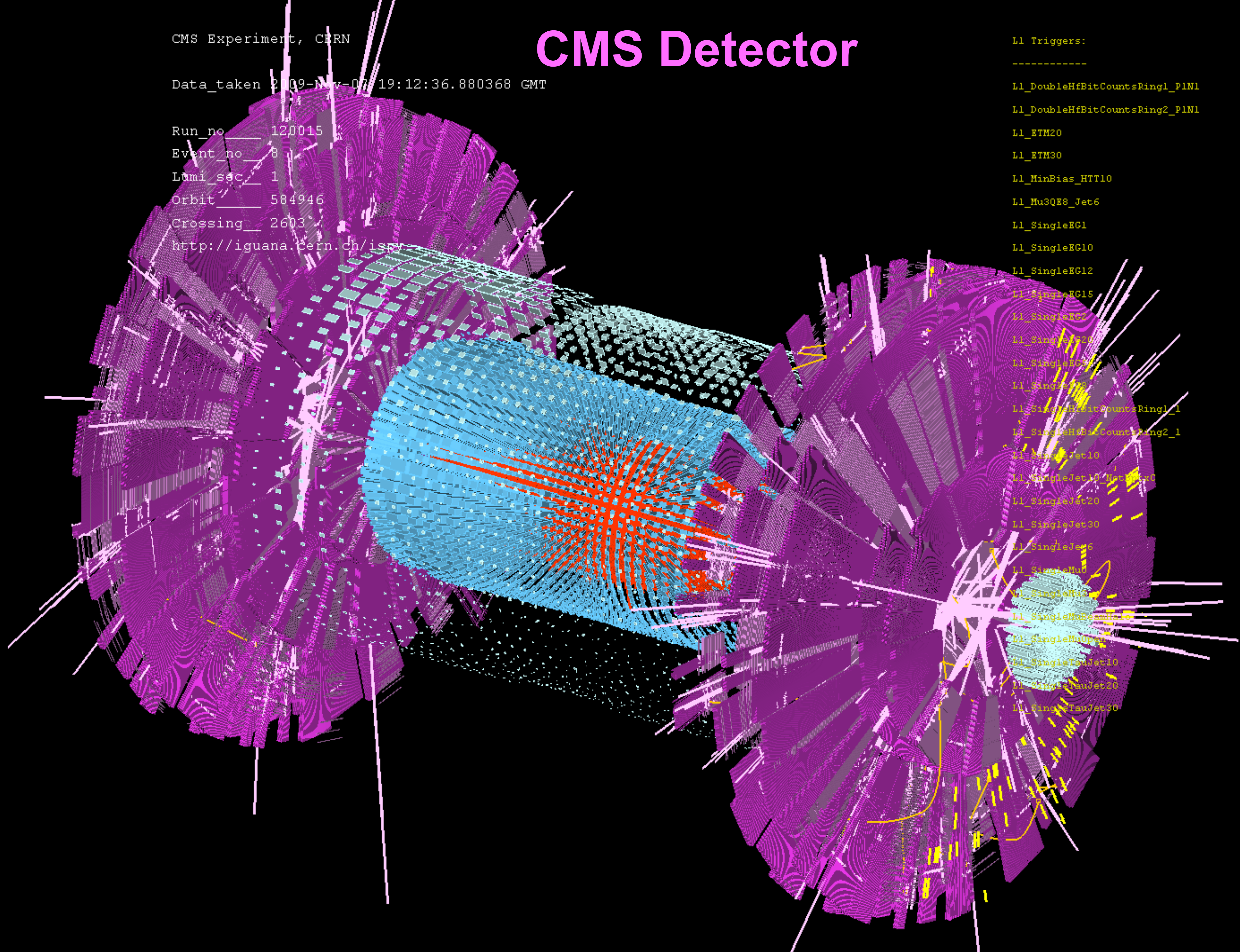




← **Particle detectors constructed at Westwood, now at LHC, CERN**

Sept 15, 2008 Issue

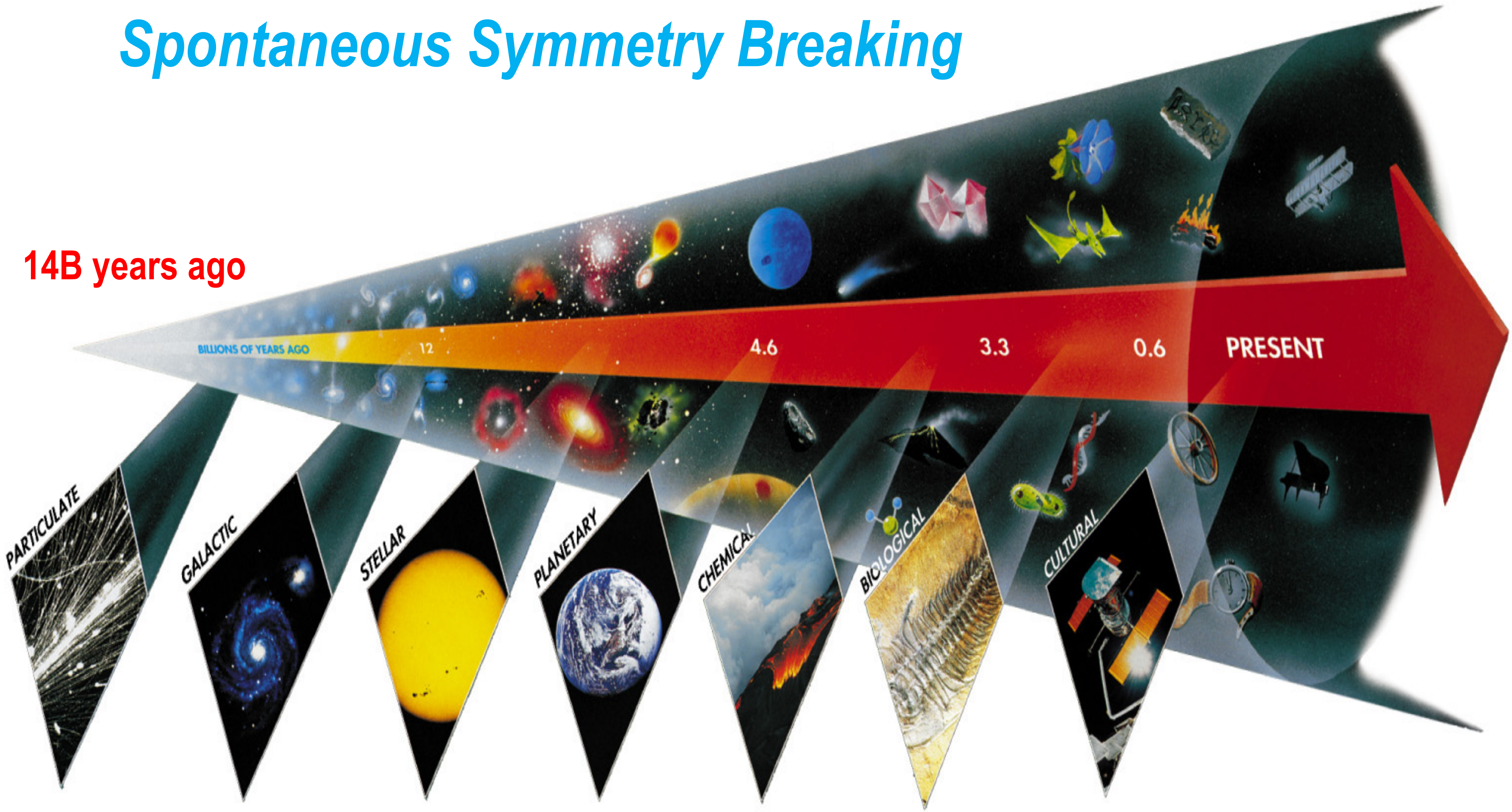
CMS Detector



First Event at LHC – Recreation of the Big Bang! (Nov 7, 2009)

Seven steps of cosmic evolution

Spontaneous Symmetry Breaking



Simple ⇨ Coherent Complex System

What is Life?

- **Emergent Property**
  - Strongly-interacting, complex system
  - ~10^4 of different proteins in one cell
  - ~10^{14} cells in one life
  - ~10^{11} neurons in our brain, ~10^{14} connections
- **Continuous, countless "symmetry breaking" towards coherent states**
  - Origin of life
  - Evolution of life
  - Growth from a single cell to a multi-cell body
  - Learning and memory

How to observe the Life and Consciousness ?

- We must look for "Live Life"
- Exactly the same way as we look for the "Origin of Universe"

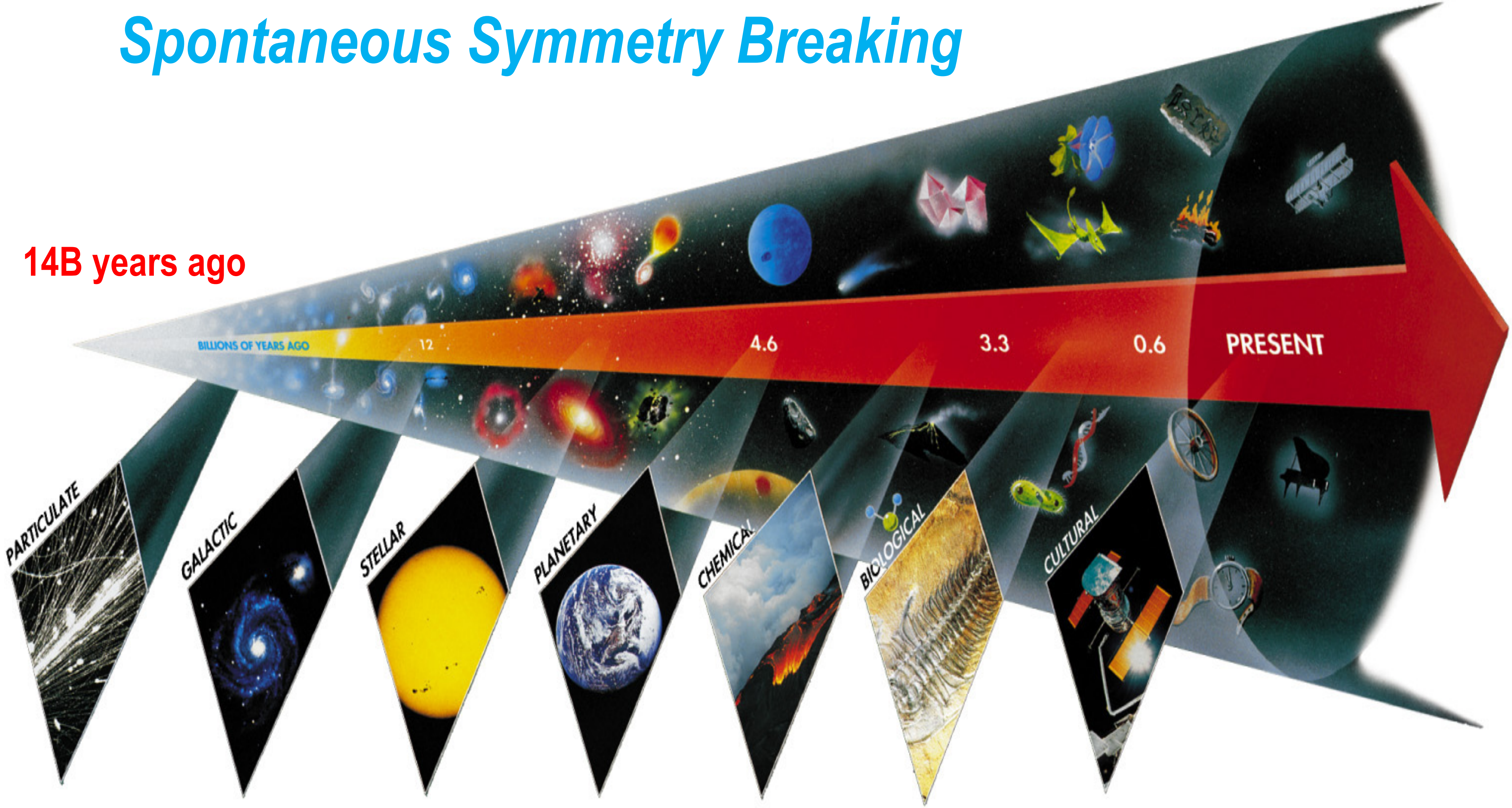
Telescope ↔ Microscope

- Take advantages of the state of art "Photon Detectors" in particle physics.

Seven steps of cosmic evolution

Spontaneous Symmetry Breaking

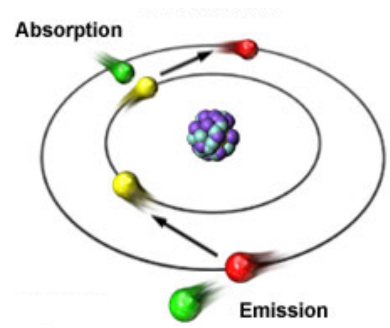
14B years ago



Accelerator ⟷ Telescope ⟶ ⟵ Microscope ⟶

Principle of Optical Microscopes

A Brief Overview of the Physics of Light

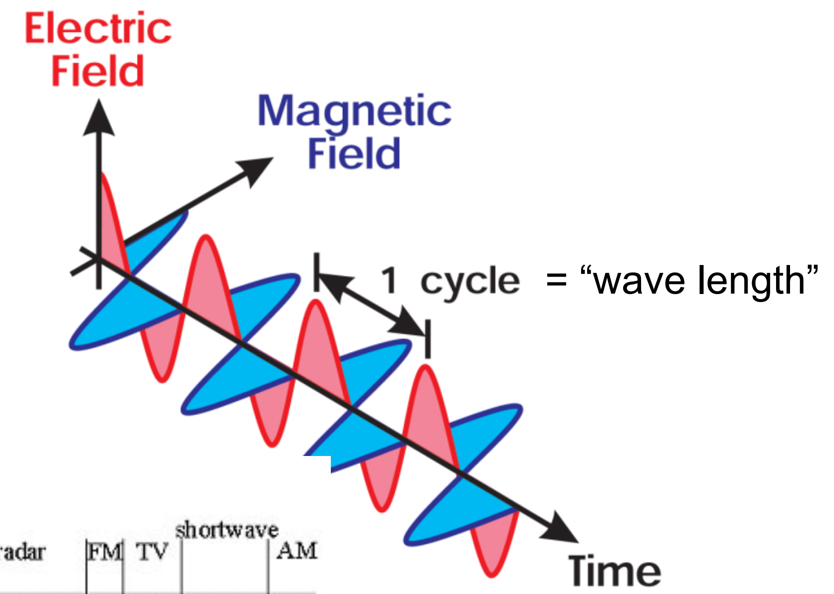


Origin of <u>a Light Wave</u>: When the valence electrons of atoms absorb energy, they are lifted from a ground level to more energetic states. After a very short time, the electrons drop back to ground level, releasing the energy in the form of a **photon,** an energy quantum associated with an **electromagnetic wave.**

<u>Properties</u> of a Light Wave:

has an **electric vector E** and a **magnetic vector B.**
has an **wave length λ,** an **amplitude** and **polarity (E).**

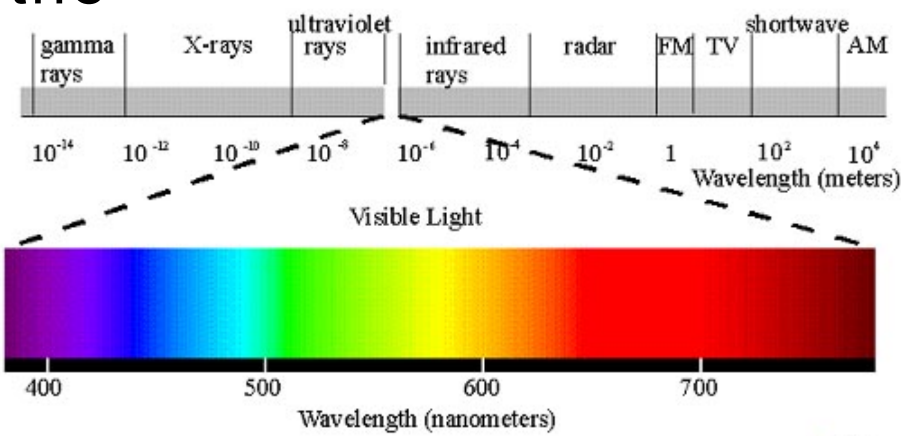
High energy photon = shorter λ = Bluer color
Low energy photon = longer λ = redder color



Direction of Propagation

<u>Color Vision</u> of the Human Eye:

Violet	410 nm
Blue	475 nm
Green	530 nm
Yellow	580 nm
Red	670 nm



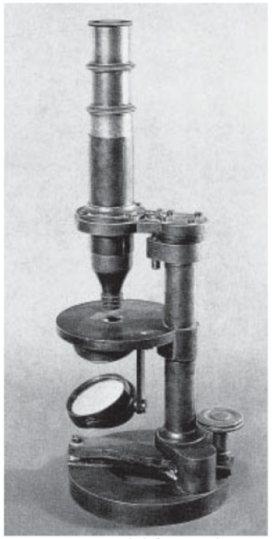
= natural white light

Modern Microscope Component Identification

1847

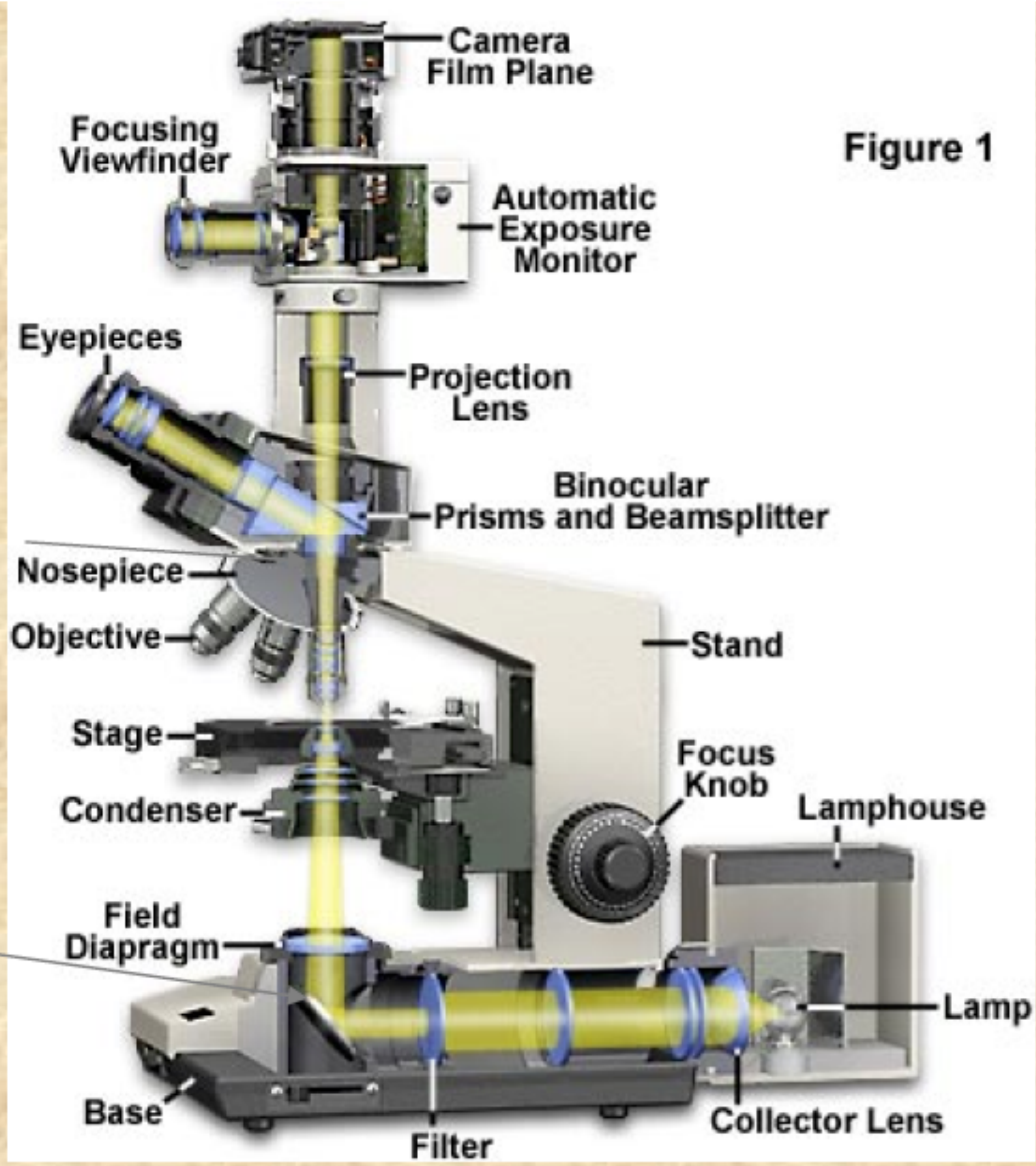
Simple ...

compound ...



1857

Prisms Used to Re-Direct Light In Imaging Path While Mirrors Are Used in Illumination Path

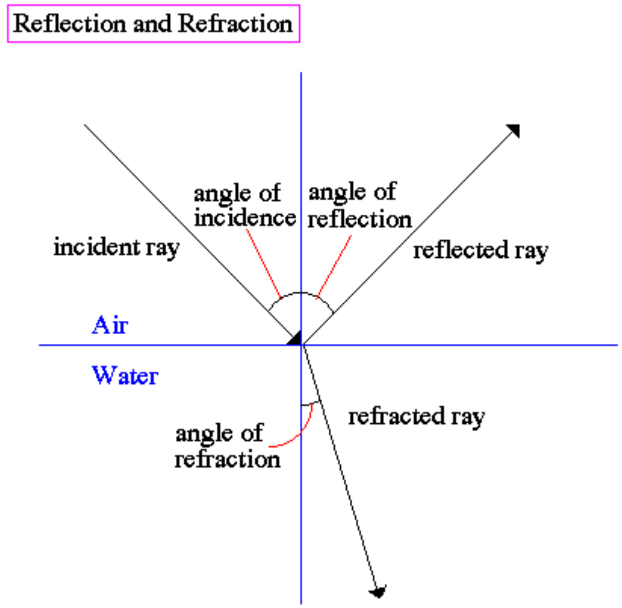


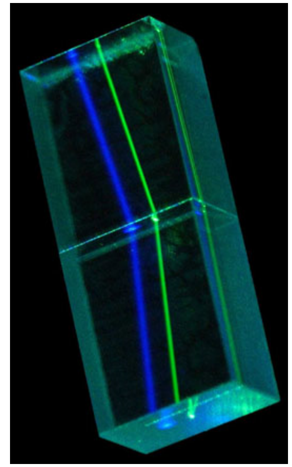
Light Microscopy Timeline

1595	Invention of the microscope (Milestone 1)
1858	First histological stain (Milestone 2)
1871	Synthesis of fluorescein (Milestone 2)
1873	Diffraction limit theory (Milestone 3)
1911	First fluorescence microscopy (Milestone 4)
1929	First epifluorescence microscope (Milestone 4)
1935	Phase contrast microscopy (Milestone 5)
1939	Polarization microscopy (Milestone 6)
1942	Immunofluorescence (Milestone 7)
1955	Differential interference contrast (Milestone 8)
1961	Concept of confocal microscopy (Milestone 9)
1967	The dichroic mirror (Milestone 4)
1972	Fluorescence correlation spectroscopy (Milestone 10)
1976	FRAP (Milestone 10)
	FRET (Milestone 11)
1980	Calcium probes (Milestone 12)
1981	Video-enhancement differential interference contrast (Milestone 8)
	TIRF microscopy (Milestone 13)
1983	Deconvolution microscopy (Milestone 14)
1987	Realization of confocal microscopy (Milestone 9)
1990	Two-photon microscopy (Milestone 15)
1993	Light sheet microscopy (Milestone 16)
	Single molecule microscopy (Milestone 17)
1994	GFP (Milestone 18)
1997	Fluorescent protein-based biosensors (Milestone 19)
1999	Red fluorescent proteins (Milestone 20)
2000	Breaking the diffraction limit: STED (Milestone 21)
2002	Photoactivatable fluorescent proteins (Milestone 20)
2006	Breaking the diffraction limit: PALM/STORM (Milestone 21)

http://www.nature.com/milestones/light-microscopy

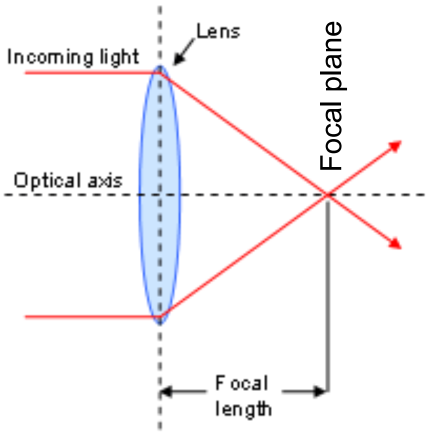
Some Properties of Lenses



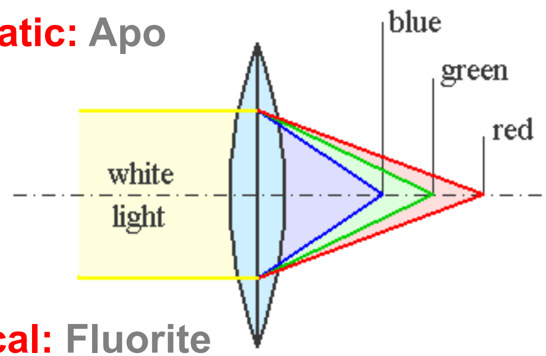


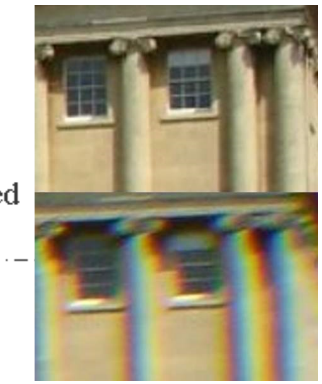
Refraction: When a beam of light passes between substances with different **refractive indices**, such as air (n=1) into water (n=1.333), it is bent in a characteristic fashion (wavelength dependant).

Focal Length



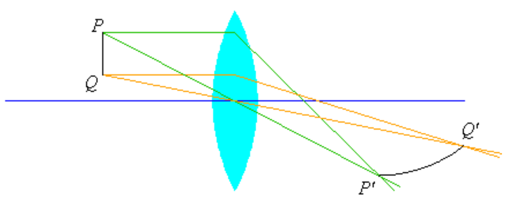
Chromatic: Apo



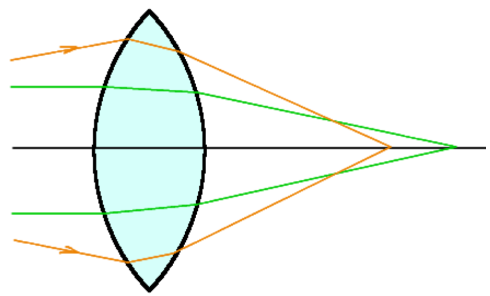


Lens Aberrations & Corrections :

Spherical: Fluorite



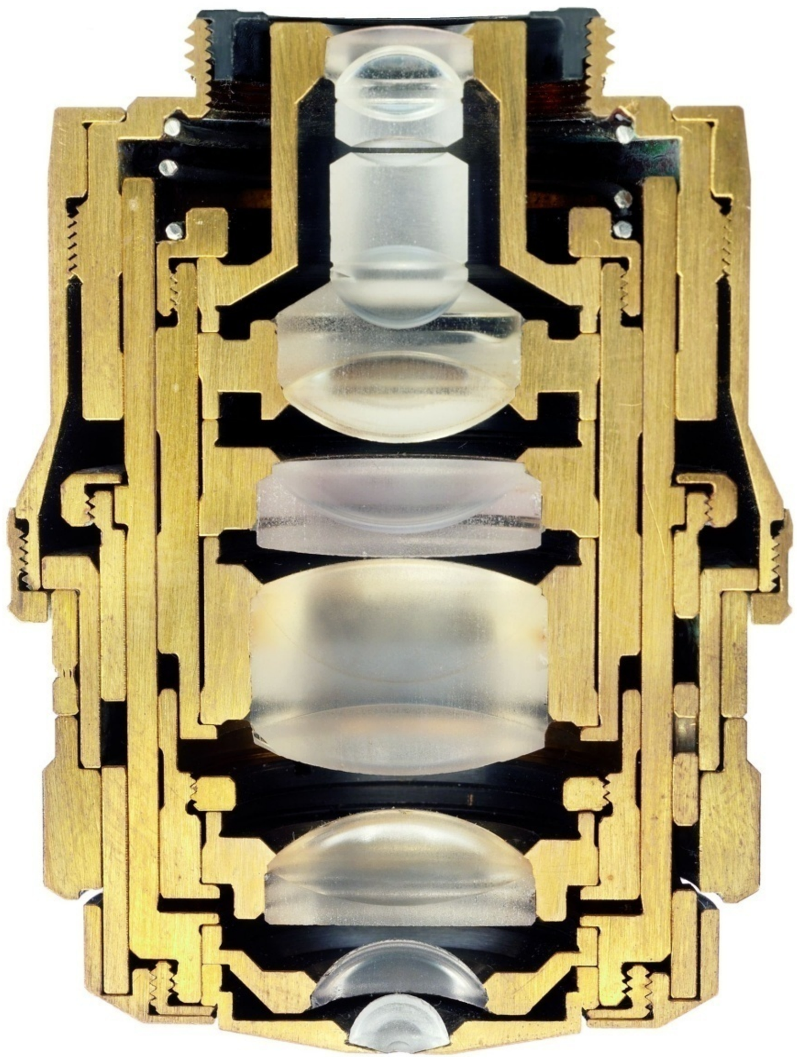
Curvature of Field: Plan



Key Component: the Objective

Objective Design Criteria Most Critical for Fluorescence:

- Numerical Aperture
- Immersion choices
- Magnification
- Transmission UV/Vis/IR
- Chromatic Correction
- Coverslip vs Chamber
- Optical Correction
- Working Distance



Achromats: corrected for chromatic aberration for red, blue

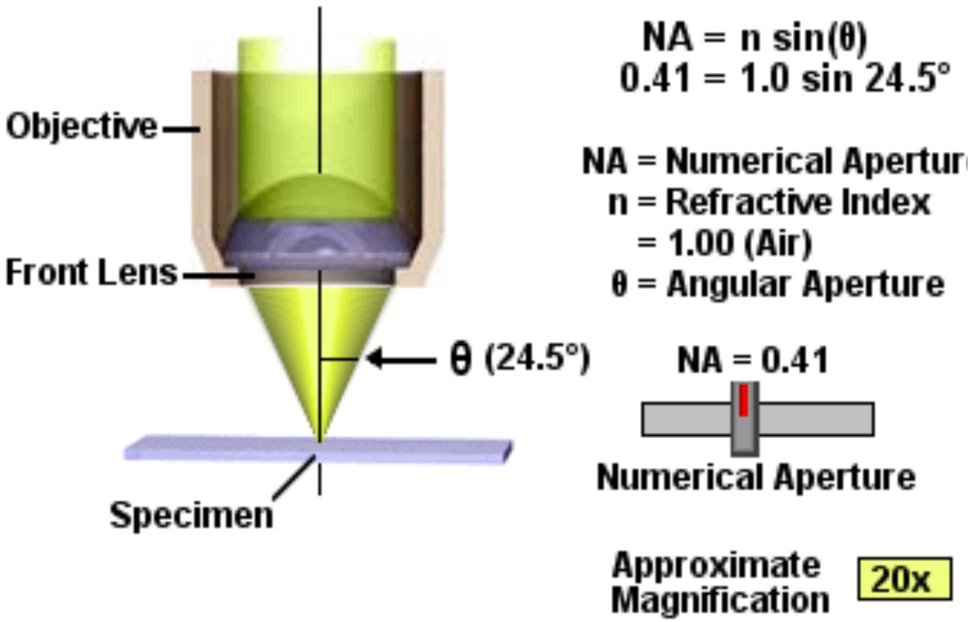
Fluorites: chromatically corrected for red, blue; spherically corrected for 2 colors

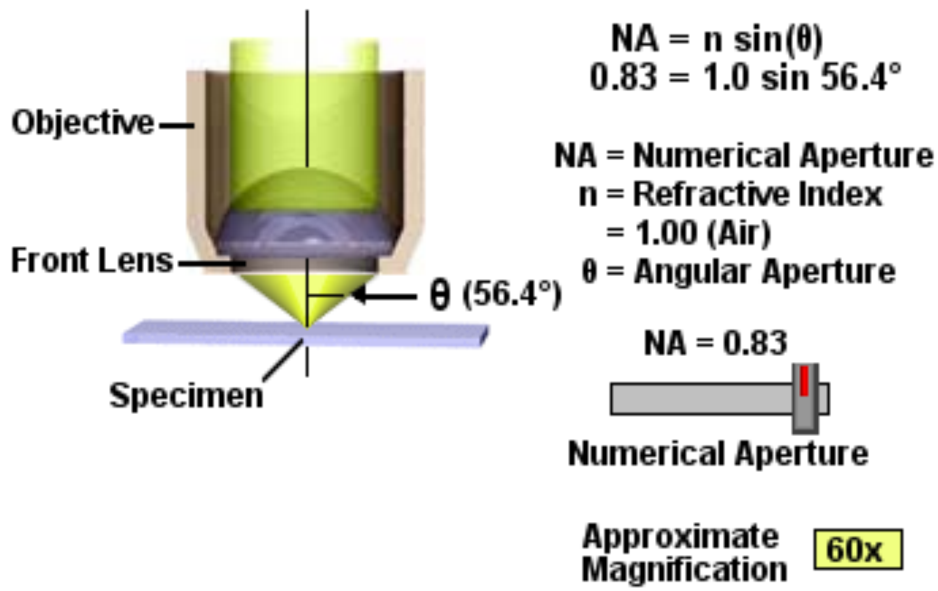
Apochromats: chromatically corrected for red, green & blue; spherically corrected for 2 colors

Plan-: further corrected to provide flat field

Some Functional Parameters of the Microscope Objectives

Numerical Aperture (NA): Light-gathering ability of the objective (NA=n.sinθ). Thus, the NA is directly related to the resolving power of the lens.





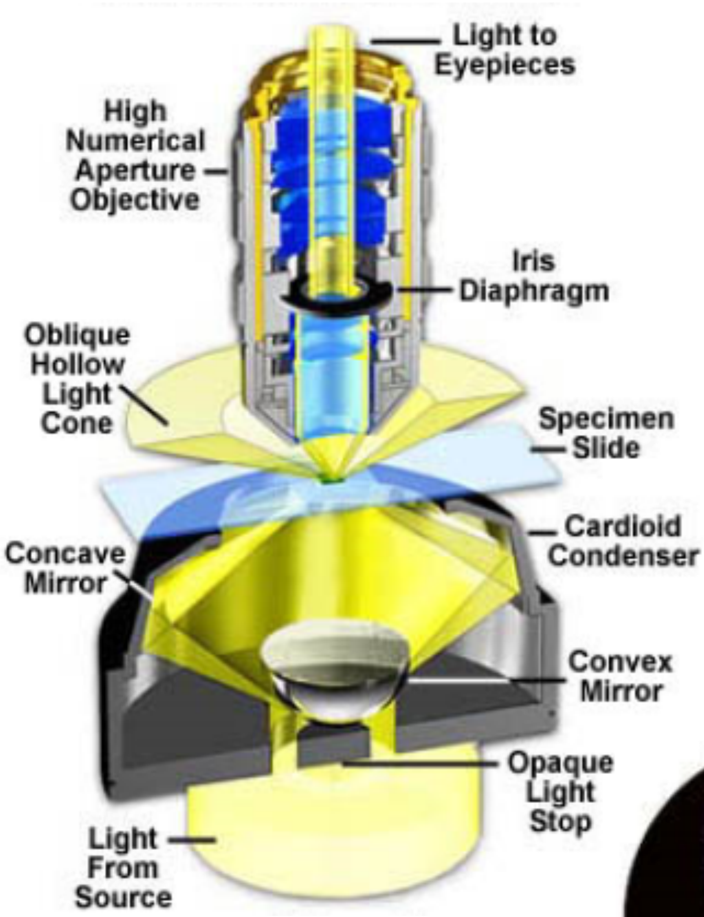
Resolution: Defined as the smallest distance between two points on a specimen that can still be distinguished as two separate entities.

$$R = 0.61\lambda/NA$$

Magnification: Product of the magnifications of objective and ocular.

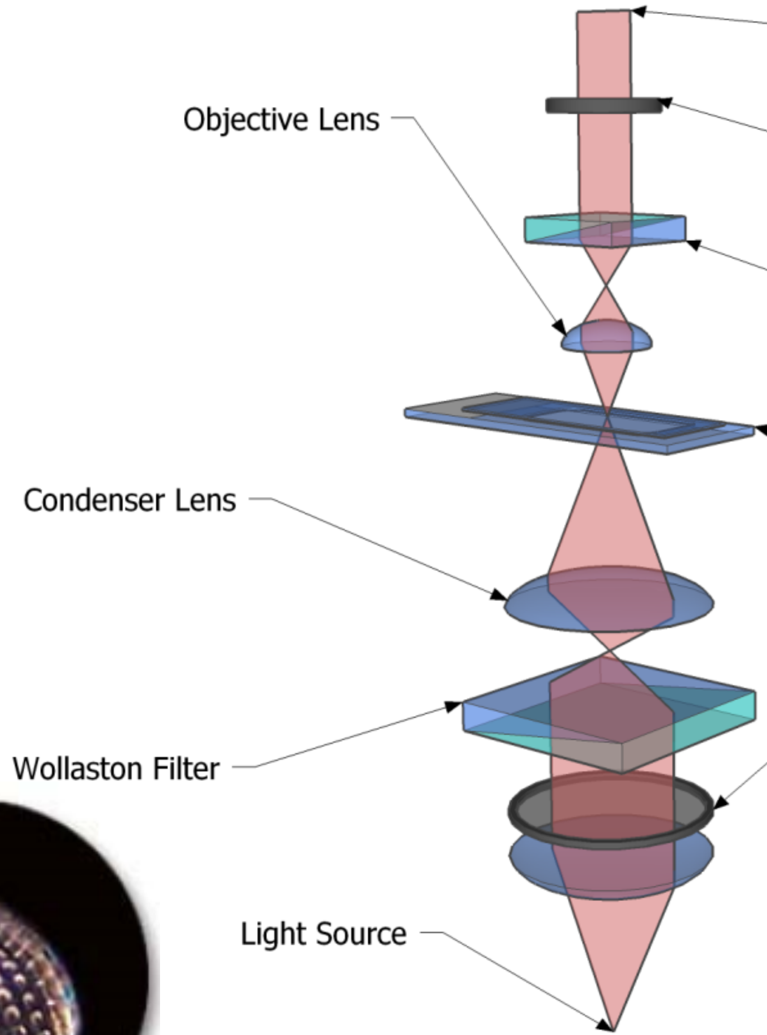
Specialized Types of Light Microscopes (Unstained Specimens)

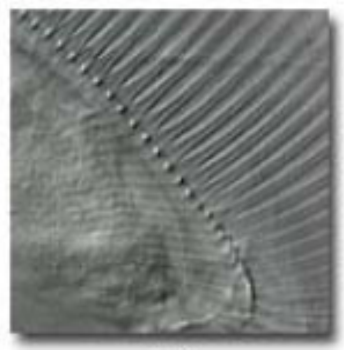
Darkfield Illumination



(b)

Differential Interference Contrast (DIC)

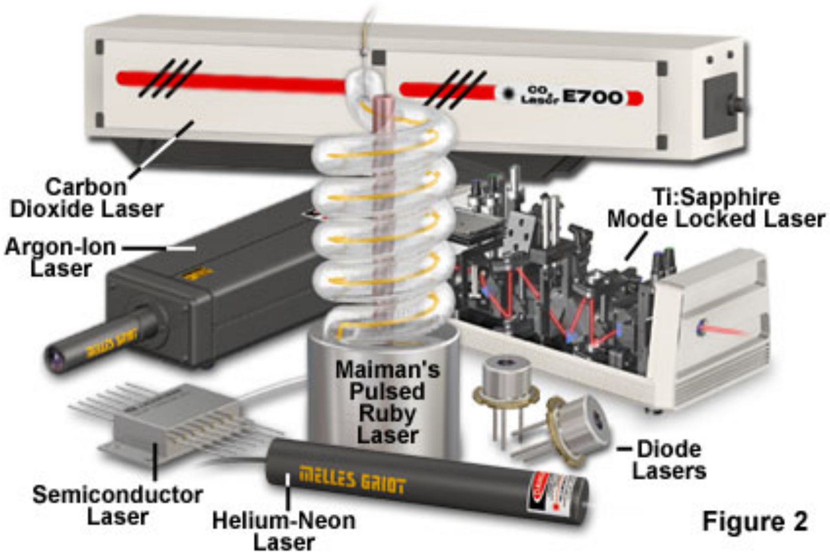




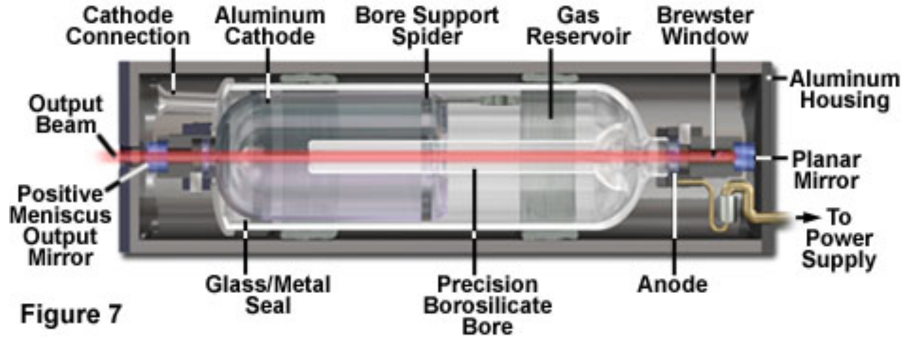
Common Light Sources

Arc lamp

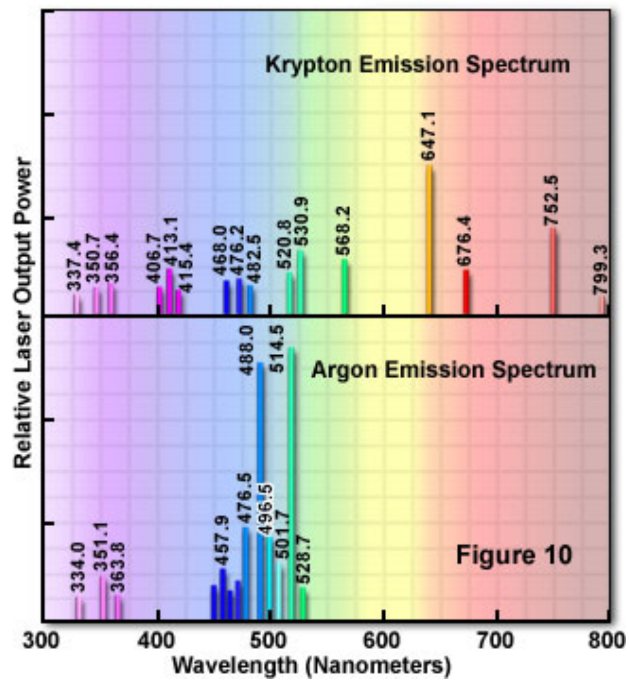
Common Laser System Configurations



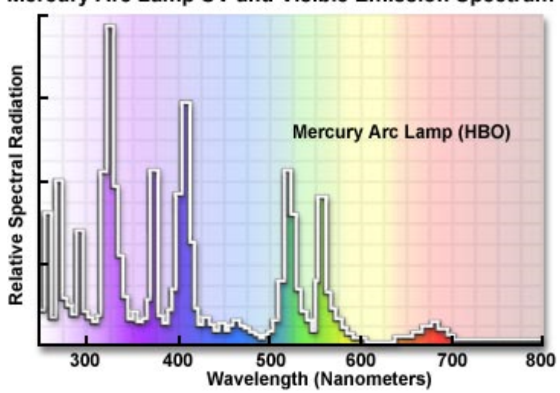
Anatomy of the Helium-Neon Laser



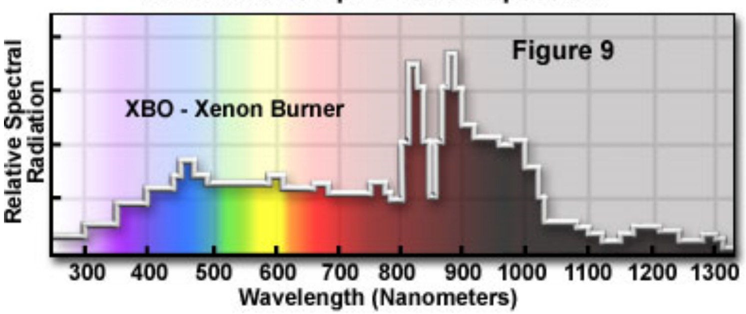
Laser Illumination Source Emission Spectra



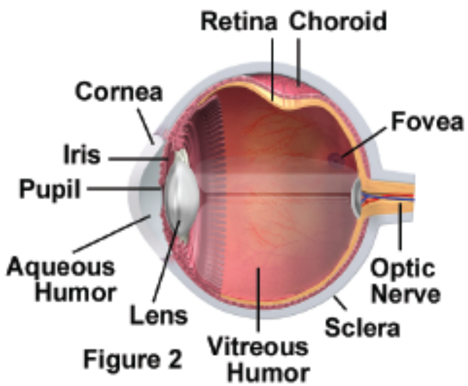
Mercury Arc Lamp UV and Visible Emission Spectrum

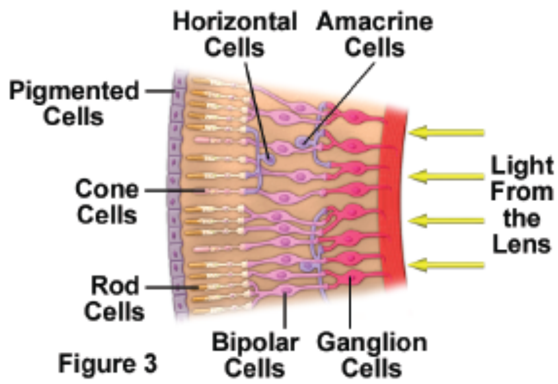


Xenon Arc Lamp Emission Spectrum



The Light Detectors

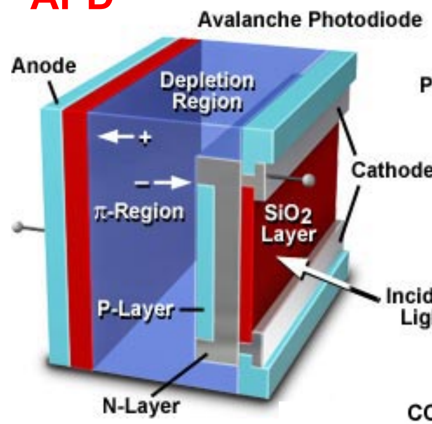




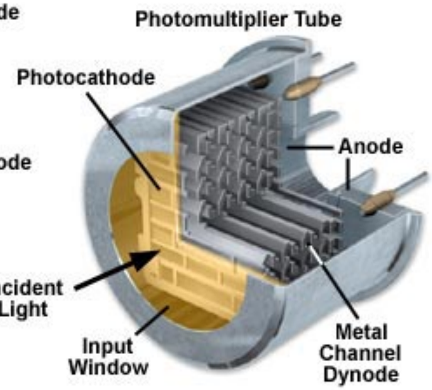
Human eye

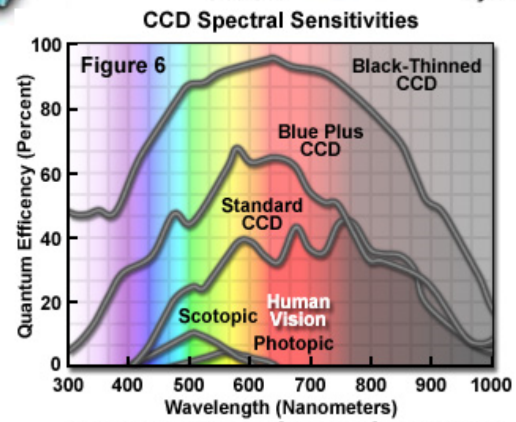
Electronic Light Detectors

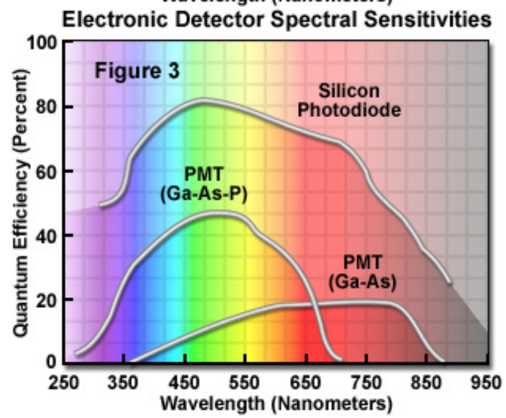
APD

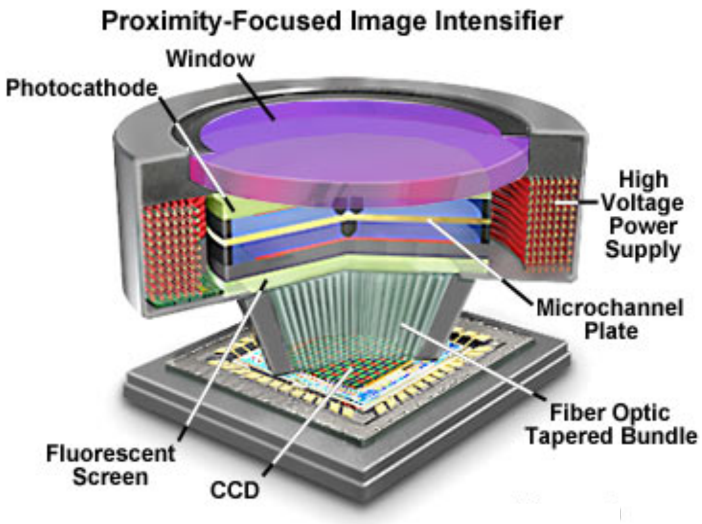


PMT

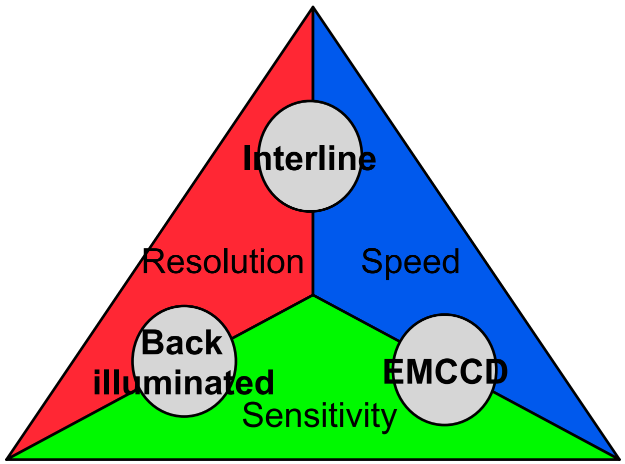






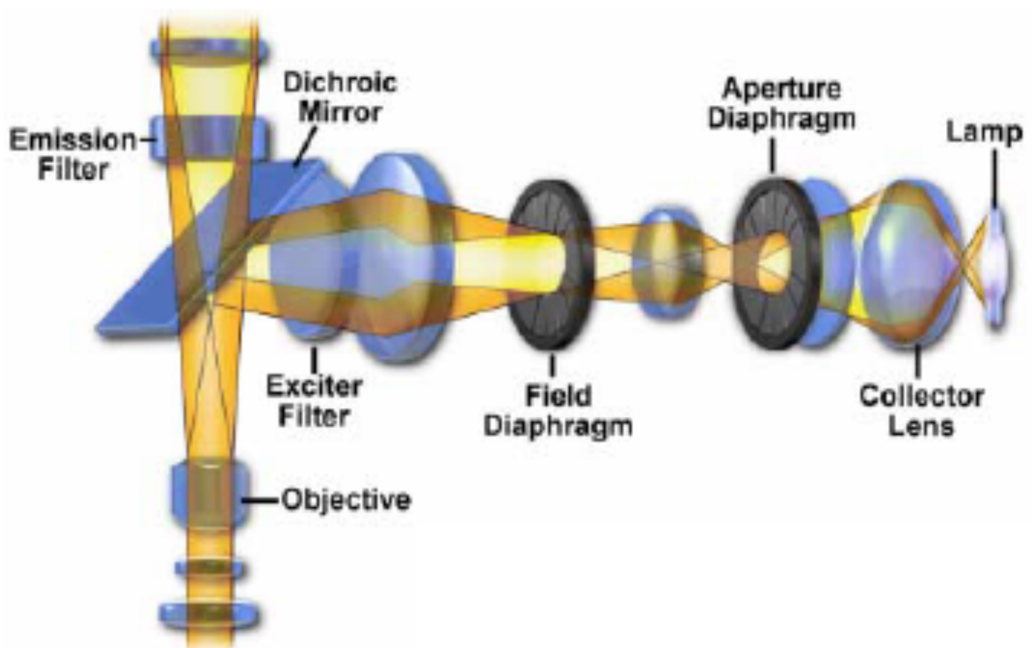


ICCD

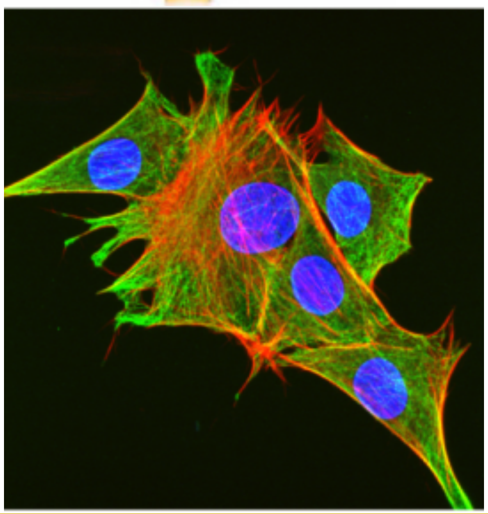


The Fluorescence Microscope (Stained Specimens)

In **fluorescence**, a molecule is excited to higher energy states by radiation of specific wavelengths

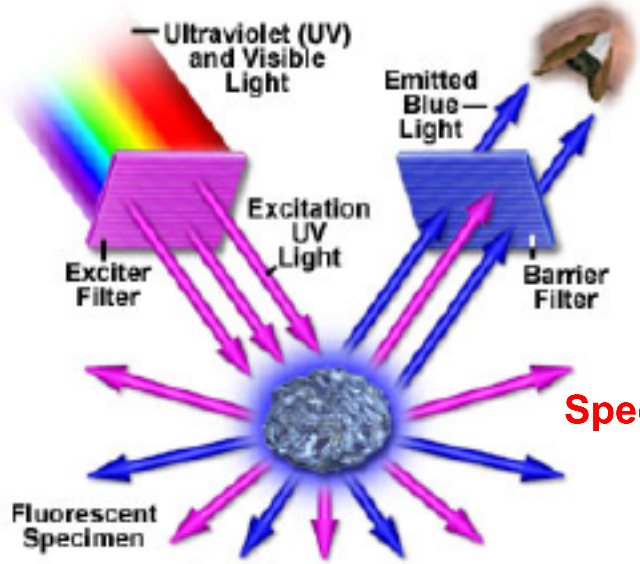


Imaging detector



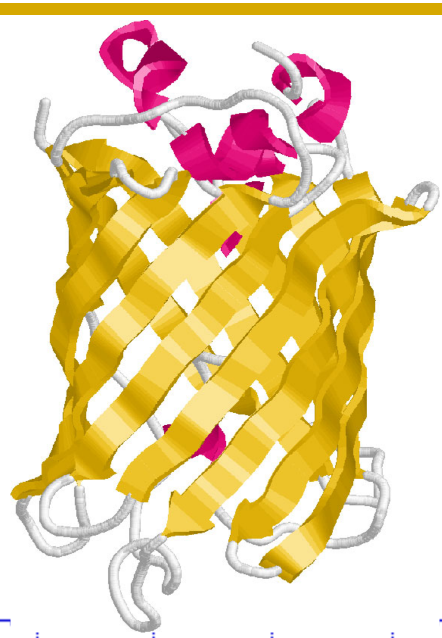
Light Sources

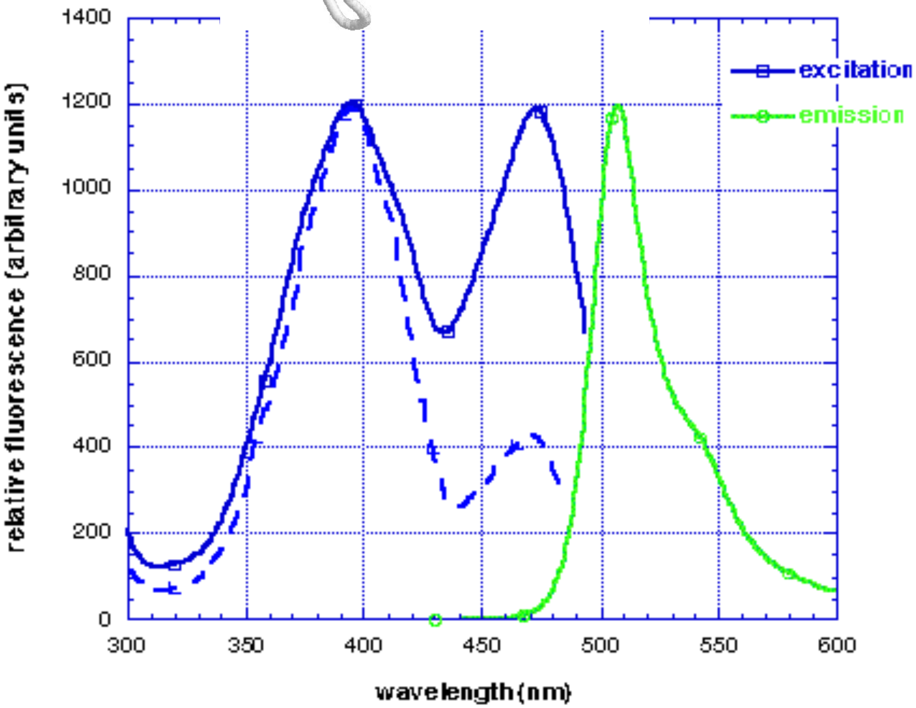
Fluorescing dye (Fluorophore)

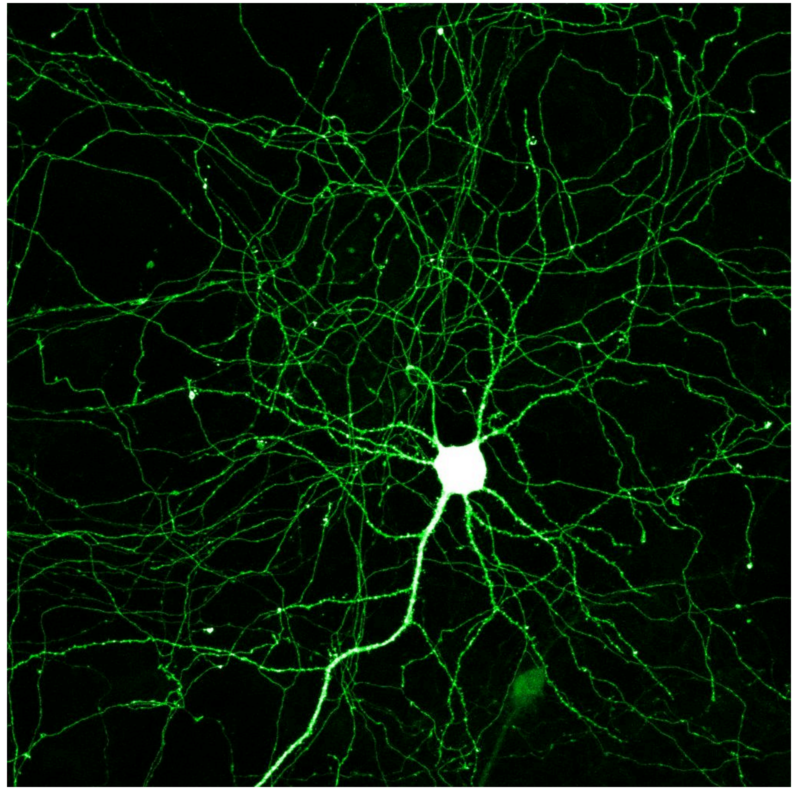


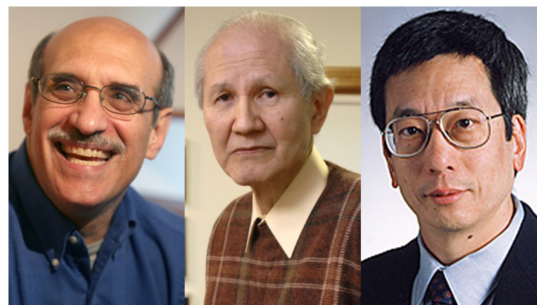
Spectral Filters

GFP (Green Fluorescent Protein)





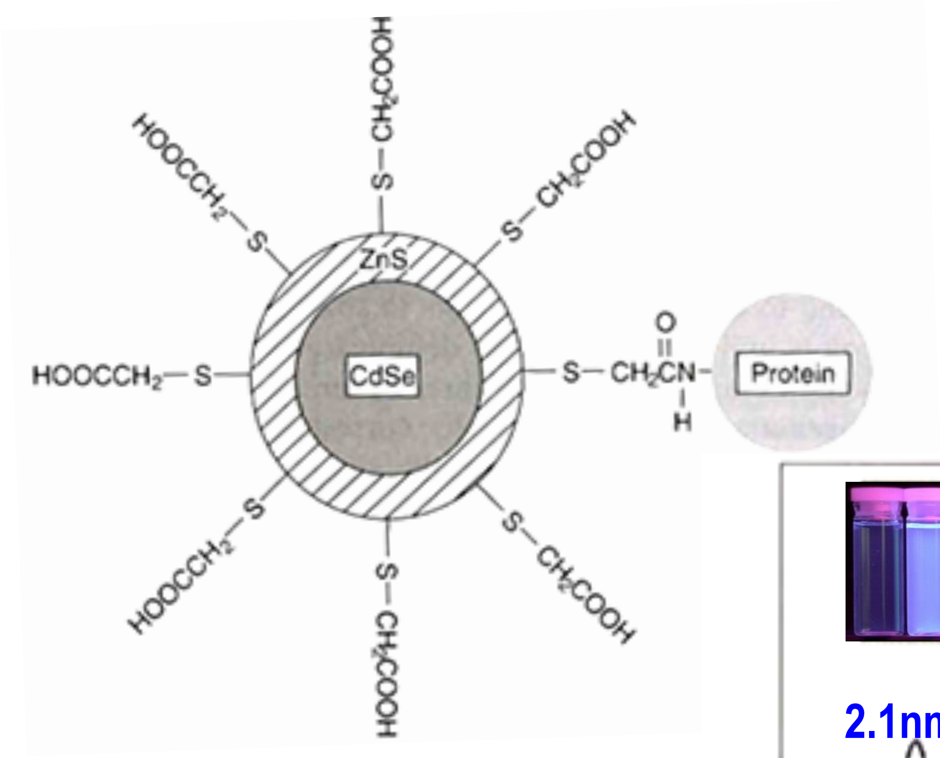


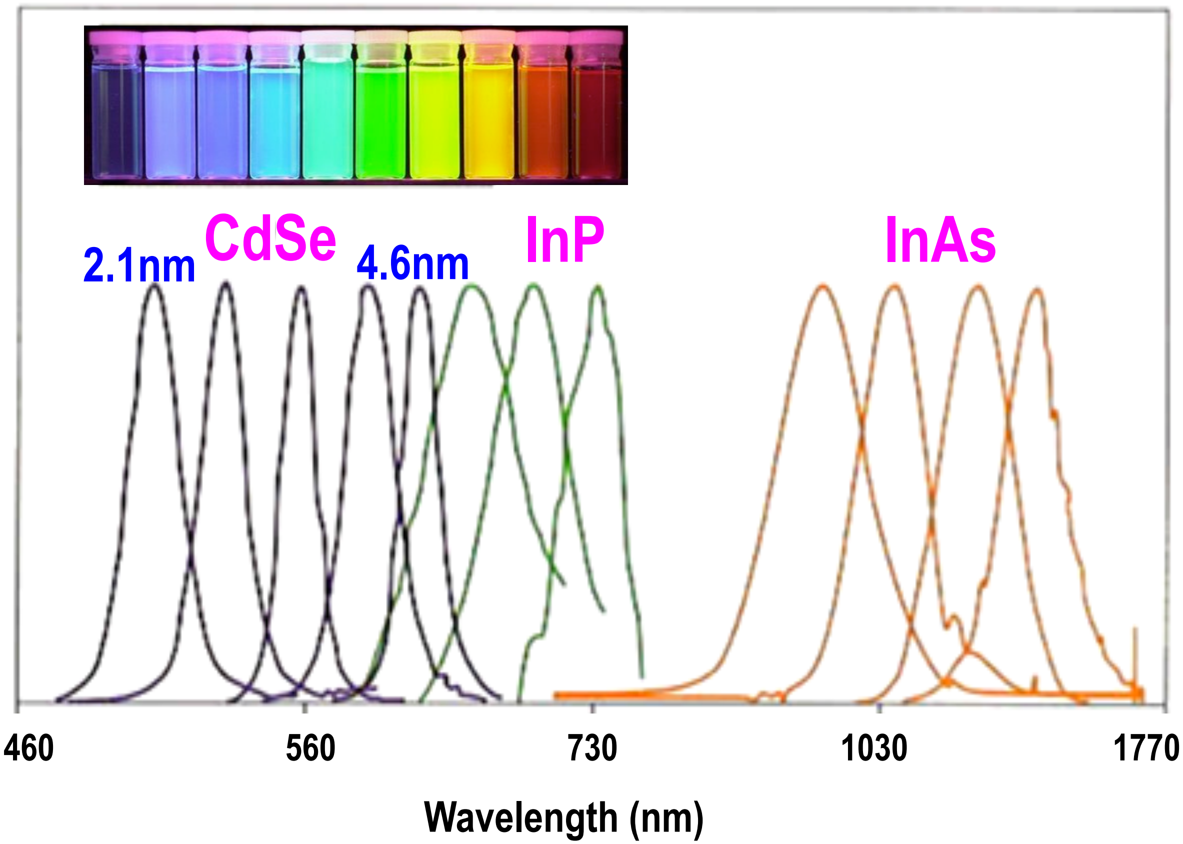


Chalfie, Shimura,Tsien

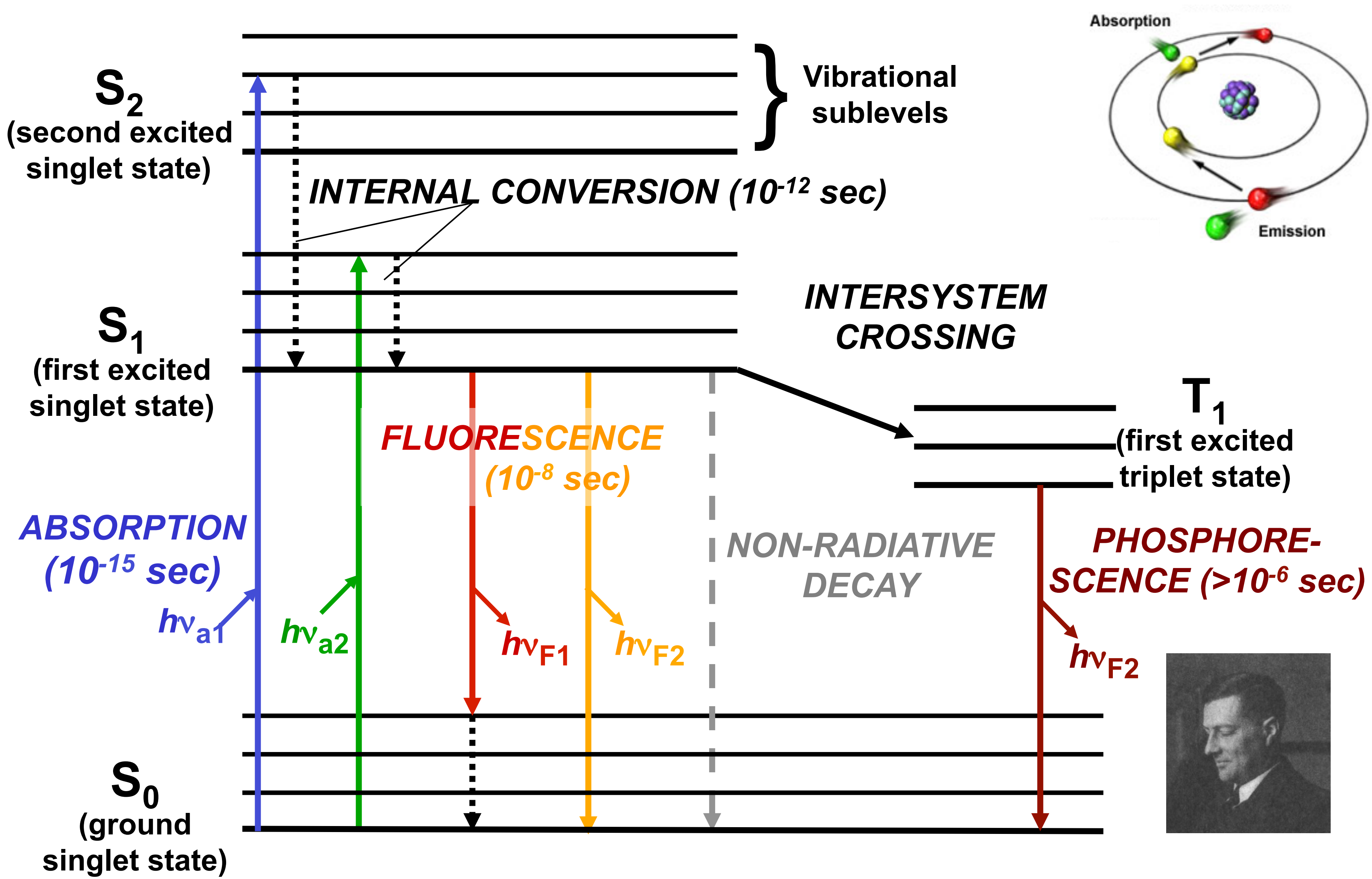
Emission of Quantum Dot

Shimon Weiss (Chemistry)

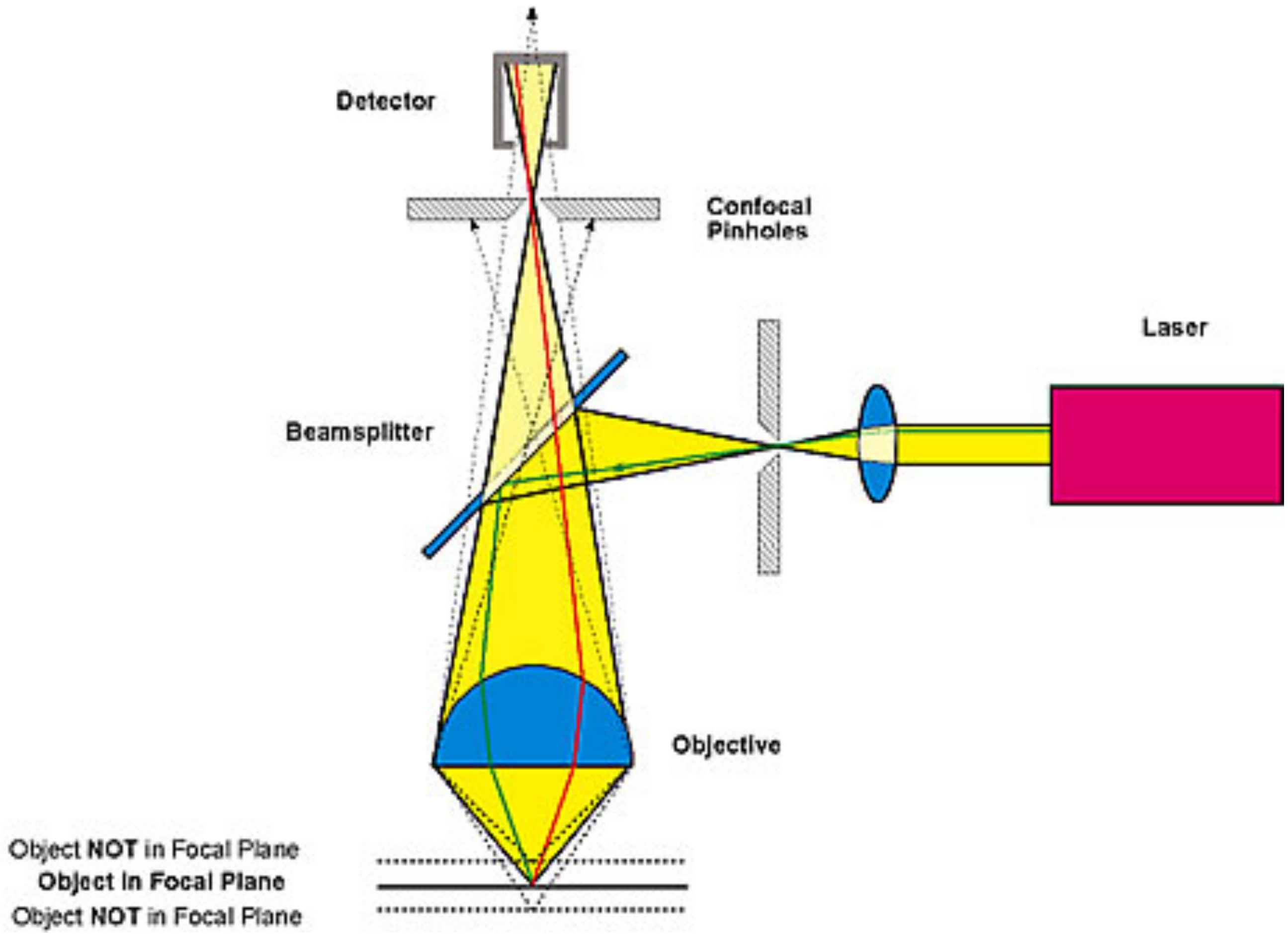




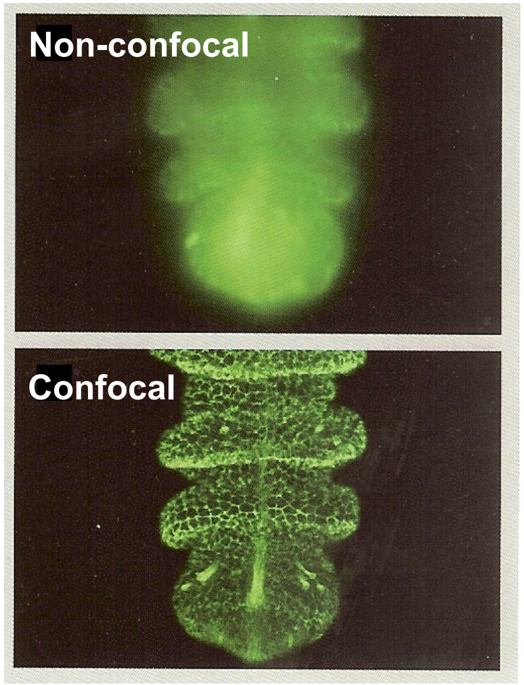
Electronic Transitions: Jablonski Diagram



Principle of Confocal Microscopy



Focused + out-of-focus light



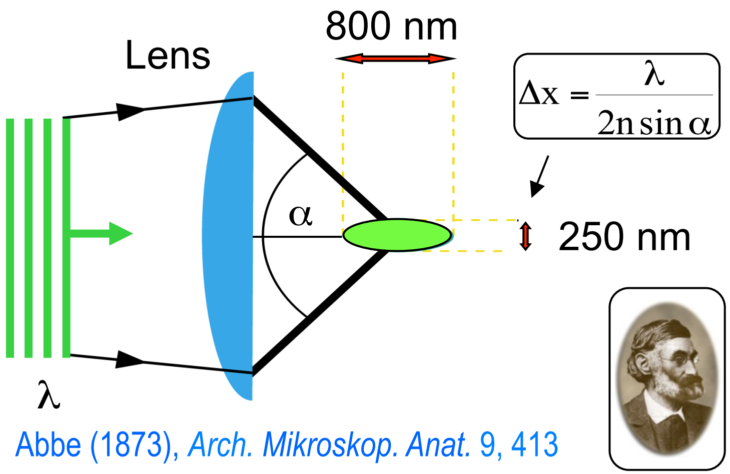
Out-of-focus light suppressed

- An aperture (detection pinhole) allows 3D optical sectioning and suppression of out-of-focus light
- Sample is scanned with point laser beam in the x- and y-directions.
- The sample is moved along the optical axis (z-direction)

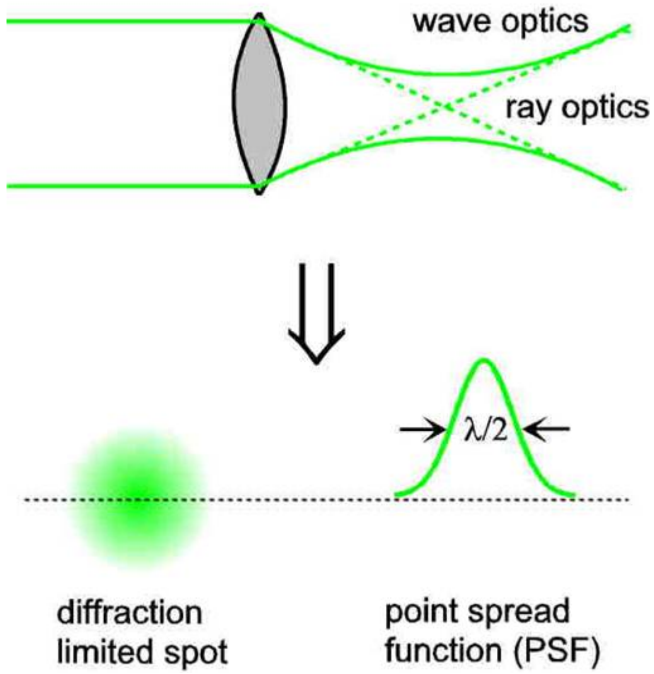
Advanced Microscopes

Super Resolution

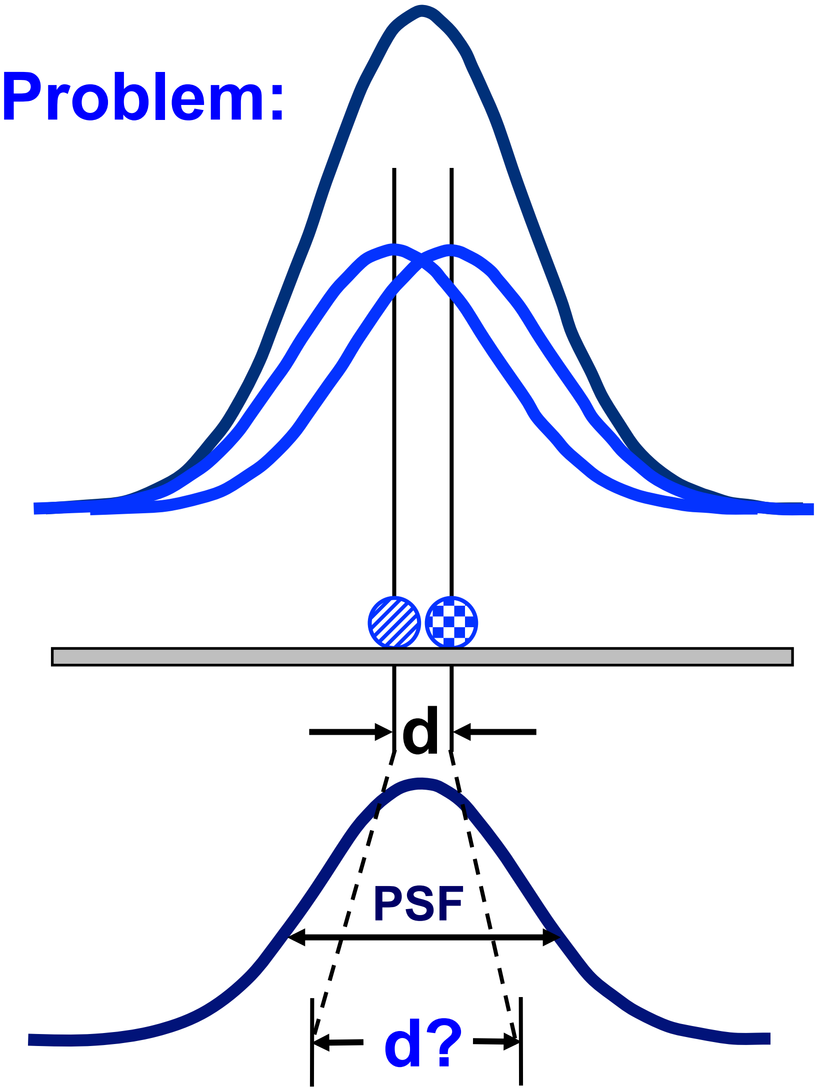
Optical Diffraction Limit



Abbe (1873), *Arch. Mikroskop. Anat.* 9, 413



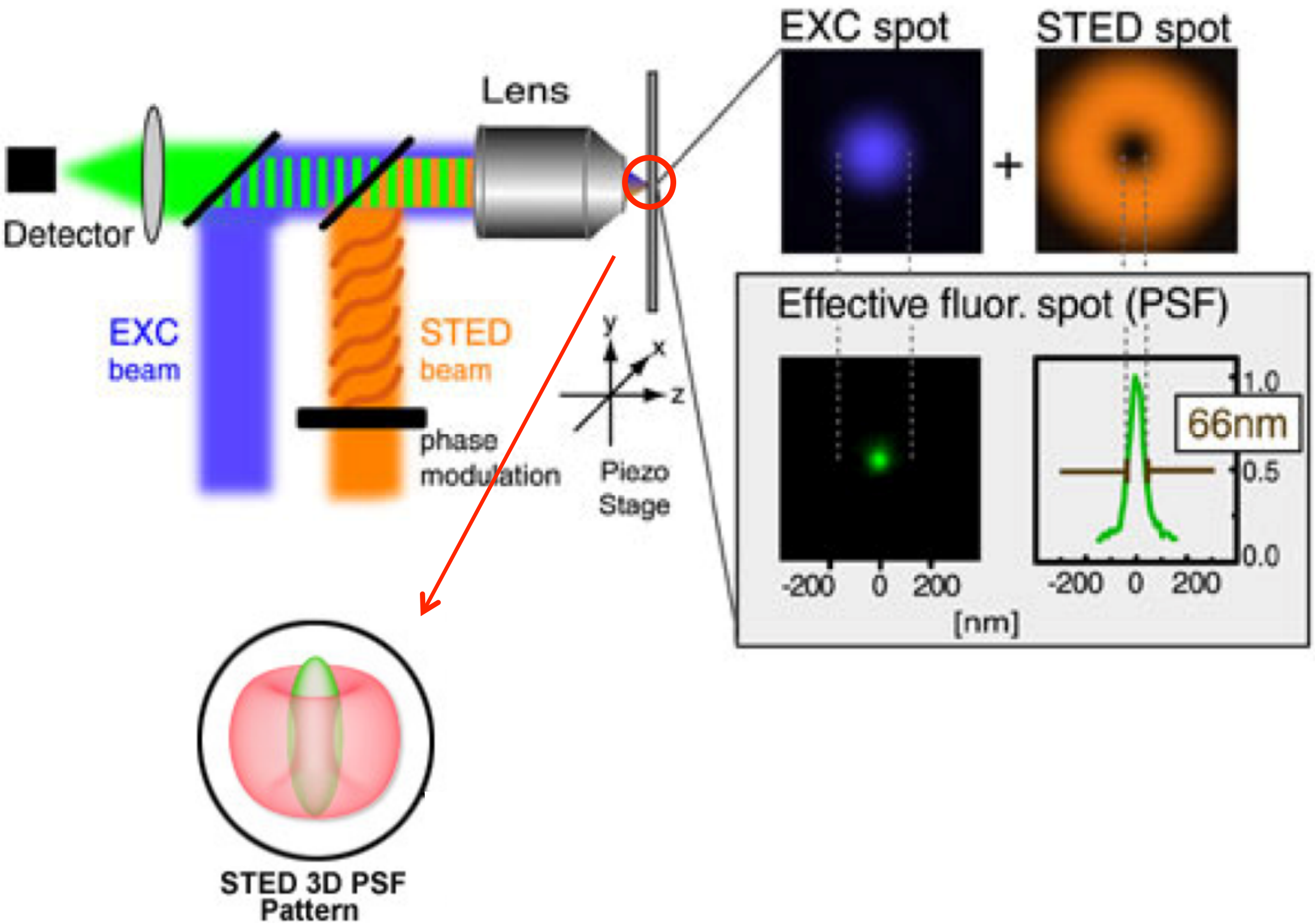
Problem:

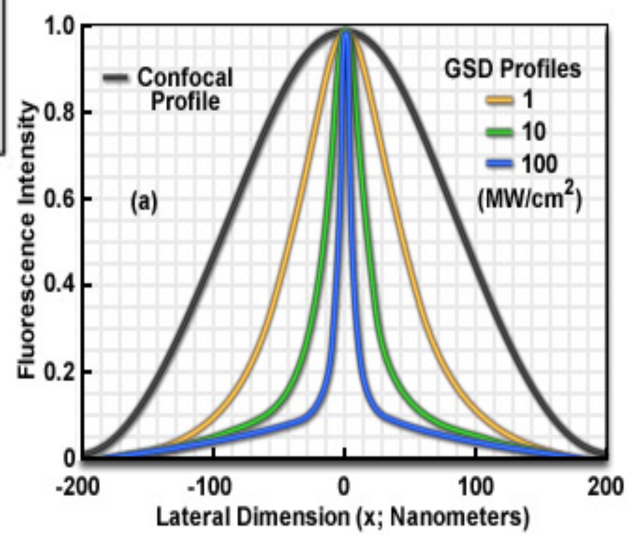


PSF > d

Microscopy at the Nanoscale: Stimulated Emission Depletion (STED)

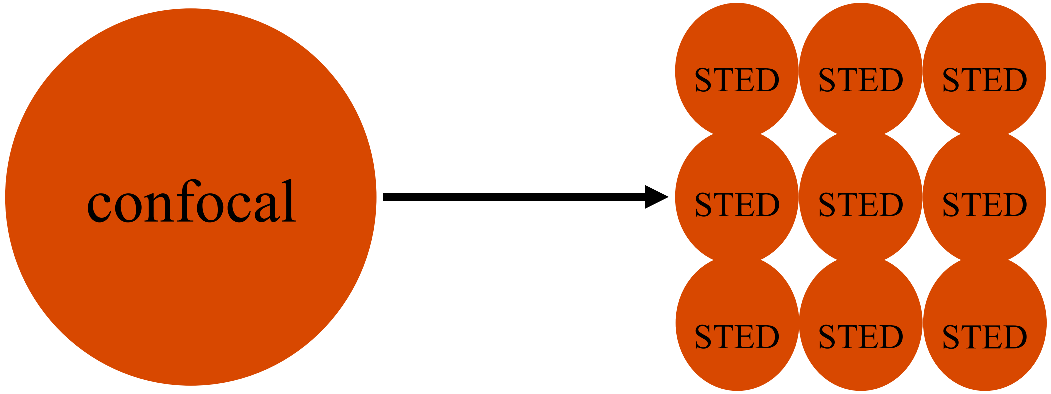
1st physical concept to break the diffraction barrier in *far-field* fluorescence microscopy (Stefan Hell)





Summary: STED Resolution

- Not limited any more by the wavelength of light!
- Just depends on the level of fluorescence depletion.
- Practically, diffraction unlimited resolution (lateral resolution < 90 nm)



A threefold improvement in resolution along the *x/y* focal plan

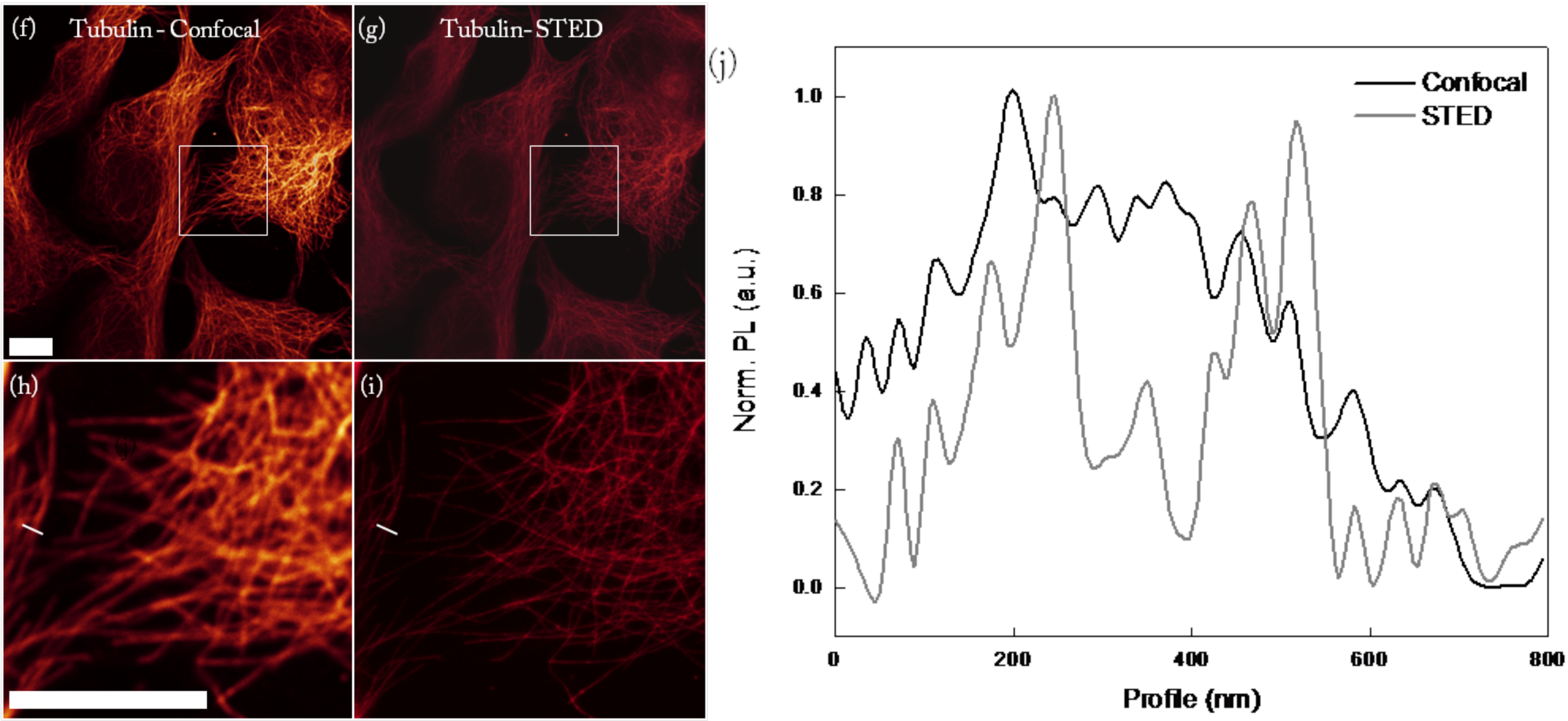
→ 9 effective scanning spots created out of 1 !

- 1st physical concept to break the diffraction barrier in *far-field* fluorescence microscopy with visible light and regular lenses!
- Light microscopy at the nanoscale = nanoscopy!
- New law; a modification of Abbe's law:
- First STED microscope in the USA!

$$\Delta x \approx \frac{\lambda}{2n\sin\alpha\sqrt{1 + I/I_{sat}}}$$

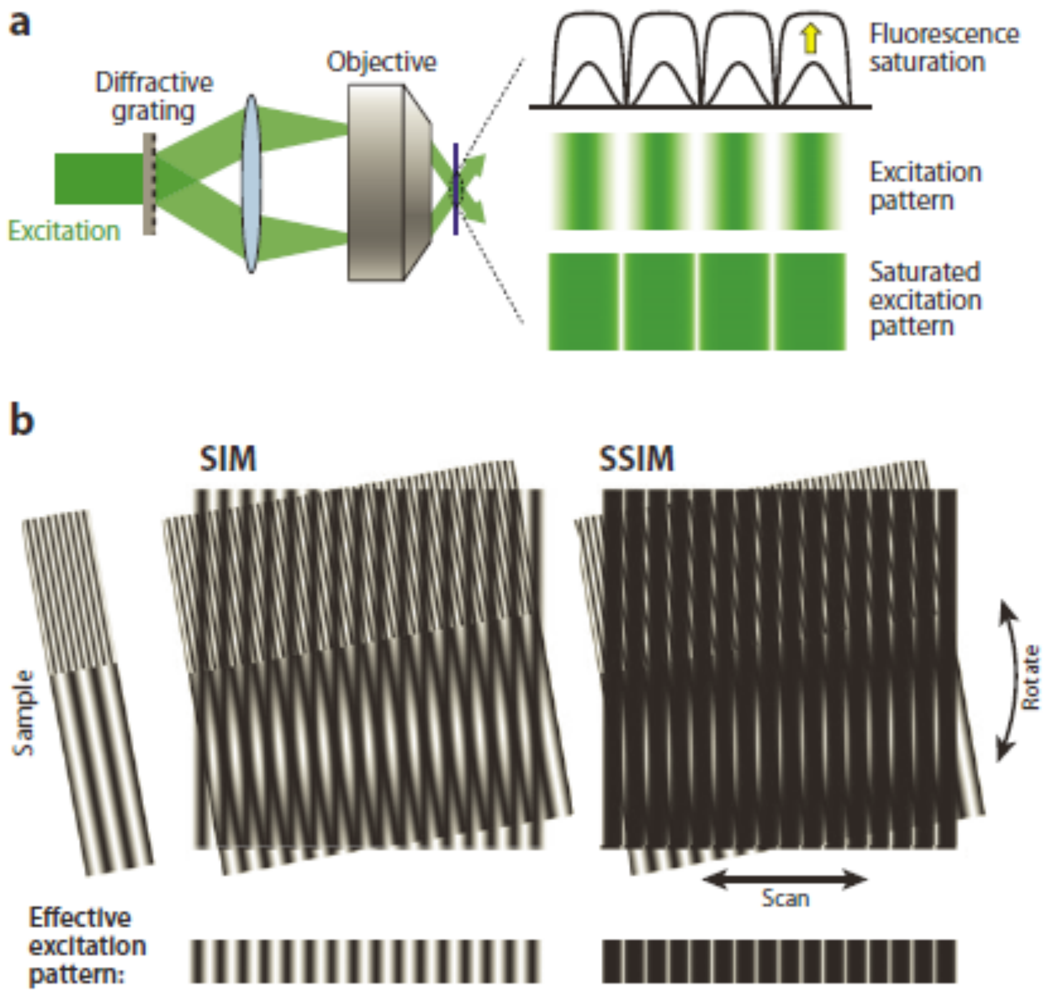
V. Westphal & S.W. Hell (2005) *Phys. Rev. Lett, 94, 143903.*

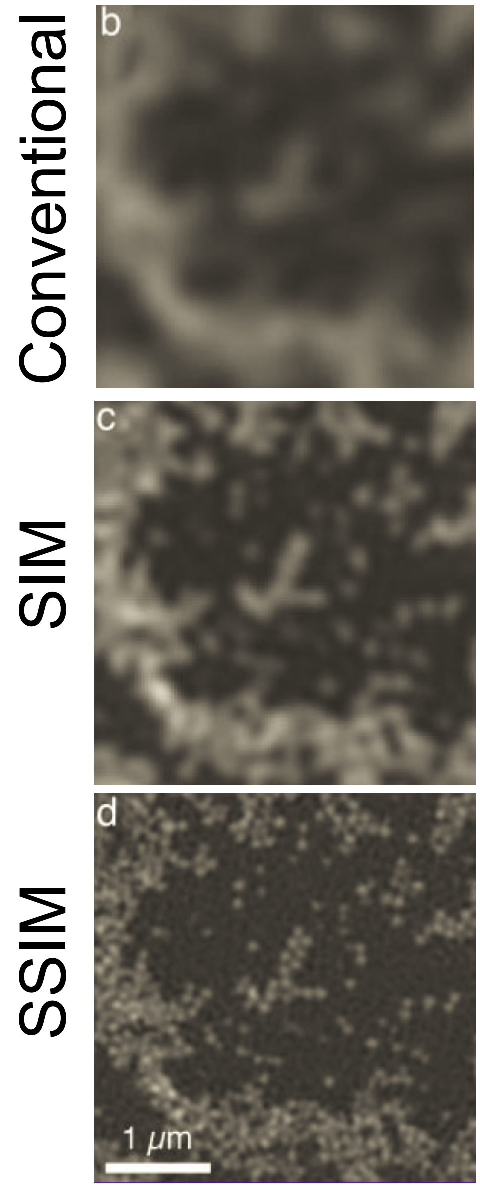
Application of STED



Farahani, Schibler and Bentolila (2010) *Microscopy: Science, Technology, Applications and Education*, Vol. II, pp 1539-1547.

Saturated Structured-Illumination Microscopy (SSIM)



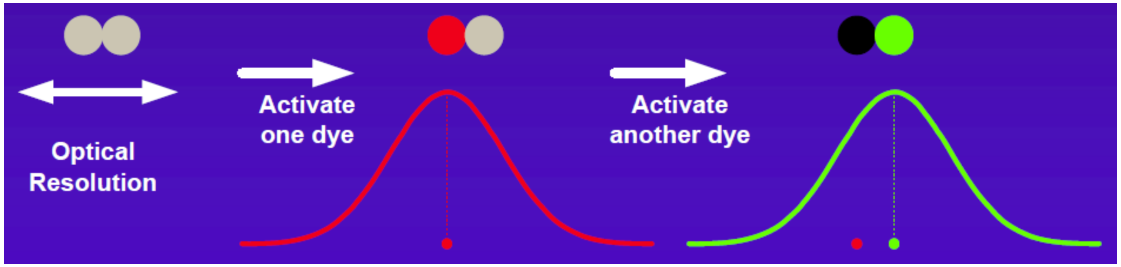


Gustafsson MGL. (2005) PNAS102:13081–86

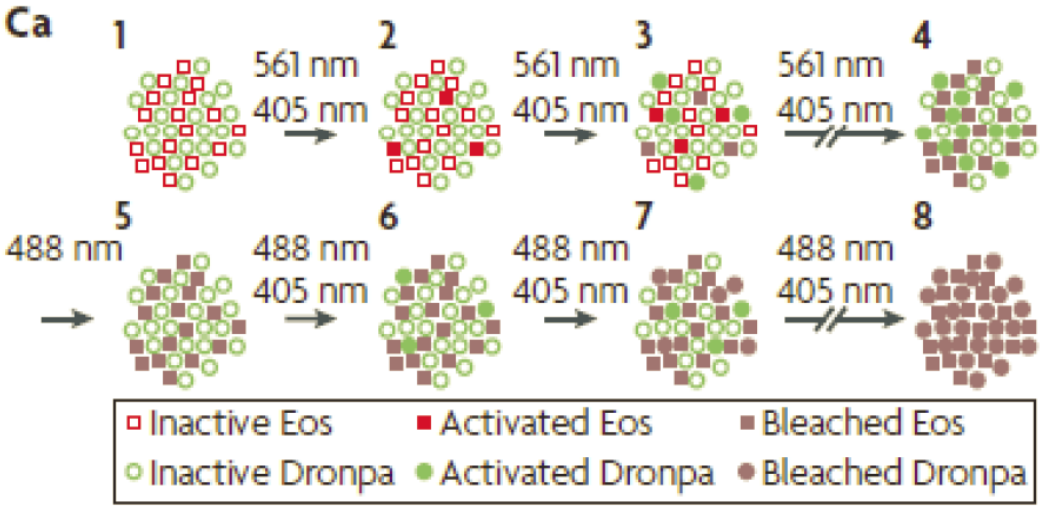
Use Moire pattern effect to detect diffraction limited objects.
A resolution of 100 nm in the lateral direction and 300 nm in the axial direction has been achieved.

Photo-activated Localization Microscopy (PALM)

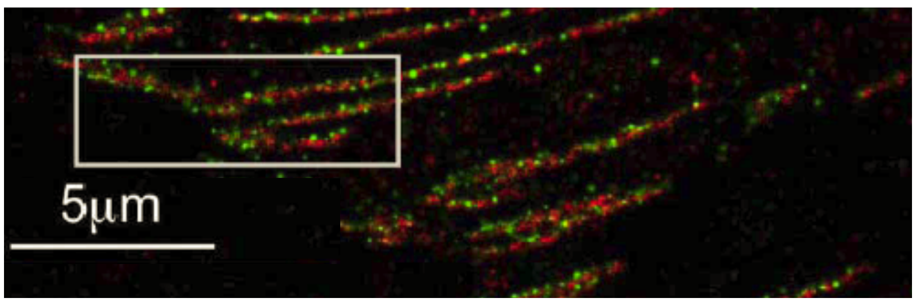
Same concept as STORM but different Dyes (FPs: EoS and Dronpa)



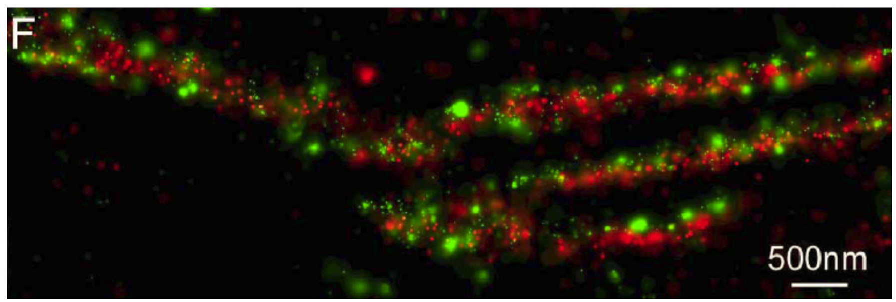
Shroff et al, (2007) PNAS 104:20308



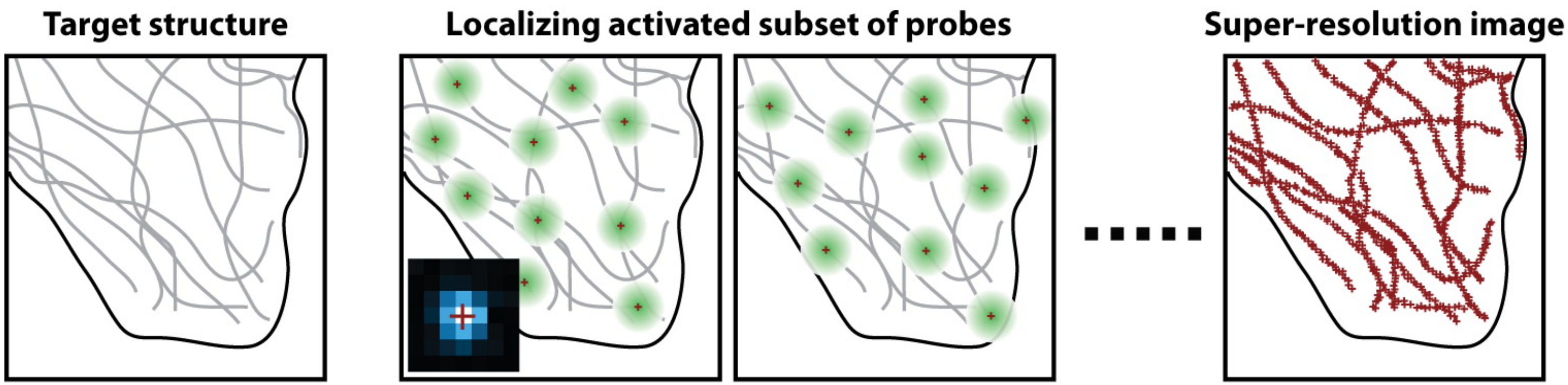
1) Activate Eos with 405
2) Image activated Eos with 488
3) Activate Eos
4) Continue to image all Eos
5) Deactivate all Dronpa with strong 488
6) Activate Dronpa with 405
7) Image activated Dronpa
8) Continue to image all Dronpa



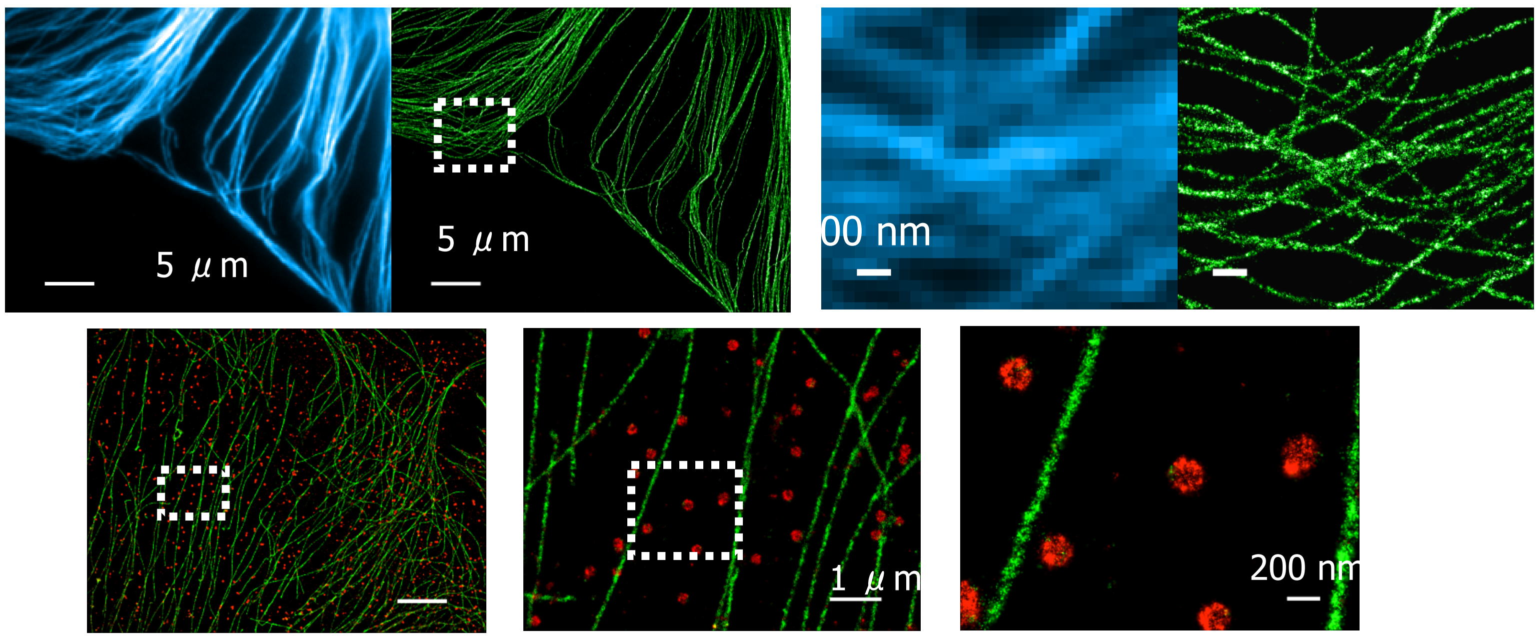
Cytoskeletal α-actinin and adhesion complex localized vinculin



Stochastic Optical Reconstruction Microscopy (STORM)



B-SC-1 cell, Microtubules stained with anti-β tubulin Cy3 / Alexa 647 secondary antibody



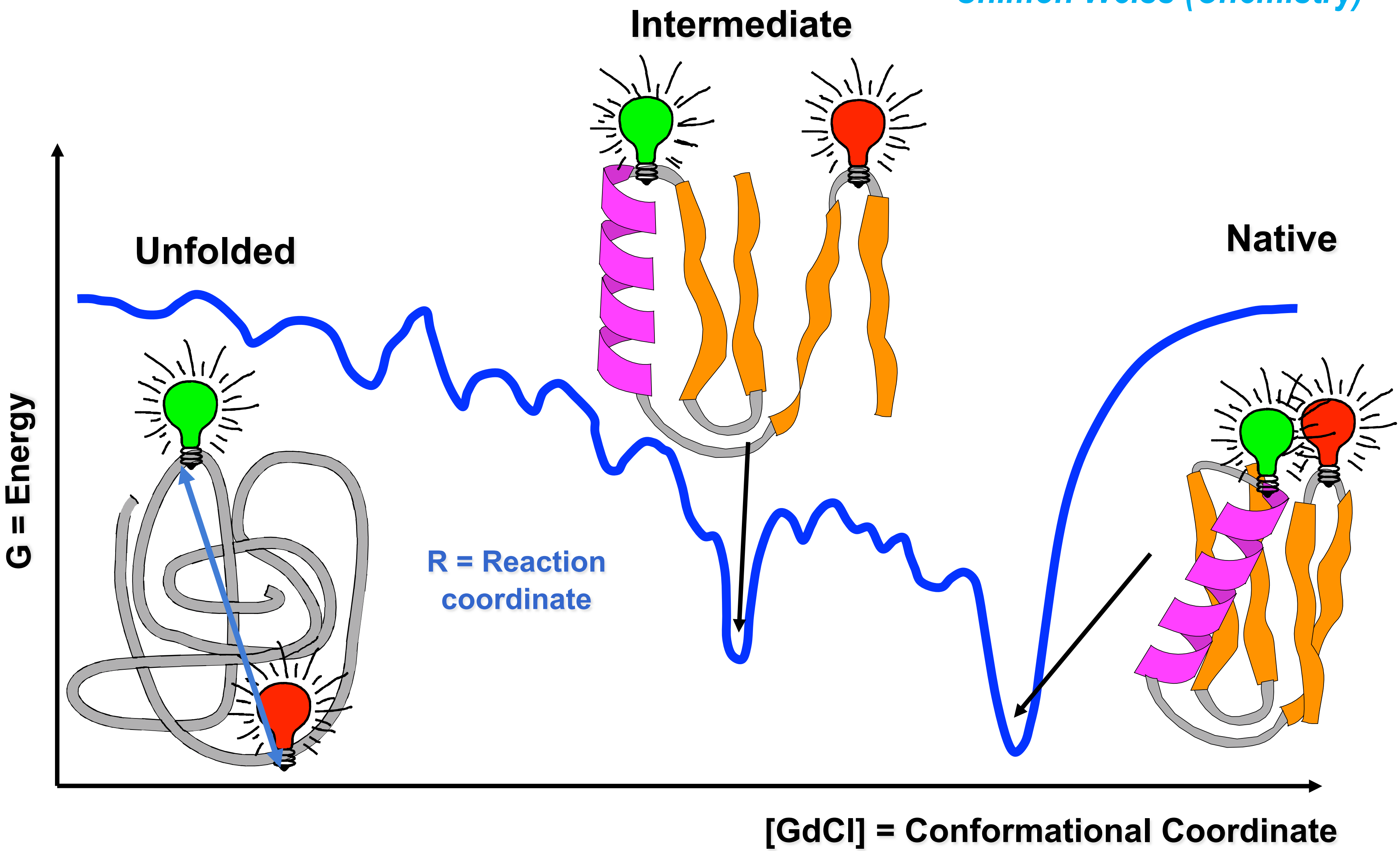
Cy3 / Alexa 647: Clathrin, Cy2 / Alexa 647: Microtubule

Bates et al, *Science* **317**, 1749 – 1753 (2007)

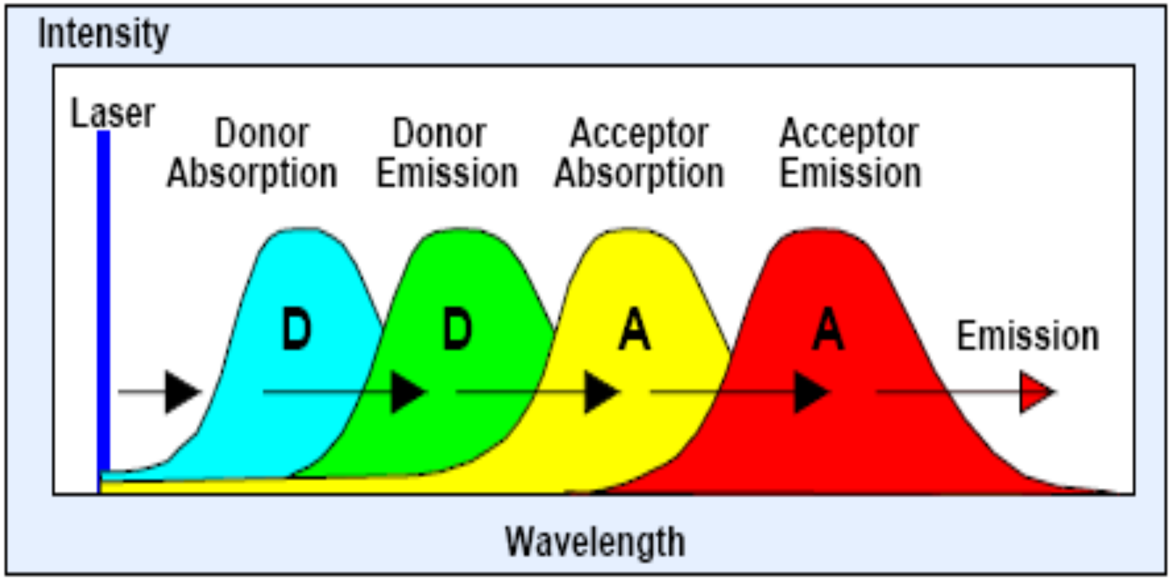
FLIM
(Fluorescence Life time Imaging)

Protein Folding by single pair Förster Resonant Energy Transfer (spFRET)

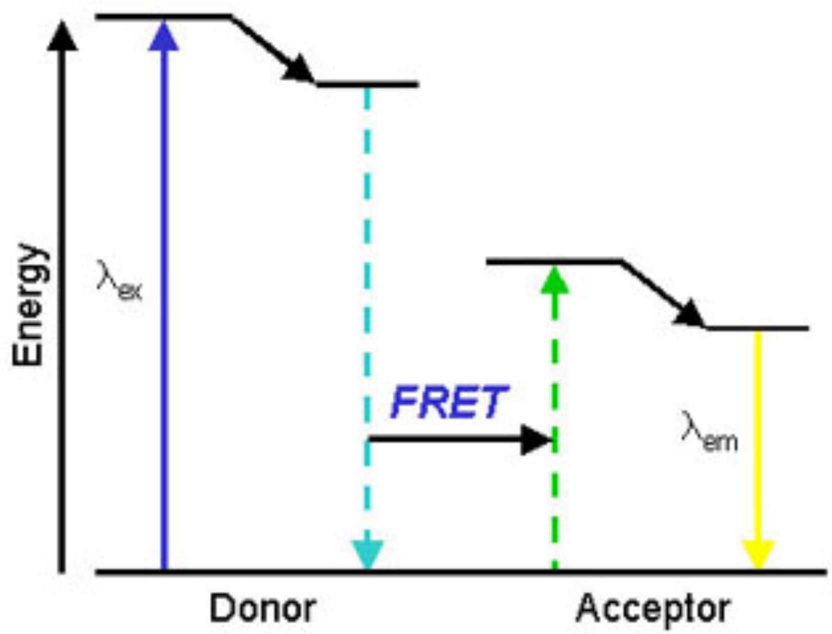
Shimon Weiss (Chemistry)

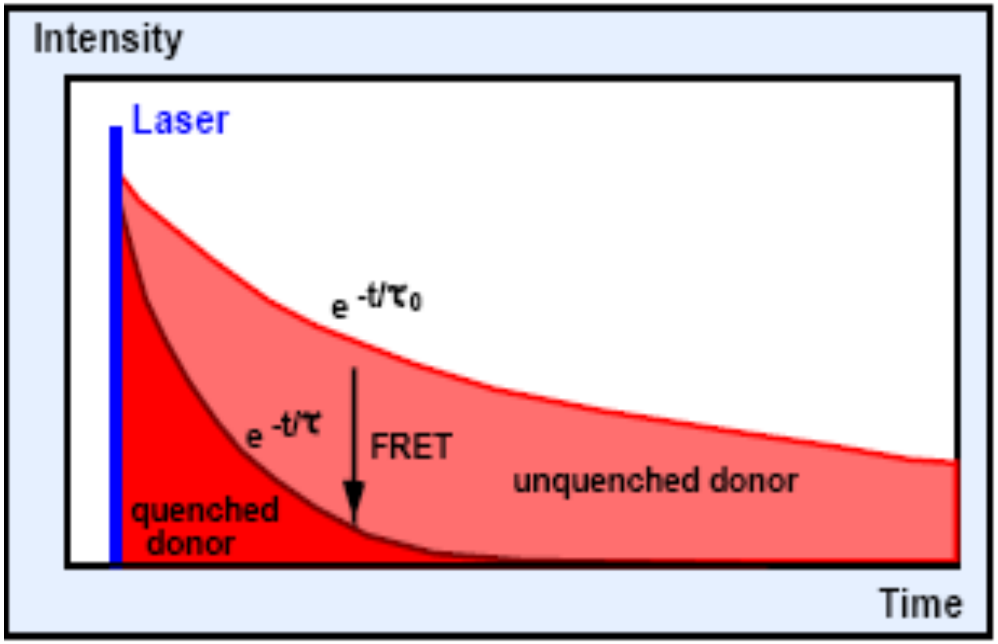


Förster Resonant Energy Transfer (FRET)



nm → nsec





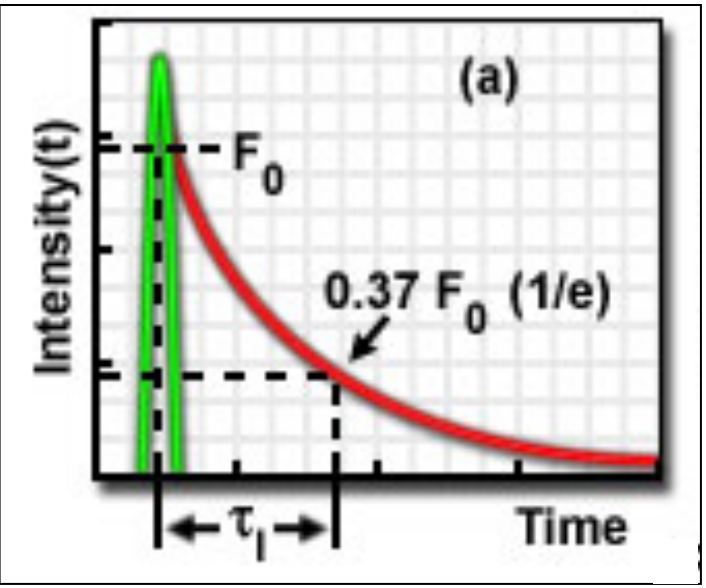
Fluorescence Lifetime Imaging (FLIM)

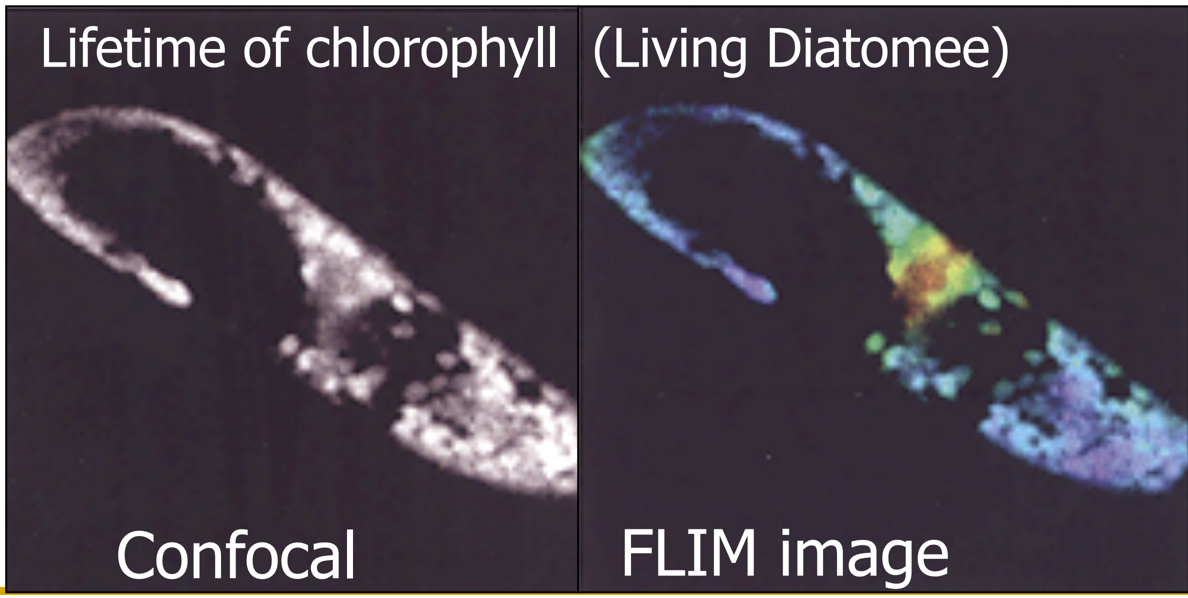
Principle

- Each fluorescent dye has its own lifetime in the excited state
- In live cells, fluorescence lifetime is affected by the local environment
- FLIM is insensitive to fluctuations in fluorochrome concentration and excitation light intensity
- It is based on time-correlated single photon counting technology

Applications

- Mapping of local environment such as pH, oxygen, ion concentrations, intracellular signal transduction, FRET, and membrane potential



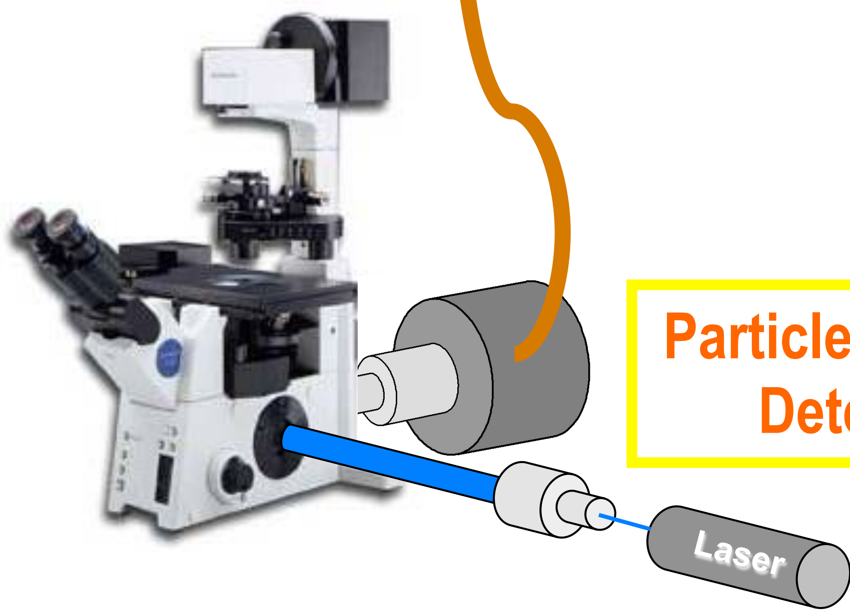


High-speed Microscopes

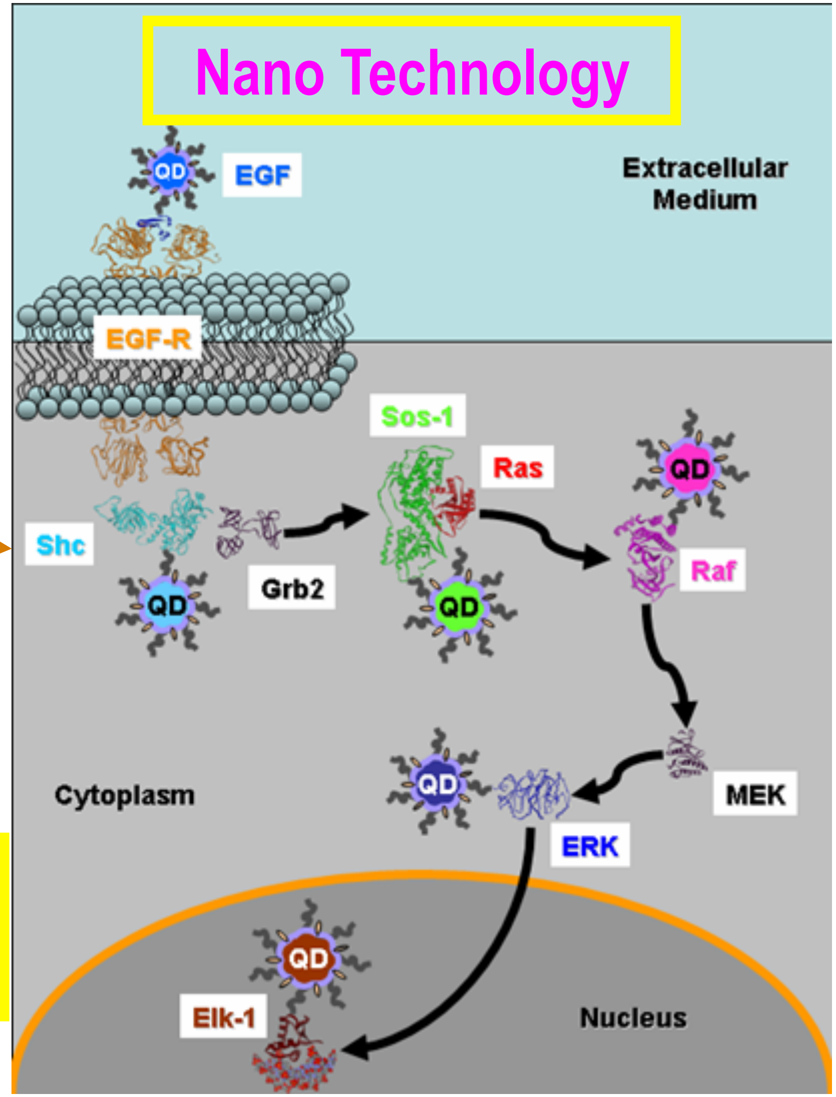
Single Molecule Imaging

January 2006

Shimon Weiss (Chemistry)

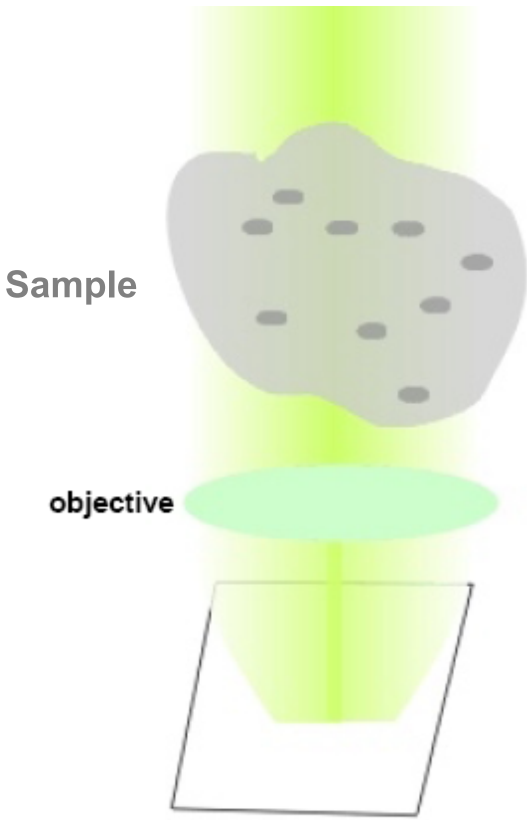


Particle Physics Detector



Principle of High-speed Bio Imaging

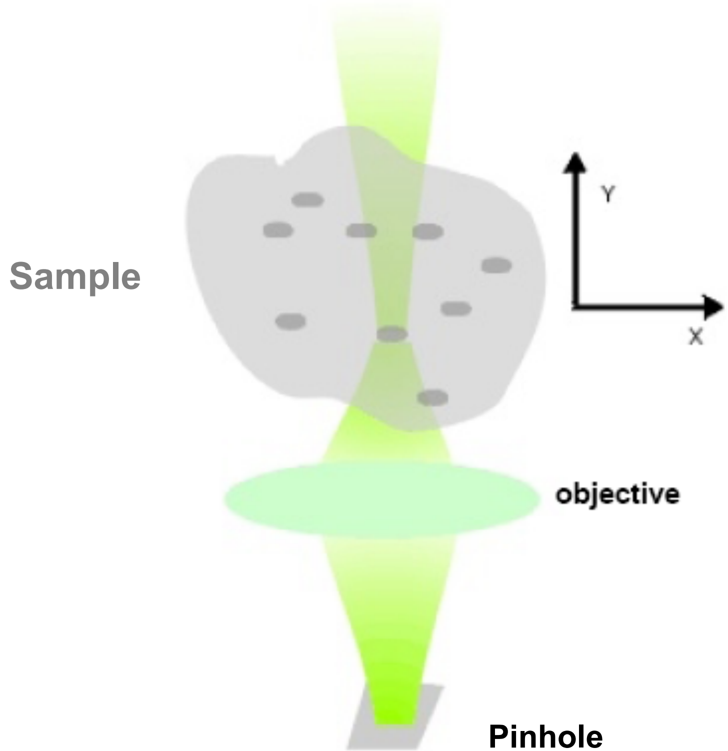
Wide Field



CCD + FADC (10 – 50 MHz)

CMOS [FADC (50 MHz) * 100]

Confocal



PMT + FADC (10 – 50 MHz)

[HAPD + FADC (1 GHz)] * 64

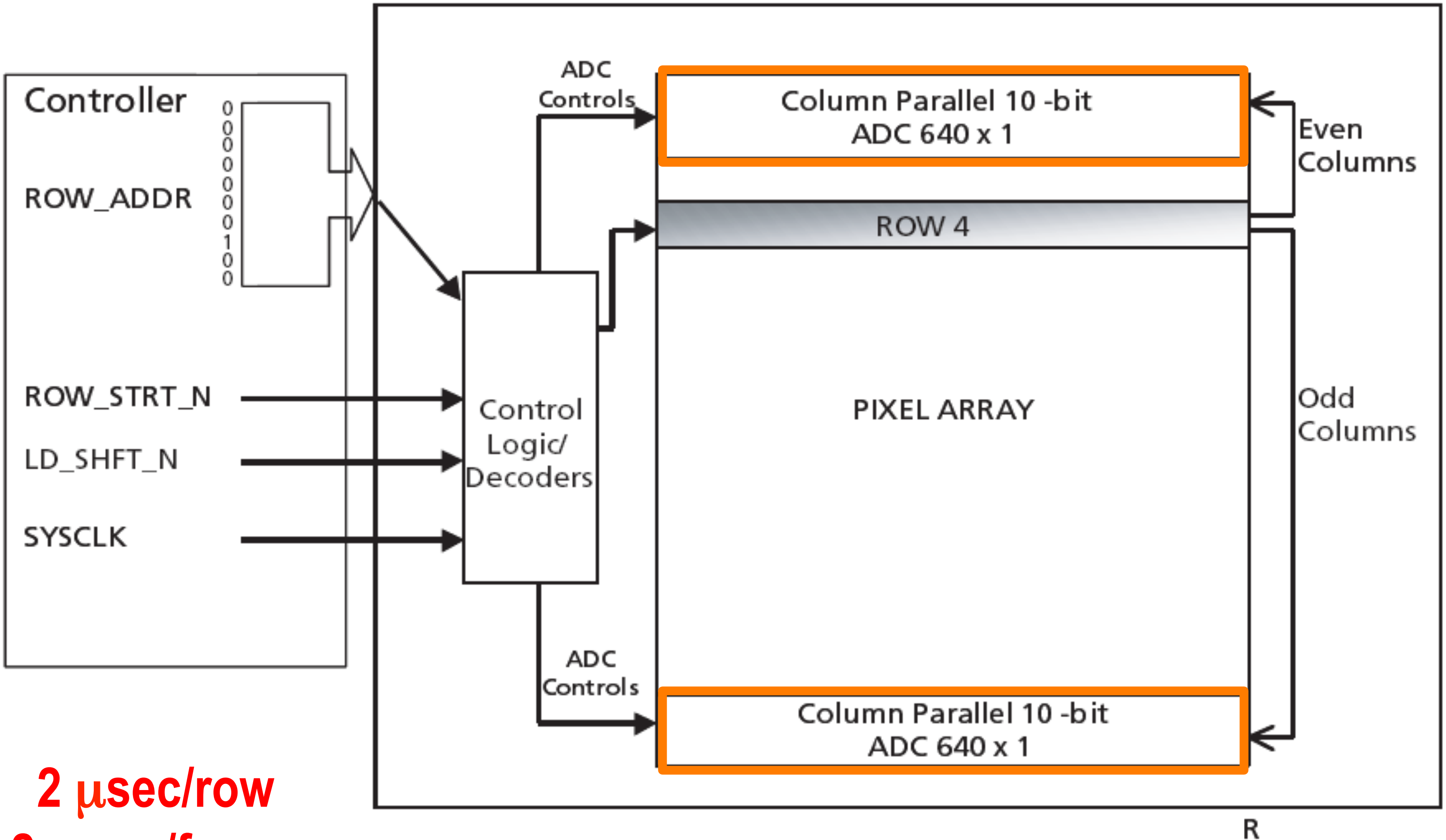
How to speed up microscopes

- All the existing microscopes are limited by the narrow bandwidth of readout.
  - Just one channel of FADC (Flash Analog to Digital Converter) running at 10 – 50 MHz
  - So-called Video Rate (30 frame/sec)

- The first step is to adopt multiple channels of FADC for massive parallel processing.
  - Like high energy experiments (such as LHC)

- In addition, we need Single Photon Sensitivity with high Quantum Efficiency.

Micron 1.3M-Pixel CMOS Sensor



2 μsec/row
2 msec/frame

(10 bits, 66MHz)

Photron FASTCAM SA-1

PRELIMINARY SPECIFICATIONS:

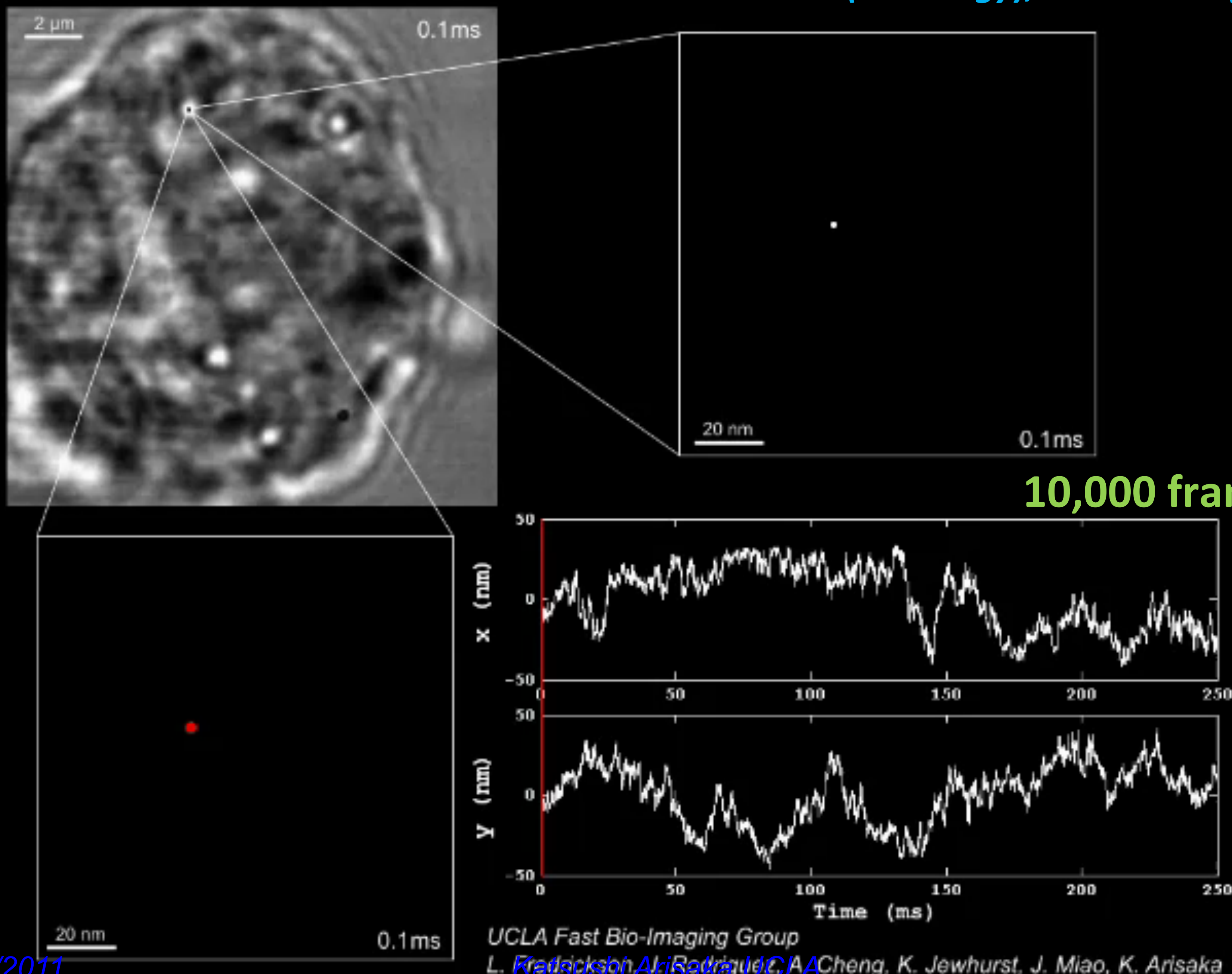
- 5,000 full mega pixel resolution fps (frames per second)
- Two microsecond global shuttering
- Two memory configurations available:
  - 8GB (6 sec. @ 1,000 full fps)
  - 16GB (12 sec. @ 1,000 full fps)
- Genuine twelve-bit resolution
- Maximum speed at reduced resolution is 150,000 fps
- Full control via Gigabit Ethernet or remote keypad with built in LCD display
- Superior light sensitivity
- IRIG/GPS
- Light weight and compact
- DC operation
- SDI and RS-170 video outputs

Photron USA, Inc.

5000 frame per sec
(200 nsec/row)

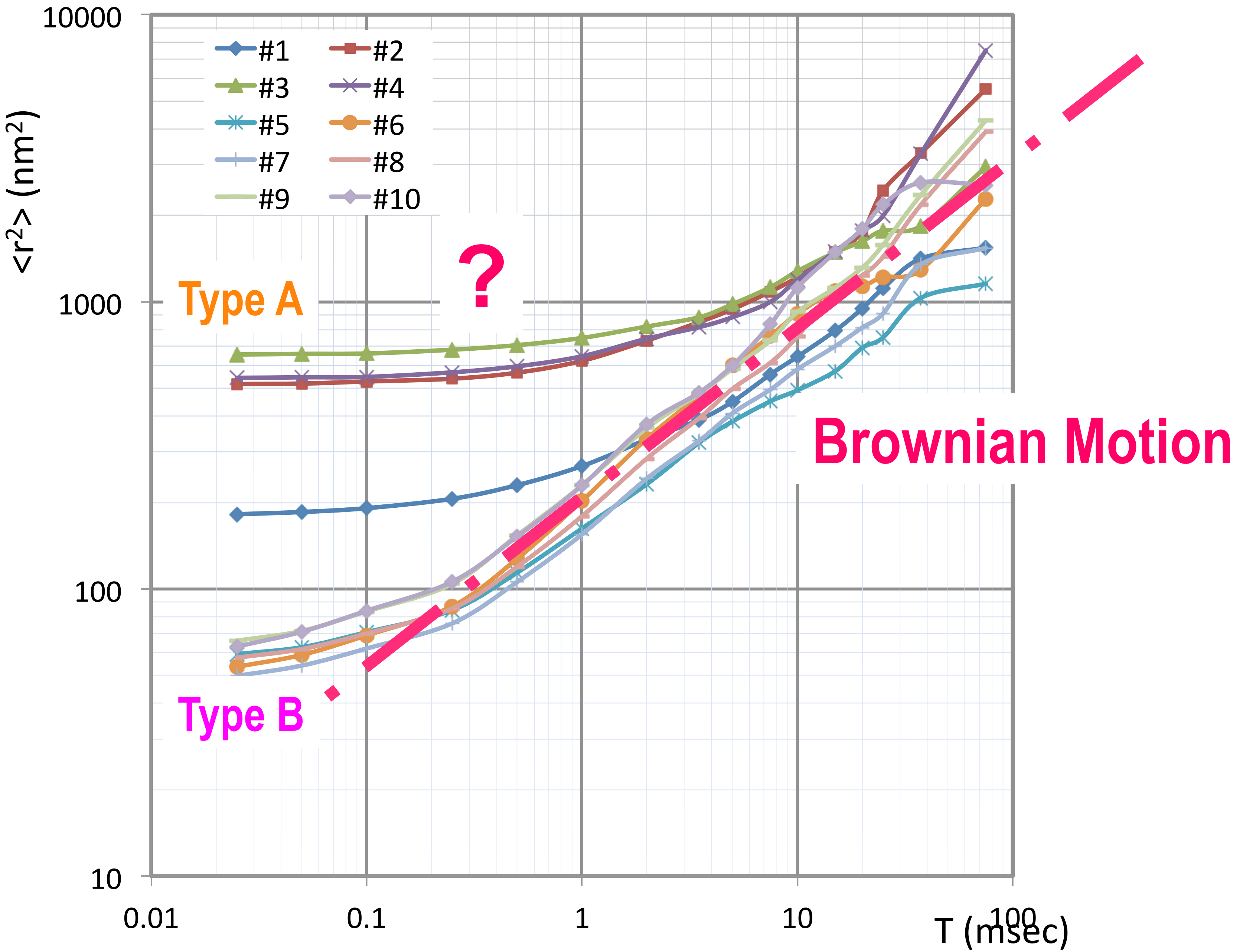
Gold nano particle (40nm) attached to Transferrin Receptor (TfR) on Cancer Cell

Manuel Penichet (Oncology), John Miao (Physics)

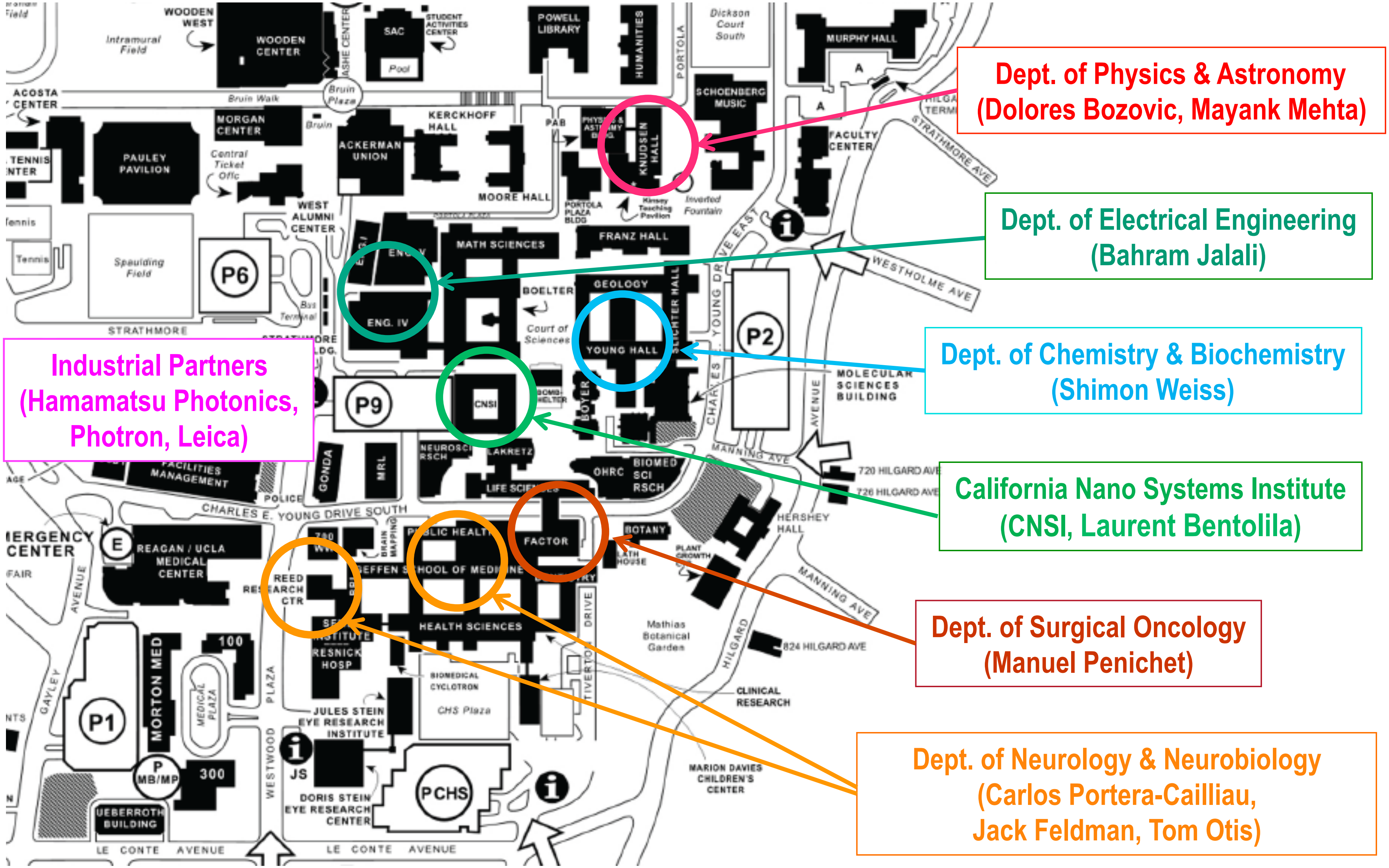


10,000 frame/sec

Mean Squire Displacement <r^2> of TfR on a Human Multiple Myeloma Cell vs. Time



Arisaka's Campus-wide Collaborations on High-Speed Bio-imaging



User-shared Core Facility of High-speed Microscopes at CNSI

CNSI (California Nano Systems Institute)

CNSI Core Lab Open House

Feb 17 (Thu)

9:00am — **Breakfast and Registration**
CNSI Lobby

9:30-11:30am — **Core Lab Presentations**
CNSI Auditorium

Welcoming Remarks
Paul Weiss, CNSI Director and Fred Kavli Chair in NanoSytems Science

Global Bio Lab
Room 6310
Hilary Godwin, Faculty Director

Integrated Systems Nanofabrication Cleanroom
A Level
Brian Matthews, Research Engineer

Integrated NanoMaterials Lab
Rooms 2133, 2139
Baolai Liang, Technical Director

Electron Imaging Center for NanoMachines
Rooms B120, B140, B146
Xing Zhang, Technical Director

Molecular Screening Shared Resource
Room 2145
Robert Damoiseaux, Scientific Director

Nano and Pico Characterization Lab
Room B133
Adam Stieg, Technical Director

Advanced Light Microscopy/Spectroscopy (with Macro-Scale Imaging Facility)
Room B145
Laurent Bentolila, Scientific Director

11:30-3:00pm — **Core Lab Tours & Demonstrations**
Levels A, B, 2, 6

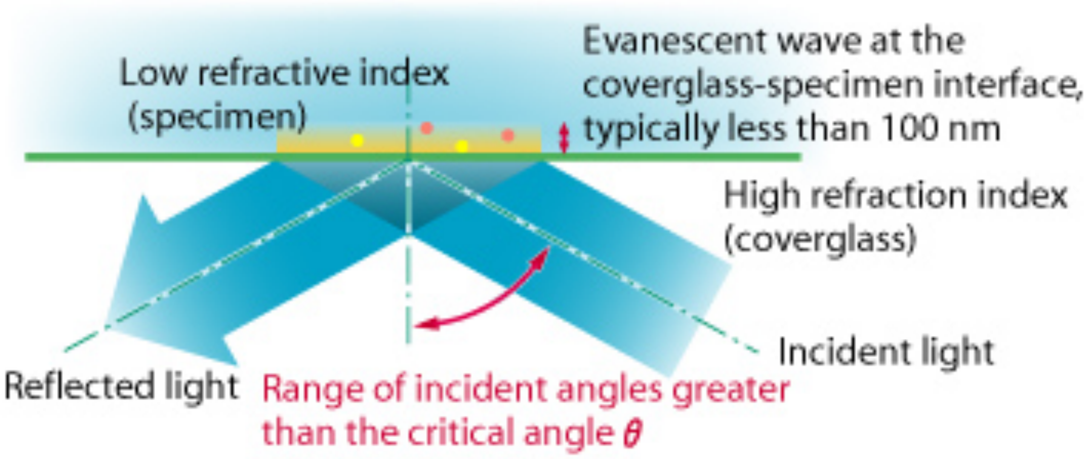
All labs will be open to view equipment and learn more about each lab's specialty.

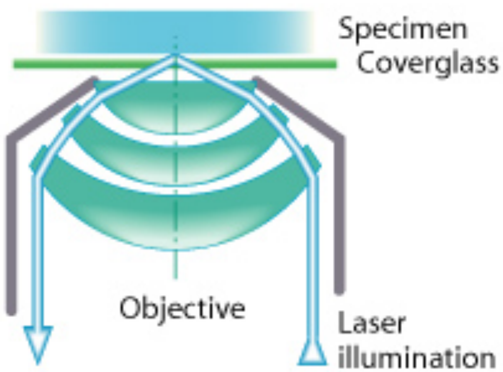
Demonstrations of the Equipment Reservation System will be available throughout the building.

1:00pm — **Lunch**
CNSI Lobby

Guests who participate during the presentations or visit a core lab will receive lunch.

Nikon Microscope TE200E with TIRF at CNSI





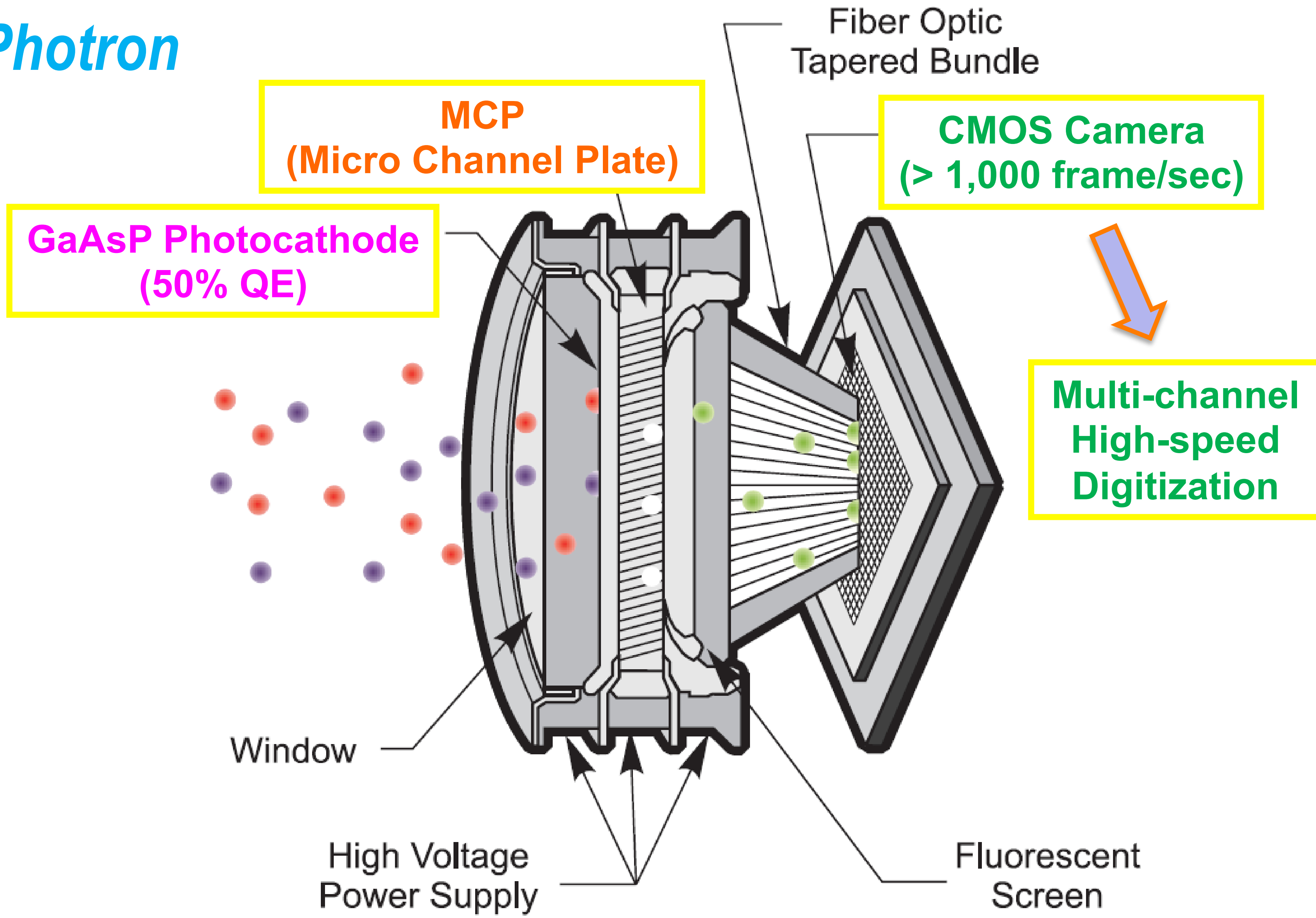
Laurent Bentolila (CNSI)

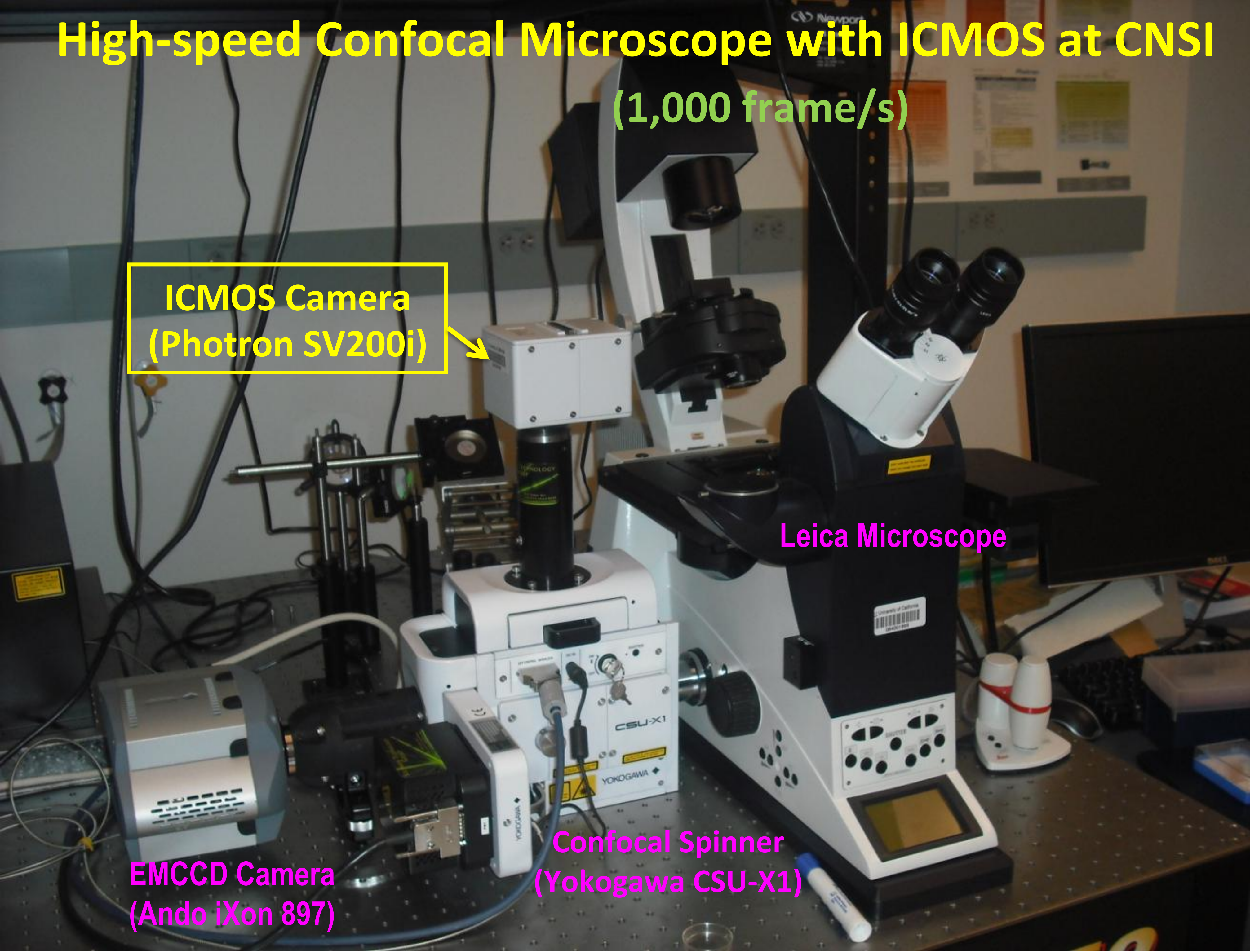
5k – 500k fps

CMOS Camera
Photron SA-1

Image Intensified CMOS Camera

Photron

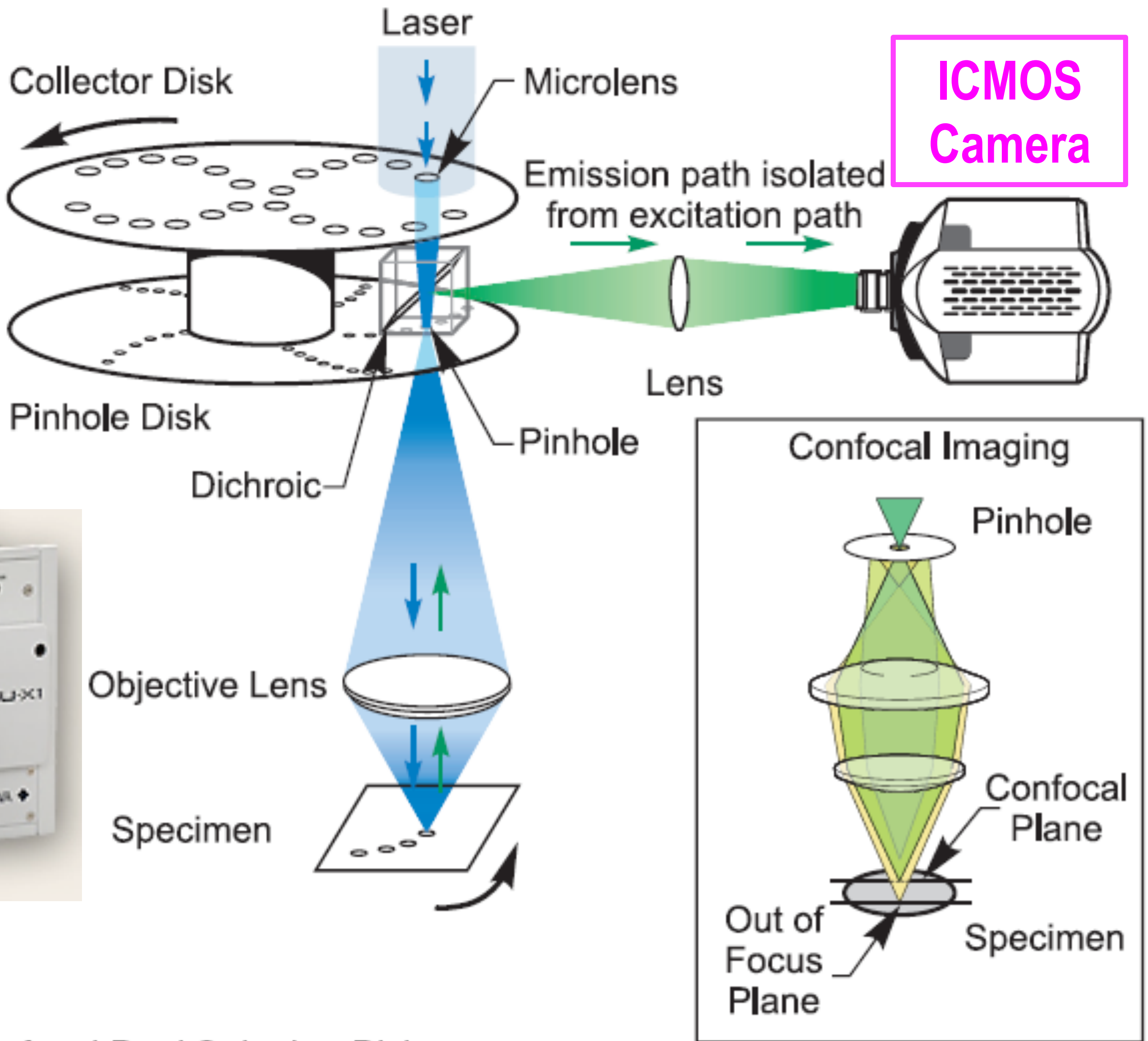



High-speed Confocal Microscope with ICMOS at CNSI
(1,000 frame/s)
ICMOS Camera
(Photron SV200i)
Leica Microscope
Confocal Spinner
(Yokogawa CSU-X1)
EMCCD Camera
(Ando iXon 897)
CSU-X1
YOKOGAWA

Yokogawa CSU-X1

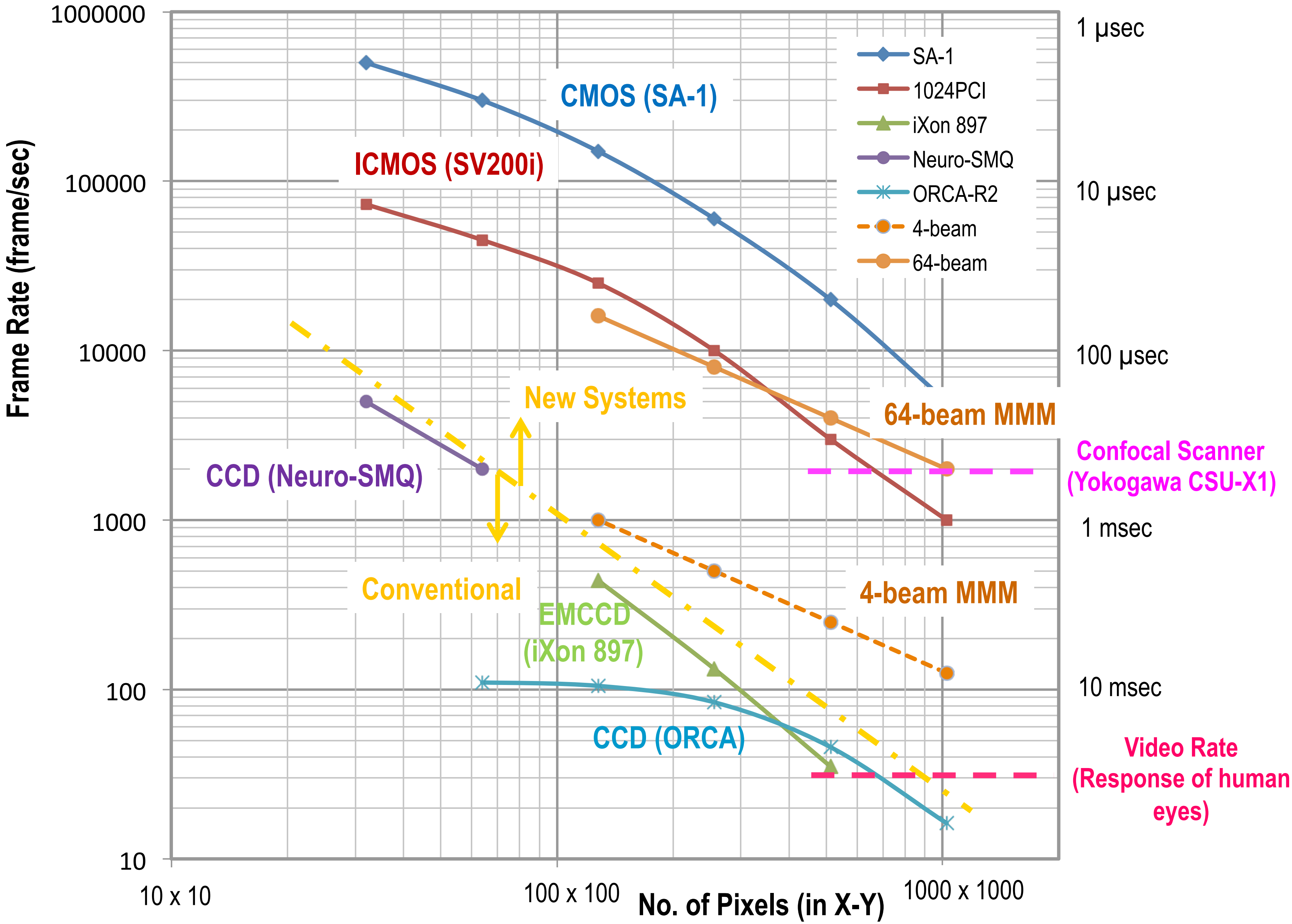
2,000 fps

ICMOS Camera



Confocal Dual Spinning Disk

Frame Rate vs. Resolution

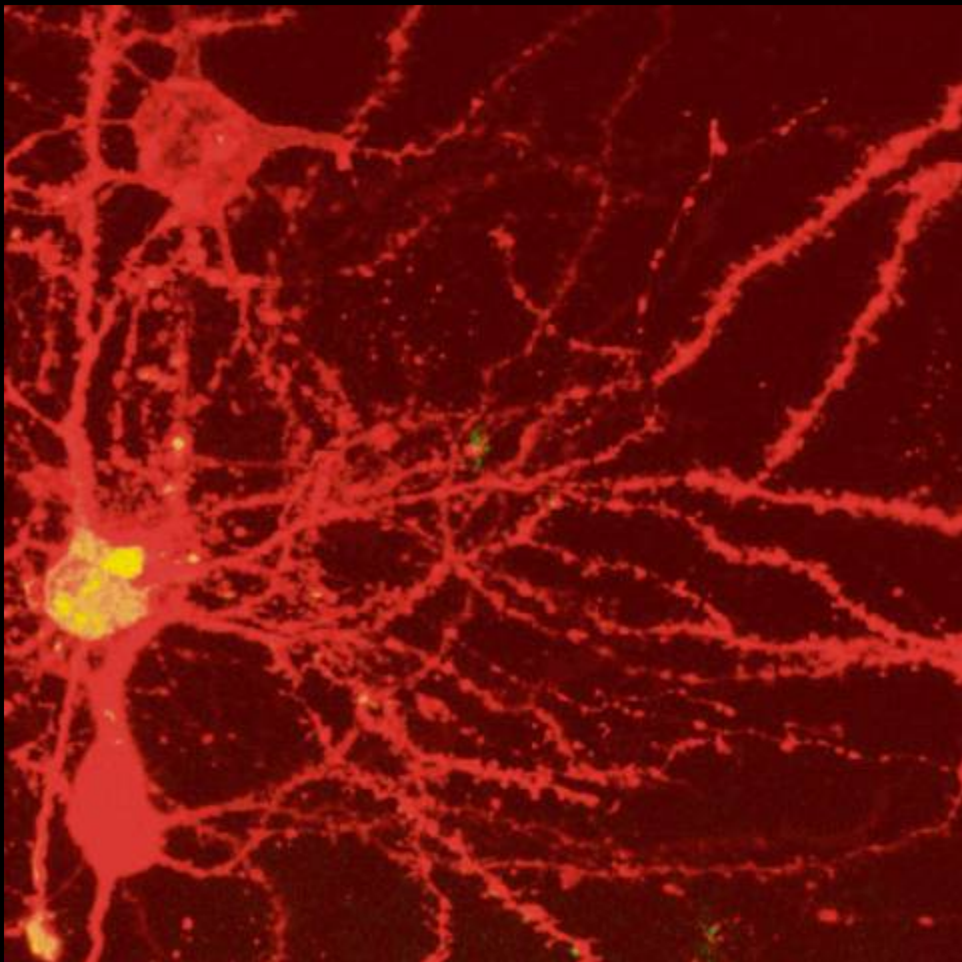


6D Bio-Imaging

- Ideally observation of Live cells requires the detection of photon intensity (I) in 6 dimension: I (x, y, z, λ, τ, T)
  - x:
  - y:
  - z: Location in depth
  - λ: Wave length of emitted photons
  - τ: Time delay of emitted photons after excitation
  - T: Frame rate.
- Photo-detectors have lower dimension:
  - PMT: I(T) at 50 MHz
  - CCD: I(x, y, T) at 30 Hz
  - CMOS: I(x, y, T) at 5 kHz
- Therefore, "compactification of extra dimension" is required.

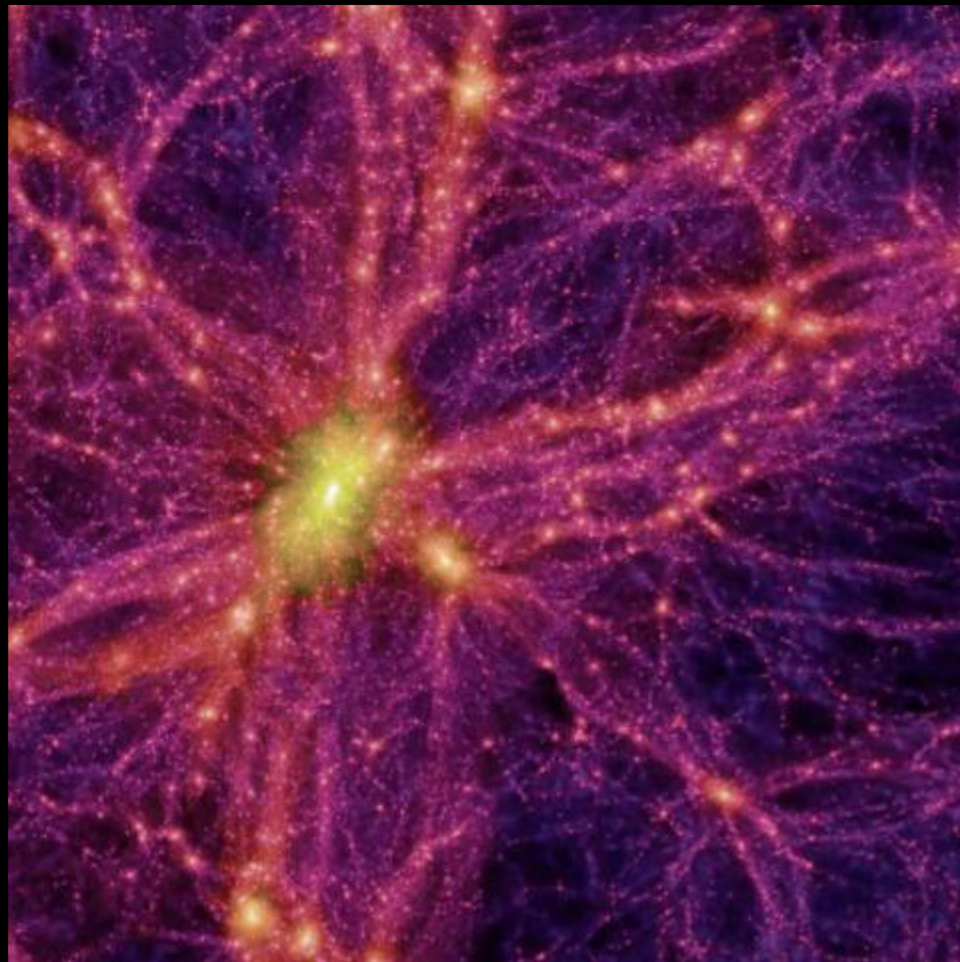
Applications to Neuroscience

Brain



100 Billions Neurons

Universe



100 Billions Galaxies

New York Times 8/21/2006

Ca^{2+} Signal in cultivated Rat's Brain by Confocal Microscope

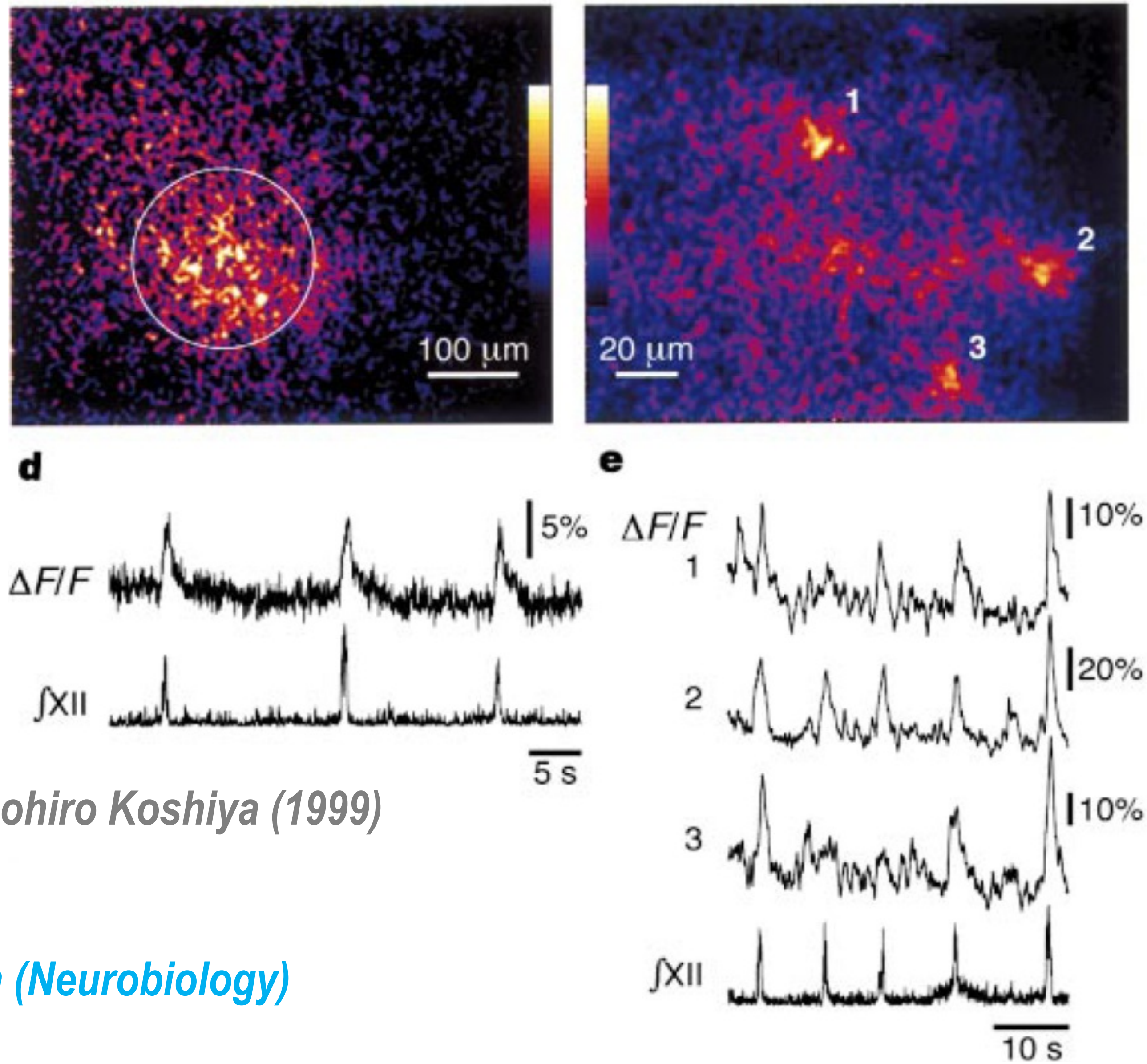
Comparison of Imaging

Methods	Electrophysiology Tetrodes	Optical Microscope Two Photon Excitation	fMRI BOLD
Sensitive to	Electric potential	Calcium iron	Metabolism
Position resolution	10 μm	1 μm	200 μm
Temporal Resolution	0.1 msec	10 msec	1 sec
Coverage	~200 μm cube	≤500 μm cube	Whole brain
Penetration depth	Any depth	up to 500 μm	Whole brain
Advantages	Single spike resolution	Anatomical identification of neurons	Whole brain imaging, non-invasive
Limitations	Invasive, can't identify active neurons	Shallow penetration, poor time resolution	Poor spatial and temporal resolution

High-speed observations

Neural Networks for Breathing

~300 neurons in rat's brain (pre-Botzinger Cells) responsible for breathing

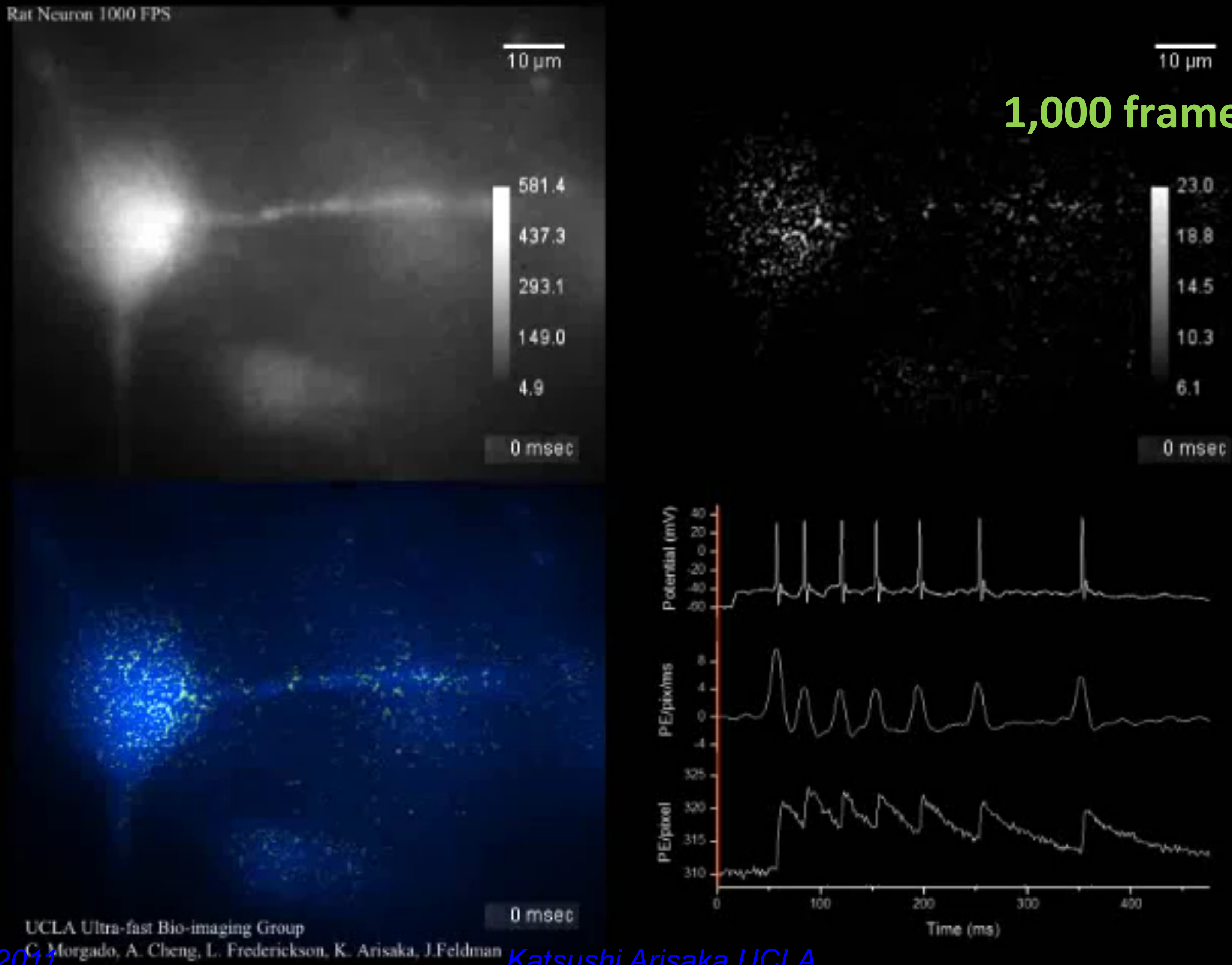


Nature by Naohiro Koshiya (1999)

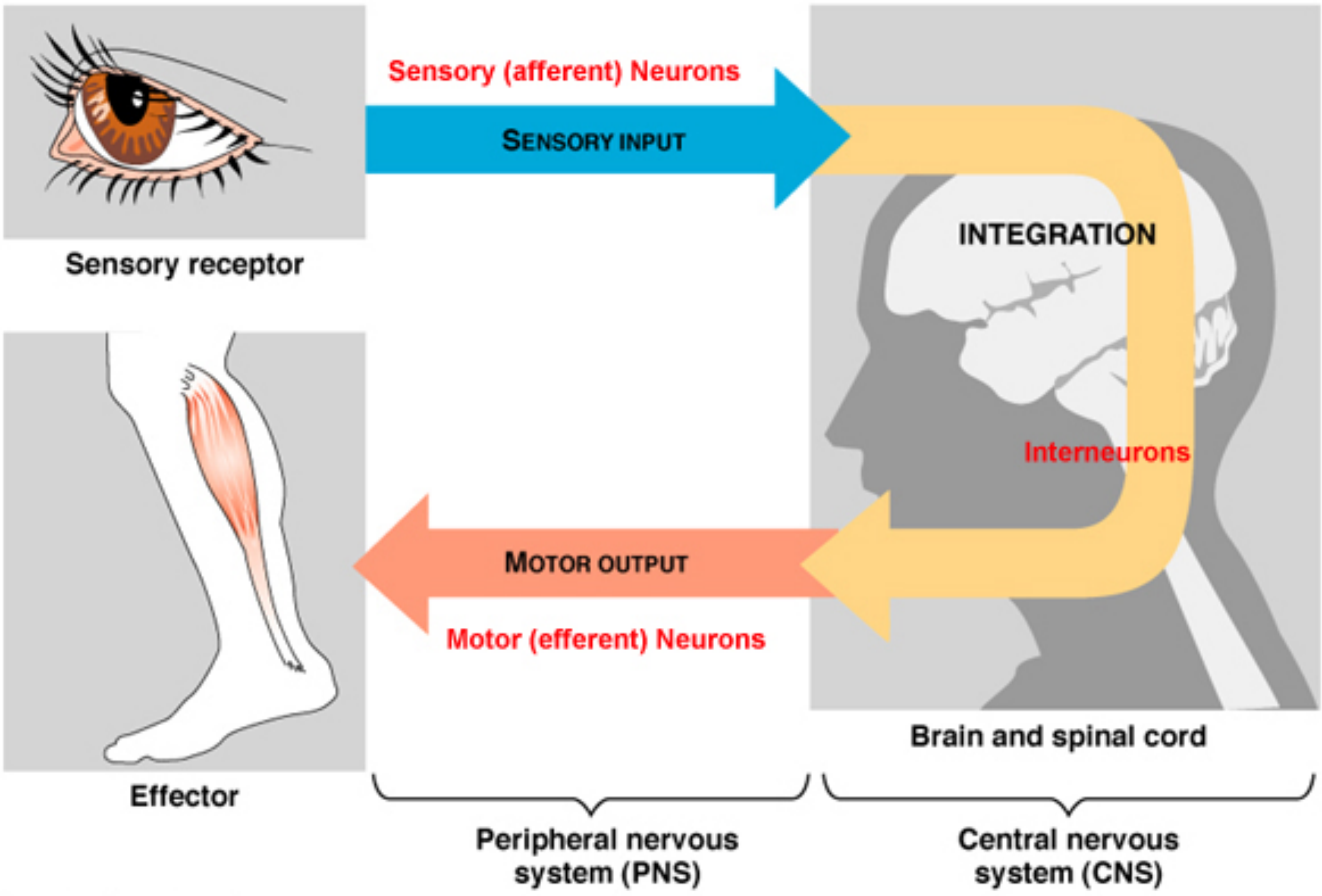
Jack Feldman (Neurobiology)

High-speed Ca^{2+} Imaging of pre-Botzinger Cells of Rats

Jack Feldman (Neurobiology)

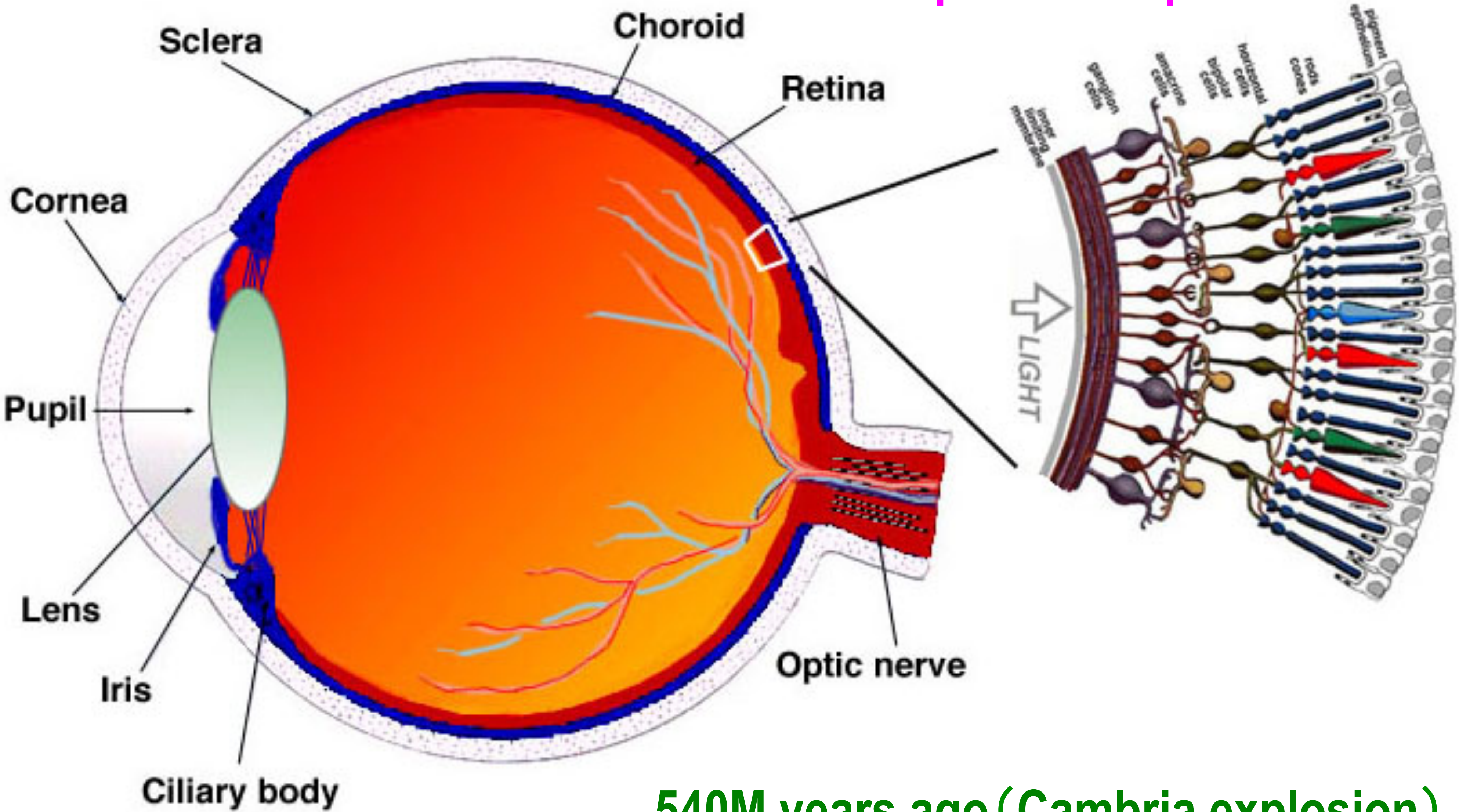


Sensory Input and Decision Making in Brain



Human Eyes

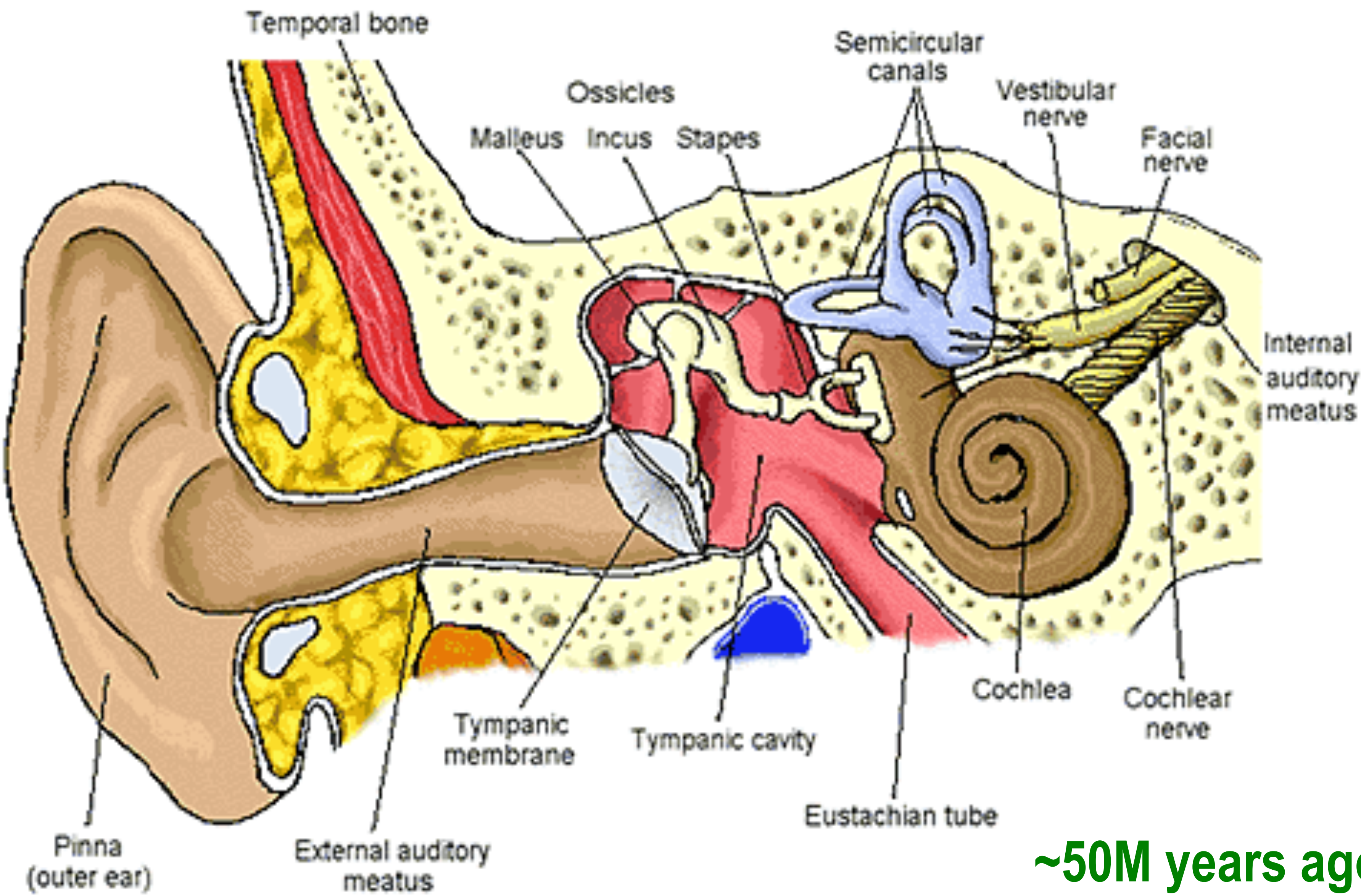
~100M photo receptors



540M years ago（Cambria explosion）

Human Ears

~10,000 Hair Cells

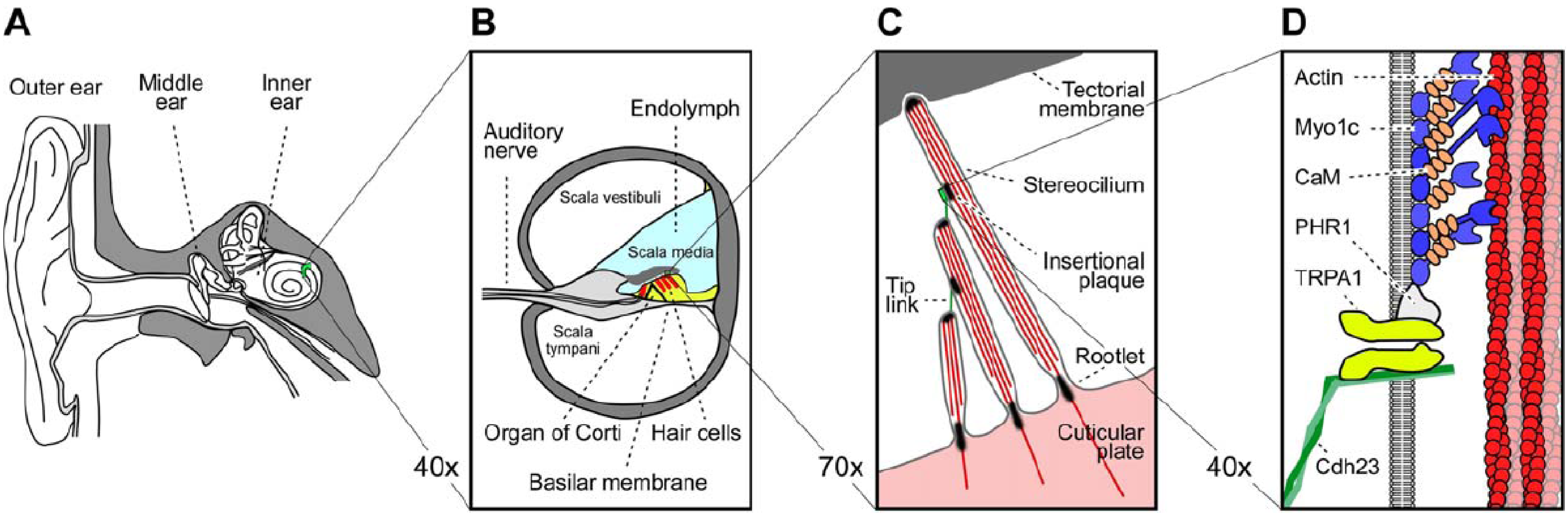


~50M years ago

Anatomy of Inner Ear

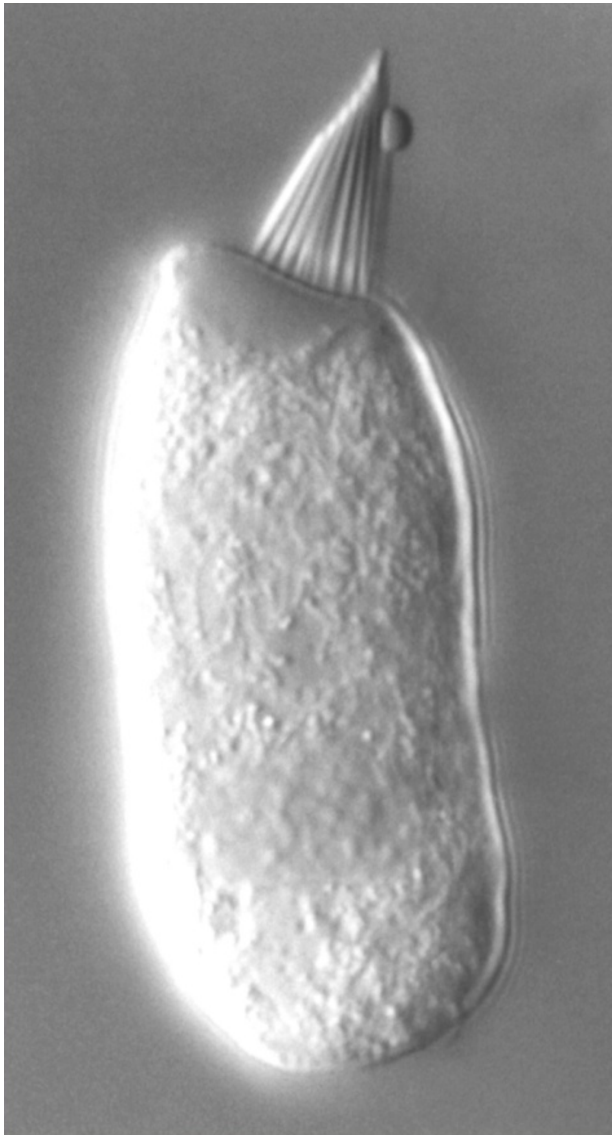
Dolores Bozovic (Physics)

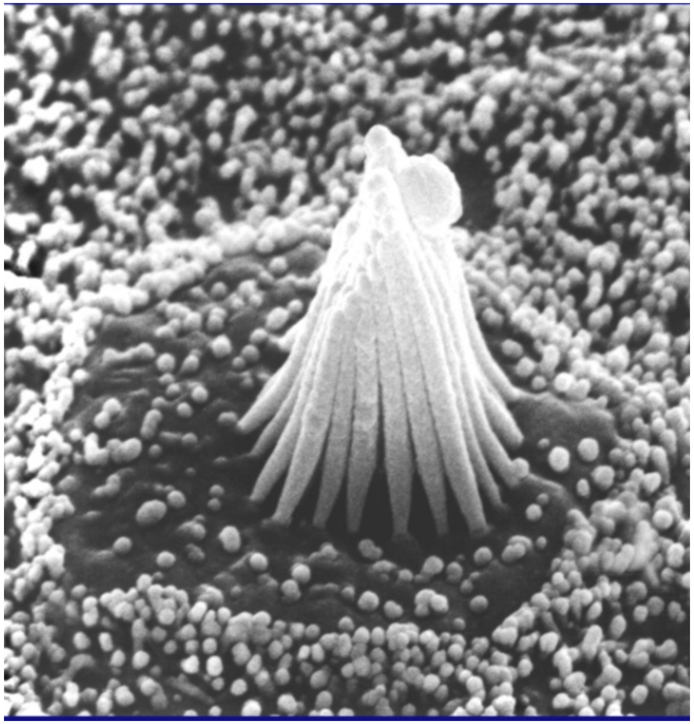
Human auditory system — **Cross-section of the cochlear** — **Hair bundle** — **Molecular mechano-transduction machinery**

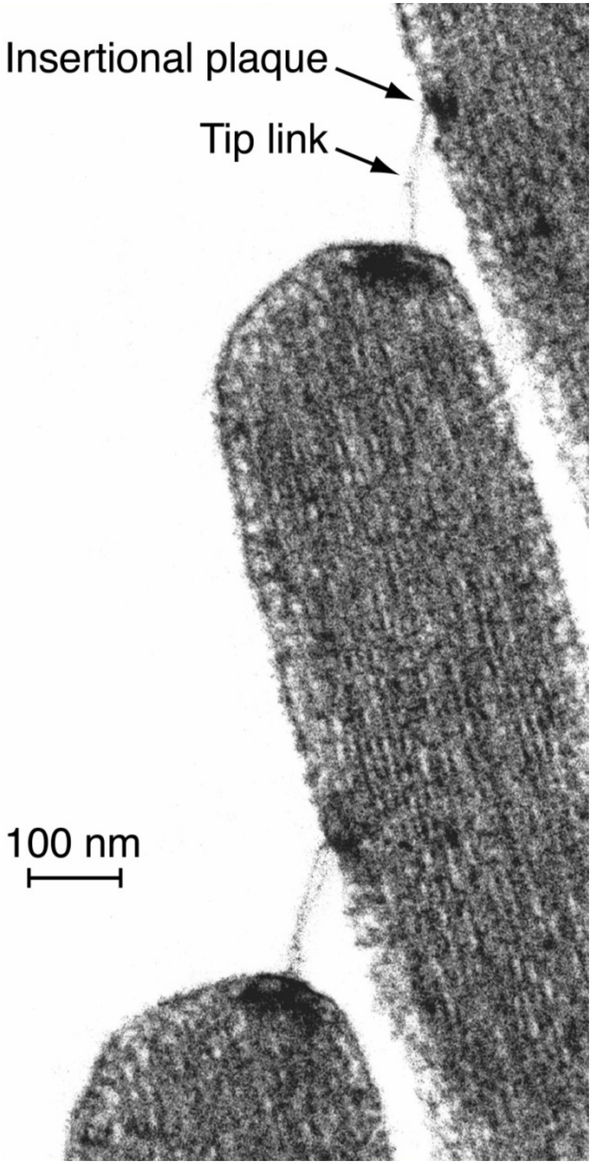


Meredith LeMasurier and Peter G. Gillespie, Neuron, Vol. 48,2005

Hair cell, bullfrog sacculus

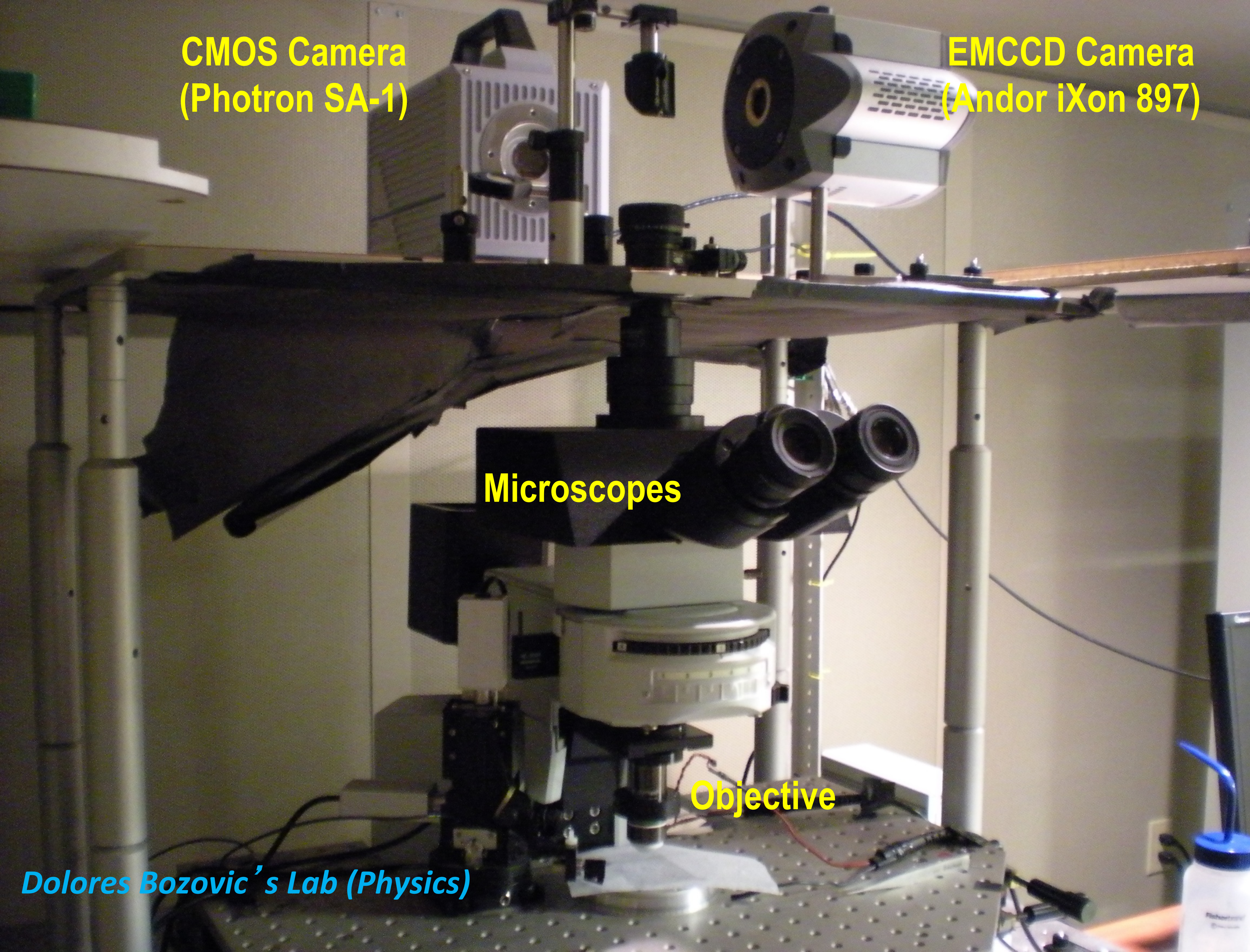






A. J. Hudspeth, Rockefeller University

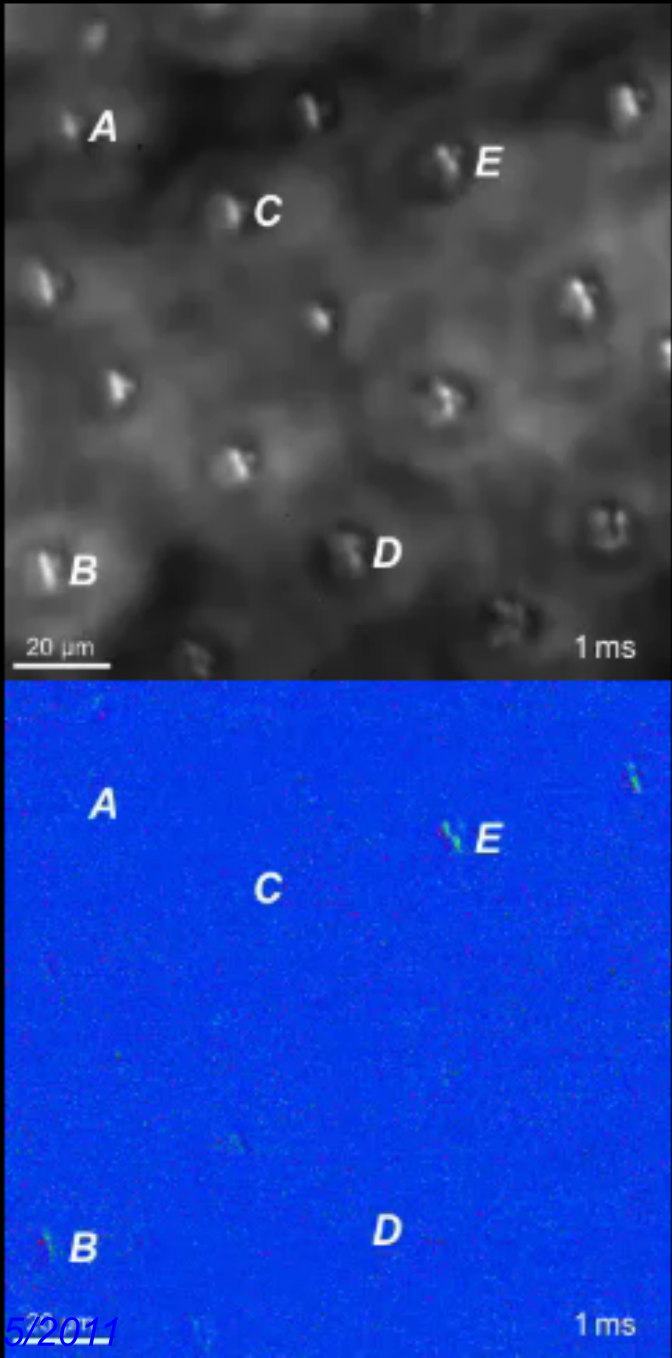
Hudspeth, A. J. & Gillespie, P. G., *Neuron* **12**:1-9 (1994).

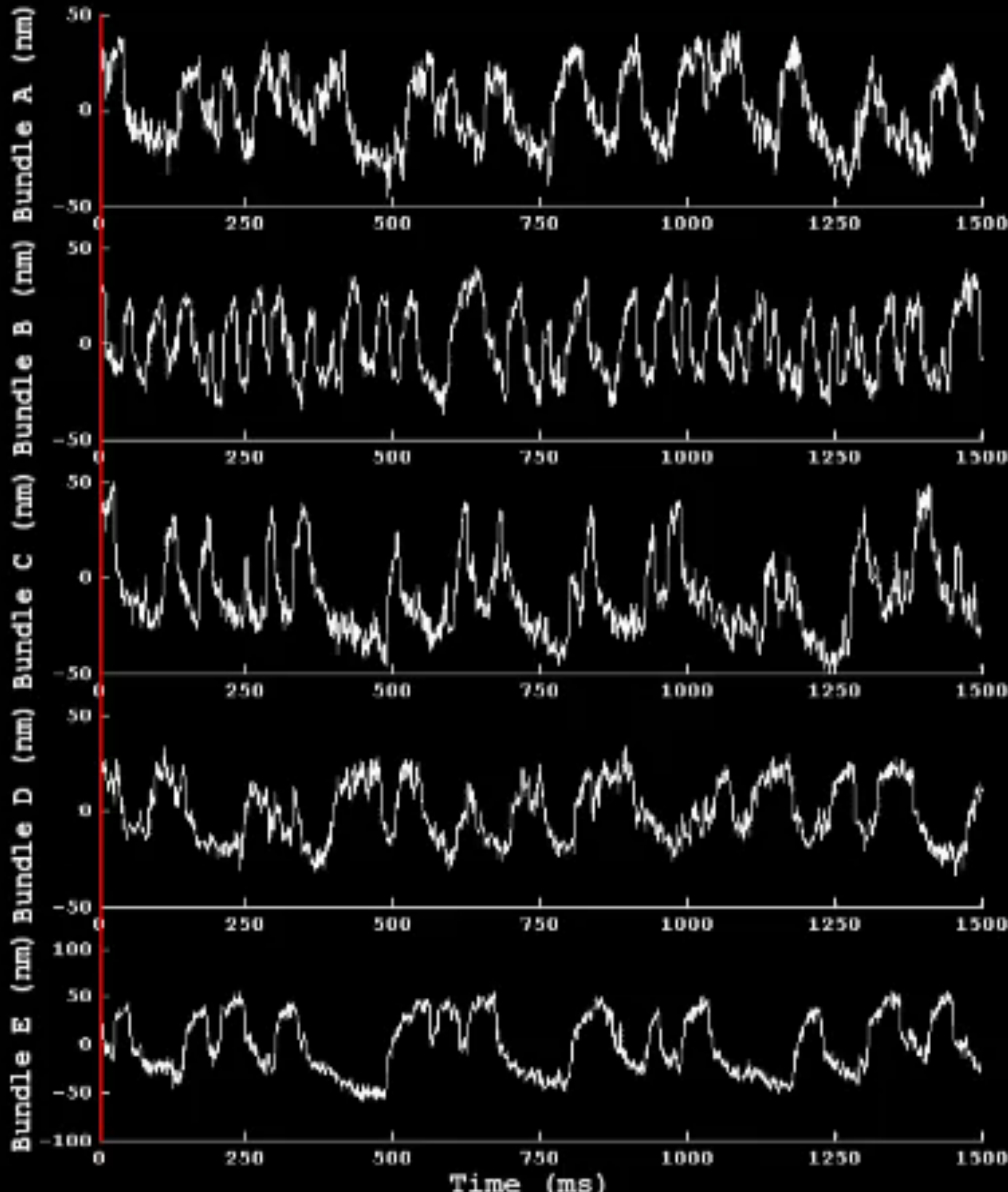

CMOS Camera
(Photron SA-1)
EMCCD Camera
(Andor iXon 897)
Microscopes
Objective
Dolores Bozovic's Lab (Physics)

Mechanical Motion of Hair Cells in Inner Ear

Dolores Bozovic, Lea Fredrickson (Physics)

1,000 frame/sec



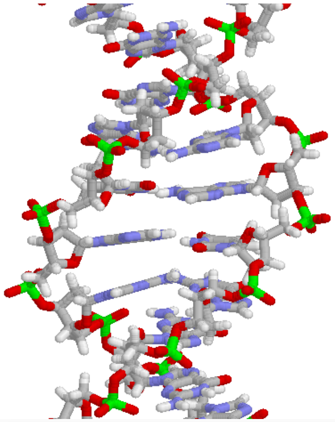


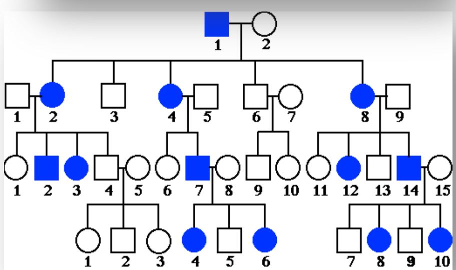
UCLA Fast Bio-Imaging Group

L. Fredrickson, A. Cheng, K. Jewhurst, C. E. Strimbu, D. Bozovic, K. Arisaka

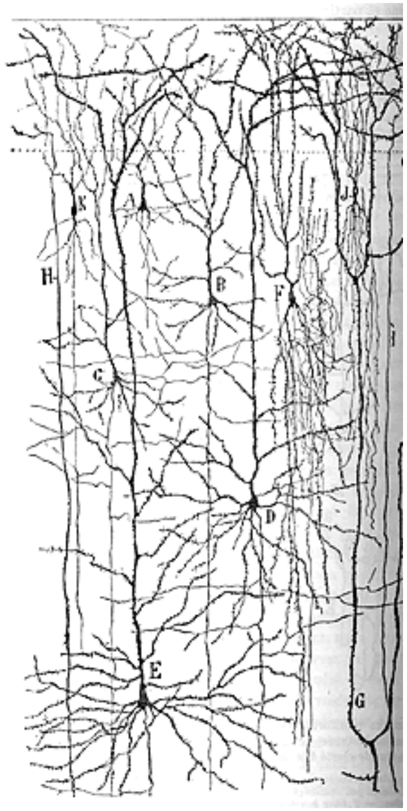
Neural Networks

Nature vs. Nurture

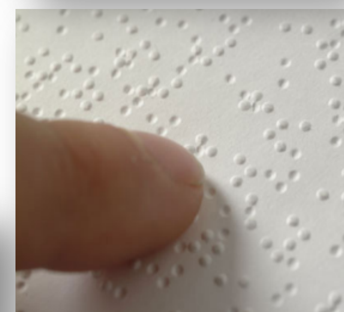


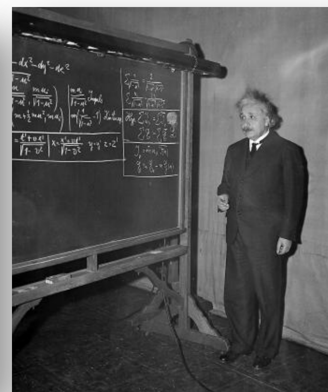


Nature



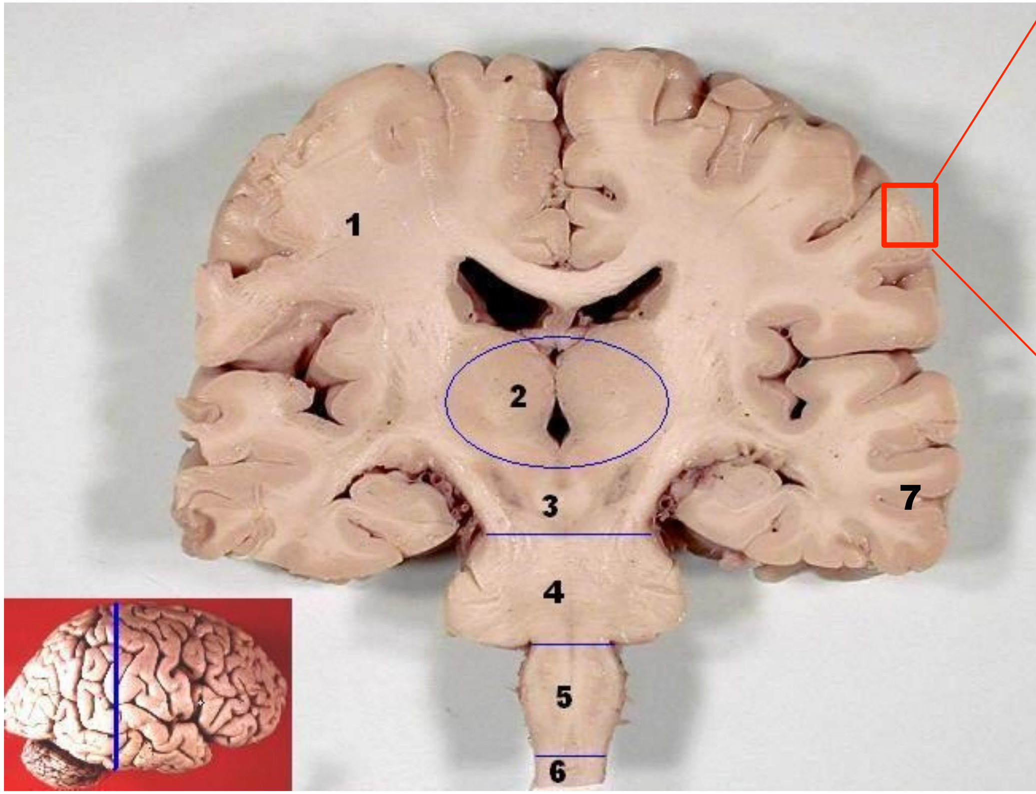
Nurture



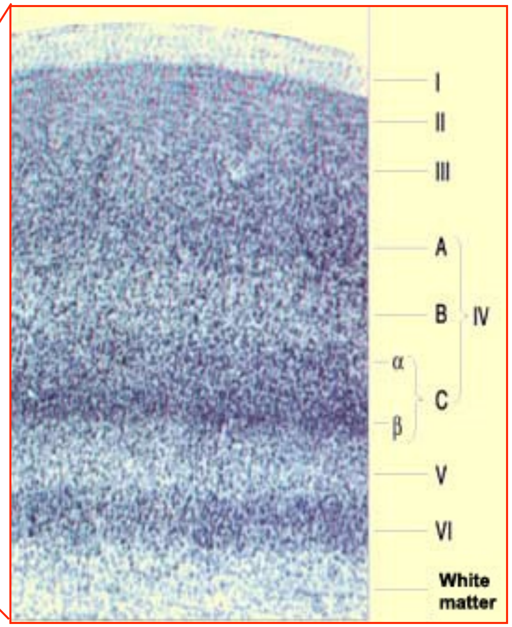


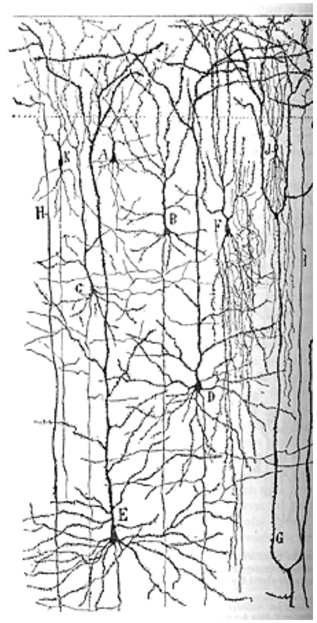
The Cerebral Cortex

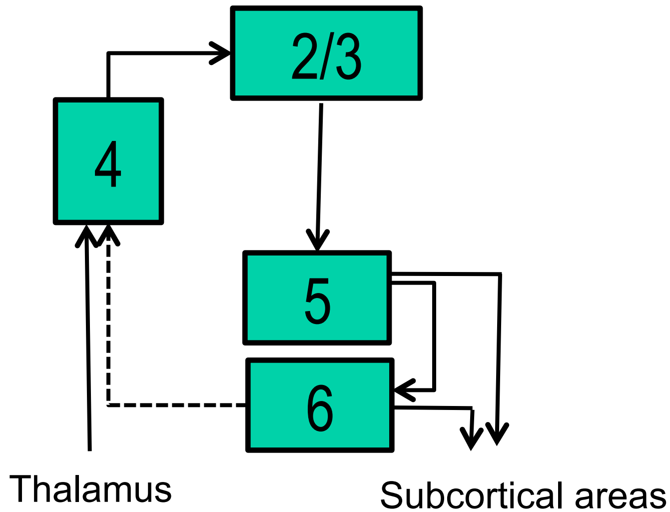
Conscious



Unconscious

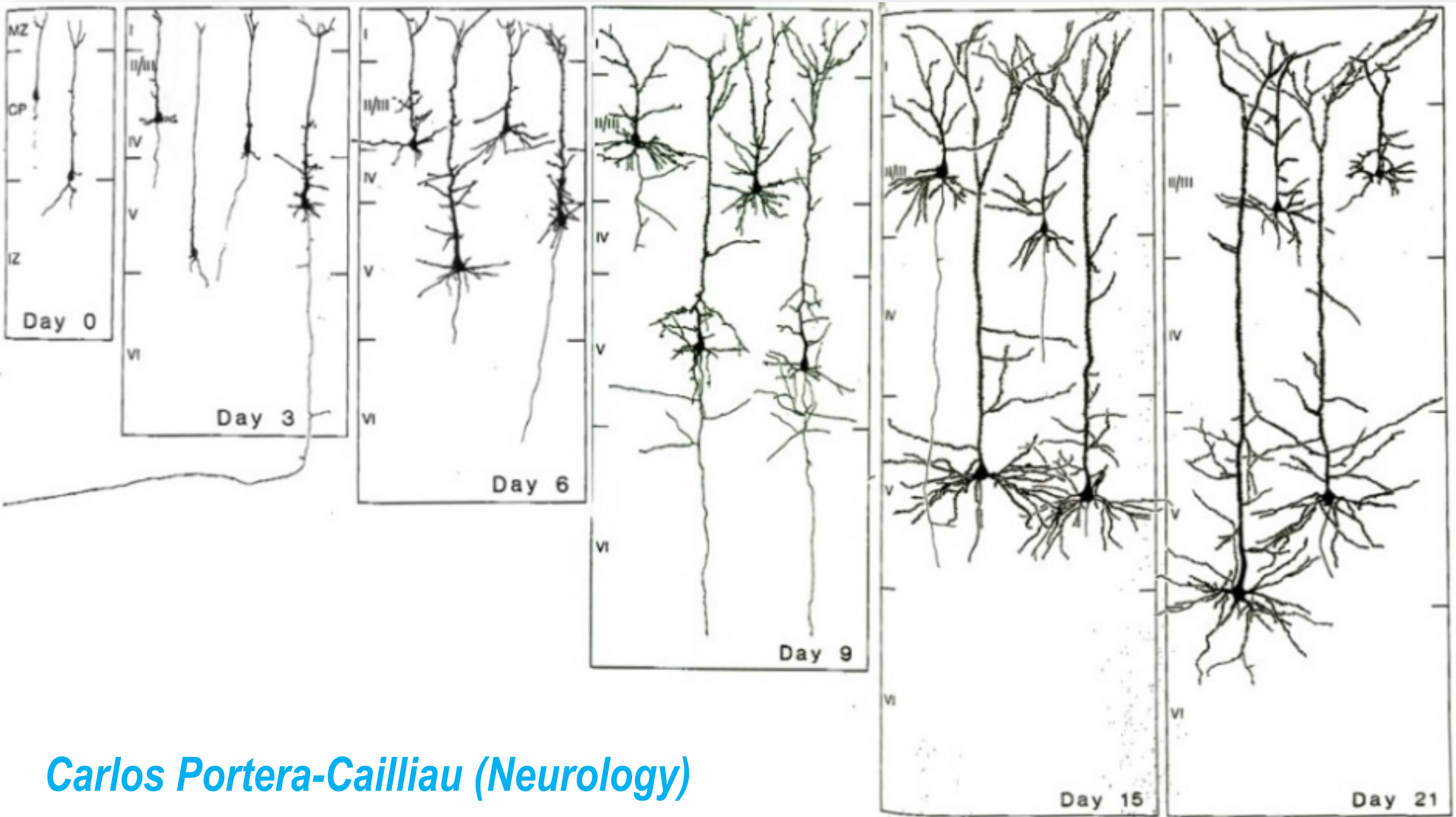






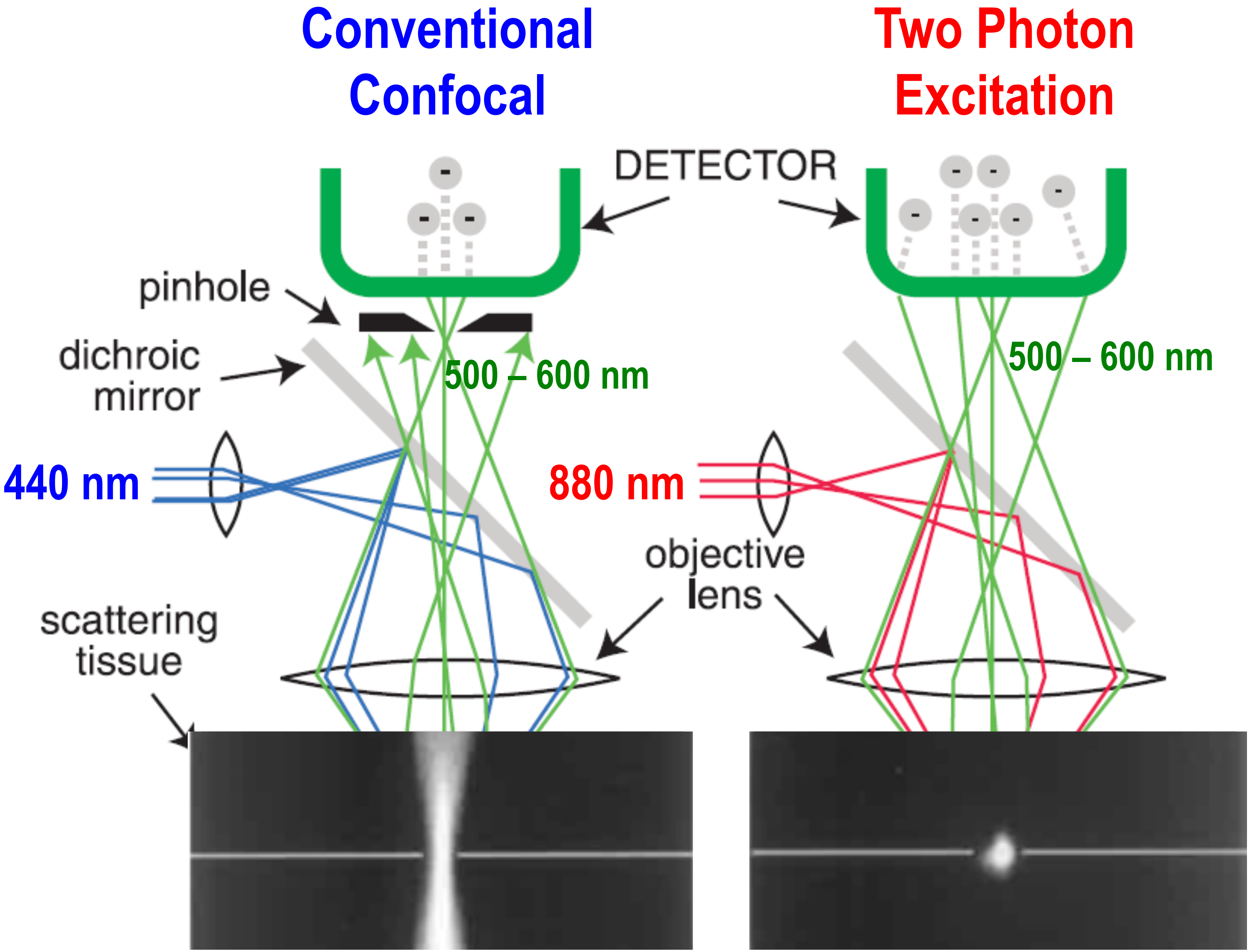
Assembly of rat's cortical circuits during development

How/when do neurons establish networks? → *Symmetry Breaking*

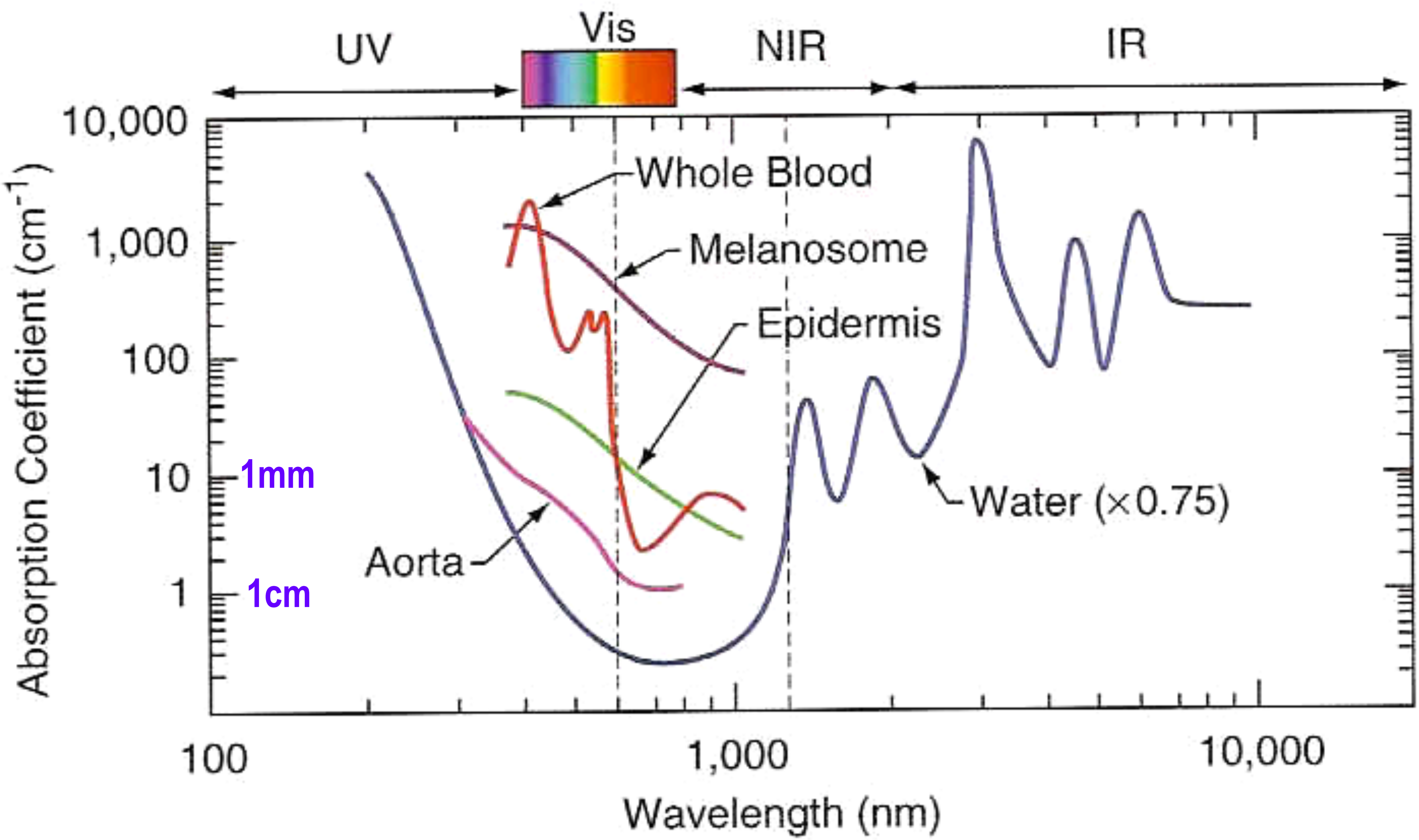


Carlos Portera-Cailliau (Neurology)

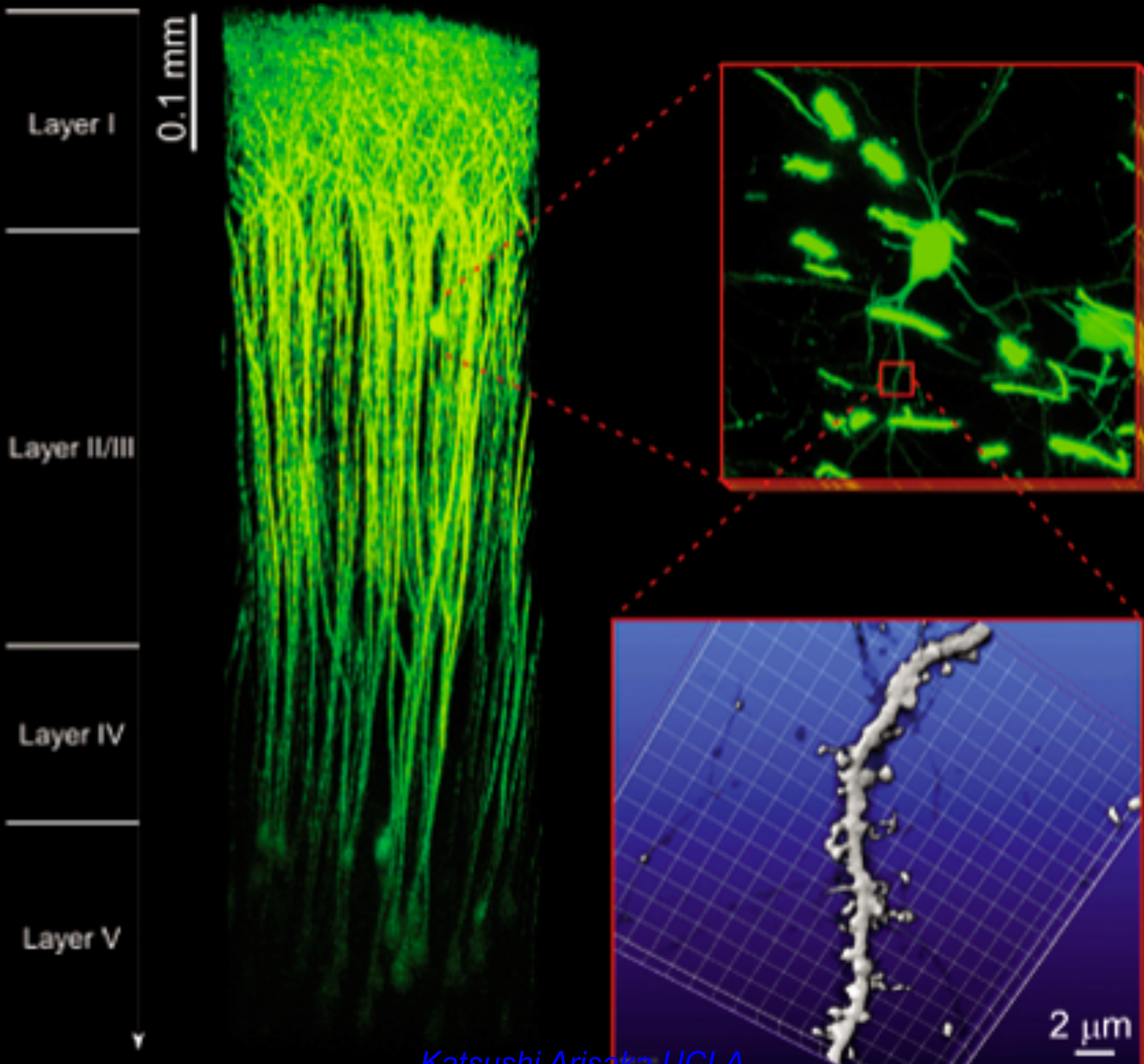
Mutiphoton Microscope



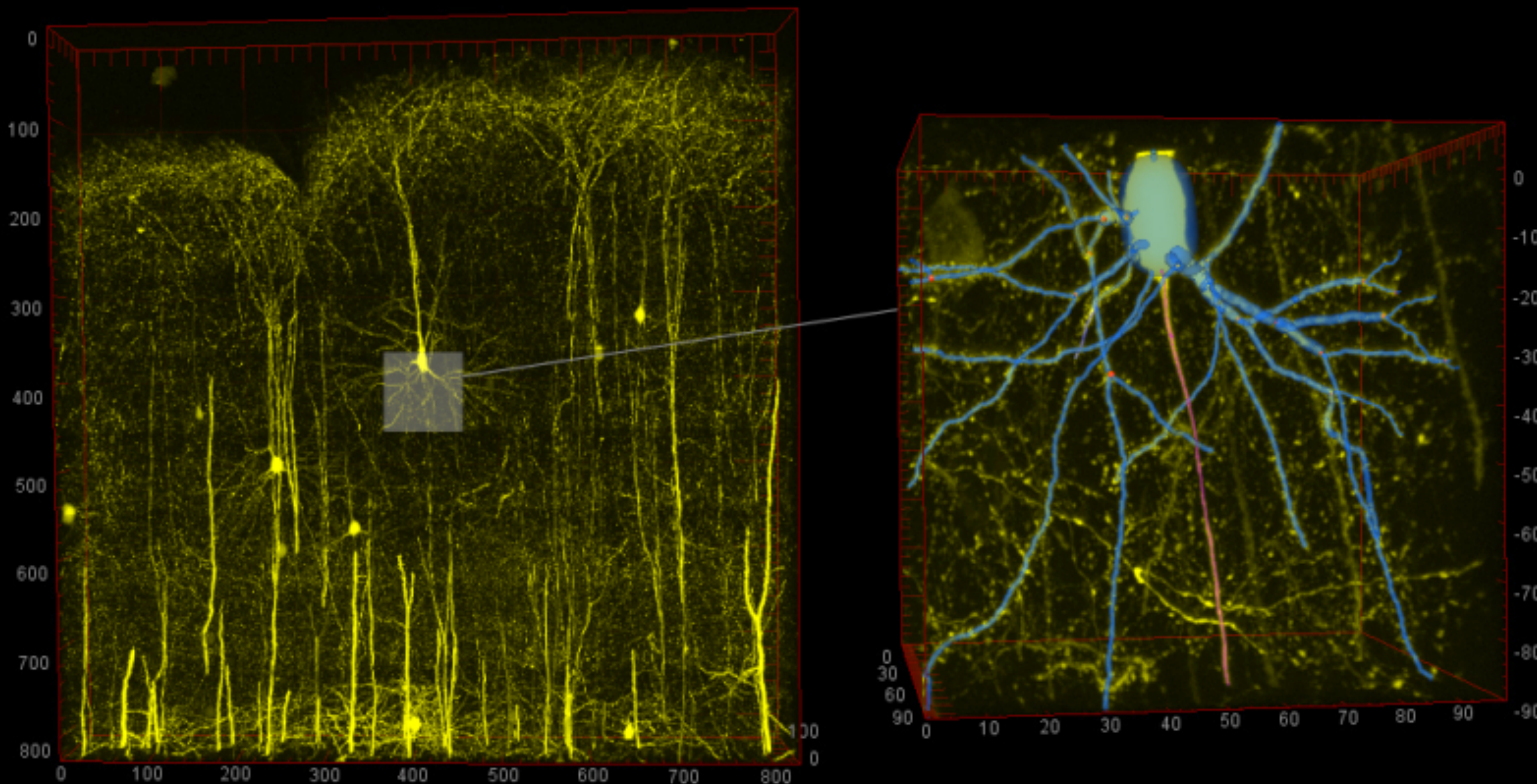
Absorption of light



Neural Network in Vivo
3D image by two photon microscope



Neural Network
3D image by two photon microscope

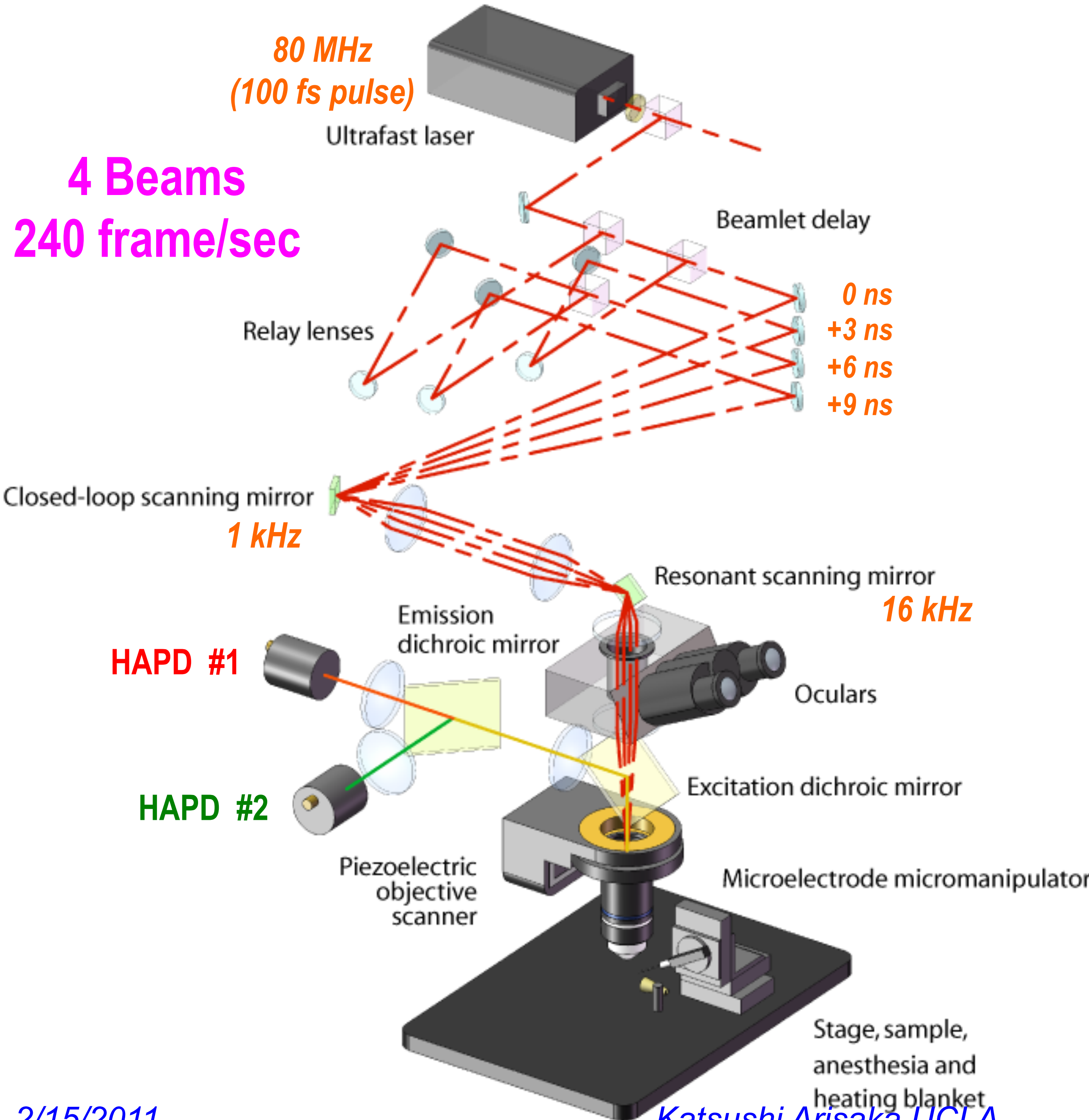


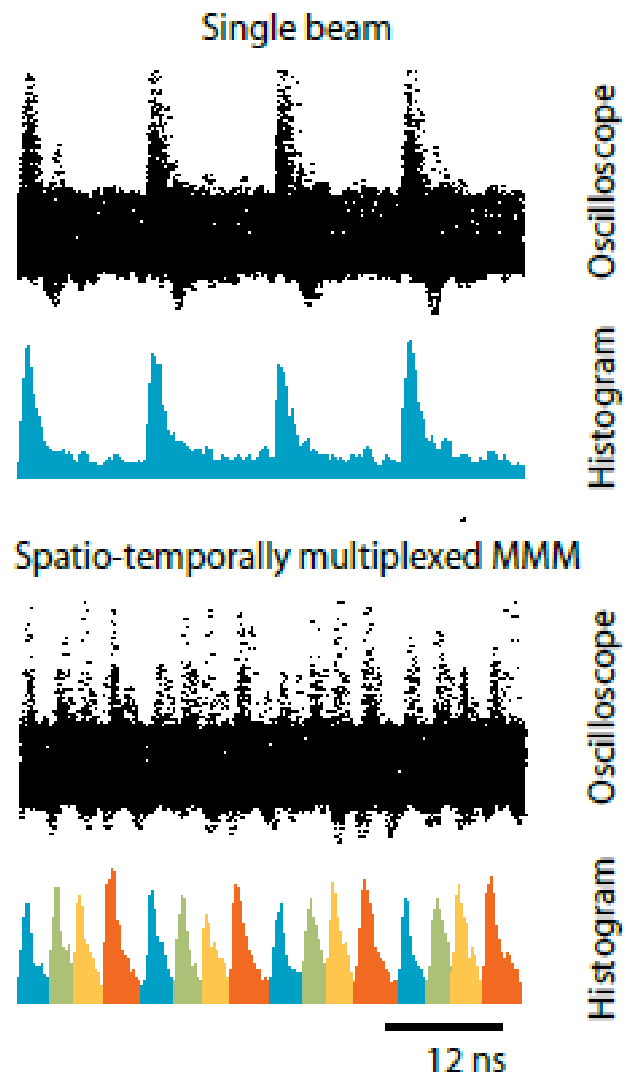
Cortical neurons in a fixed, 100 um-thick brain slice from a transgenic mouse with sparse neuronal GFP expression. Left: Mosaic of 81 high-resolution image stacks acquired on a 2-photon laser-scanning microscope, part of a larger data set spanning several consecutive brain slices. Right: Individual stack from this data set, containing a GFP-expressing cortical layer 2/3 pyramidal neuron. Its dendritic (cyan) and axonal (magenta) compartments were identified and traced within the 3D data containing many other neuronal structures, some of which appear to make contact with the highlighted cell. Images: Miguel Vaz Afonso.

Spatio-Temporal Excitation-Emission Multiplexing (STEM) Microscope

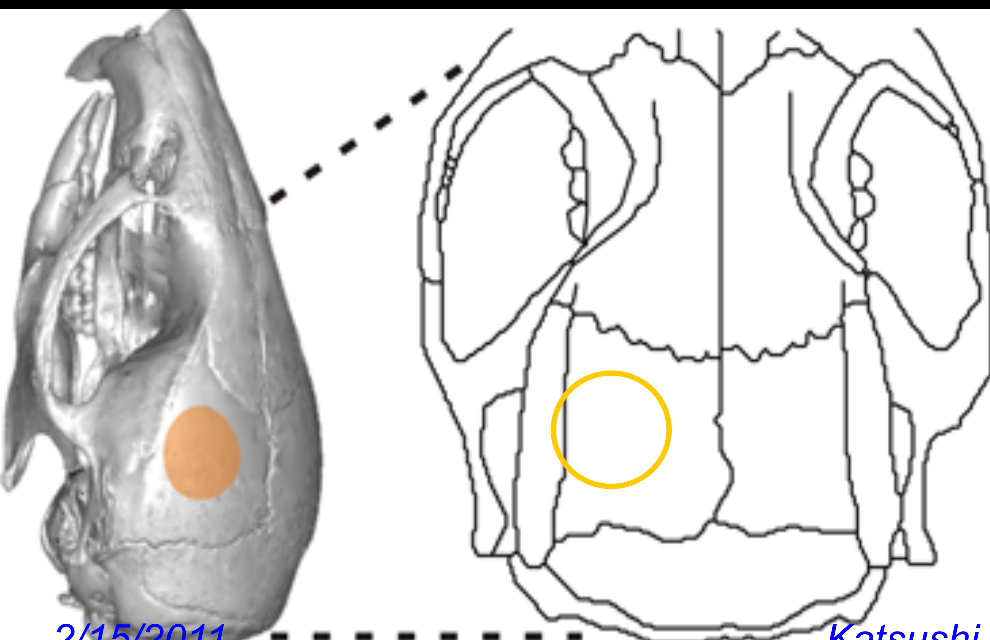
4 Beams
240 frame/sec

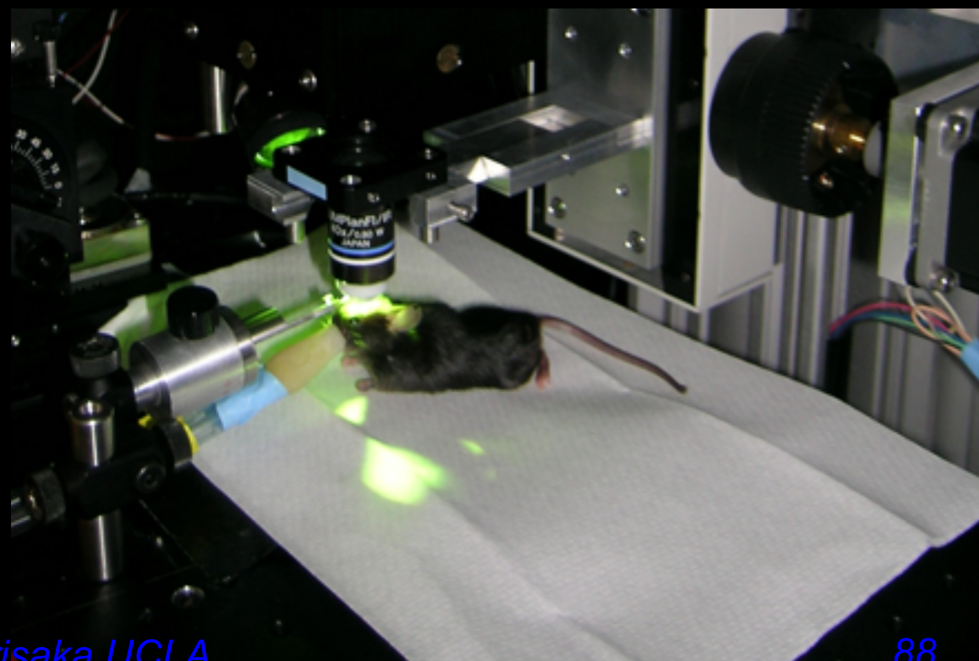
Adrian Cheng (Physics)



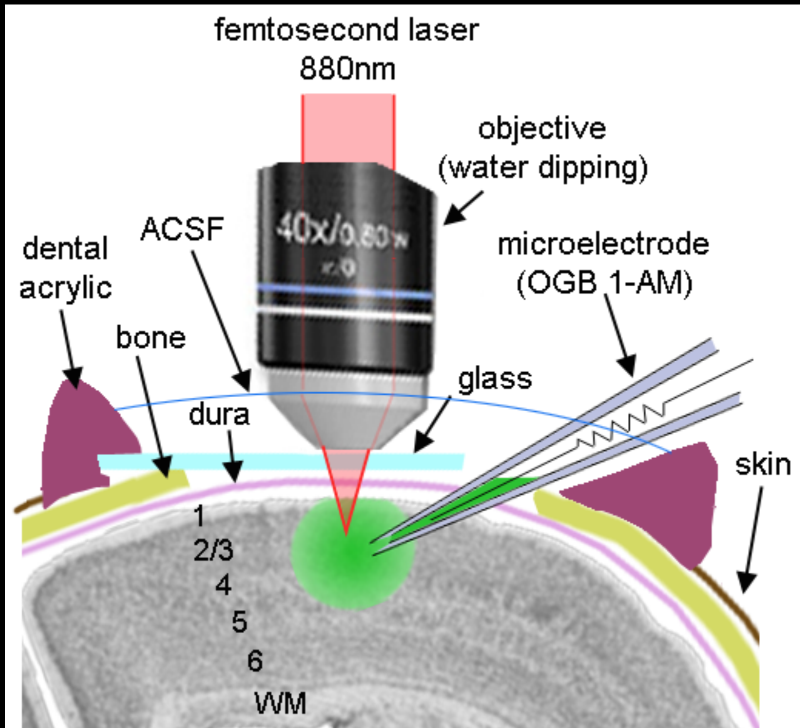


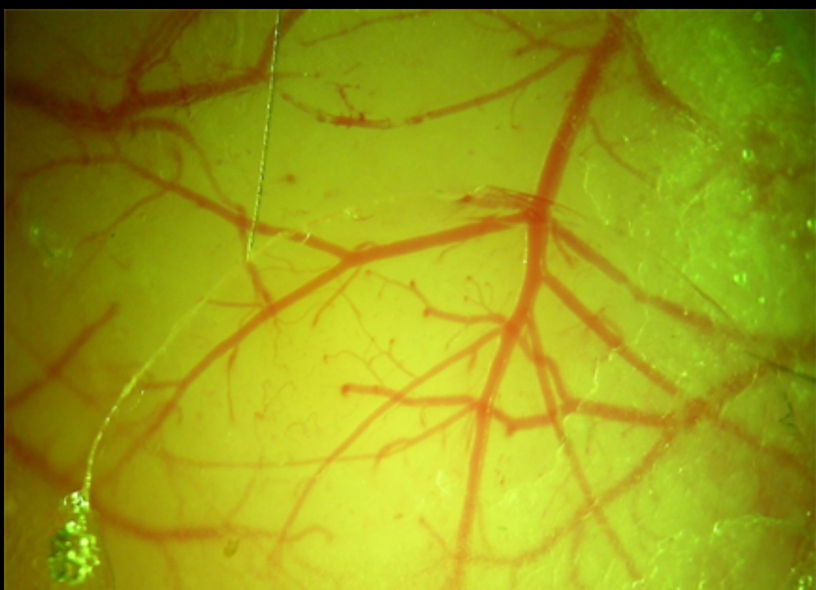
Surgery to Open a Cranial window
Prof. Carlos Portera-Cailliau

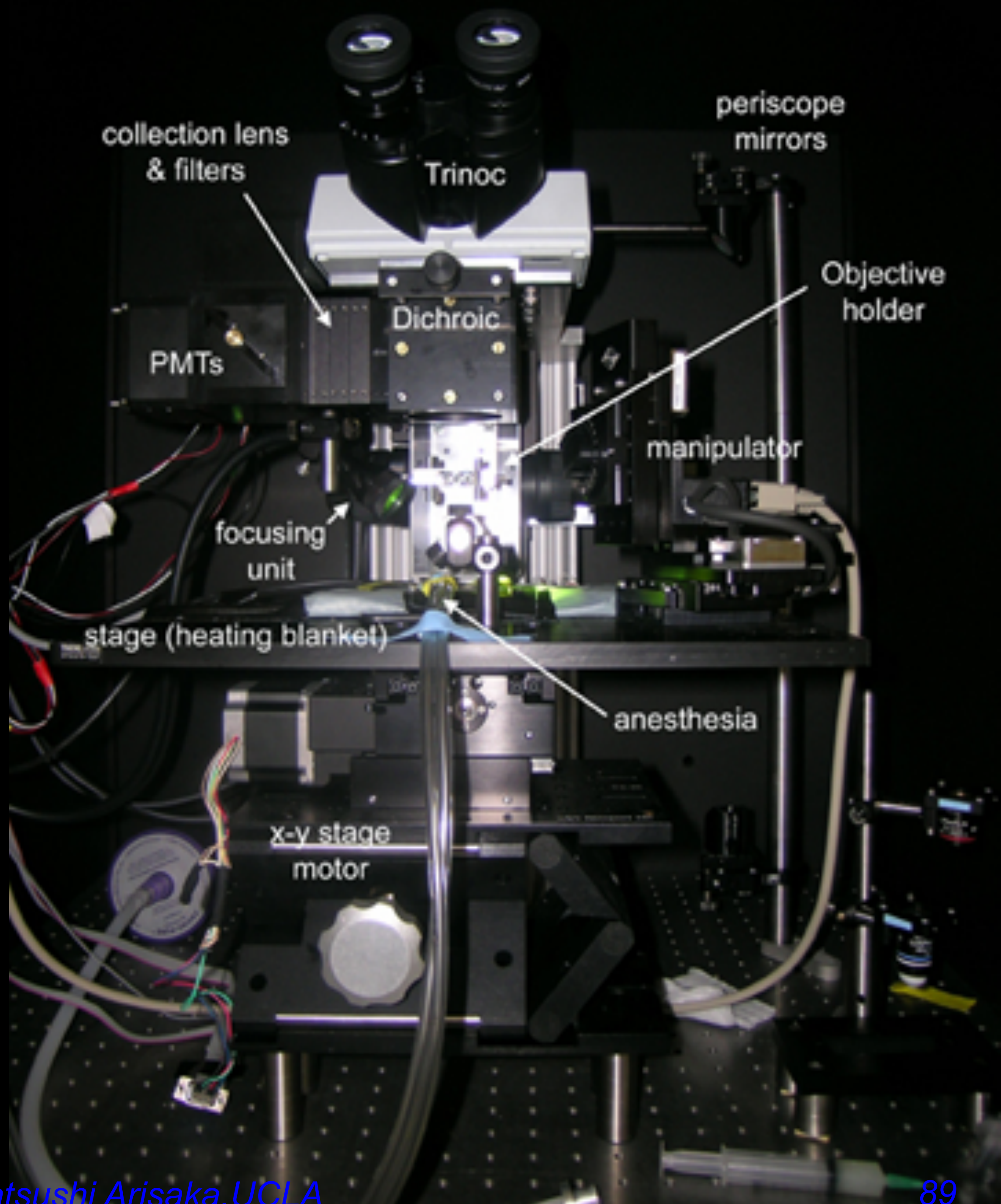




In vivo calcium imaging of neuronal activity








SPATIOTEMPORAL MULTIPLEXING 2-PHOTON MICROSCOPE
University of California, Los Angeles, Depts. Physics and Neurology
Profs. Carlos Portera-Cailliau/Katsushi Arisaka (A. Cheng, J. T. Gonçalves *et al* Nat Methods 2011)
UCLA

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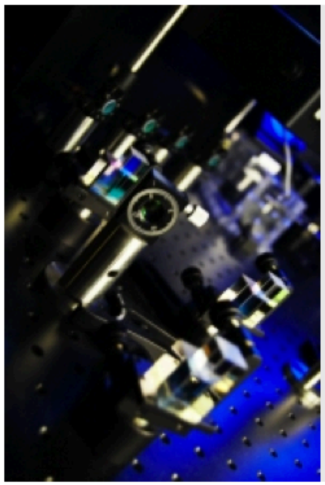
New UCLA-designed microscope records firing of thousands of individual neurons in 3-D

Imaging system could help reveal 'miscommunications' in autism, schizophrenia

By Mark Wheeler | January 11, 2011



Some disorders of the brain are obvious — the massive death of brain cells after a stroke, the explosion in the growth of cells that marks a tumor. Other disorders, such as autism, schizophrenia and mental retardation show no physical signs of damage and are believed to be caused by problems in how brain cells communicate with one another.

To understand the root of the problem of these latter diseases, visualizing brain activity is key. But even the best imaging devices available — fMRIs and PET scans — can only give a "coarse" picture of brain activity.

UCLA neuroscientists have now collaborated with physicists to develop a non-invasive, ultra–high-speed microscope that can record in real time the firing of thousands of individual neurons in the brain as they communicate, or miscommunicate, with each other.

"In our view, this is the world's fastest two-photon excitation microscope for three-dimensional imaging *in vivo*," said UCLA physics professor Katsushi Arisaka, who designed the new optical imaging system with UCLA assistant professor of neurology and neurobiology Dr. Carlos Portera-Cailliau and colleagues.

Their research appears in the Jan. 9 edition of the journal Nature Methods.

Because neuropsychiatric diseases like autism and mental retardation often display no physical brain damage, it's thought they are caused by conductivity problems — neurons not firing properly. Normal cells have patterns of electrical activity, said Portera-Cailliau, but abnormal cell activity as a whole doesn't generate relevant information the brain can use.

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Media Contacts

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mwheeler@mednet.ucla.edu

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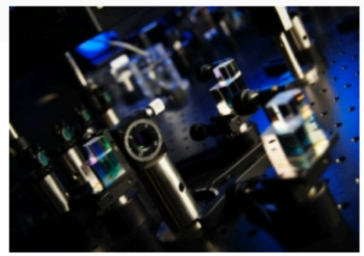
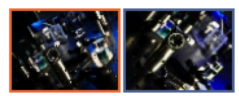


STEM microscope designed at UCLA



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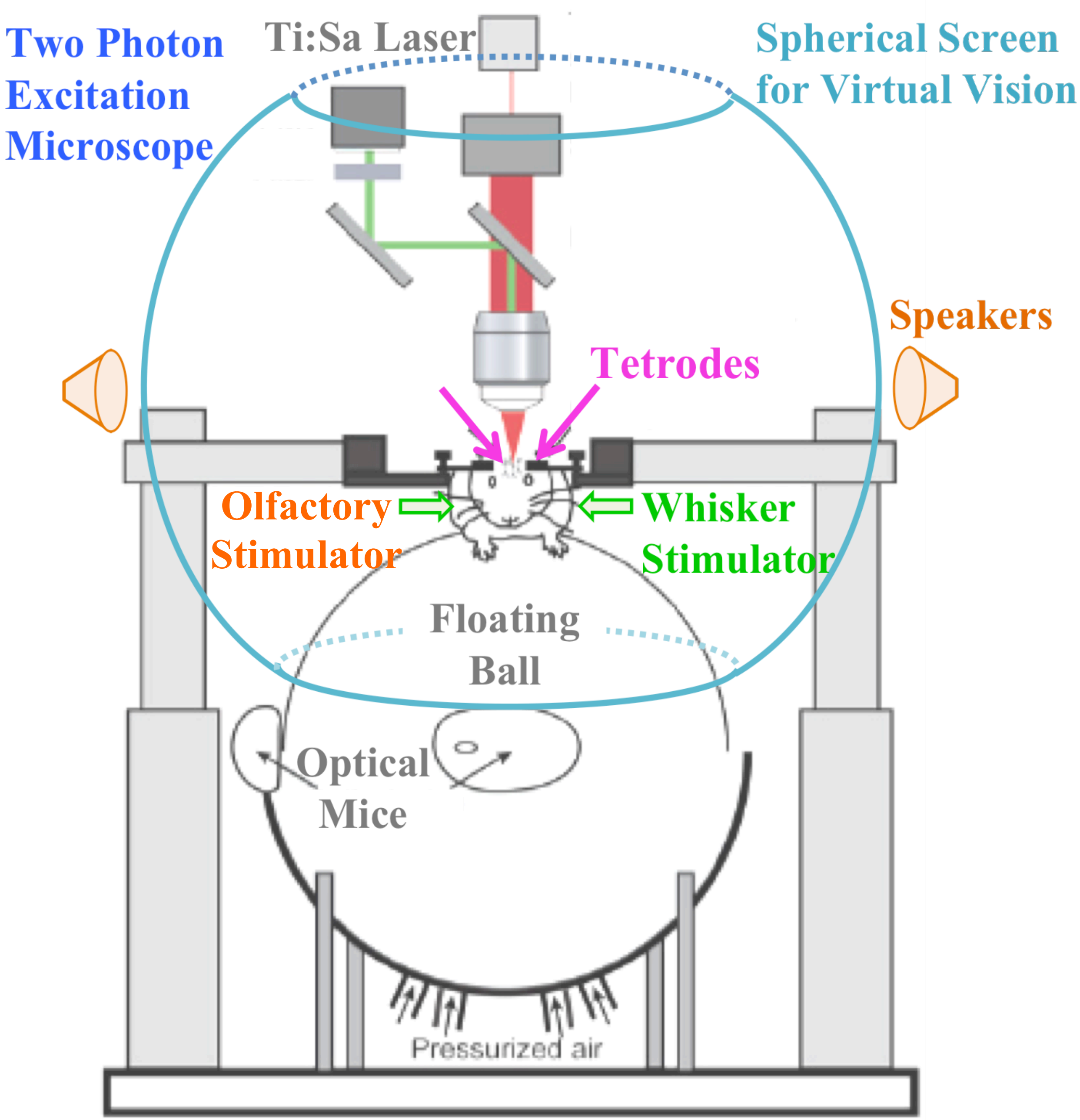
Future Directions

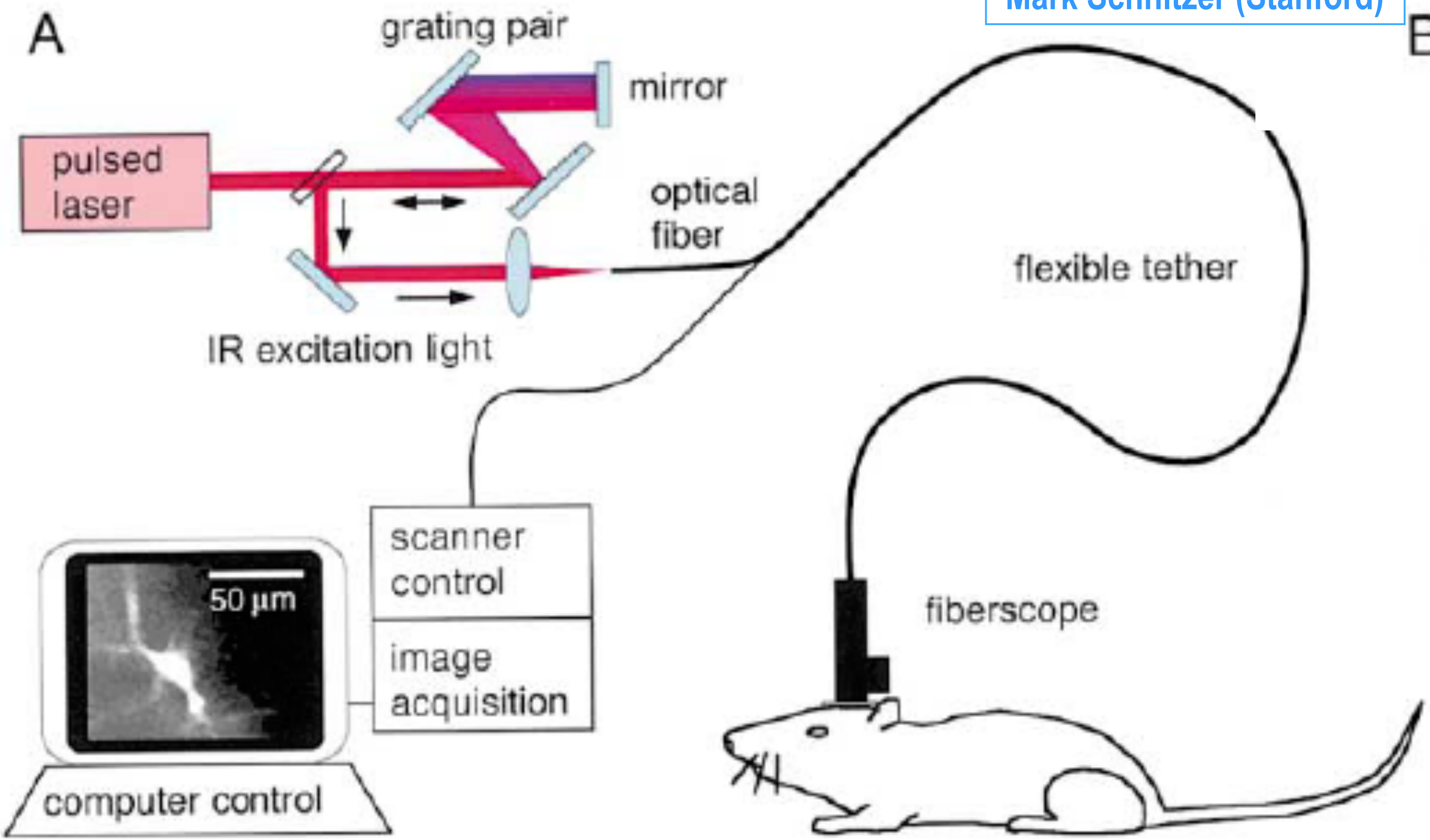
Virtual Reality Experiment on Awake Rats



Mayank Mehta
Daniel Aharoni
Bernard Willers
(Physics)

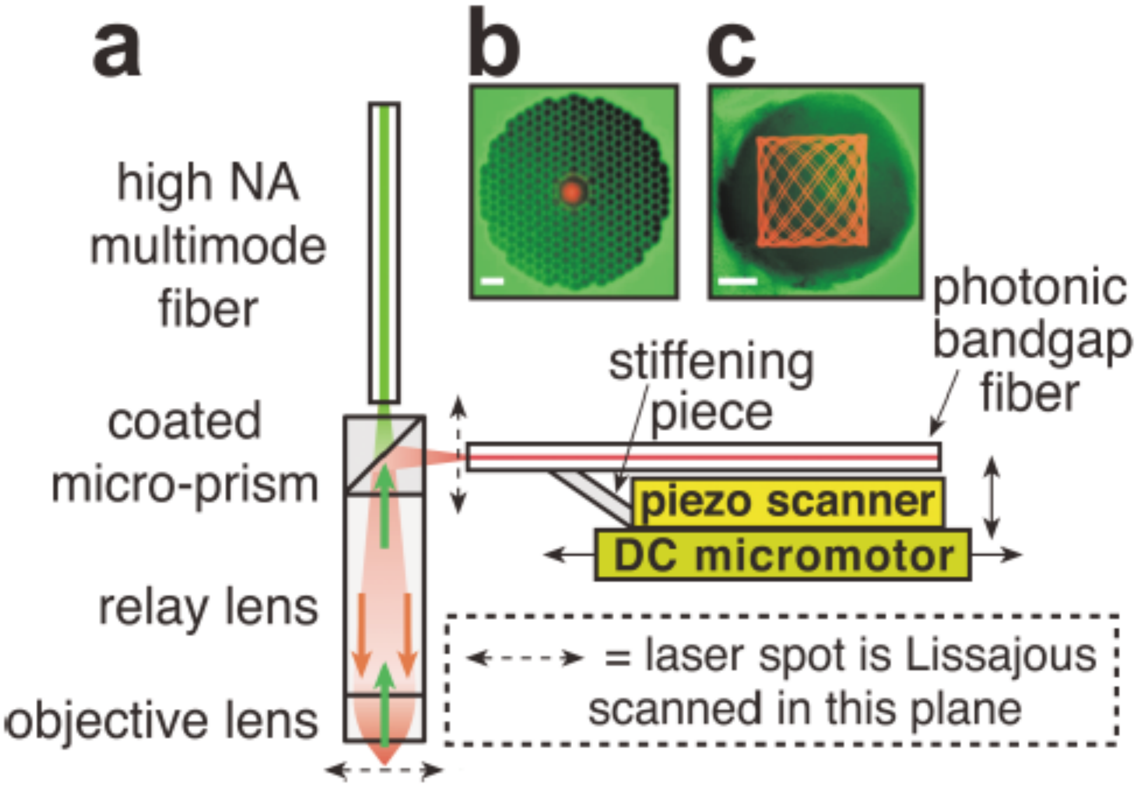
GRIN-based Two photon excitation Endoscope

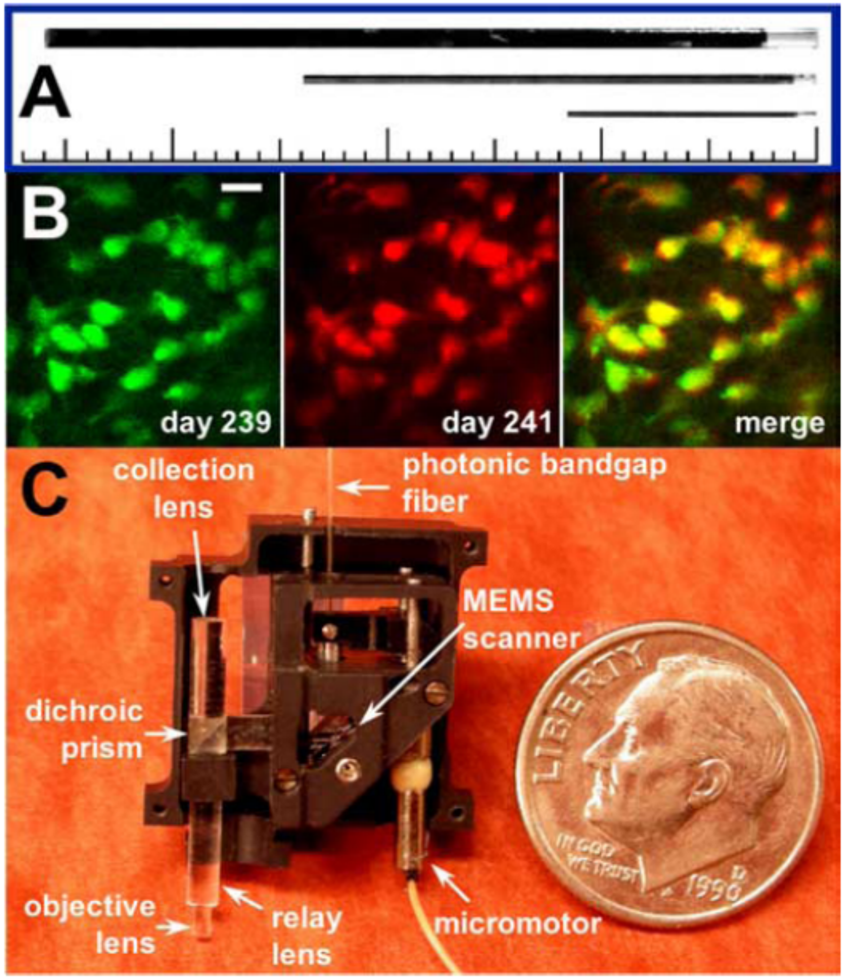
Mark Schnitzer (Stanford)



GRIN 2PE Endoscope

Mark Schnitzer (Stanford)



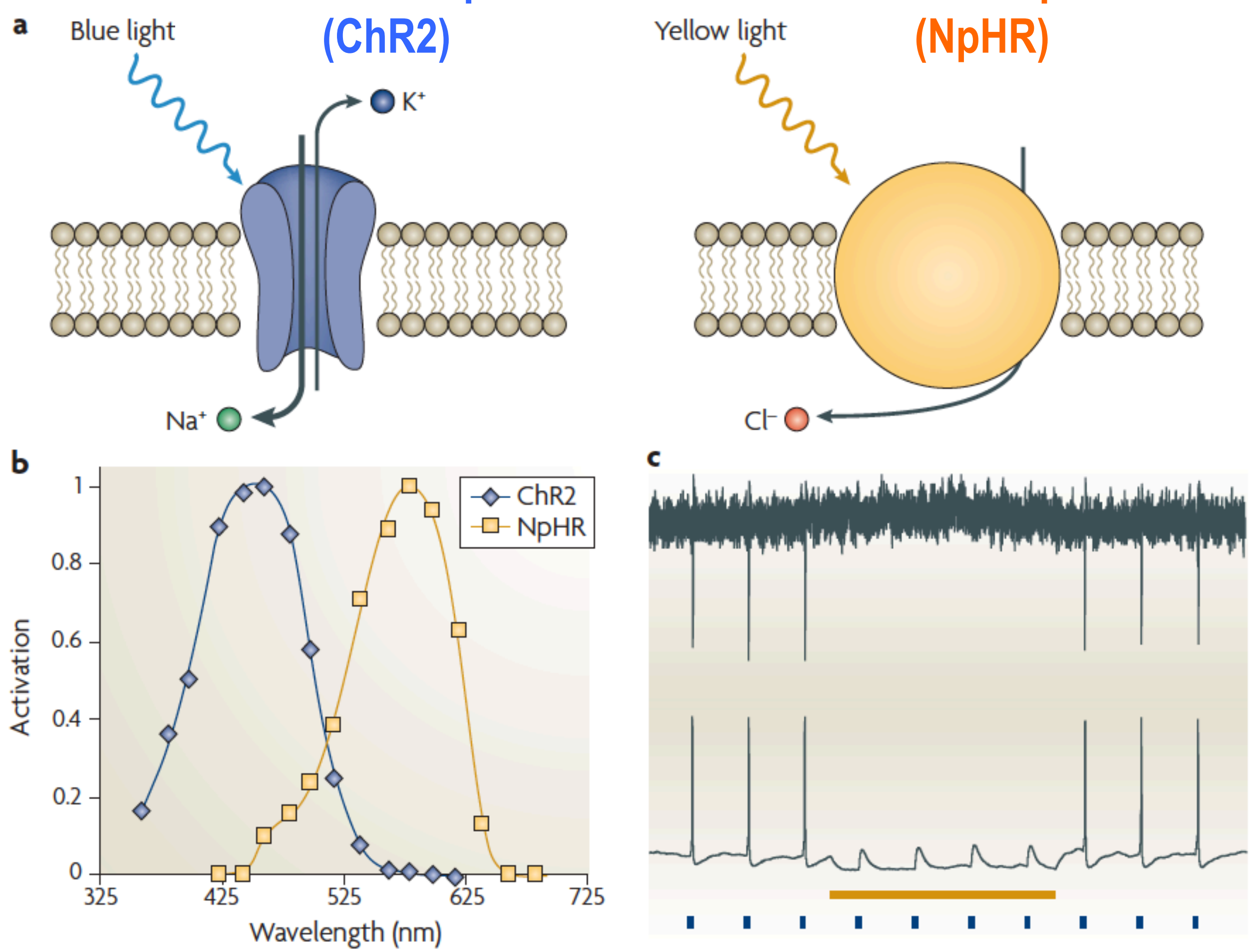


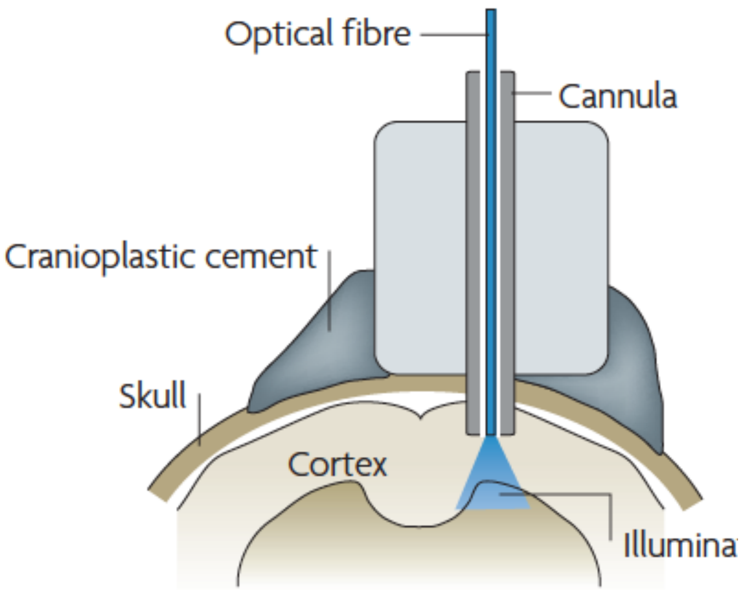
Optogenetic Excitation of Neurons

Karl Deisseroth (Stanford)

Excitation by Channelrhodopsin-2 (ChR2)

Inhabitation by Halorhodopsin (NpHR)



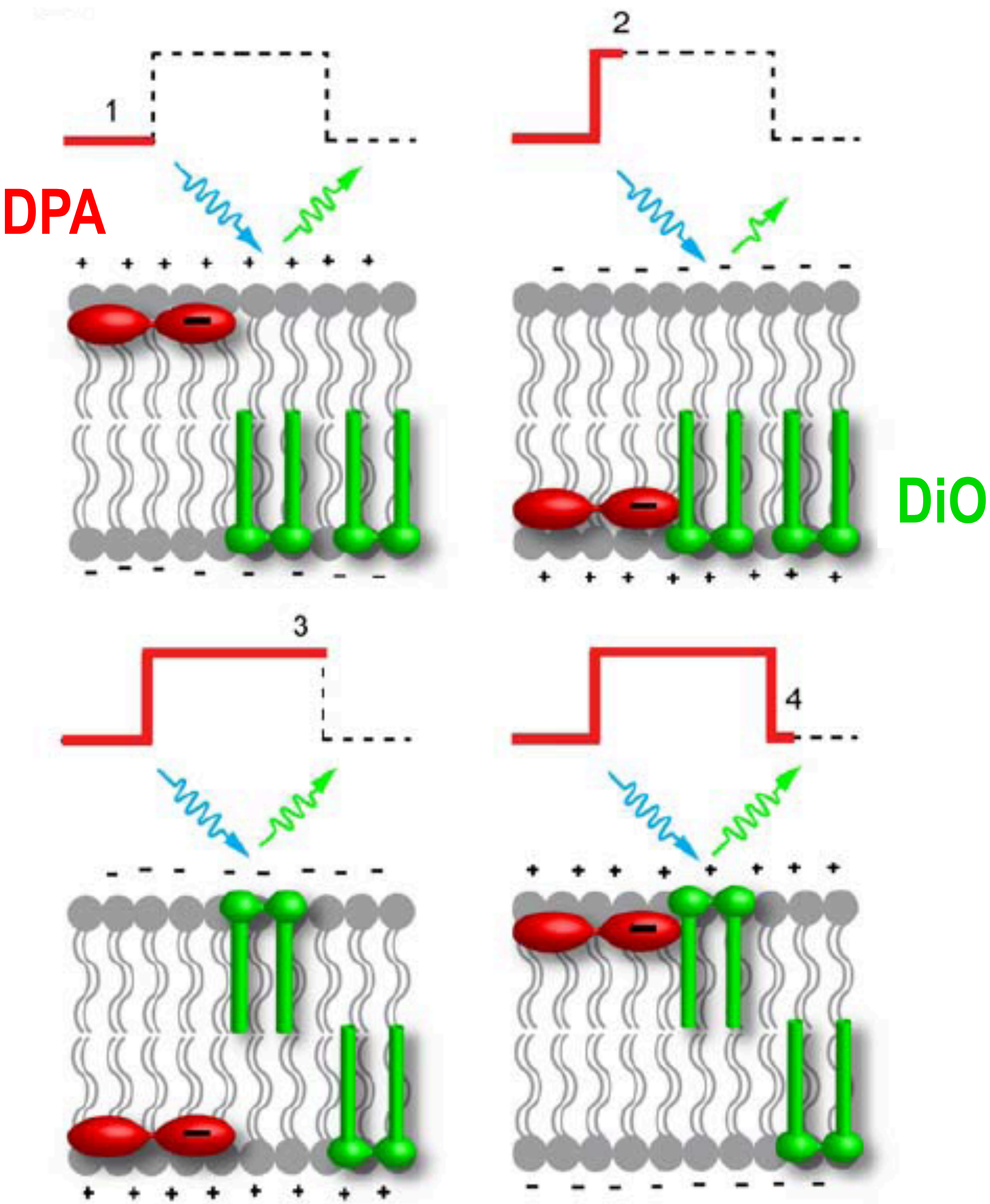


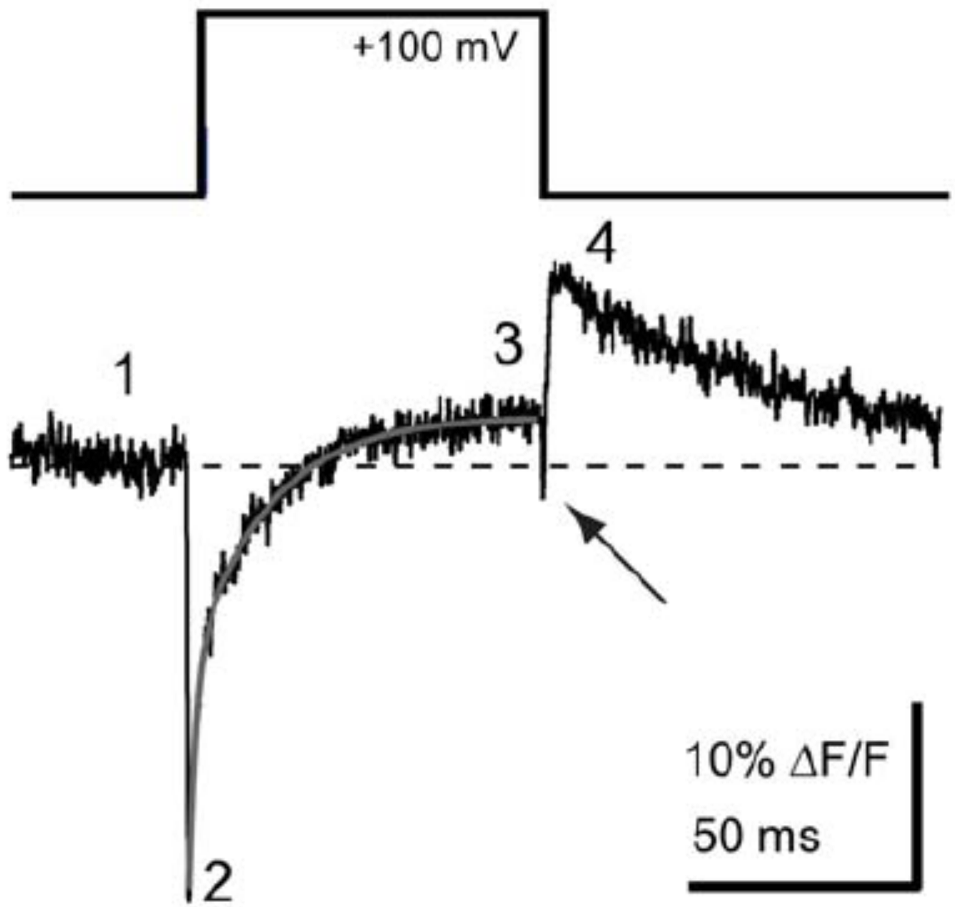
Outer world vs. Inner word

- Outer world : Five senses → Manipulate by Virtual Reality
  - Vision
  - Sound
  - Touch
  - Smell
  - Taste
- Inner world → Manipulate by Photo Excitation of single neurons
  - Neural network in brain
- Establish direct link between Inner world & Outer world
  - Control outer world – Virtual reality
  - Control inner world – Neural reality

Voltage Sensing Dye by FRET

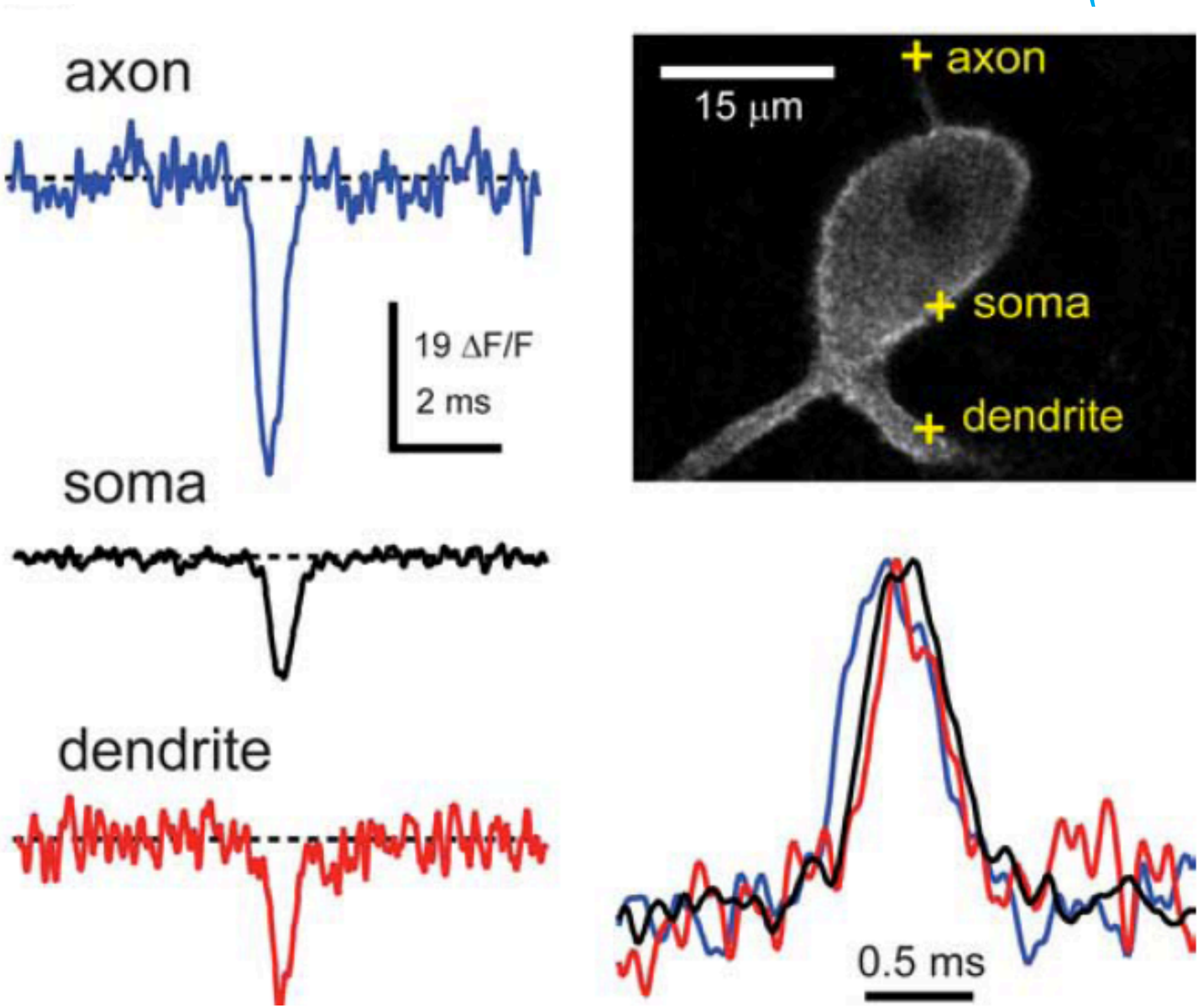
Tom Otis (Neurobiology)





Voltage Sensing Dye

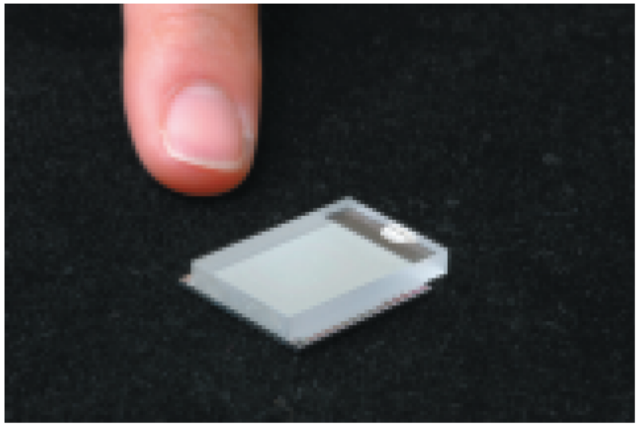
Tom Otis (Neurobiology)



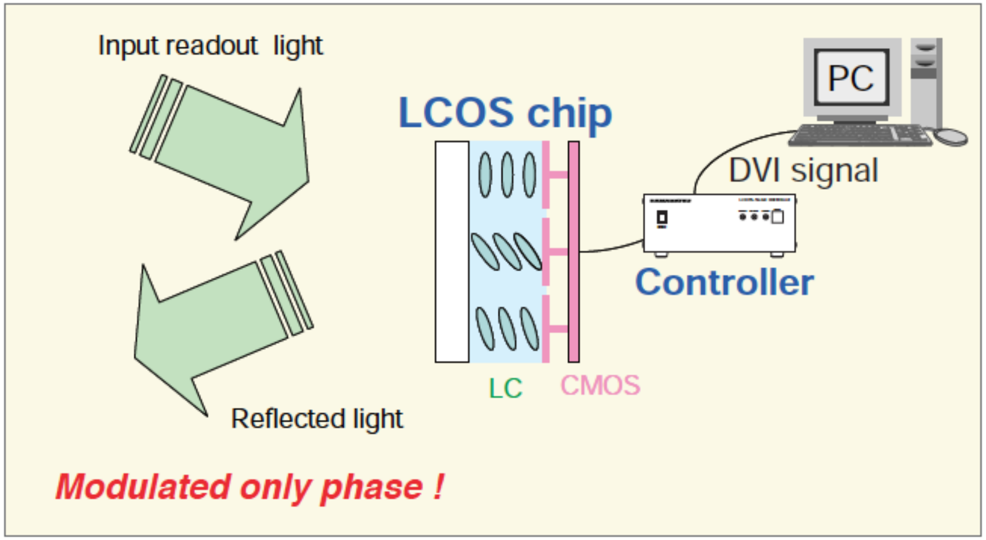
LCOS (Liquid Crystal on Silicon) for SLM (Spatial Light Modulator)

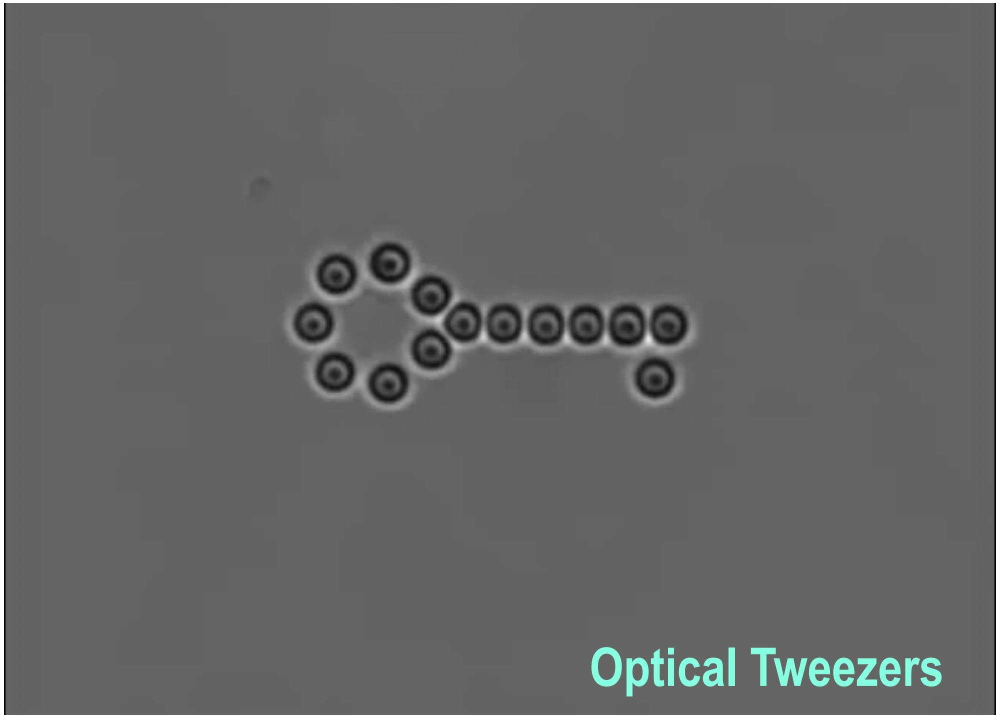
Hamamatsu

X10468 Head and Controller

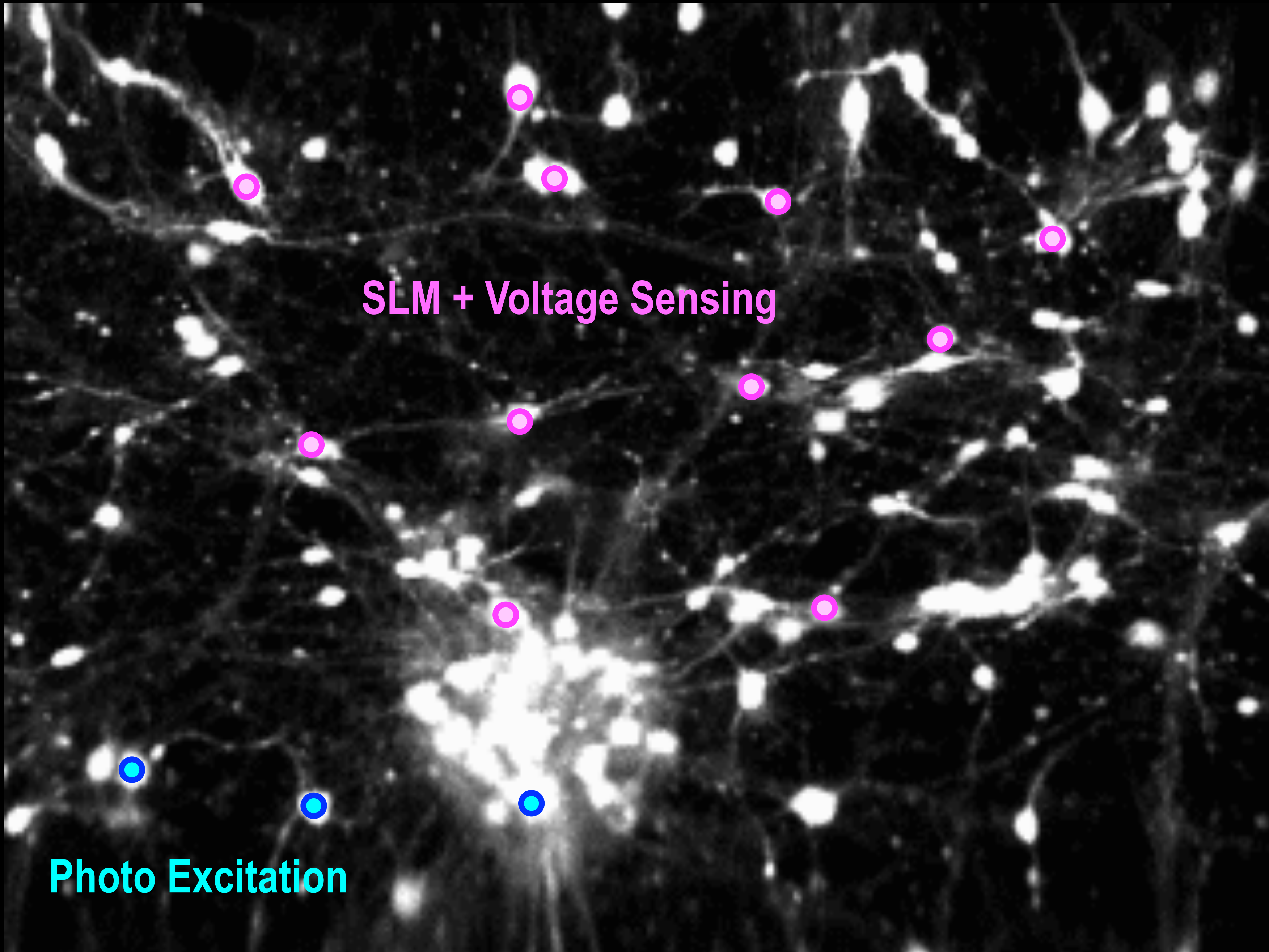


LCOS chip inside the Head



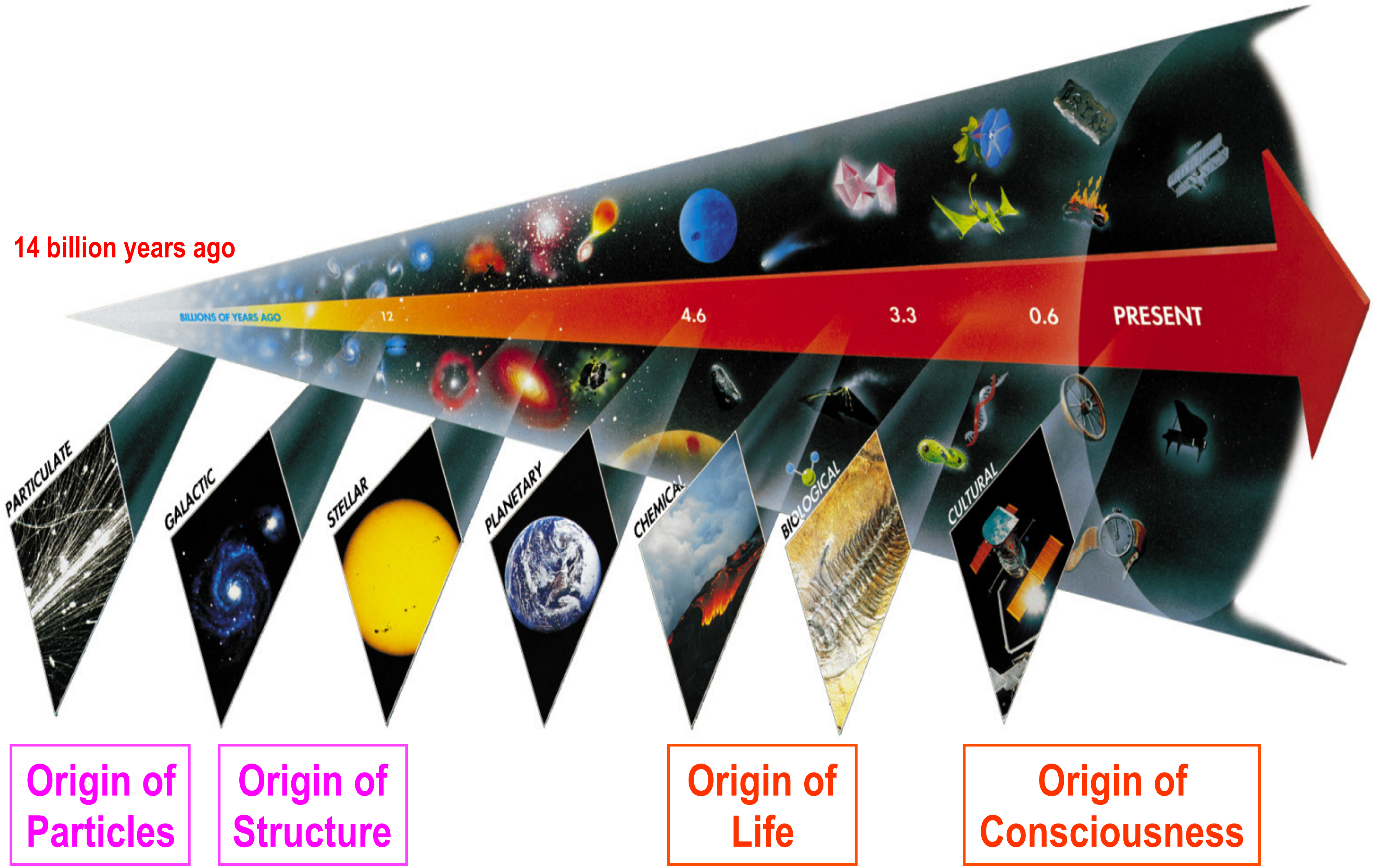


Ca^{2+} Signal in cultivated Rat's Brain by Confocal Microscope



Summary

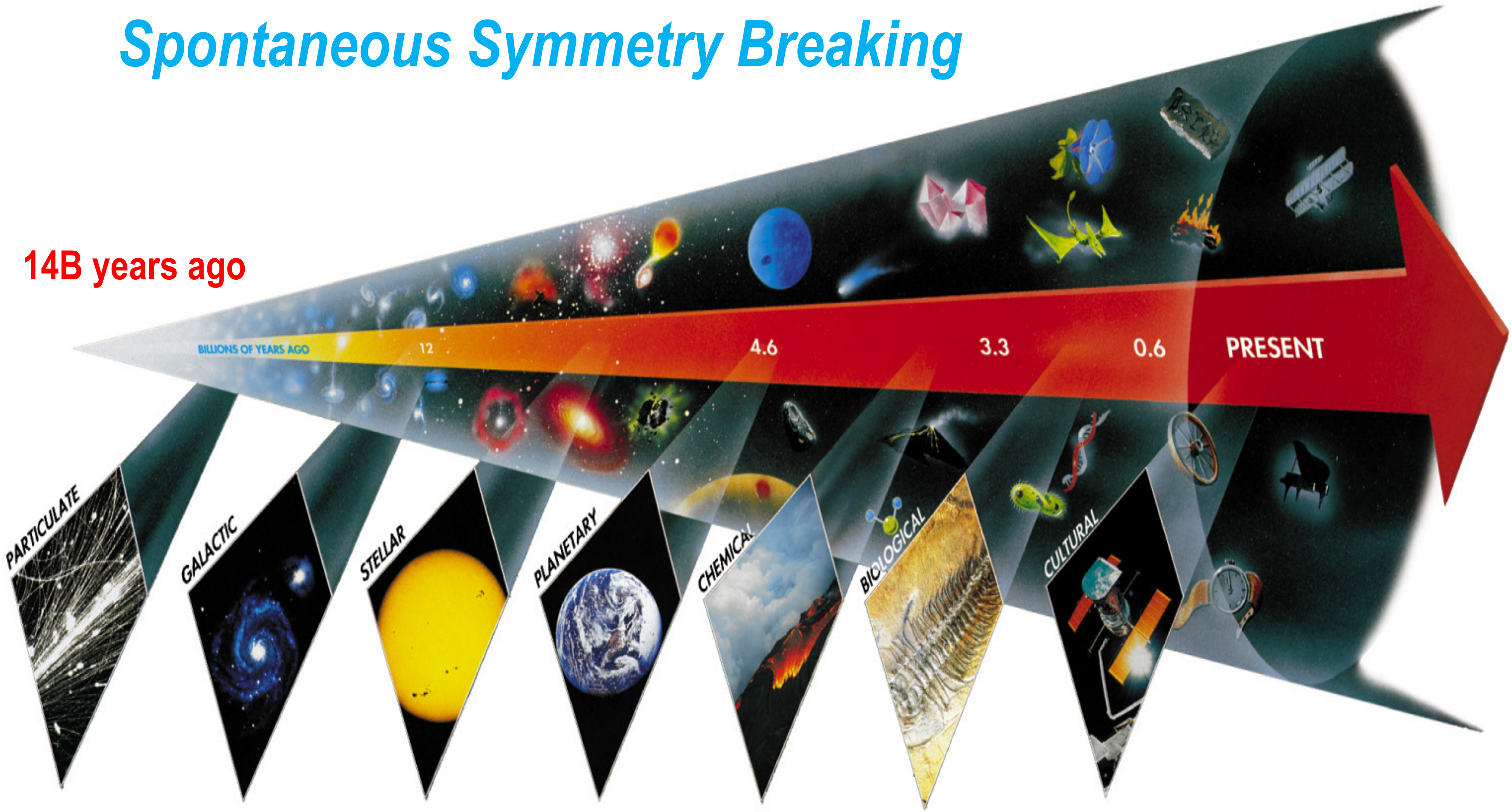
Seven Phases of Cosmic Evolution



Seven steps of cosmic evolution

Spontaneous Symmetry Breaking

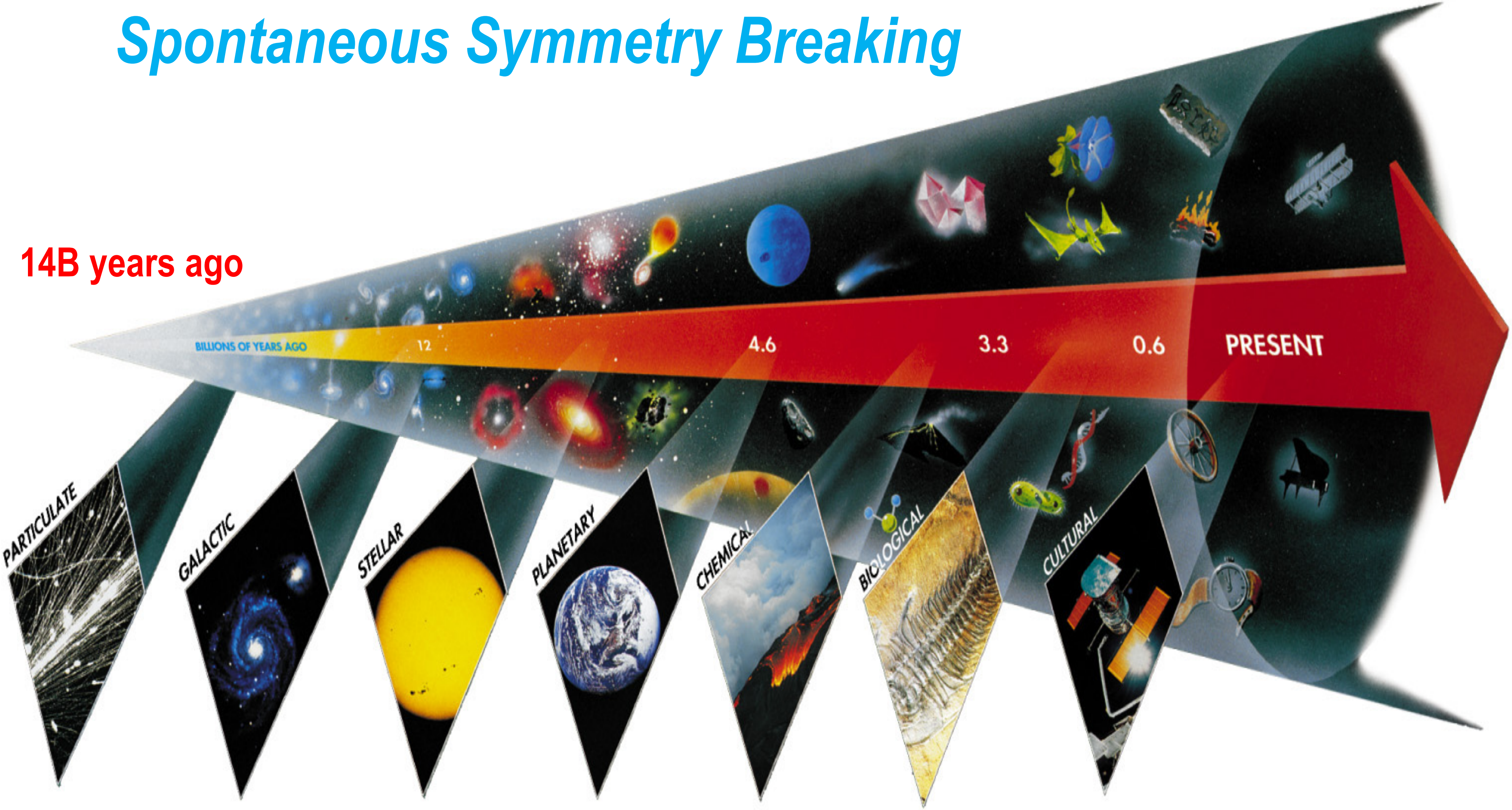
14B years ago



Simple ⇨ Coherent Complex System

Seven steps of cosmic evolution

Spontaneous Symmetry Breaking



Accelerator ← Telescope → ← Microscope →

Four Major Science

Origin of Particles
Particle Physics

Origin of Universe
Cosmology

Origin of Life
Molecular Biology

Origin of Consciousness
Neurophysics

Concluding Remarks

- Life, in particular, our brain is a complex system in 4 dimensional space-time.
  - Emergent property
  - Strongly interacting
- Countless "spontaneous symmetry breakings" during the evolutional and developing process of life
- Fully controlled experiments by "Virtual Reality" under way.
  - Outer world (environment) vs. Inner world (brain)
- "Super-resolution high-speed 4D imaging" may reveal the fundamental principle of the most complex system in nature – our brain.
  - How can life overcome thermal fluctuation?
  - Networks in a cell and between cells (neurons)