Modeling, simulations, data analysis in neuroscience and application to medical prediction using Model-Machine-Learning

Lectures 2019-20

D. Holcman

ENS Paris

1- www.biologie.ens.fr/bcsmcbs/

2- http://bionewmetrics.org

Practical info

- Oct 2020-Jan 2021
- Wednesday. 17h30-20h30.
- **Starting date: Oct 15**
- **WHERE** "Salle 511":
- ENS 46 rue d’Ulm, 75005 Paris
- **Class common to PSL-ENS-Sorbonne University**

Practical info

- Youtube class organized in www.Bionewmetrics.org
- **http://bionewmetrics.org/stochastic-processes-and-applications-to-modeling-cellular-microdomains/**

- Listen and try to redo the class
- Join Zoom Meeting https://us02web.zoom.us/j/83845723162?pwd=V1BpM3IwMzZGK2xXK3I1T3IvakxPdz09
- Meeting ID: 838 4572 3162
  Passcode: XYajB1

Projects: creativity, construction, depth in modeling, simulations, rigor to finish a project:

2 pages summary
1 ppt presentation
40-70 hours of work
possible publication

Exam, project 6 months +PhD thesis

- Exam: one project (40hs/20 min ppt presentation+10min questions/2 pages summary)
- 2 to 3 Master positions available
- 2 PhD positions.
- Interested students: contact me now.

Content of the class

- General notion of cells, neurons, cell compartments
- Physical modeling
- Mathematical methods and simulations
- Data analysis, extraction of parameters and features

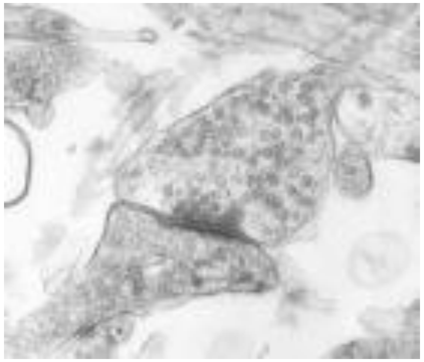
Expectation from the class

- Research in applied mathematics, physical biology
- New methods of data analysis beyond classical statistics
- Methods for multiscale simulations
- Publish in interdisciplinary J., math, physics and biology as independent researcher
- Produce models, simulations, data analysis

Biological Microstructures

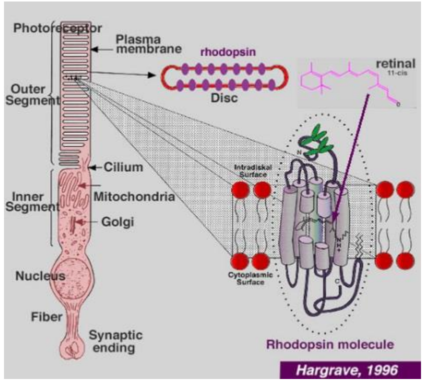
Definition:

Part of a cell, driven by molecular interactions underlying a physiological unit.



- **Synapses** (transduce information between neurons)

- **Outer segment of photoreceptors** (a photon induces a hyperpolarization)



Why modeling microstructures?

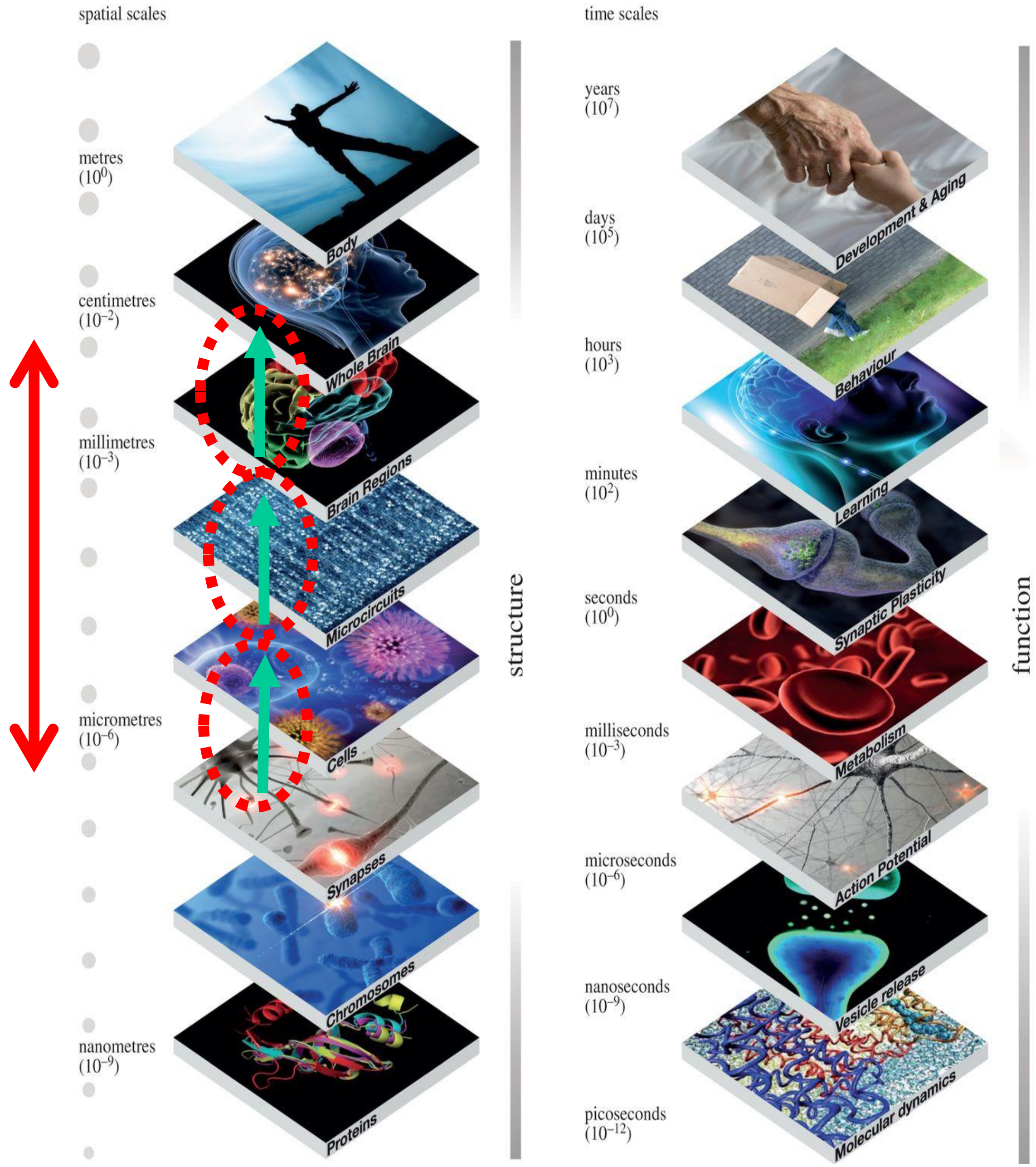
1. **Understand** the function of microdomains and analyze the cell behavior in normal and pathological conditions.

2. **Account for** :
   - small size structures.
   - low number of molecules (buffers, dyes introduced experimentally may perturb the function).
   - How to study a molecular cascade ?
   - Predict the effect of drugs/ molecule/removing proteins…

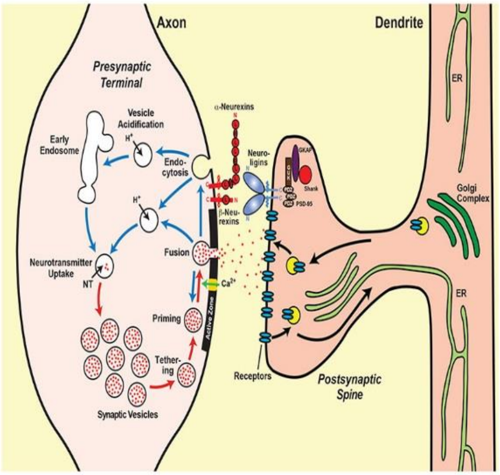
Studying multicale changes

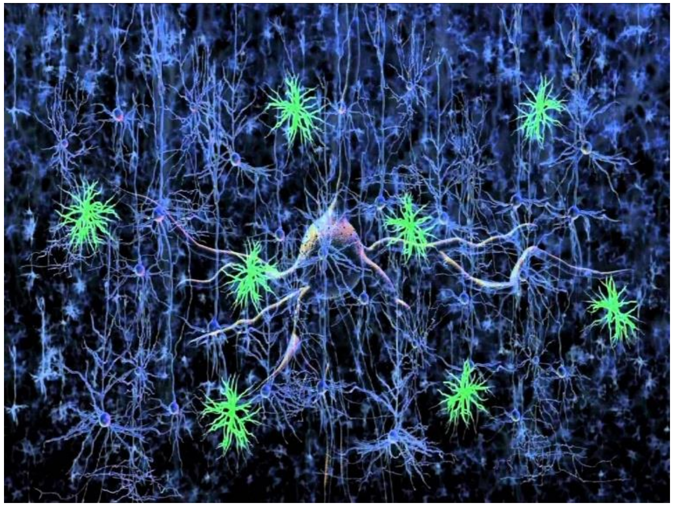
Temporal and spatial scales

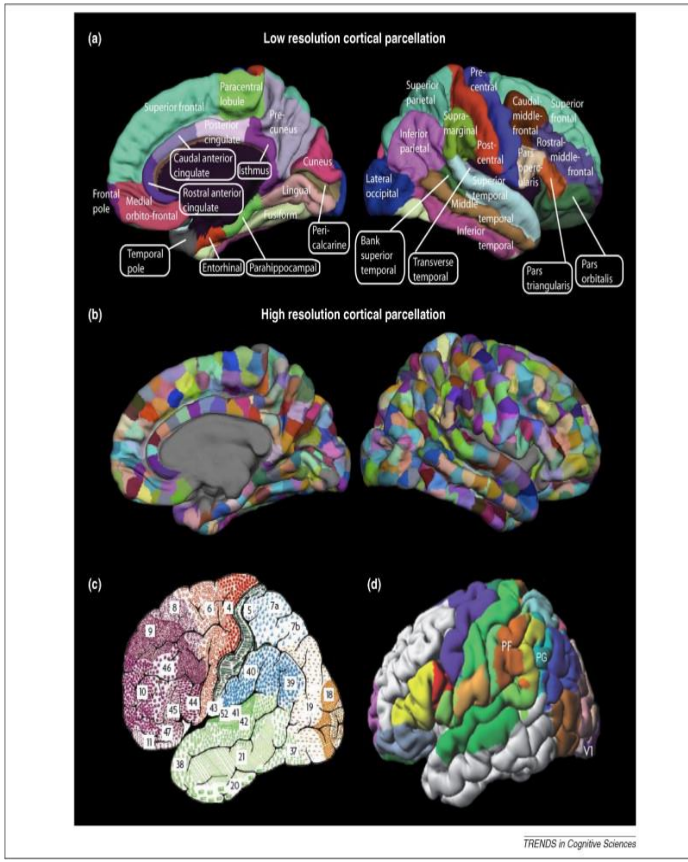
Multiscale Models, Analysis Simulations

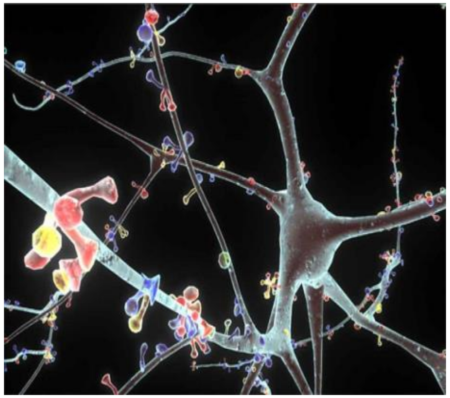


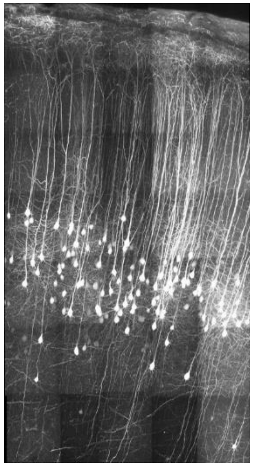
Phenomena at different scales











Entire brain

Synapses: from molecules→cells

Network: cell→population

Syllabus

Part I: Molecular level

- Stochastic processes, Fokker-Planck equation
- Recovering a stochastic process from noisy trajectories: application to the reconstruction of synapses and cellular organelles.
- Exit problem and boundary layer for linear PDE and Mean First Passage Time Equations.
- Small hole theory: search for a small target: application to neuronal signaling
- Extreme statistics and redundancy principle to study rare events.
- Diffusion in the cleft+ method of simulations. Calcium dynamics in a dendritic spine.
- Fast simulations of rare events.
- Model of vesicular release and calcium in the pre-synaptic terminal. Diffusion in microdomains: Molecular and vesicular trafficking. Hybrid (Markov and mass-action) model of reaction-diffusion.

Part II and III: sub-cellular-cellular

- Analytical method of single particle trajectories analysis for calcium channel, calreticulin, AMPAR, NMDA, Gly,..receptors: Model of reconstruction for high-density regions, potential wells analysis, based on density statistics and vector field reconstruction. Introduction to the vector field index.
- ER-network: concept of active Graph and interpreting photo-activation data.
- Model facilitation-depression, Bursting and Up-Down states, distribution of time in the Up-state by studying the non-selfadjoint Fokker-Planck and the full spectrum.
- Large-scale model of Neuron-glia interactions.
- Model of electro-diffusion, asymptotic and singularities, simulations. Electro-neutrality.
- Deconvolution of time series (voltage dyes).
- EEG analysis. Band spectral analysis.
- Machine learning classification, feature extractions. Applications to Coma, Anesthesia and sleep.

Possible projects

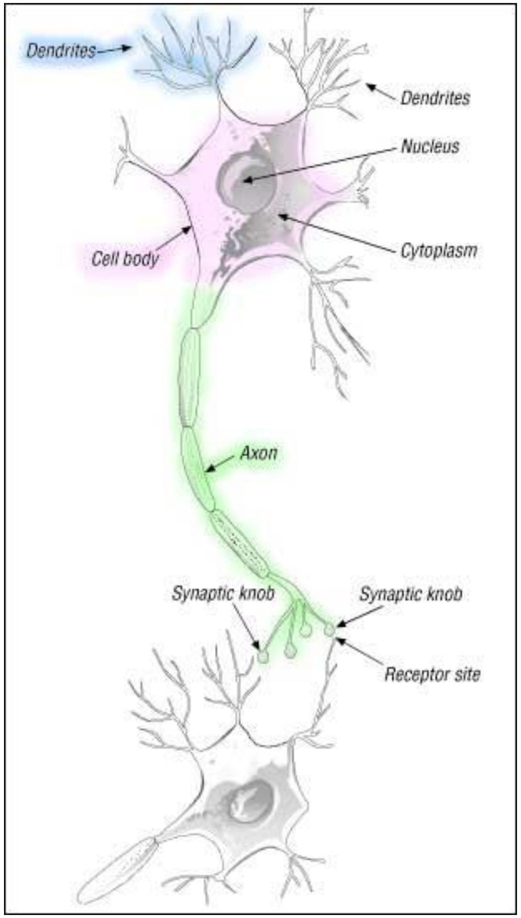
- Stochastic simulations in microdomains: role of exteme statistics in activation
- Fast oscillation in the Brain: Ripples activity at the end of the critical period.
- Analysis of coma from auditory cortex stimulation and EEG
- Asymptotic analysis of PDE for escape: Up down states.
- Modeling cell sensing
- Modeling and multiscale analysis of signal transduction in olfactory receptor neurons
- Extract flow: vector field from trajectories
- MFPT in the ER network
- Data blood flow: reconstruction+ coupling neuronal activity
- Analysis minis and evoked actvity: reconstruct and analyze column at synapses.
- Hi-C
- Effect of noise in computation anomalous exponents
- Extreme stat and calcium signaling in neurons

References

- -D. Holcman Z. Schuss, Stochastic Narrow Escape: theory and applications, Springer 2015
- -D. Holcman, Z. Schuss, Asymptotics of Singular Perturbations and Mixed Boundary Value Problems for Elliptic Partial Differential Equations, and their applications, Springer 2018
- -Schuss, Z., Theory and Applications of Stochastic Processes (Hardback, 2009) Springer ; 1st Edition. (December 21, 2009)
- **Basics :**
- D. Holcman Z. Schuss, 100 years after Smoluchowski: stochastic processes in cell biology, *J. Phys. A* (2016).
- Z. Schuss D. Holcman, The dire strait time, SIAM Multicale Modeling and simulations, 2012.
- D. Holcman Z. Schuss, the Narrow Escape Problem, SIAM Rev 56 no. 2, 213–257, 2014.
- D. Holcman, Z. Schuss Control of flux by narrow passages and hidden targets in cellular biology, *Reports on Progress in Physics* 76 (7):074601. (2013).
- Z. Schuss, Brownian Dynamics at Boundaries and Interfaces, Springer series on Applied Mathematics Sciences, vol.186 (2013).
- **Advanced :**
- D. Holcman N.Hoze, Statistical methods of short super-resolution stochastic single trajectories analysis, *Annual Review of Statistics and Its Application, 4, 1-35* (2017).
- N Rouach, KD Duc, J Sibille, D. Holcman, ionic fluxes regulated neurons and astrocytes. Dynamics of ion fluxes between neurons, astrocytes and the extracellular space during neurotransmission, *Opera Medica et Physiologica* 4 (1), 1-18, 2018.
- J Cartailler, P Parutto, C Touchard, F Vallée, D Holcman, Alpha rhythm collapse predicts iso-electric suppressions during anesthesia, Communications biology 2 (1), 1-10 2019.

Crash course on neuronal function

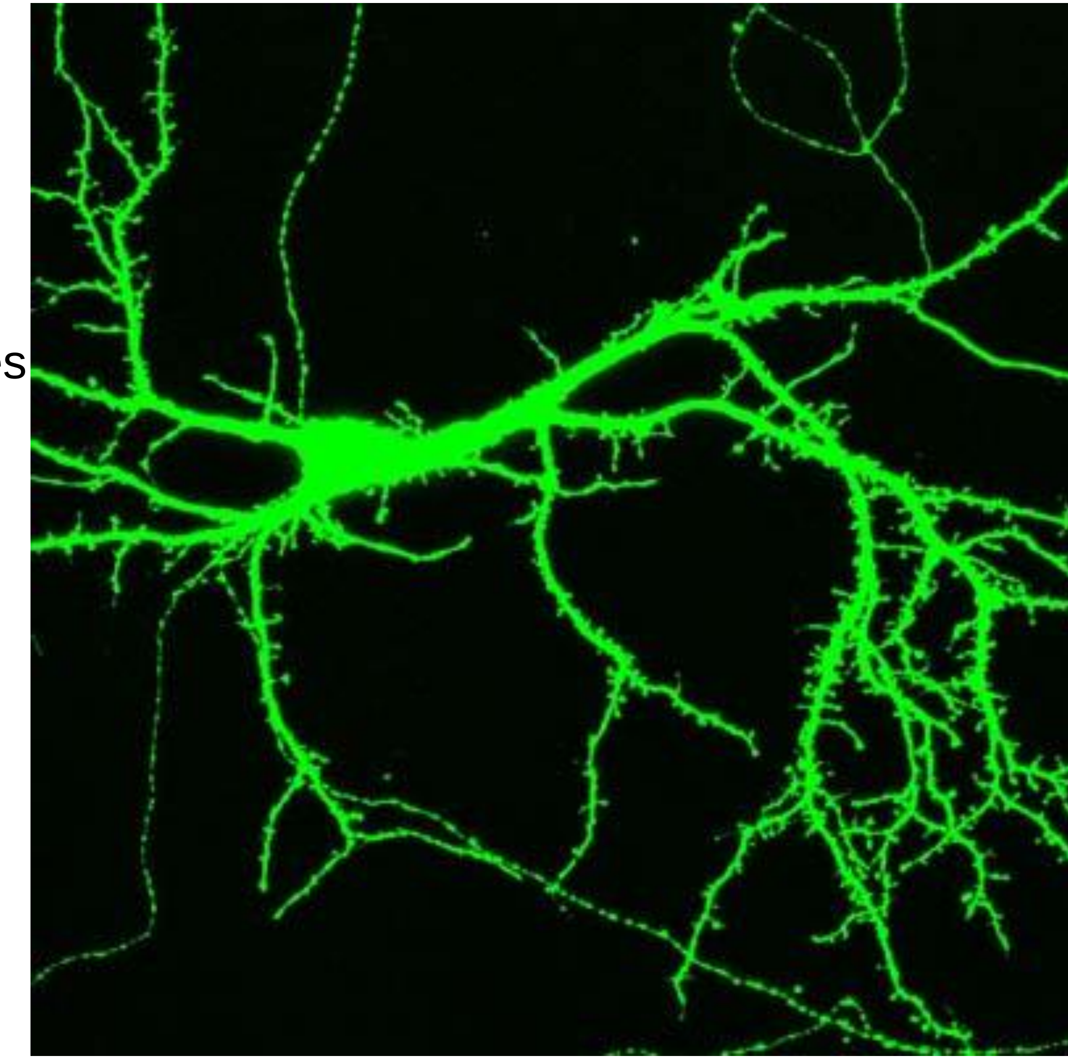
Neurons



-Dendrites

-Soma

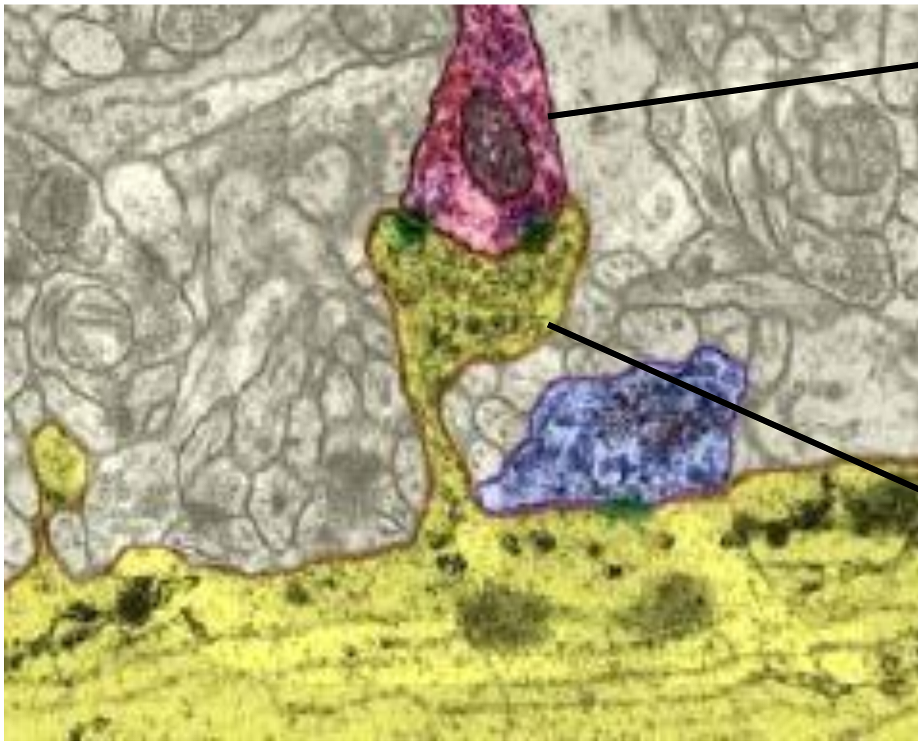
-Axons

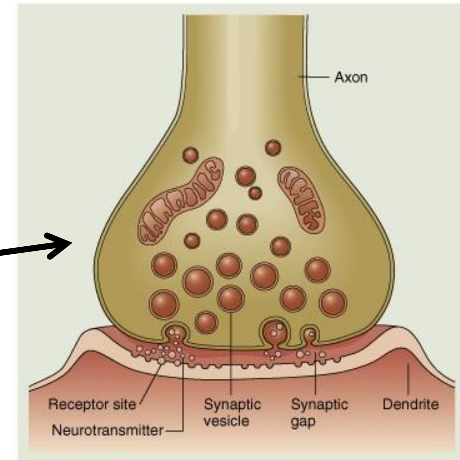


Hippocampal neurons

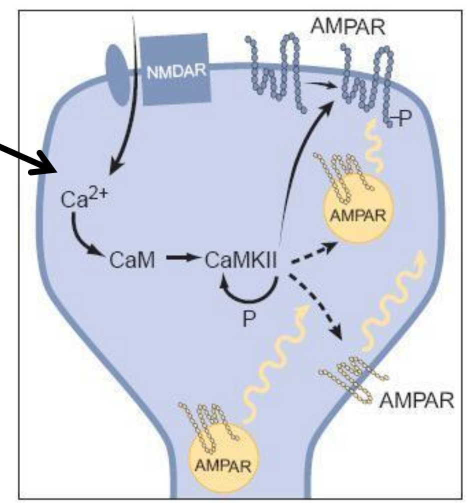
Synapses

Pre-



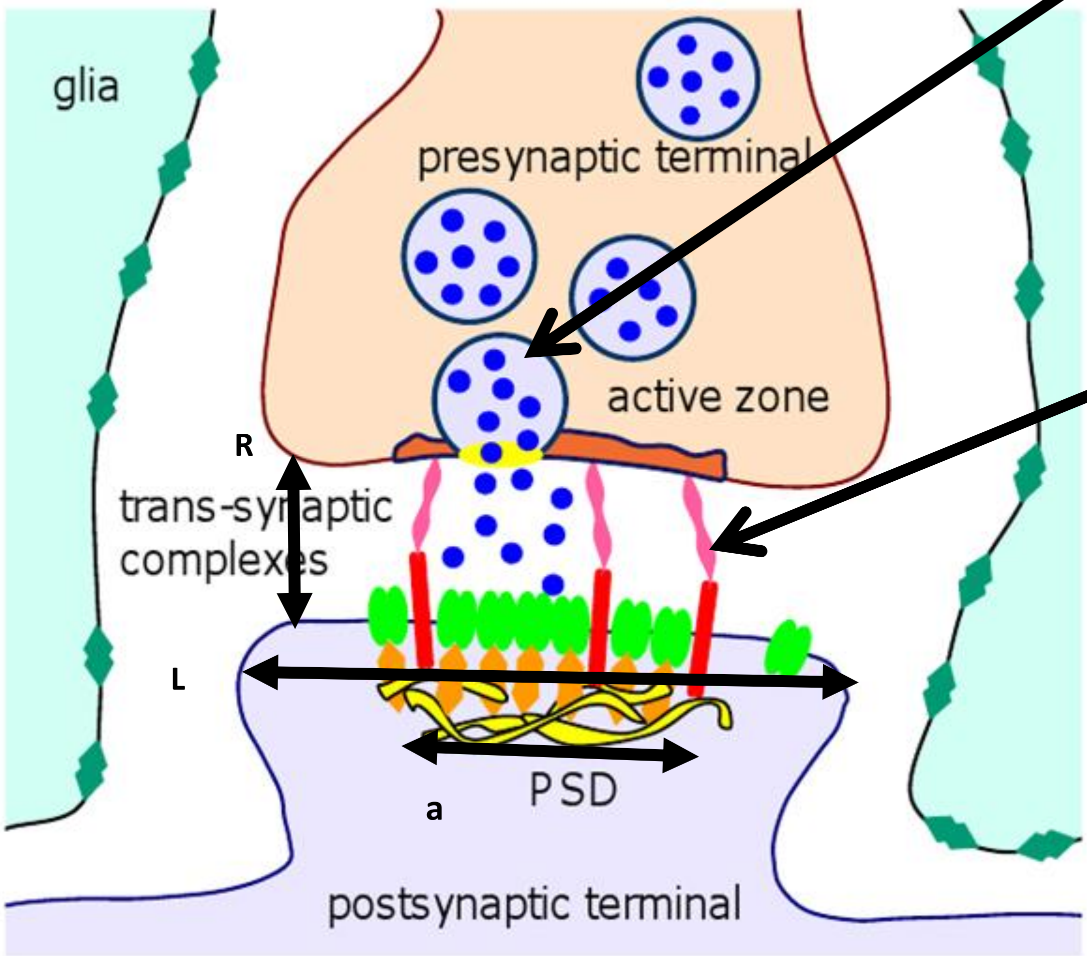


Picture sourse: R.C. Malenka and R. A. Nicoll



Post-

Diffusion in synaptic microdmains



Calcium diffusion between Vesicles: position of calcium channels

$$\tau_{Target} = \frac{|\Omega_{terminal}|}{4\pi D_{Ca,c}\varepsilon},$$

Guerrier-Holcman, SIAM MMS 2015

Guerrier-Holcman, submitted

Diffusion law in the synaptic cleft. Probability of finding a receptor

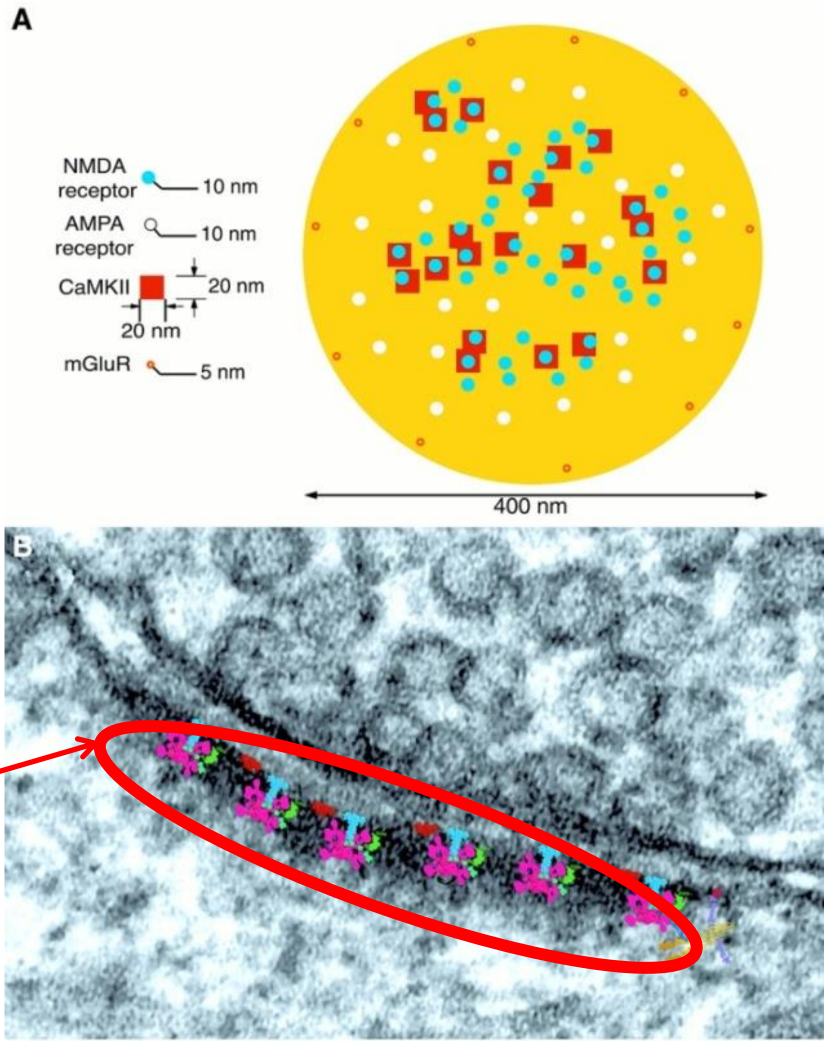
$$\Pr\{\tau_{\text{hole}} < \tau_{S_r}\} = \frac{4a}{\pi R}\sum_{m=1}^{\infty}\frac{1}{\gamma_{0,m} J'_0{}^2(\gamma_{0,m})\sinh\frac{\gamma_{0,m}L}{R}} + O\left(\frac{a^2}{L^2}\log\frac{a}{L}\right).$$

-Reingruber et al , *SIAM Multiscale Modeling Simulation*. 9, pp. 793-816 (2011)

-Holcman, Rep Prog Phys. 2013 76(7):074601.

Conclusion: the number of bound receptors is independent of the diffusion coefficient

Organization of receptor at the PSD



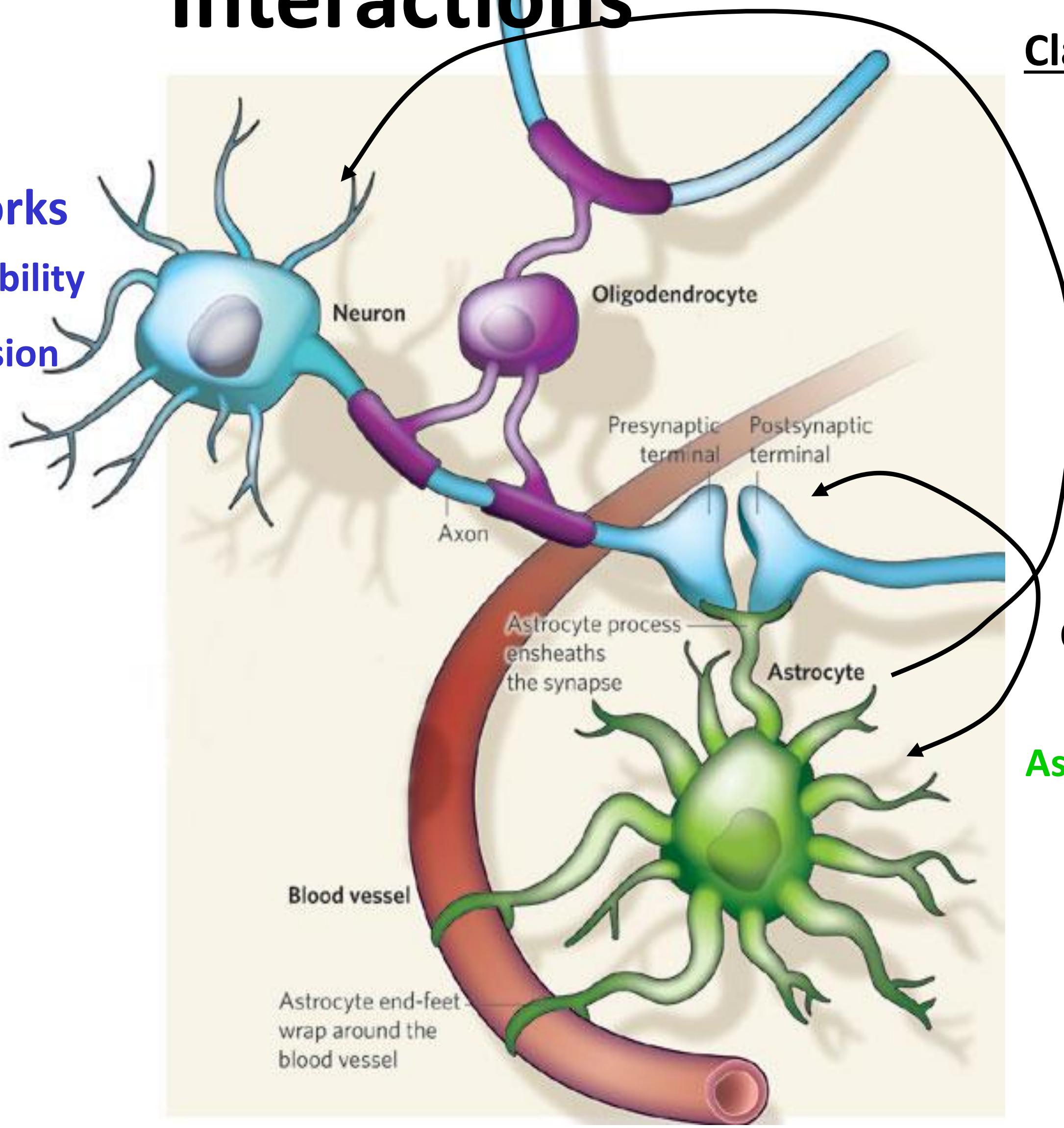
PSD

M. Kennedy Science 2000

Few numbers of receptors shape the synaptic response

Population in the Brain: Neuron-Glia-Interactions

Neuronal networks
- Electrical excitability
- Neurotransmission



Classic concept:
Structural, metabolic and trophic support

New concept:
Calcium excitability, Gliotransmission

Astrocyte

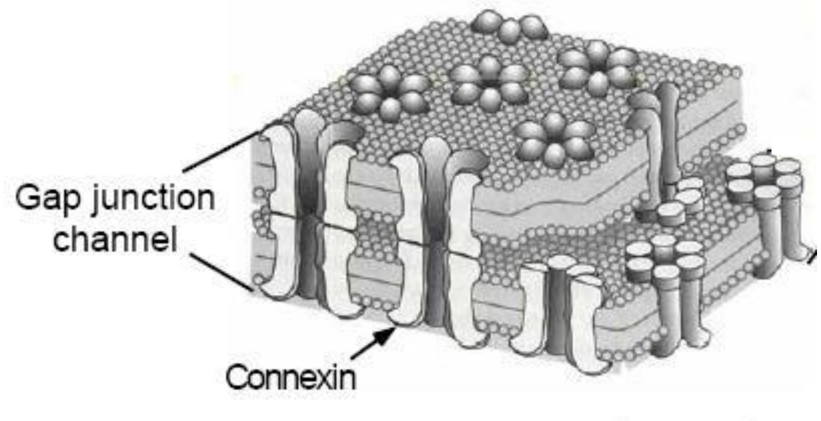
Allen & Barres 2009, Nature

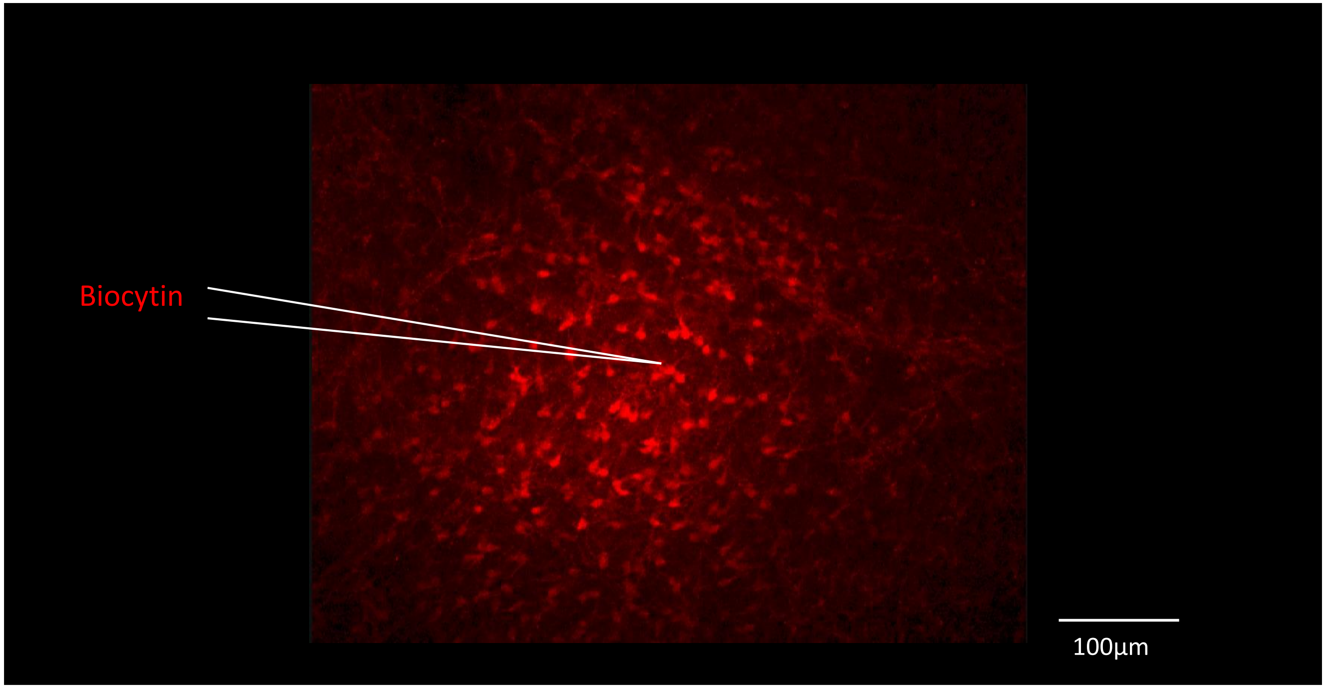
Astrocytic Connexins: network organization

Connexin Connexon intracellular channel

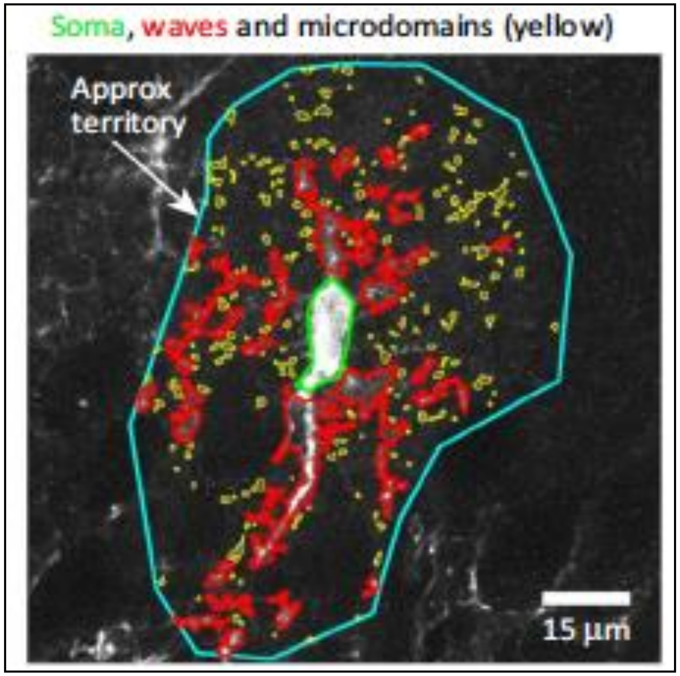
Connexin 43

Connexin 30

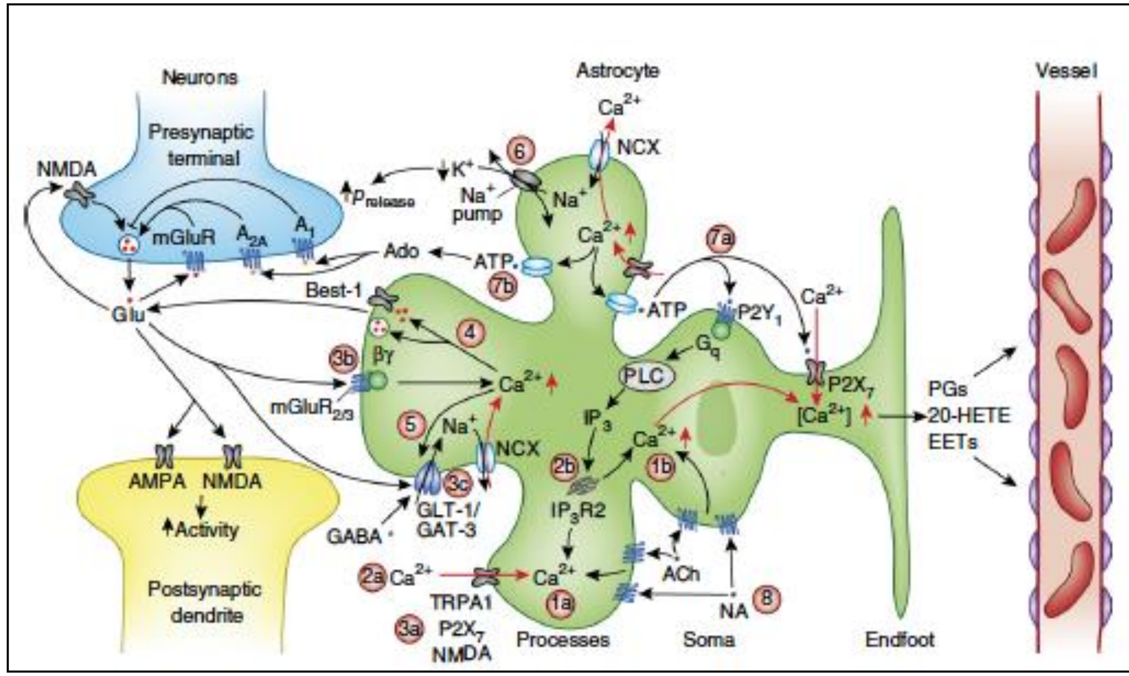




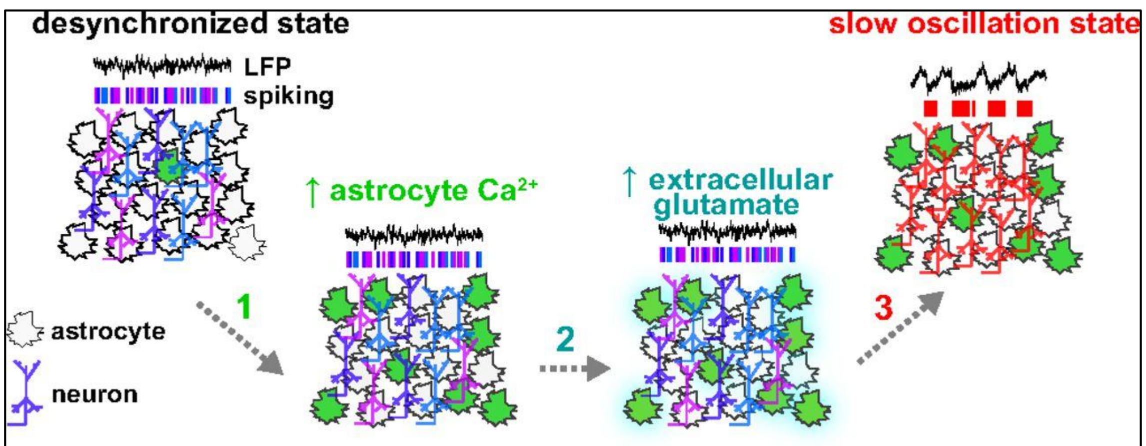
Astroglial Ca^{2+}



Srinivasan et al., 2015



Narges Bazargani & David Attwell, 2016



Kira Poskanzer and Rafael Yuste, 2016

Dopamine Elevates and Lowers Astroglial Ca^{2+} Through Distinct Pathways Depending on Local Synaptic Circuitry

Alistair Jennings,[1] Olga Tyurikova,[1,2] Lucie Bard,[1] Kaiyu Zheng,[1] Alexey Semyanov,[2,3] Christian Henneberger,[1,4,5] and Dmitri A. Rusakov[1,2]

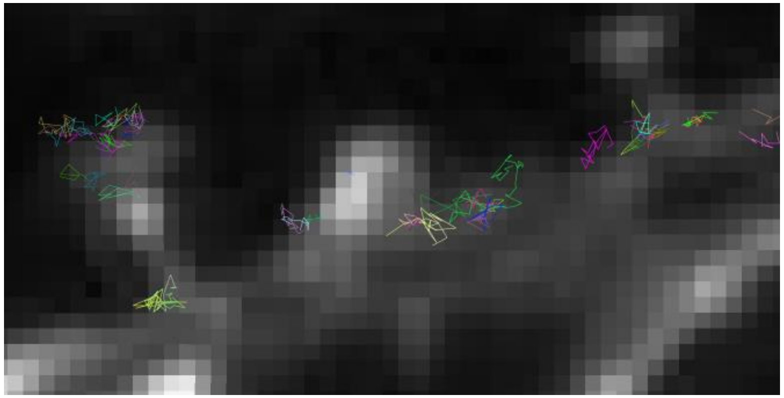
LETTER

doi:10.1038/nature20145

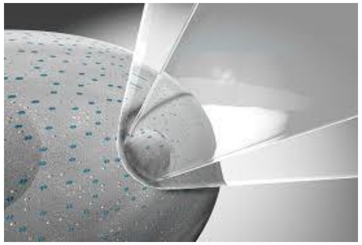
Neuromodulators signal through astrocytes to alter neural circuit activity and behaviour

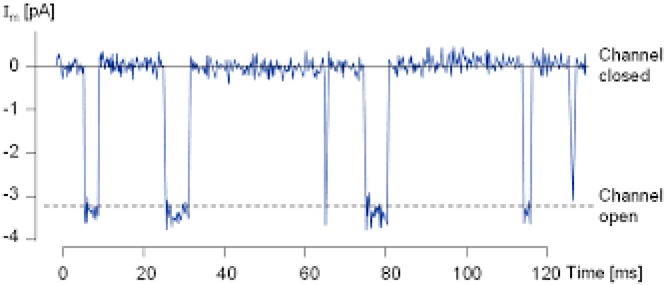
Zhiguo Ma[1], Tobias Stork[1], Dwight E. Bergles[2] & Marc R. Freeman[1]†

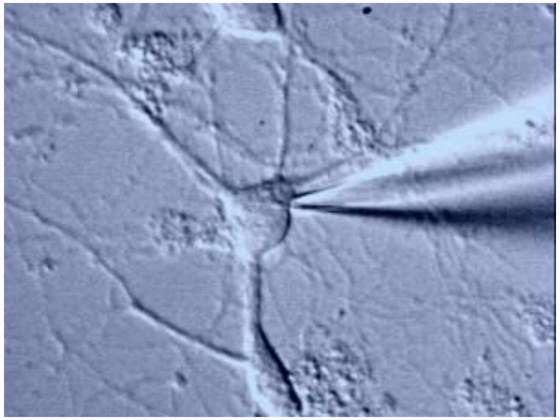
Type of recordings

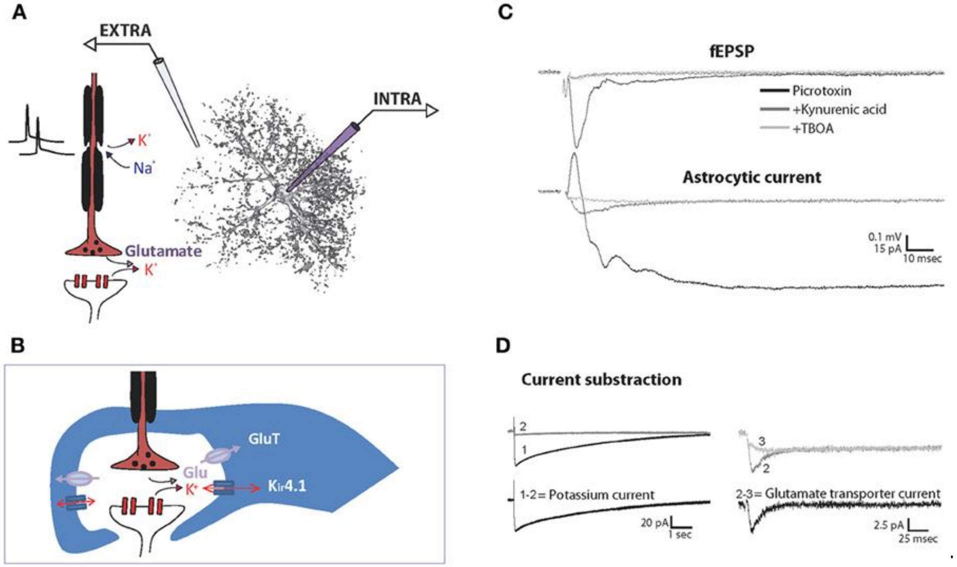


- Molecule/cellular (SPTs, calcium)
- Patch
- Field recording



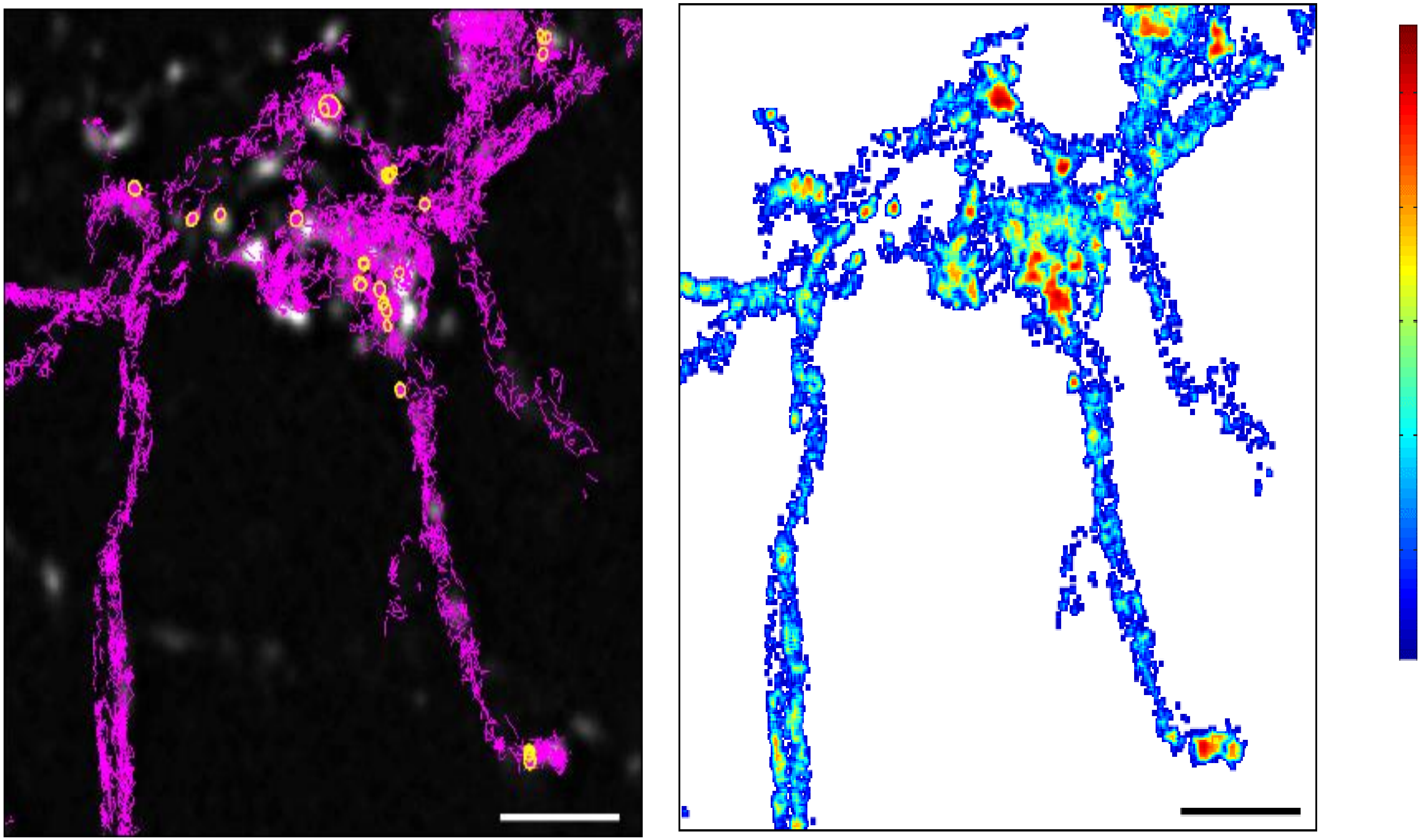






Synaptic nano-domains

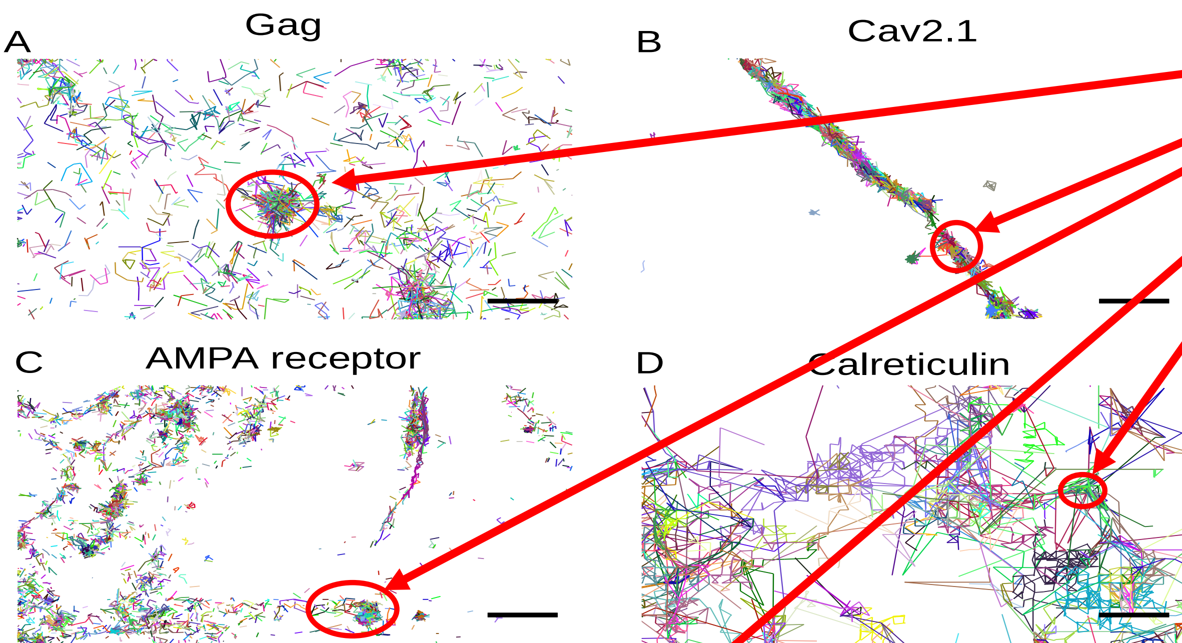
1. **Neuronal nanodomain definition: calcium ions, channel and receptors**



2. Empirical definition using Single Particle Trajectories

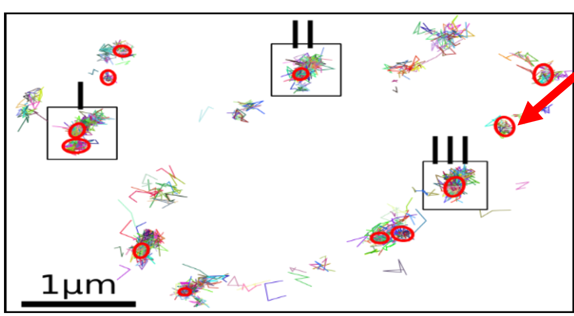
Nano-domains revealed by super-resolution Single particle trajectories

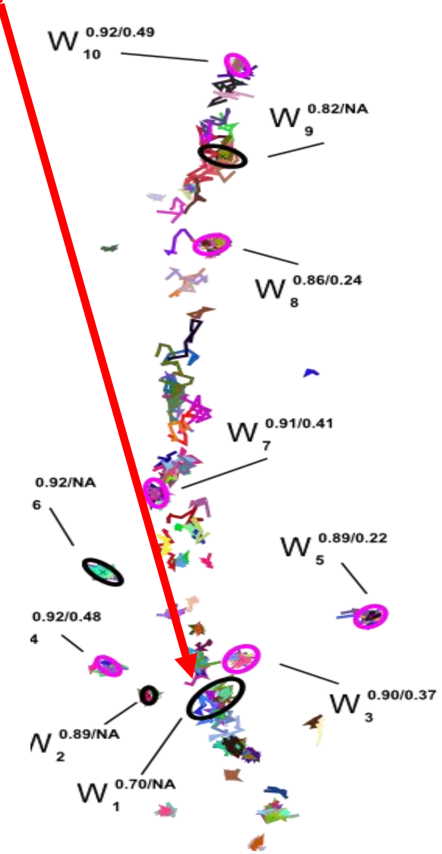
High density regions



E CaV (membrane) at Neuro-muscular junction in drosophila

Hoze et al , Ann. Rev. 2017



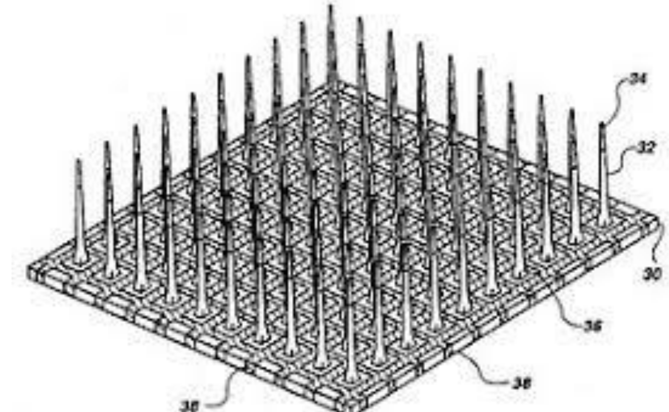


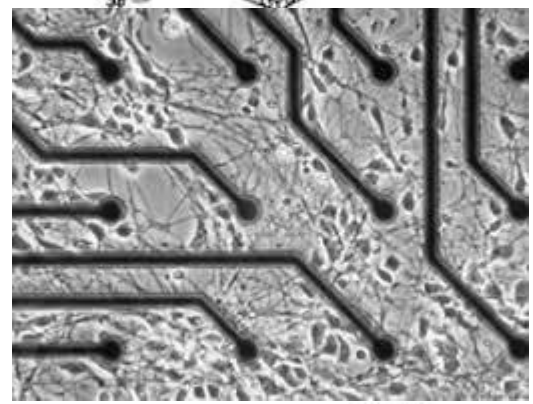
Nanodomains=region of high density revealed by SPT

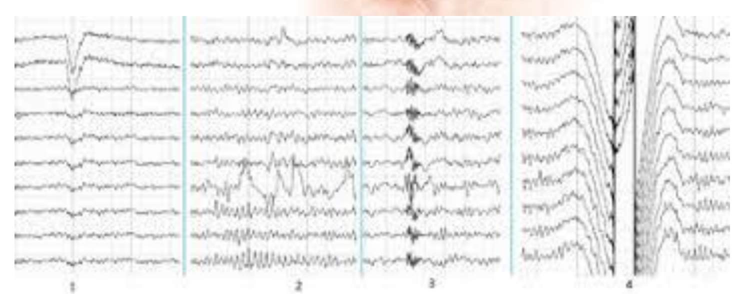
F-CaV2.1 on axon

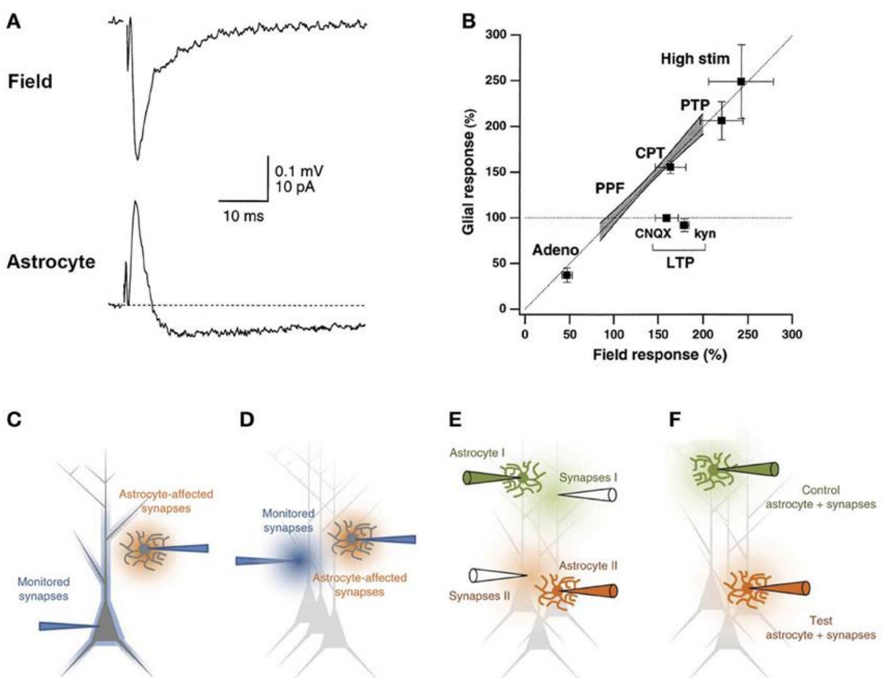
Type of recordings

- Field recording
- MEA (multi-ElectroArray)
- EEG

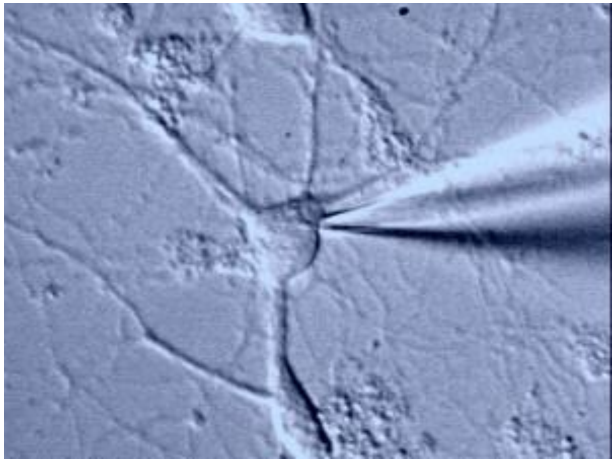


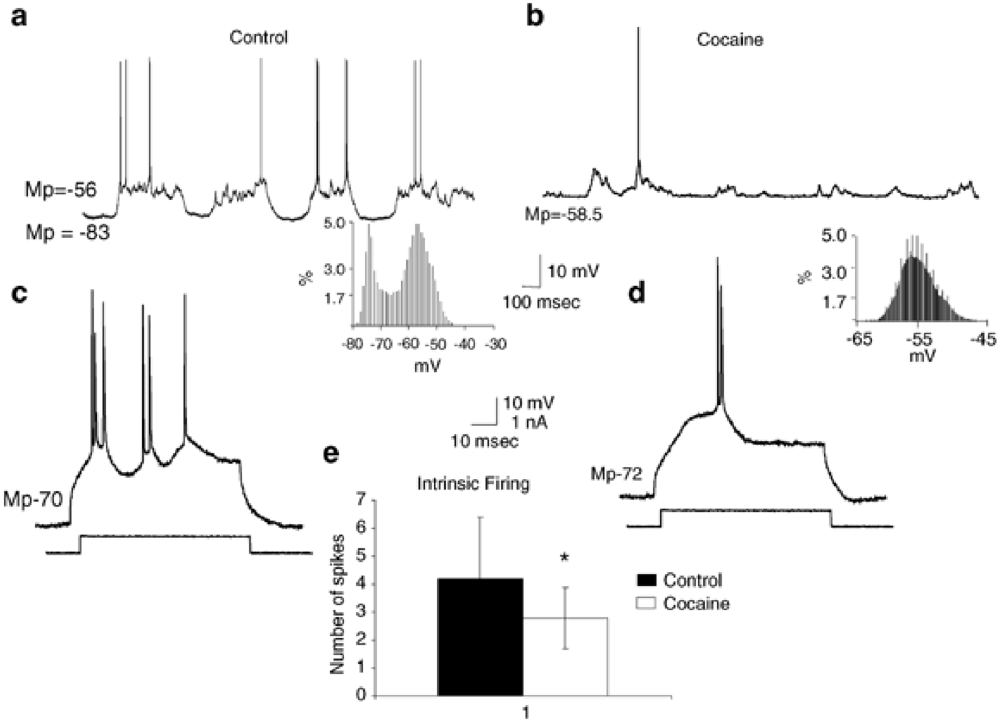




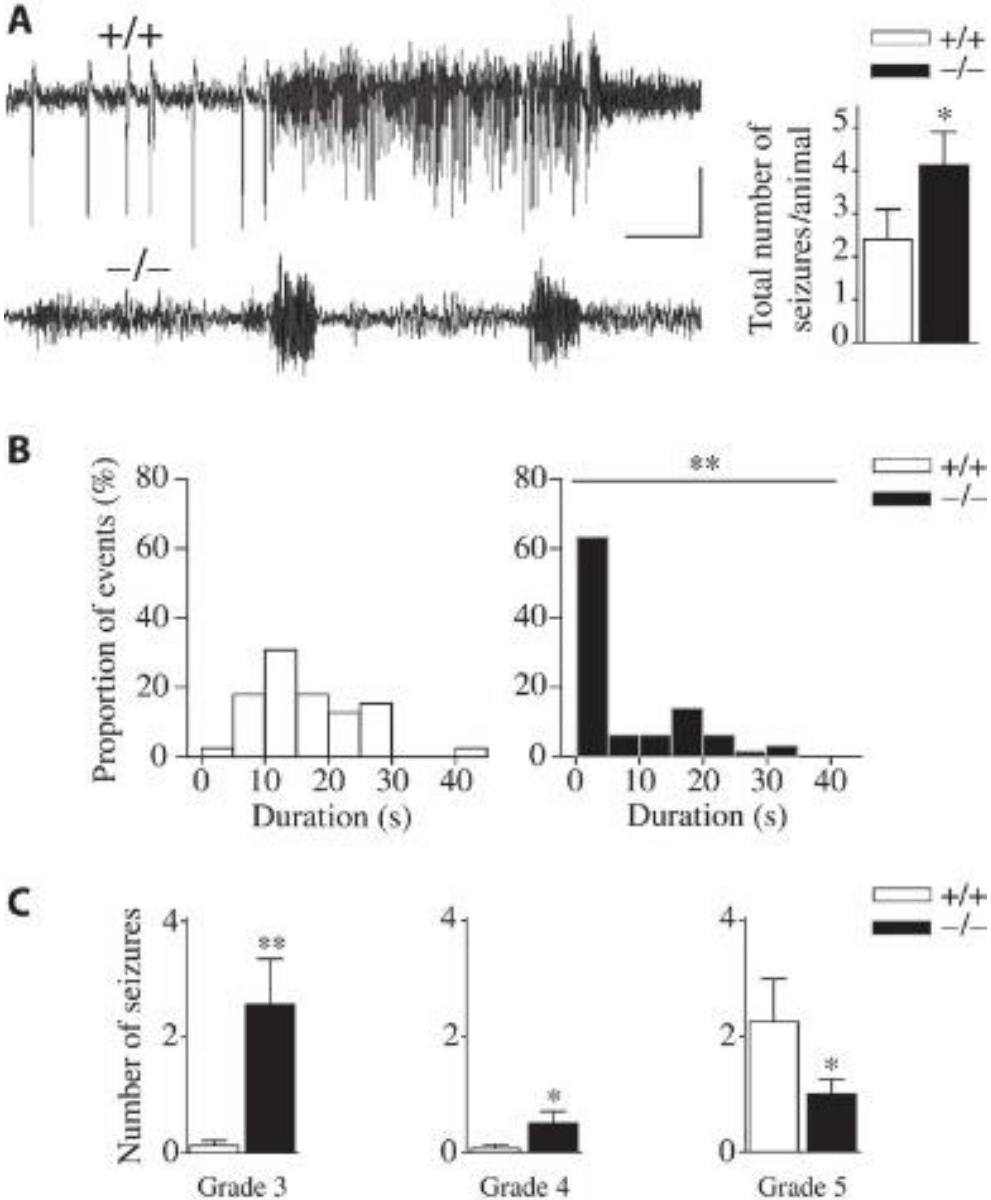


Electrical activity of Neurons

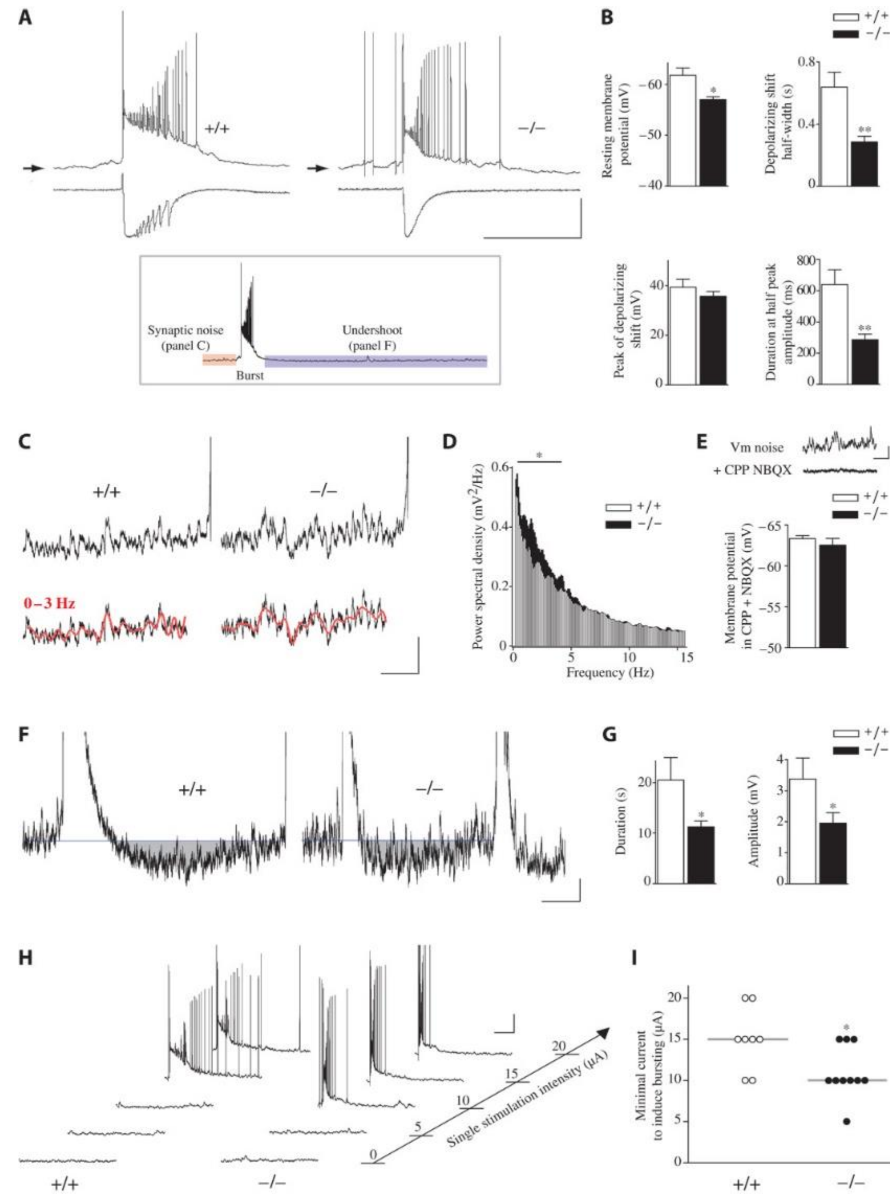




Bursting

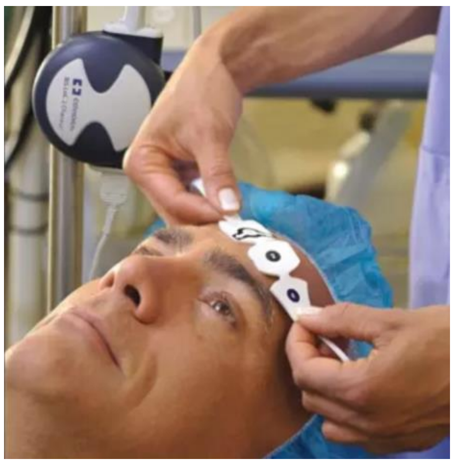


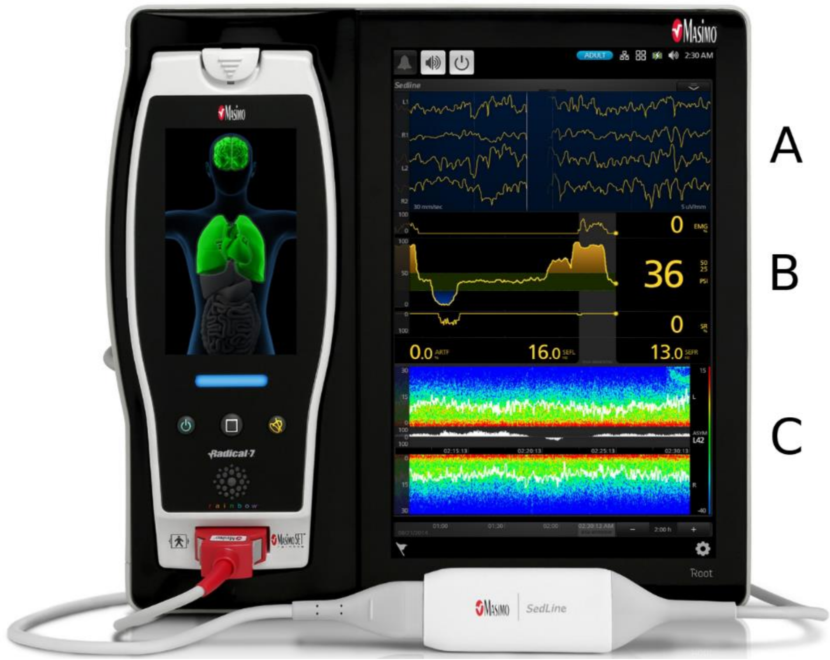
A
+/+
−/−
+/+
−/−
Total number of seizures/animal
*
B
Proportion of events (%)
Duration (s)
**
C
Number of seizures
**
*
*
Grade 3
Grade 4
Grade 5



A
+/+
−/−
Synaptic noise (panel C)
Burst
Undershoot (panel F)
B
Resting membrane potential (mV)
Depolarizing shift half-width (s)
Peak of depolarizing shift (mV)
Duration at half peak amplitude (ms)
C
0–3 Hz
D
Power spectral density (mV²/Hz)
Frequency (Hz)
E
Vm noise
+ CPP NBQX
Membrane potential in CPP + NBQX (mV)
F
G
Duration (s)
Amplitude (mV)
H
Single stimulation intensity (μA)
I
Minimal current to induce bursting (μA)

Brain monitoring today





Les Entreprises:

- **Patient State Index**
  Masimo, USA
- **Bispectral Index System**
  Covidien, USA
- **Narcotrend Compact M**
  MonitorTechnik, Germany

Real-time information → No prediction

Rhythm during GA vs else

Awake with eyes open

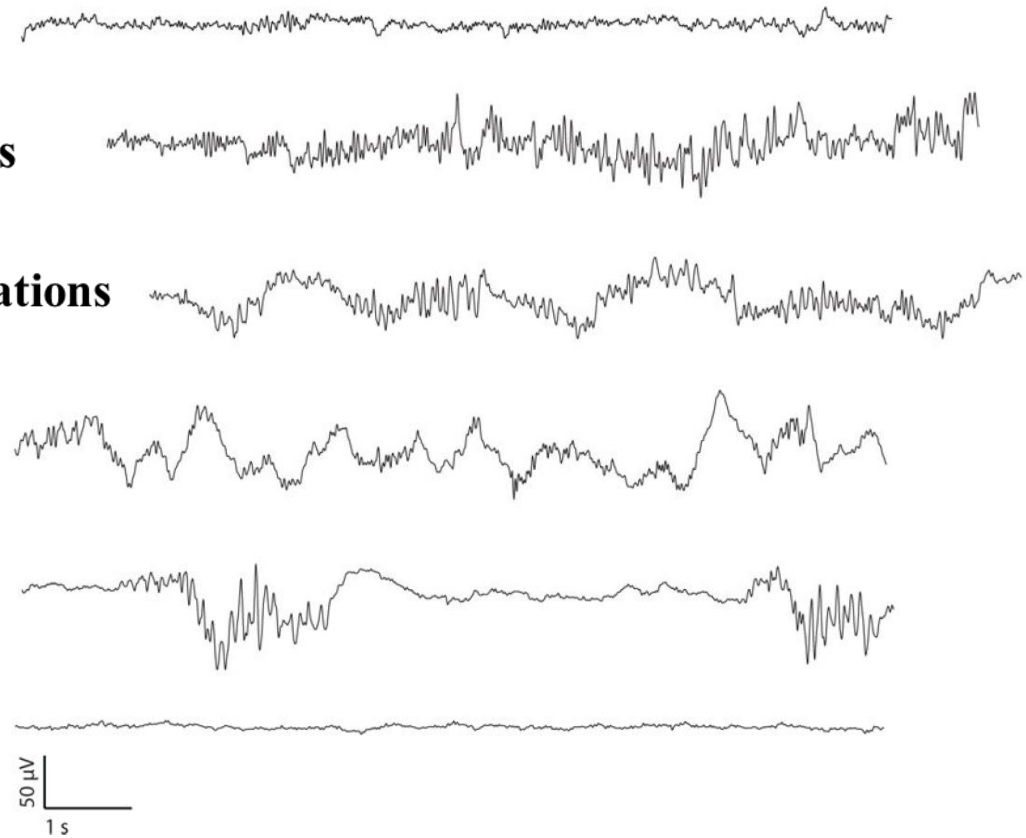
Paradoxical excitation: β Oscillations

Unconsciousness: Slow and α oscillations

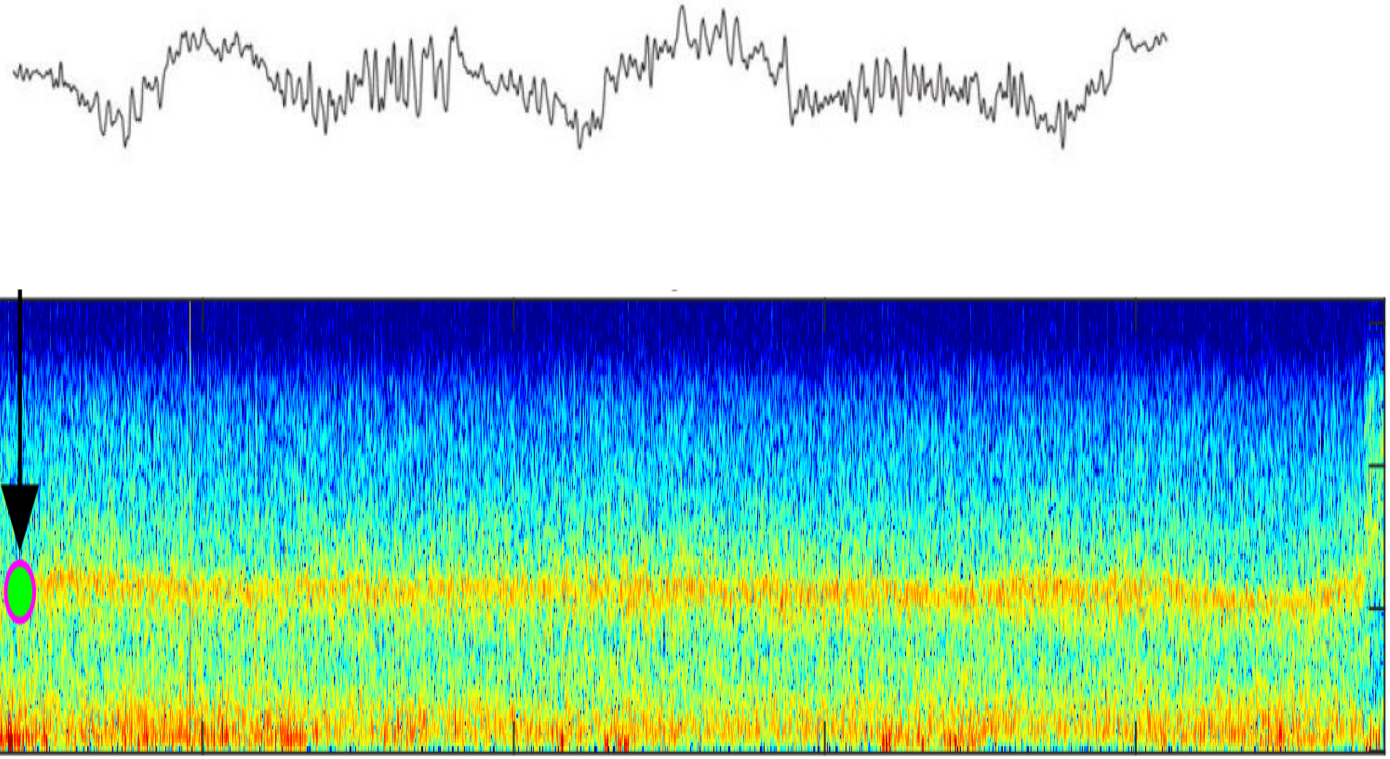
Unconsciousness: Slow Oscillations

Burst Suppression

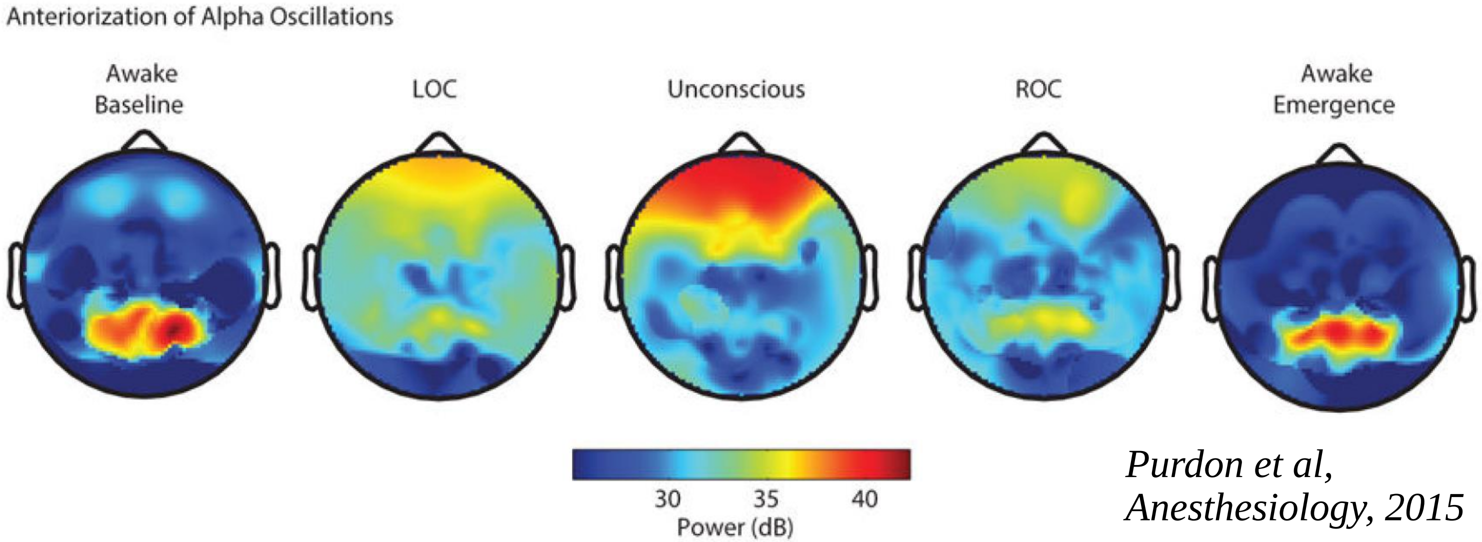
Isoelectricity



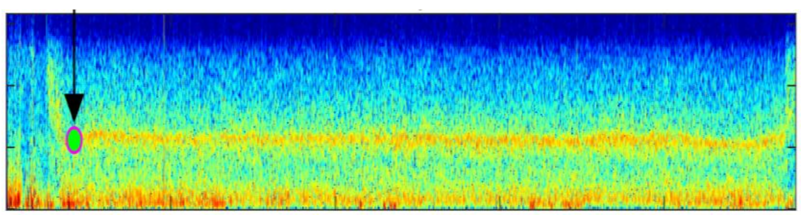
Analyse temps-frequence



Spectrogram during Propofol

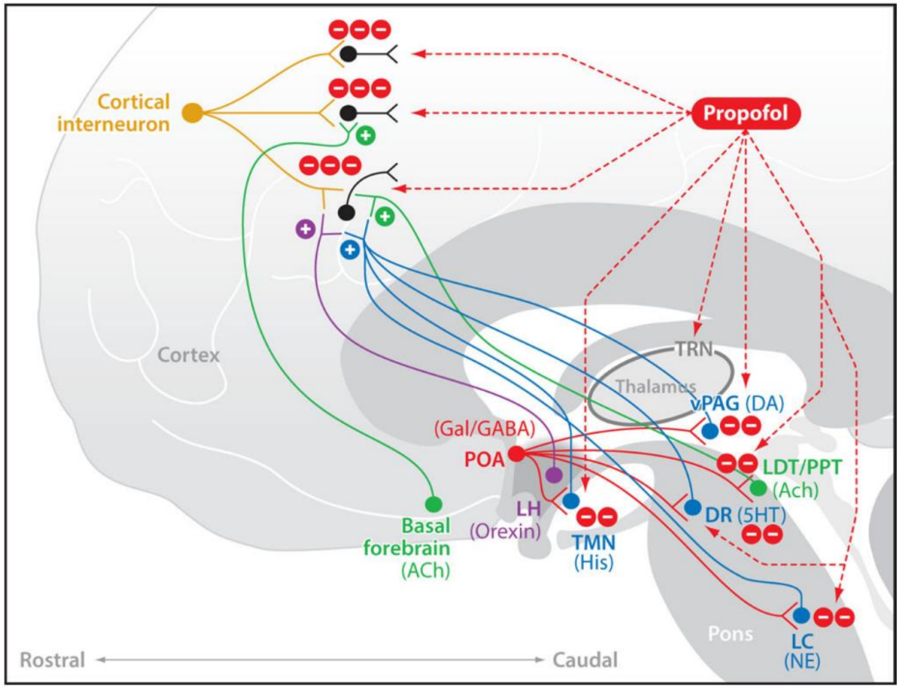


Purdon et al, Anesthesiology, 2015



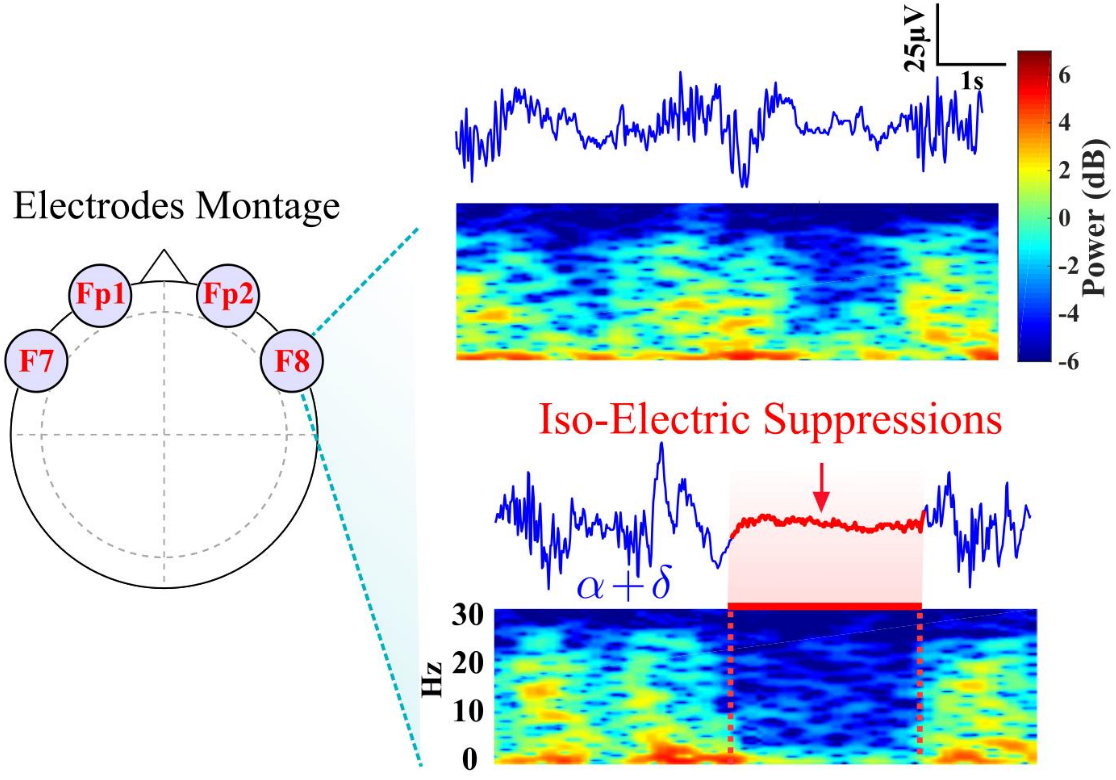
➔Frontal alpha oscillations is prominent during Propofol-based GA

Effect of Propofol on the brain



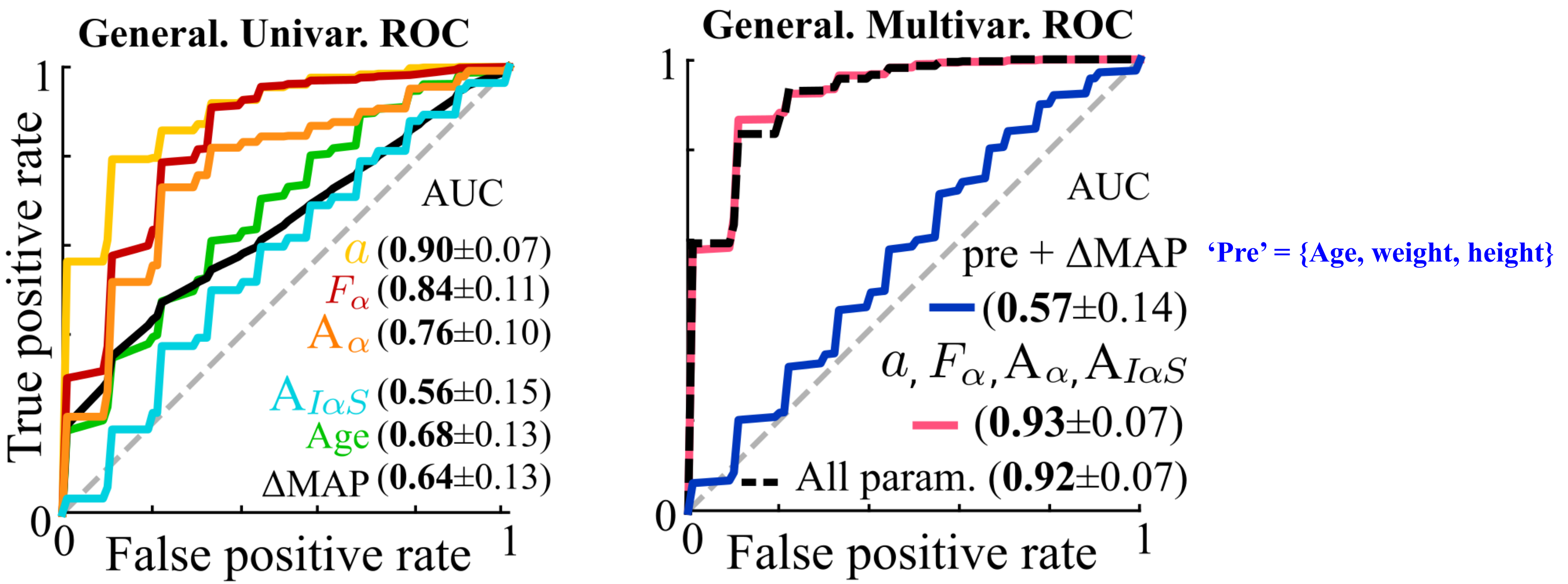
Purdon et al, Anesthesiology, 2015

Transient motif: IES during General Anesthesia



➔ IES are events that can occur during GA

Alpha-Suppression and IES: mean study



➔ αS better predict IES than known risk factors: 'age' or 'ΔMAP'