Scientific Literature Analysis In Neuroscience

Modelling the Human Brain

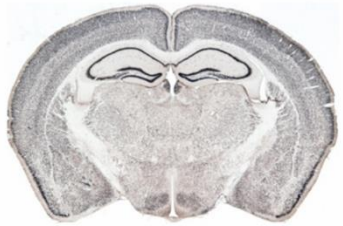
BIOENG-451

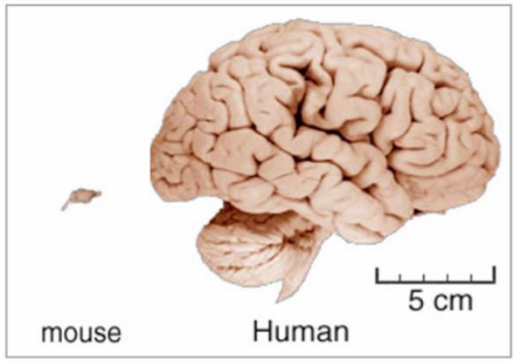
Academic year: 2025-2026

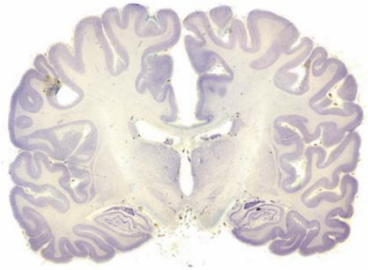
Teacher: Prof. Gioele La Manno

TA: Alessandro Valente

Why modelling the human brain?

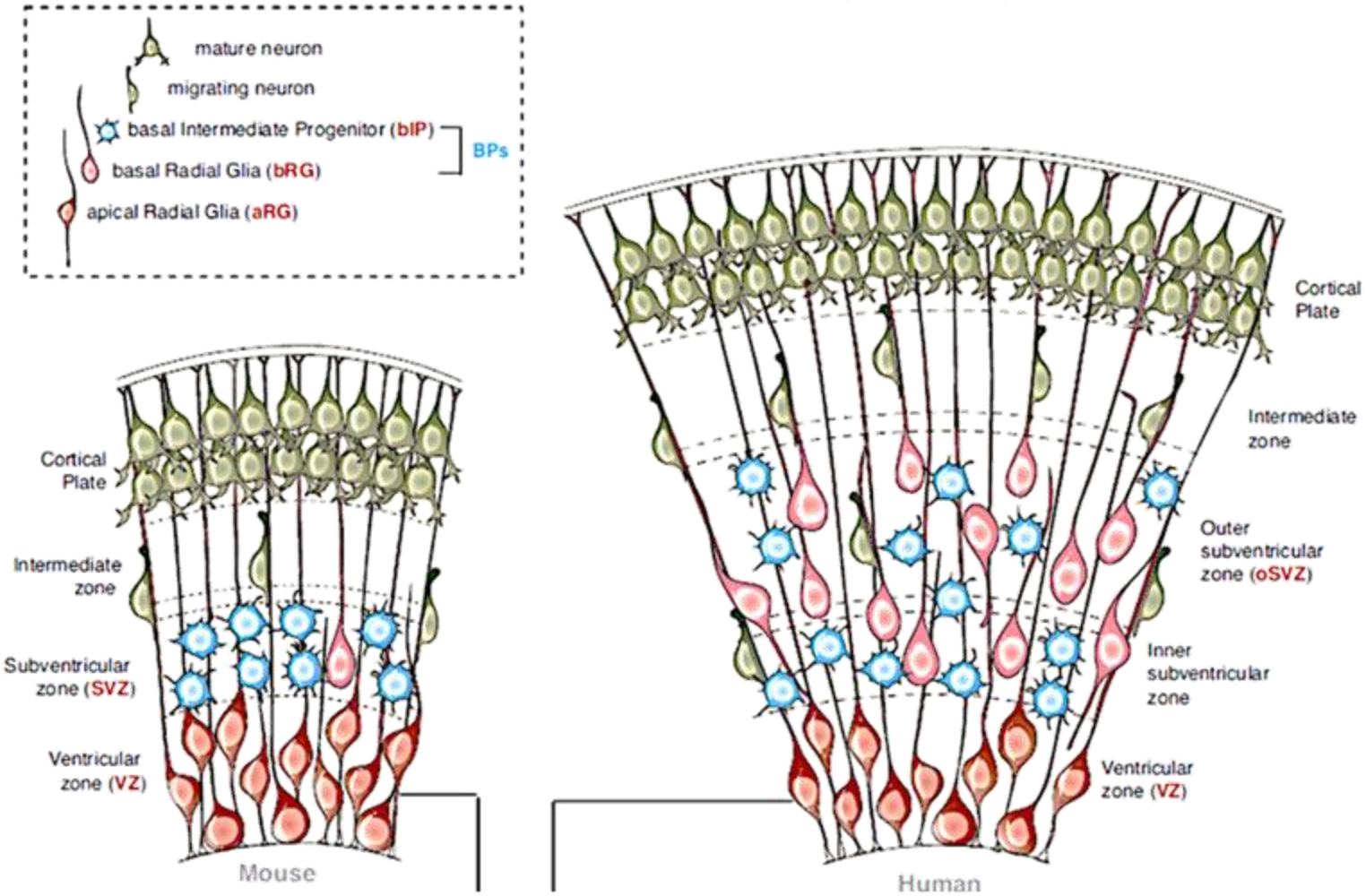




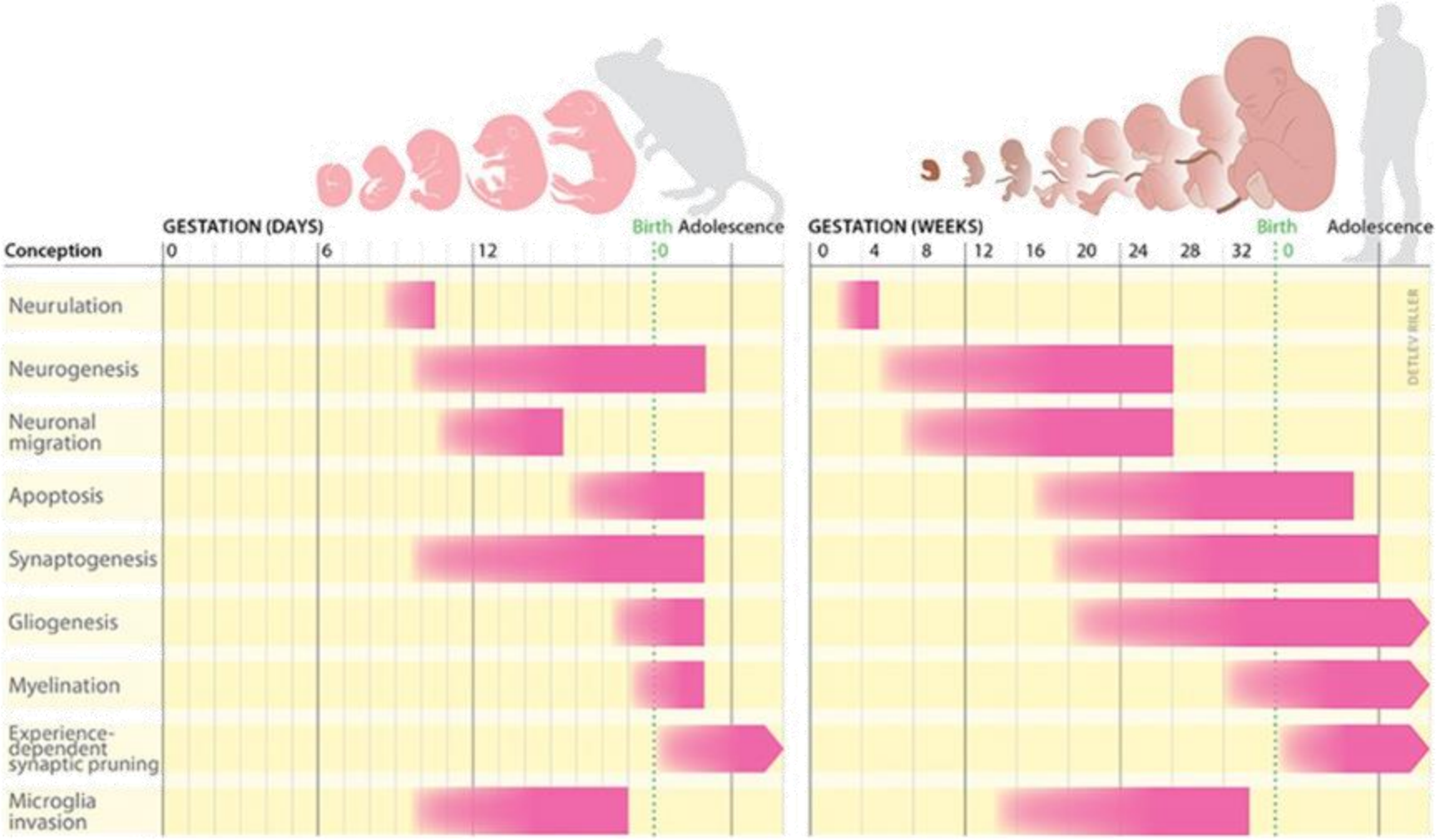


	Mouse	Human
Neurons brain	71.000.000	86.000.000.000
Neurons cortex	4.000.000	21.000.000.000
Relative to total	5,6%	25,9%
Number of Synapses	1 x 10^11	1.5 x 10^14

Humans have more complex SVZ regions and an expanded cortical plate compared to mouse



Gestational differeces between mouse and human brain development



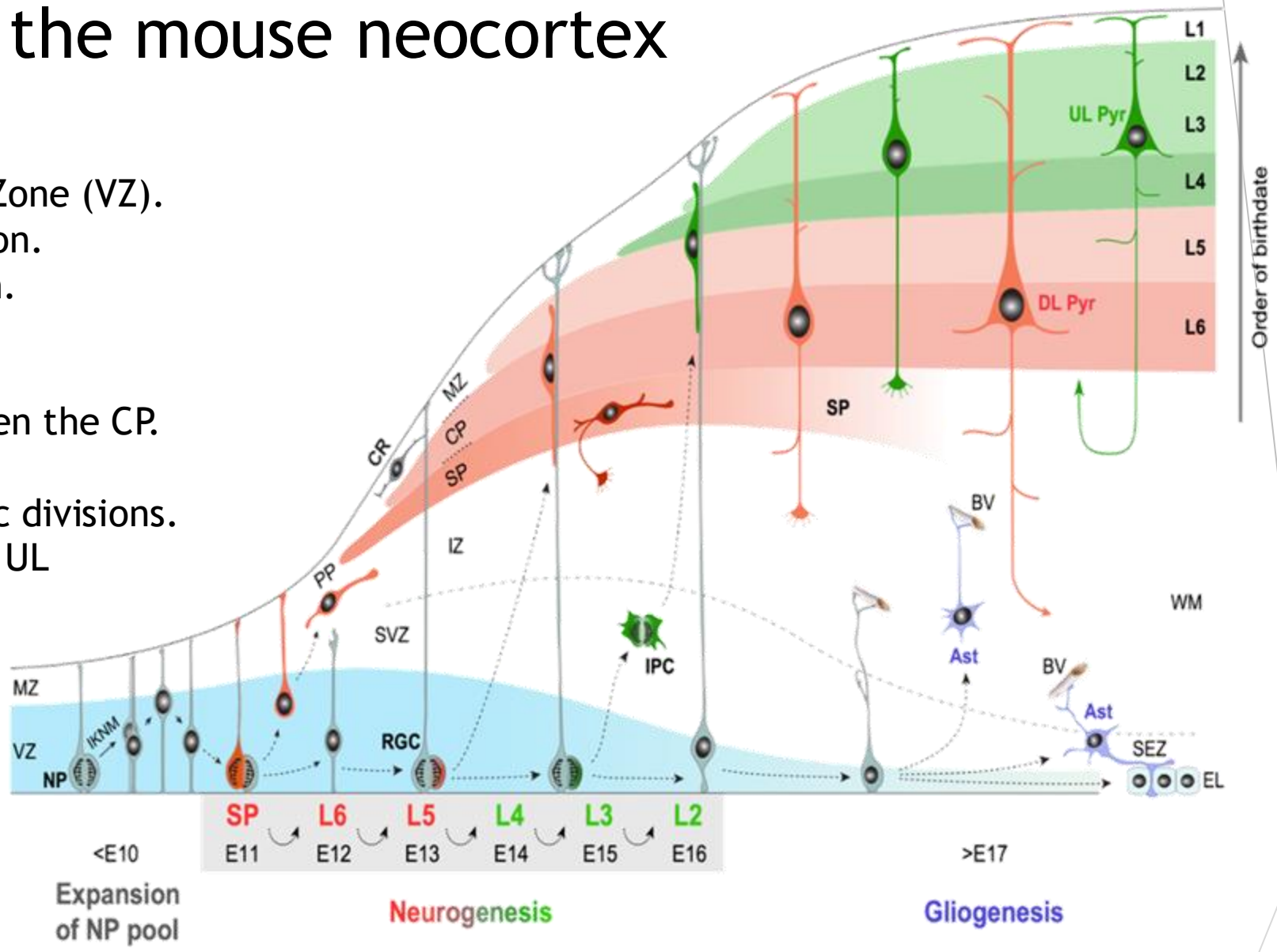
Development of the mouse neocortex

Prior Neurogenesis:

- NPs pool in the Ventricular Zone (VZ).
- Interkinetic Nuclear Migration.
- RGc and Asimmetric Division.

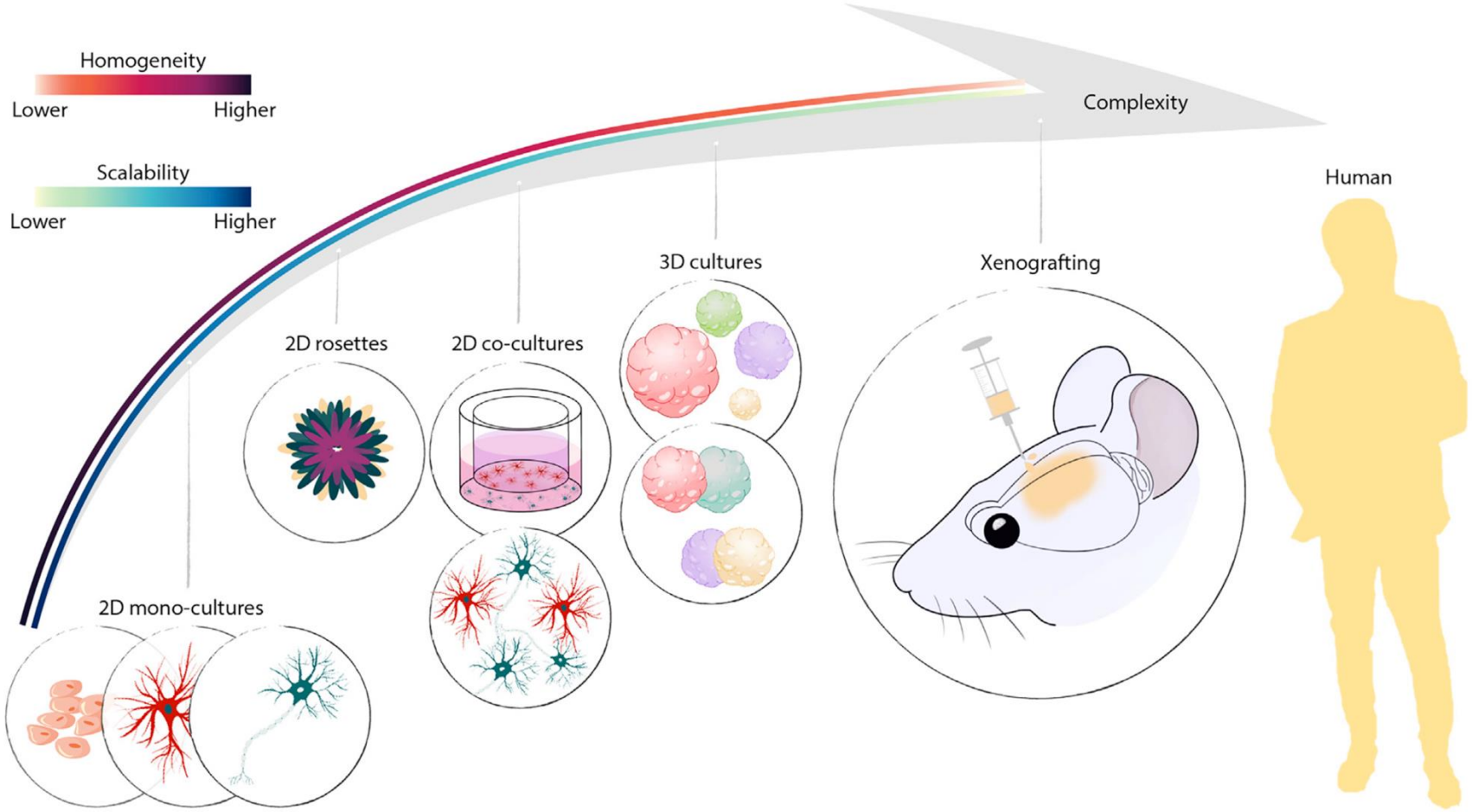
Newborn Neurons:

- Form the PP and the and then the CP.
- Inside-out Neurogenesis.
- IPCs derive from asymmetric divisions.
- IPCs contribute more to the UL neurogenesis.



Corresponding gestetional period in humans

Approaches to model human brain disorders



In and out: Benchmarking in vitro, in vivo, ex vivo, and xenografting approaches for an integrative brain disease modelling pipeline

Pereira et al. 2024

Stem cells derived Brain Organoid models

Cell

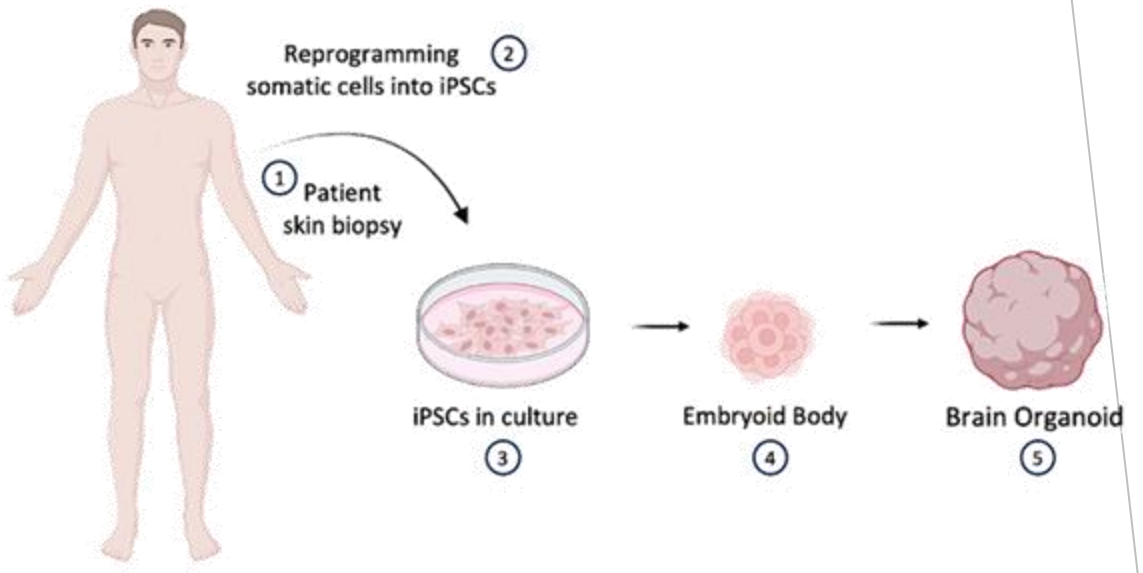
Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi[1] and Shinya Yamanaka[1,2,*]
[1]Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2]CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
*Contact: yamanaka@frontier.kyoto-u.ac.jp
DOI 10.1016/j.cell.2006.07.024

Reprograming somatic cells with Yamanaka factors:

- Myc
- Oct3/4
- Sox2
- Klf4

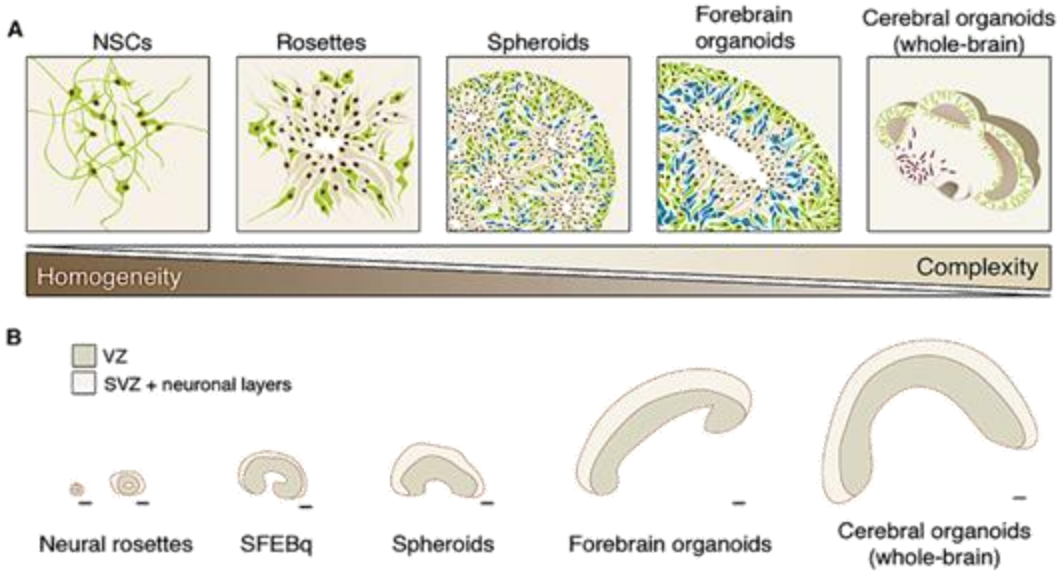
Takahashi and Yamanaka 2006



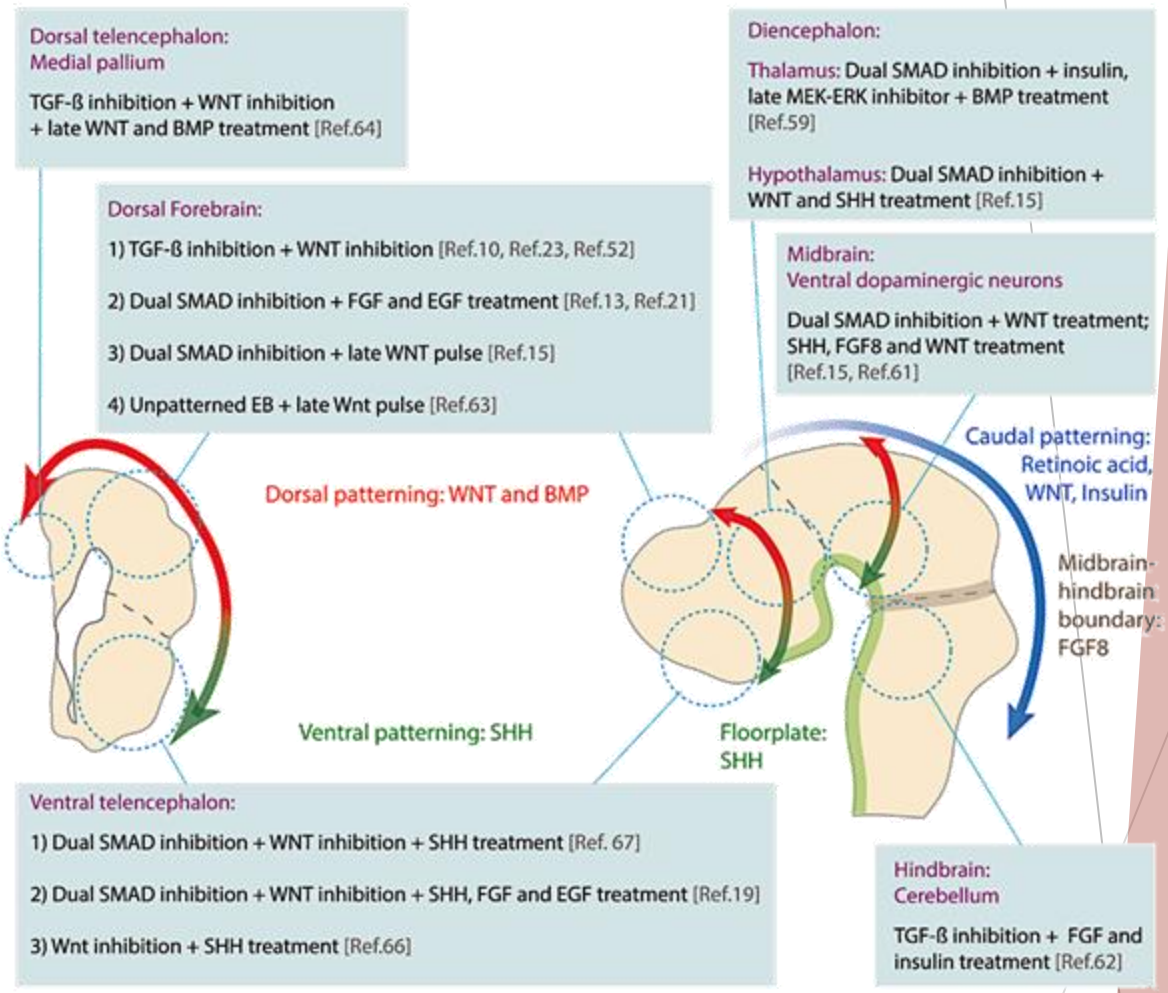
Step for the generation of brain organoids from somatic cells derived from patients.

- Yamanaka protocol for reprogramming started the new era of personalized medicine.
- Yamanaka won the Nobel price in 2012

Patterned and Unpatterned Brain organoids



Schematic representation of the main brain organoids protocols. (A) The higher is the cellular complexity, the lower is the homogeneity and vice versa. (B) Panel depicting the different organoid dimension obtained using different protocols. Scale bar is 100 µm. Adapted from Kelava and Lancaster 2016.

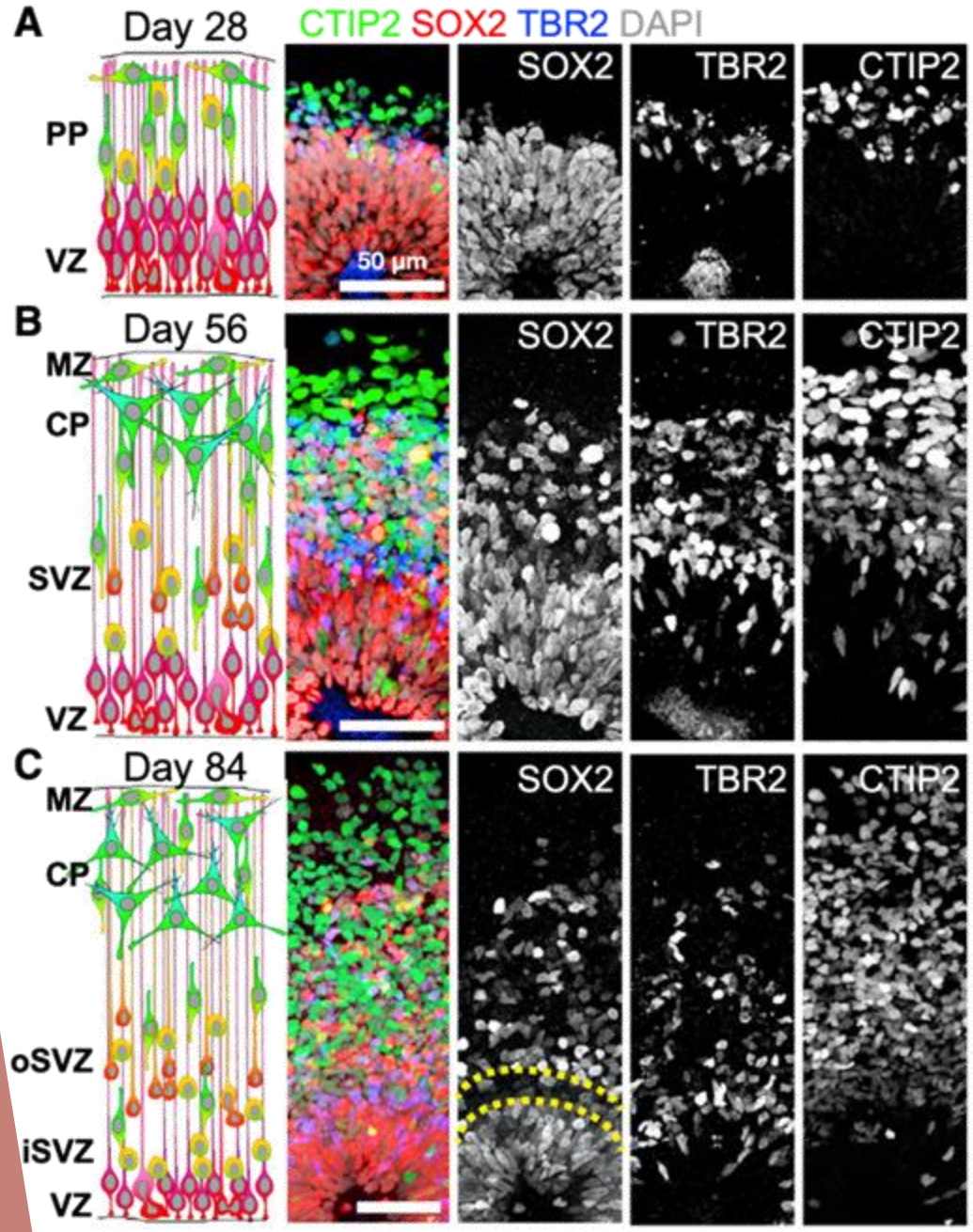


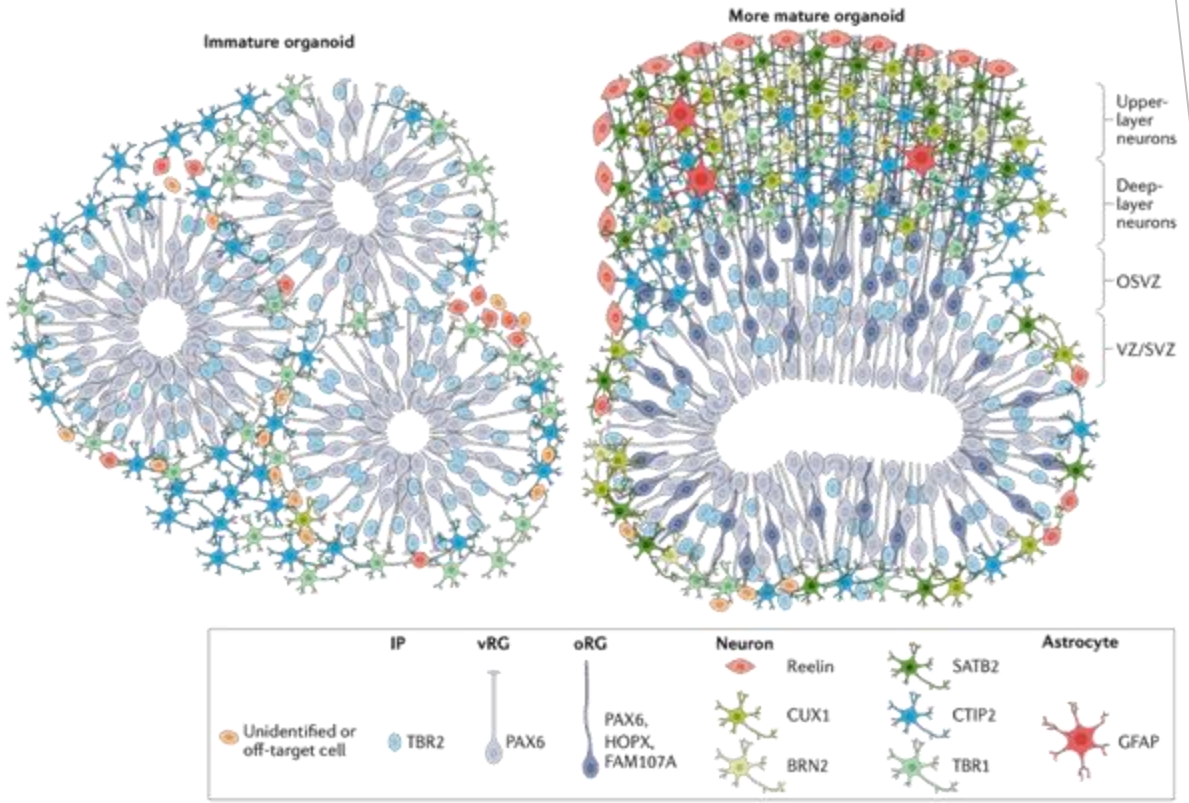
The perfect model does not exist!

Sidhaye, J., Knoblich, J.A. Brain organoids: an ensemble of bioassays to investigate human neurodevelopment and disease. *Cell Death Differ*

Brain organoids partially recapitulate the Human Brain

- Specific markers at different time points recapitulate specific neurodevelopmental stages





Schematic of cortical organoids at different stages of development. From Di Lullo and Kriegstein 2017.

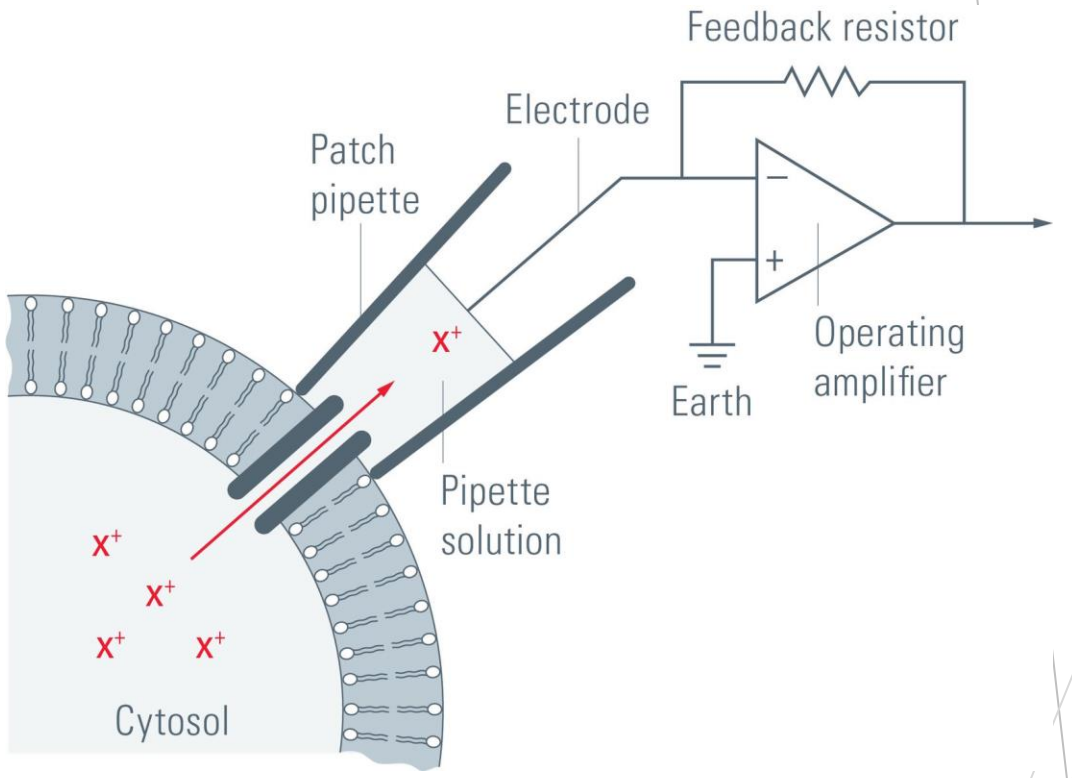
https://doi.org/10.1016/j.cell.2016.04.032

Techniques
Neuronal activity

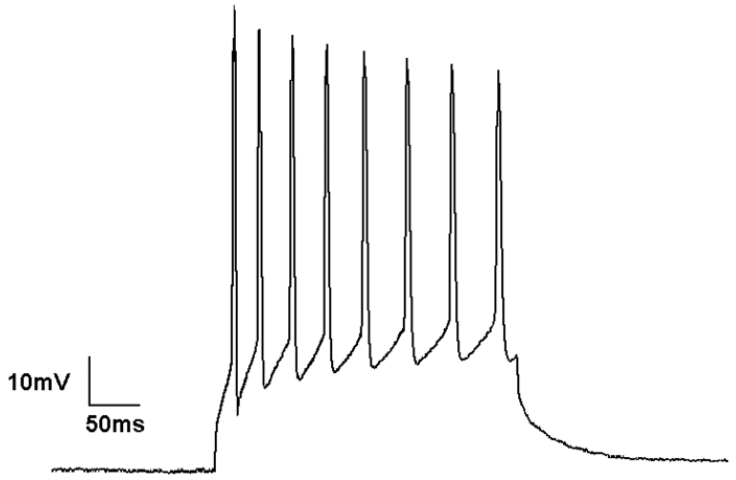
Patch Clamp Electrophysiology

Aim: Measure electrical activity and membrane properties of individual neurons

- Forms tight seal between pipette and cell membrane
- Records current flow through ion channels
- Allows manipulation of intracellular environment
- Provides high-resolution temporal data on neuronal activity



Patch Clamp Electrophysiology



Controls:

- Known ion channel blockers or activators
- Comparison with model cell parameters

Critical points:

•Cell health and viability during recording

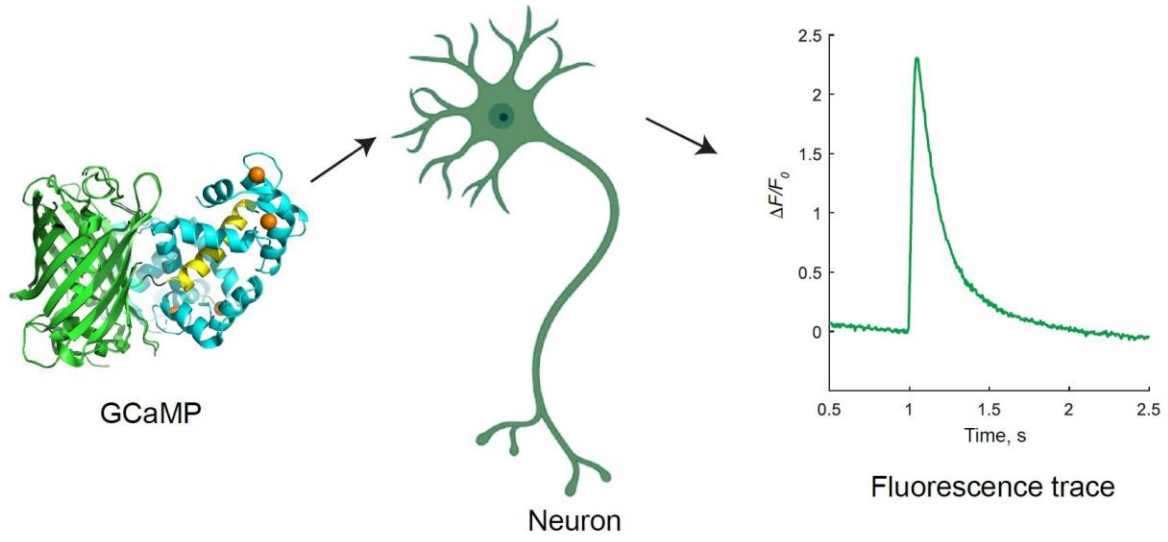
•Series resistance and capacitance compensation

•Liquid junction potential correction

Calcium Imaging with GCaMP

Aim: Visualize neuronal activity through calcium-dependent fluorescence changes

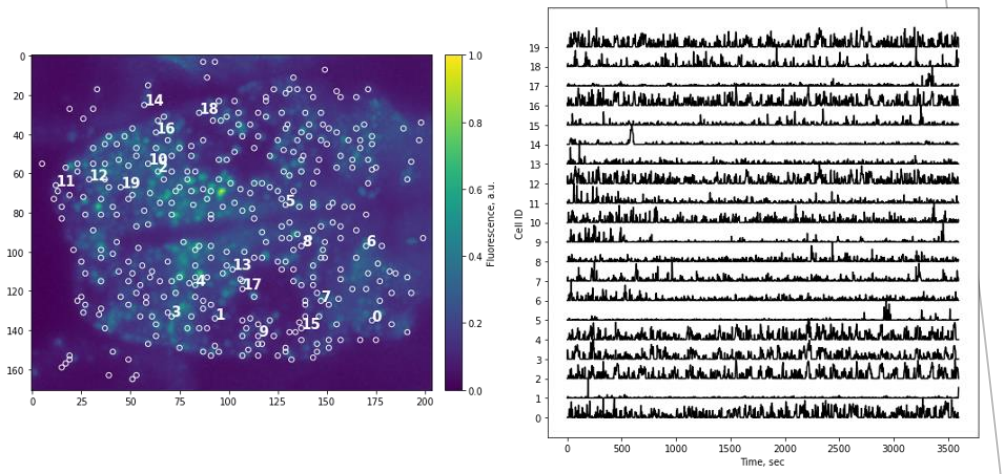
- GCaMP: Genetically encoded calcium indicator
- Binds to Ca2+ upon neuronal firing
- Increases fluorescence intensity
- Optical imaging captures activity patterns



Calcium Imaging with GCaMP

Controls:

- Calibration with known stimuli
- Comparison with electrophysiological recordings



Critical points:

- Temporal resolution and calcium dynamics
- Potential interference with cellular calcium homeostasis
- Relationship between fluorescence and spike rate