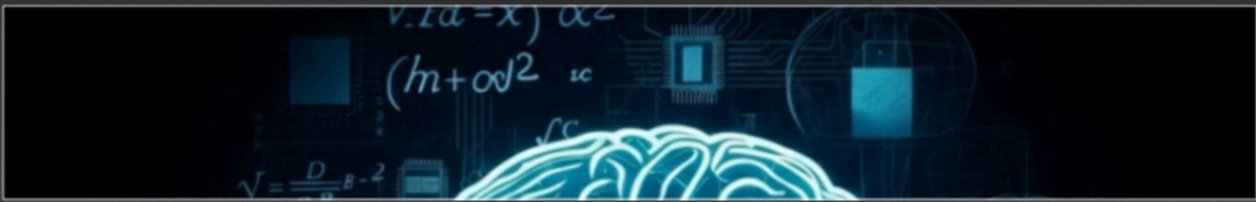
MODELLING NEURAL SYSTEMS



COMPUTATIONAL MODELLING OF NEURONS AND MICROCIRCUITS

Prof. Ing. Michele GIUGLIANO, PhD

Introductory Class

ATTENDANCE TRACKING: **today's code is 33333**

(for my own statistical purposes)

Download for iPhone

Download for Android

https://www.unimore.it/it/servizi/unimore-app

Teams - Instant messaging

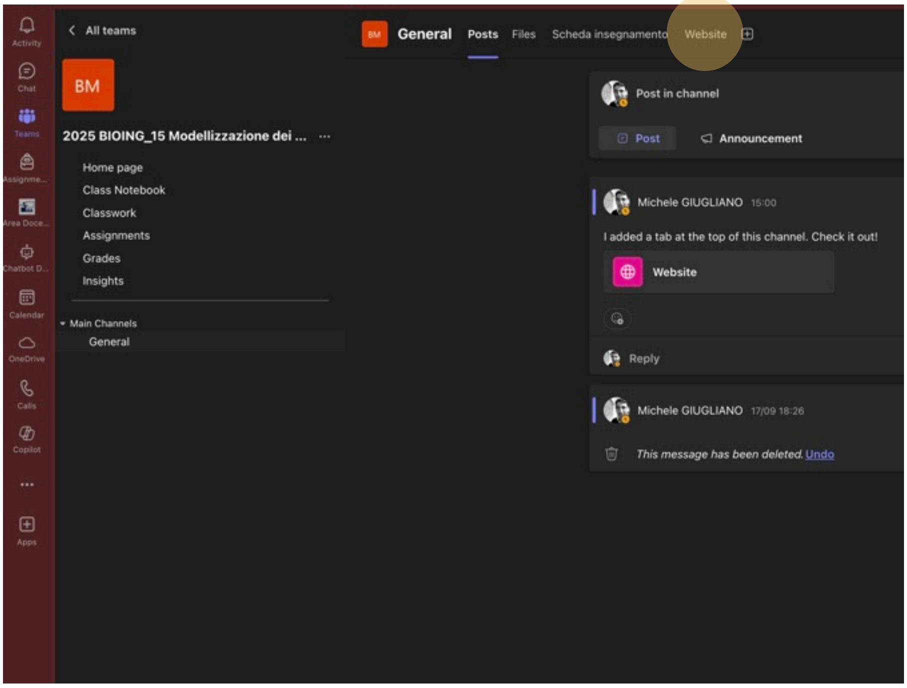
Announcements; Forum/Q&A for all !

Website and GitHub repository

https://mgiugliano.github.io/ModellingNeuralSystems

https://github.com/mgiugliano/
ModellingNeuralSystems

Website and GitHub repository



Lectures: recorded (not streamed!)

Posted (with delay / without guarantees) on

YouTube

*https://www.youtube.com/@Michele_GIU**G**LIANO*

Playlist: UNIMORE 2025 - ModellingNeuralSystems

Beware of glitches!

Organisation and Practicalities

- Classes *in person* - Slides + chalk/board
- **Interactive!** I can't read your mind (yet)
- I do **NOT** mind *stupid* questions (really!)
- **Ask** for help, explanations, guidance, books, papers, code, hints, intuition, etc.

Master thesis opportunities

- https://unimore.unifind.cineca.it/get/person/114689
- "Modeling" projects
- "Experimental" (wet-, hard-, soft-ware) projects
- "You come out with your own" projects.

Organisation and Practicalities

- **hand-outs:** made available to you upfront (web)
- **videotaping:** mostly aimed at *working* students
- **hands-on:** just need a web browser (Colab) or (if interested), install ju**py**ter on your device - **ask**

Evaluation and Exam(s)

- **<u>this</u>** module: **oral**, informal, interview (~25 min)
- Overall mark = average **weighted** by CFUs of modules
- Overall mark cum laude = 32/30
- Overall mark = **rounded** to closest integer (~~*ceil, floor*~~)
- Overall mark = **requires** both modules (none skipped)
- Each module mark expires after **24 months**

Exams and Exam sessions

- Jan 2026: 14th, 21st, 28th 16-19, 4 *slots/day*
- Feb 2026: 4th, 18th, 25th 16-19, 4 *slots/day*

- 1-2 sessions in June, TBA
- 1-2 sessions in July, TBA
- exceptionally: on appointment (1-2 slots/day)

Class organization: your call!

- Current schedule: **14:30 - 17:00**, sharp **at 14:30**
- Alternative 1: **14:15 - 16:45**, sharp **at 14:15**
- Breaks: **(1 x) after 75 min**
- Alternative: **no break**, we end 15m earlier

Study Material (chapters from)

- Sterratt (2011) *"Principles of Computational Modelling in Neuroscience"*, CUP (Cambridge Univ. Press)
- Gerstner (2014) Neuronal Dynamics, Cam. Univ. Press.
- Abbott LF, Dayan P (2001) *"Theoretical Neuroscience",* MIT Press.

- MG might circulate his own material (if stars align).

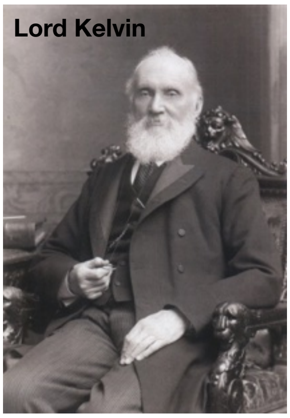
Why bother??

- Massive efforts, worldwide, last decades;
- Limits in current approaches and techniques;
- General theories or explanatory principles are scarce;

1. **measure** activity of LARGE set of neurons & circuits;
2. **analyse** and **model** those neurons and circuits;
3. **falsify** these models by actual (experimental) manipulations.

General theories or explanatory principles?

In terms of formulating a *model!*



*"I am never content until I construct a mechanical **model** of the subject I am studying.*

If I succeed in making one, I understand; otherwise I do not."

Methods to look into the brain

- Imaging (functional Magnetic Resonance Imaging)
- Electroencephalography (EEG)
- Confocal / 2photon, fluorescence, transmitted-light microscopy
- Fluorescent (genetically-encoded) reporter dyes – Ca+, potential
- *In vitro* and *in vivo* electrical recordings: intra/extra-cellular
- "Patch-clamp" recordings – individual ion channels

- **and** ..use a model (and its numerical simulation if needed) to interpret data, derive predictions, suggest novel manipulations.

Neural Sciences

"THE TASK OF NEURAL SCIENCE**S** is to understand the mental processes by which we perceive, act, learn, and remember..."

Kandel, E.R., Schwartz, J.H., Jessell, T.H.

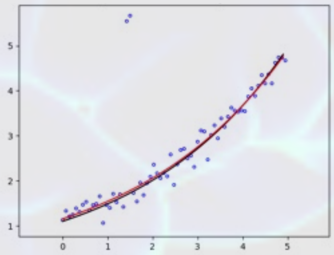
Principles of Neural Science

Computational/Theoretical Neuroscience

Quantitative study of the brain by techniques and tools from mathematics, physics, electrochemistry, psychology, etc. to uncover the ***principles*** and ***mechanisms*** that guide development, (self)organization, information representation, processing, storage, sensory, motor, & cognitive abilities of the nervous systems.

- What is a "model" ?
- Can you make other examples in science?

What is a model?



A **simplified** version of a physical system (i.e., a formula, a sentence, a *cartoon*, a set of equations, their numerical simulation), stripping away "**unnecessary**" aspects.

Abstractions of real world systems, or implementations of hypotheses to **falsify** particular scientific questions.

What is the appropriate level of description?

Molecular level

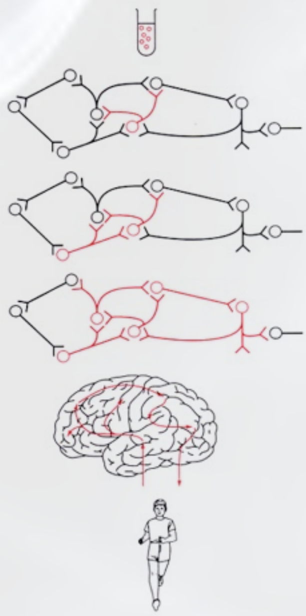
Single-cell level

Microcircuit level

Population level

System level

Behavior



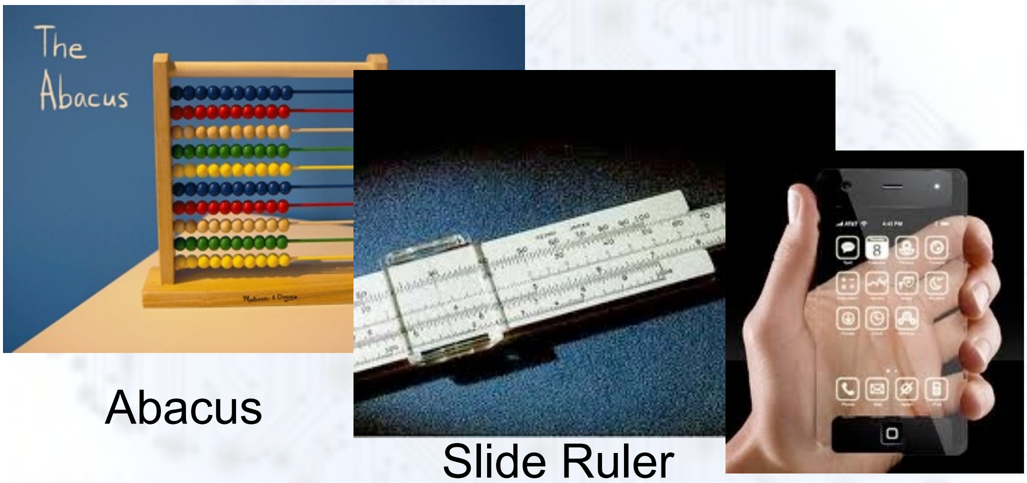
“Computational Neuroscience”

may therefore be defined in terms of

• a concept:
understanding the brain as a *computing device*
computation = representation + dynamics

• a series of useful techniques + (mathematical) ideas:
using computers to support the study the brain
manage huge data set, data analysis and interpretation
simulate mathematical models that are too complex for being approached by “paper-and-pen”

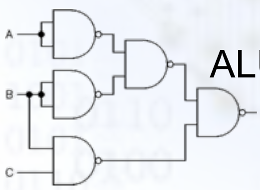
computation = representation + dynamics



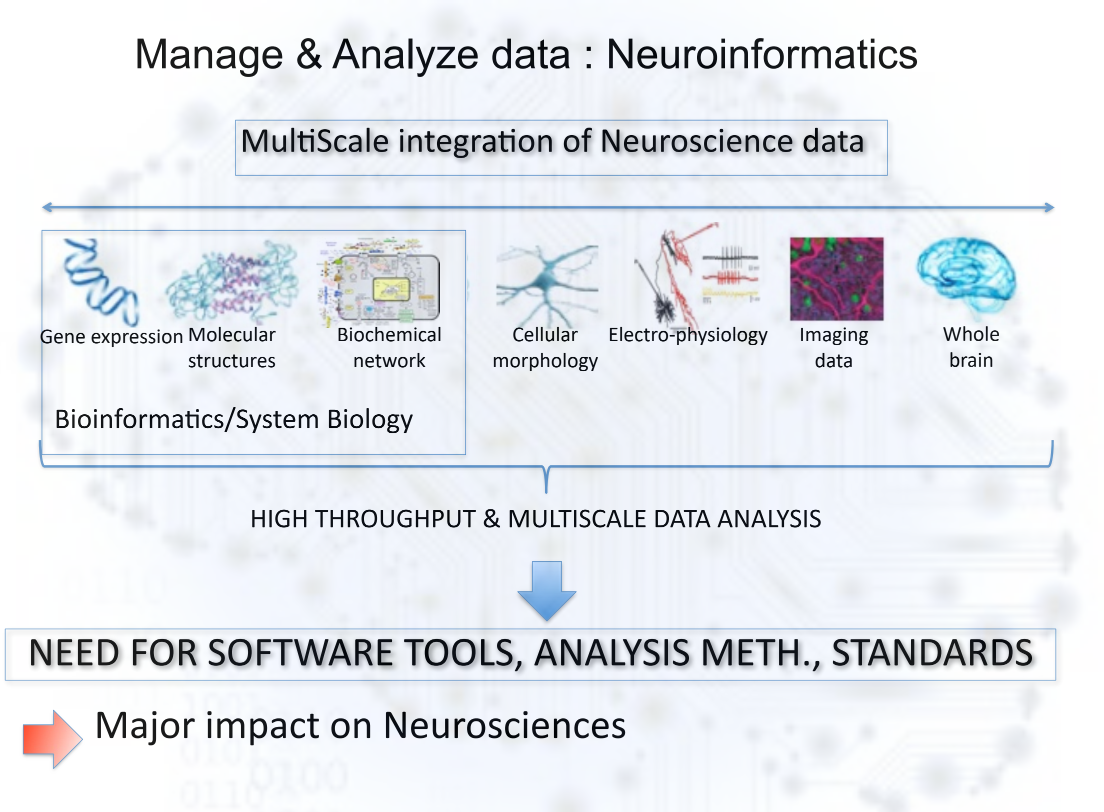
Abacus

Slide Ruler

iPhone 19 ?



ALU: “logic” electronic transistor *gates*,
AND, OR, NOT



EBRAINS

https://ebrains.eu

https://www.humanbrainproject.eu/en/

SERVICE CATEGORY Data and Knowledge	SERVICE CATEGORY Atlases	SERVICE CATEGORY Simulation
SERVICE CATEGORY Brain-Inspired Technologies	SERVICE CATEGORY Medical Data Analytics	SERVICE CATEGORY Community

Examples of still open questions in our *computational* understanding of the brain

How and how *fast*, neurons relay/process information downstream?

How do interacting cells give rise to sequences of motor activations?

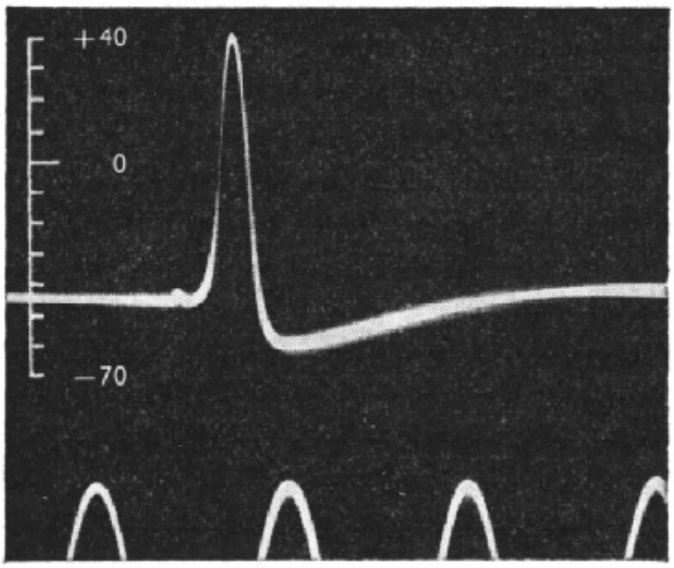
What are the mechanisms underlying oscillations in health/disease?

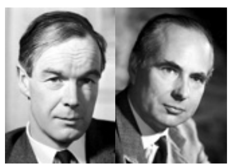
Is there a meaning to synchronous emission of nerve impulses?

How memories are recalled? What are the mechanisms of learning?

How could one interface brain tissue to an electronic artificial device?

The most successful **theory** in Neuroscience (so far)

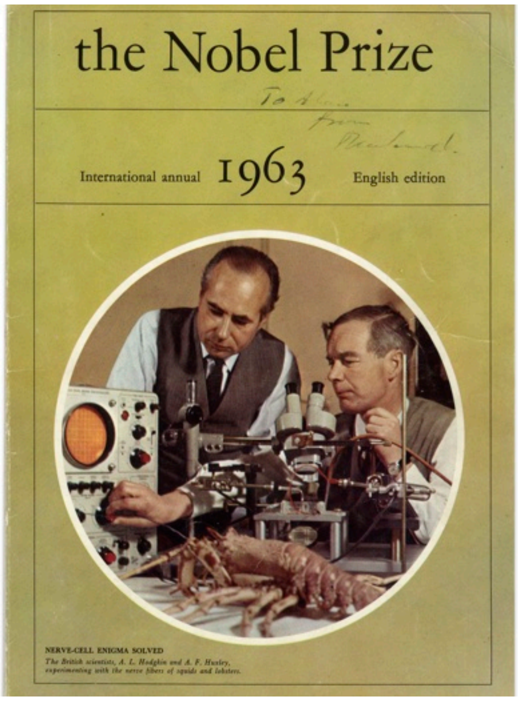


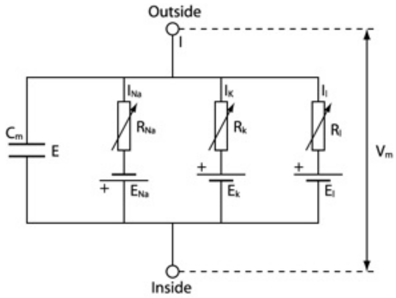


Alan Hodgkin and Andrew Huxley
1952

The nerve impulse, or Action Potential

Nerve-cell enigma solved

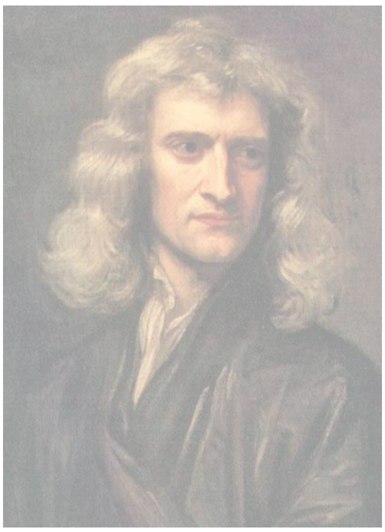




$$C\frac{dV}{dt} = g_{N_a} m^3 h (V_{Na} - V) + g_K n^4 (V_K - V) + g_L (V_L - V) + I$$
$$\frac{dm}{dt} = \alpha_m (V)(1-m) - \beta_m (V) m$$
$$\frac{dh}{dt} = \alpha_h (V)(1-h) - \beta_h (V) h$$
$$\frac{dn}{dt} = \alpha_n (V)(1-n) - \beta_n (V) n$$

Understanding by modelling

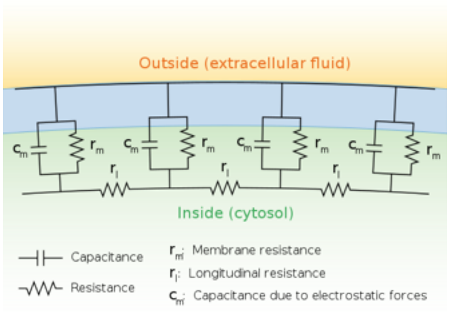
Astronomical & terrestrial motion enigma solved

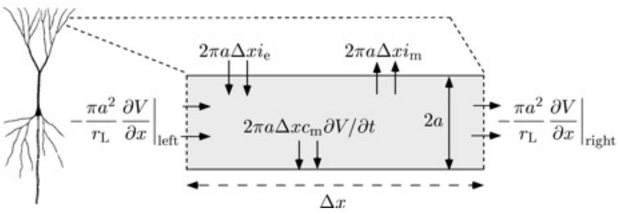


The three laws of motion and
the universal gravitation law explain
- classic mechanics and
- Kepler’s laws of planetary motion.

Understanding by modelling

Cable Theory, for AP Propagation





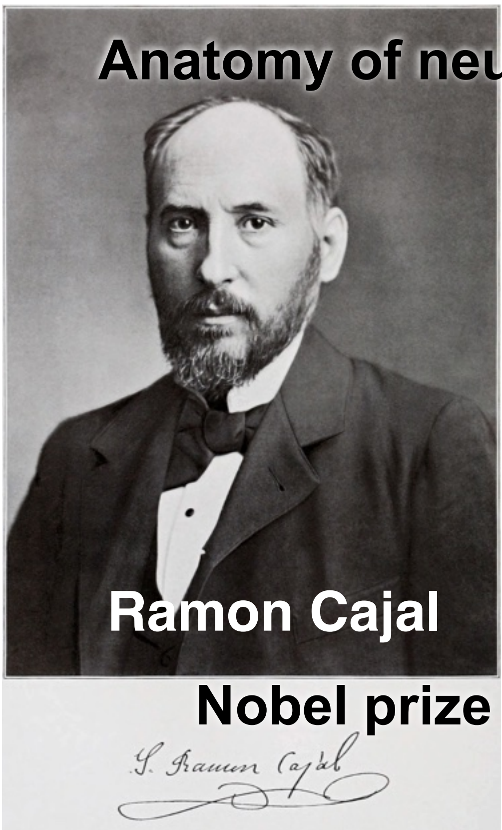
$$\left(\frac{r_m}{r_i}\right)\frac{\partial^2 V(x,t)}{\partial x^2} - r_m c_m \frac{\partial V(x,t)}{\partial t} - V(x,t) = 0$$

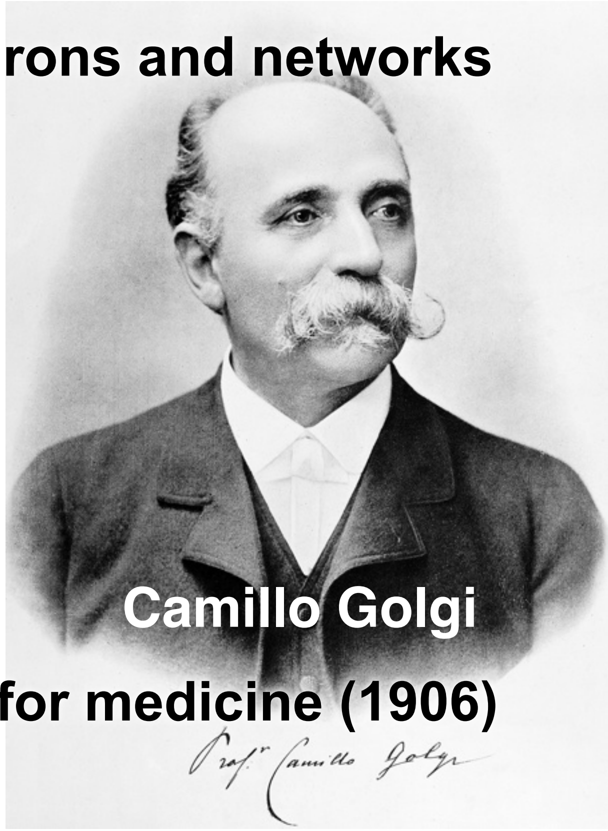
$$\frac{\partial^2 V}{\partial X^2} = \frac{\partial V}{\partial T} + V(X,T)$$

$X = x/\lambda$
$T = t/\tau_m$.

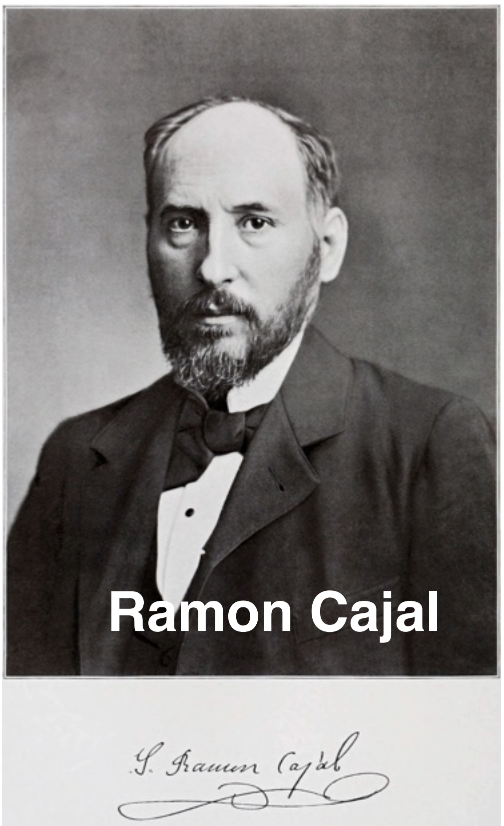
- BTW, why do I need to use the “Cable” equation and its variant?
- Biophysically, what is the limit of HH?

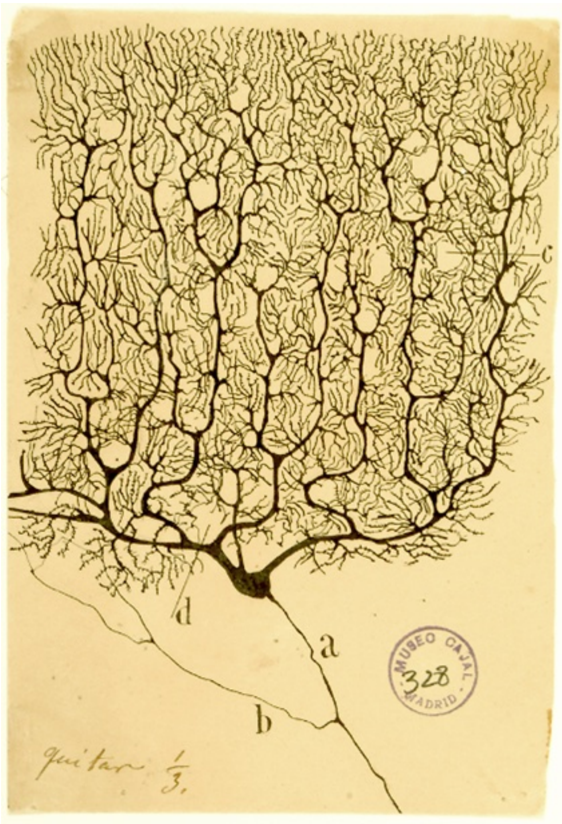
Anatomy of neurons and networks

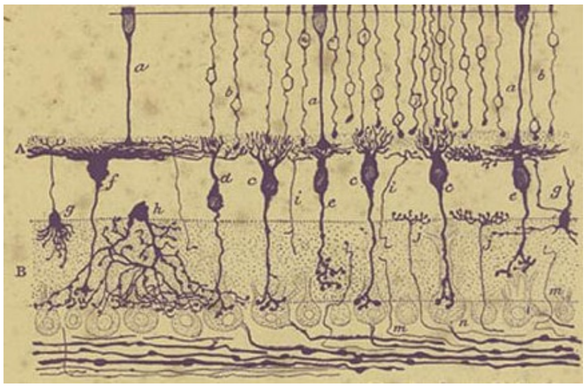


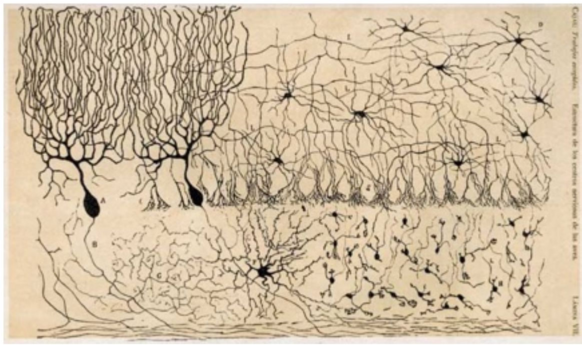


Nobel prize for medicine (1906)

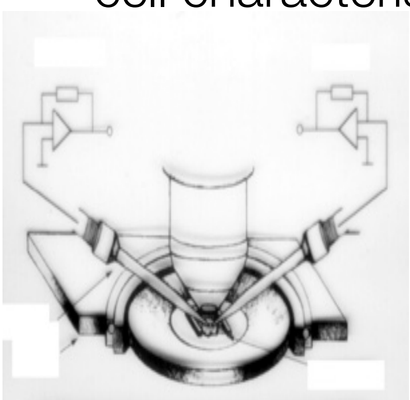


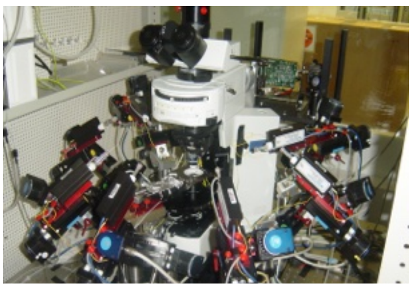


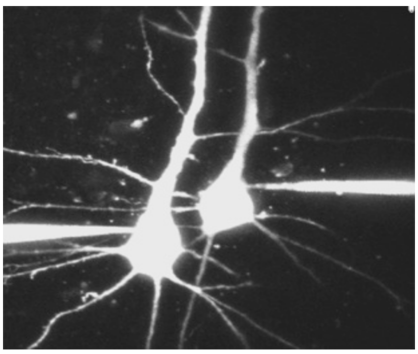




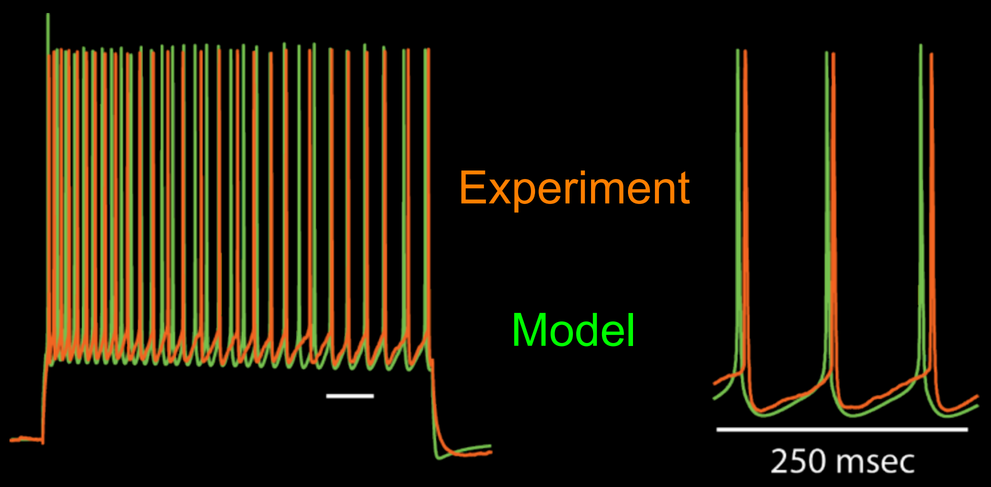
Simultaneous Morphological & Electrical
cell characterisation/digitization





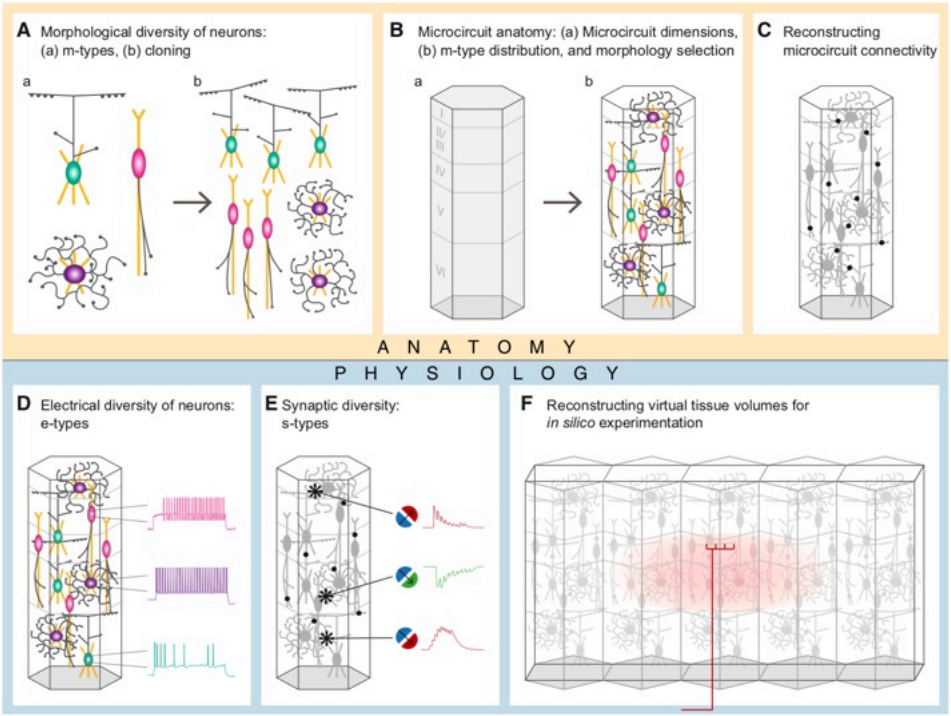


Quantitative recreation of
single-neuron electrical response:
bring to life a mathematical description of the cells

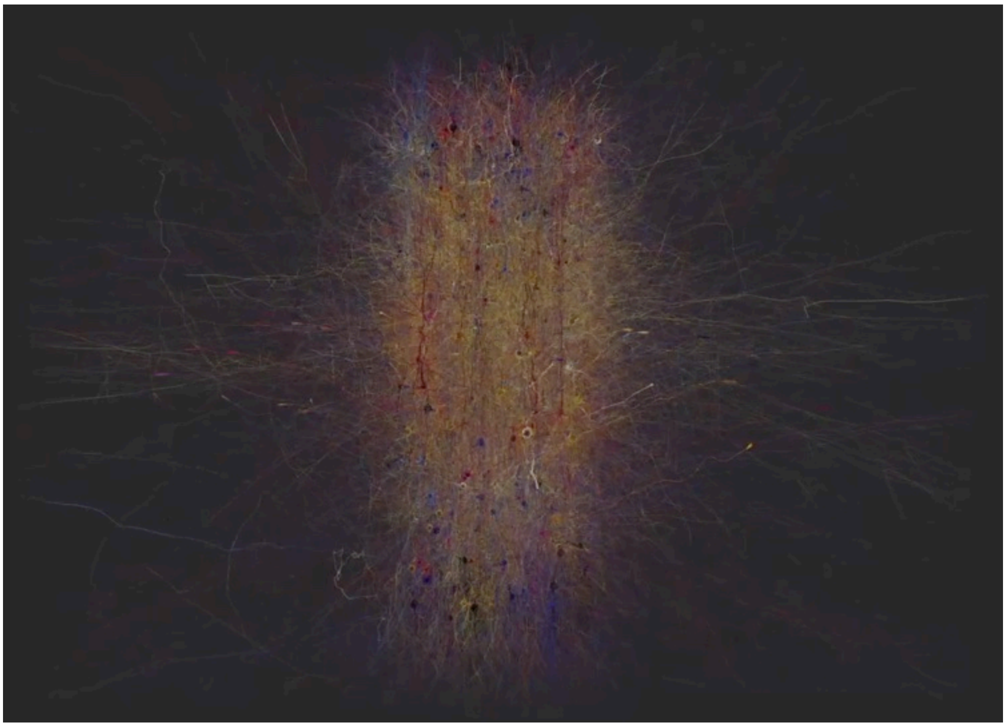


- Are you impressed by the quality of the “fit”, comparing real data and simulated data?
- What would convince you that the model captures the (bio)physical phenomenon correctly?

HBP strategy for simulating the brain



Simulating the activity of a "*cortical column*"



Highly criticised but…
undebatable value of this approach

*…**a complementary algorithmic approach** that reconstructs neuronal microcircuitry across all layers **using available sparse data** and that leverages biological principles and interdependencies between datasets **to predict missing biological data.** […]*

Cell

Resource

Reconstruction and Simulation of Neocortical Microcircuitry

Henry Markram,[1,2,19,*] Eilif Muller,[1,19] Srikanth Ramaswamy,[1,19] Michael W. Reimann,[1,19] Marwan Abdellah,[1] Carlos Aguado Sanchez,[1] Anastasia Ailamaki,[16] Lidia Alonso-Nanclares,[6,7] Nicolas Antille,[1] Selim Arsever,[1] Guy Antoine Atenekeng Kahou,[1] Thomas K. Berger,[2] Ahmet Bilgili,[1] Nenad Buncic,[1] Athanassia Chalimourda,[1] Giuseppe Chindemi,[1] Jean-Denis Courcol,[1] Fabien Delalondre,[1] Vincent Delattre,[2] Shaul Druckmann,[4,5] Raphael Dumusc,[1] James Dynes,[1] Stefan Eilemann,[1] Eyal Gal,[4] Michael Emiel Gevaert,[1] Jean-Pierre Ghobril,[2] Albert Gidon,[3] Joe W. Graham,[1] Anirudh Gupta,[2] Valentin Haenel,[1] Etay Hay,[3,4] Thomas Heinis,[1,16,17] Juan B. Hernando,[8] Michael Hines,[12] Lida Kanari,[1] Daniel Keller,[1] John Kenyon,[1] Georges Khazen,[1] Yihwa Kim,[1] James G. King,[1] Zoltan Kisvarday,[13] Pramod Kumbhar,[1] Sébastien Lasserre,[1,15] Jean-Vincent Le Bé,[2] Bruno R.C. Magalhães,[1] Angel Merchán-Pérez,[6,7] Julie Meystre,[2] Benjamin Roy Morrice,[1] Jeffrey Muller,[1] Alberto Muñoz-Céspedes,[6,7] Shruti Muralidhar,[2] Keerthan Muthurasa,[1] Daniel Nachbaur,[1] Taylor H. Newton,[1] Max Nolte,[1] Aleksandr Ovcharenko,[1] Juan Palacios,[1] Luis Pastor,[9] Rodrigo Perin,[2] Rajnish Ranjan,[1,2] Imad Riachi,[1] José-Rodrigo Rodríguez,[6,7] Juan Luis Riquelme,[1] Christian Rössert,[1] Konstantinos Sfyrakis,[1] Ying Shi,[1,2] Julian C. Shillcock,[1] Gilad Silberberg,[18] Ricardo Silva,[1] Farhan Tauheed,[1,16] Martin Telefont,[1] Maria Toledo-Rodriguez,[14] Thomas Tränkler,[1] Werner Van Geit,[1] Jafet Villafranca Díaz,[1] Richard Walker,[1] Yun Wang,[10,11] Stefano M. Zaninetta,[1] Javier DeFelipe,[6,7,20] Sean L. Hill,[1,20] Idan Segev,[3,4,20] and Felix Schürmann[1,20]

[1]Blue Brain Project, École polytechnique fédérale de Lausanne (EPFL) Biotech Campus, 1202 Geneva, Switzerland
[2]Laboratory of Neural Microcircuitry, Brain Mind Institute, EPFL, 1015 Lausanne, Switzerland
[3]Department of Neurobiology, Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
[4]The Edmond and Lily Safra Center for Brain Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
[5]Janelia Farm Research Campus, Howard Hughes Medical Institute, Ashburn, VA 20147, USA
[6]Laboratorio Cajal de Circuitos Corticales, Centro de Tecnología Biomédica, Universidad Politécnica de Madrid, 28223 Madrid, Spain
[7]Instituto Cajal (CSIC) and CIBERNED, 28002 Madrid, Spain
[8]CeSViMa, Centro de Supercomputación y Visualización de Madrid, Universidad Politécnica de Madrid, 28223 Madrid, Spain
[9]Modeling and Virtual Reality Group, Universidad Rey Juan Carlos, 28933 Móstoles, Madrid, Spain
[10]Key Laboratory of Visual Science and National Ministry of Health, School of Optometry and Opthalmology, Wenzhou Medical College, Wenzhou 325003, China

Markram et al., Cell, 2015

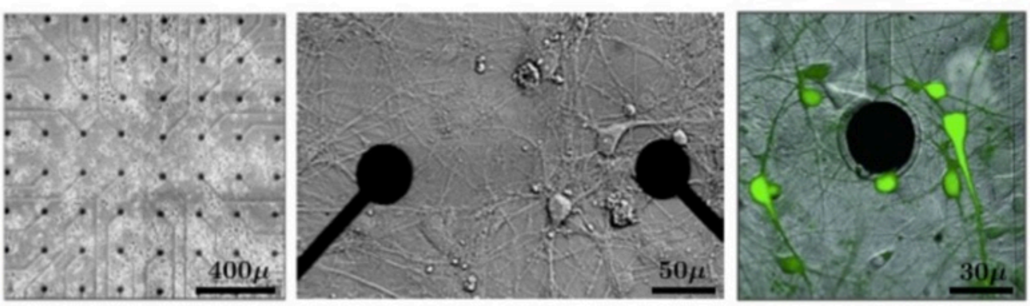
Is HH enough for single neurons?
(Is a typical experiment enough?)

16332 • The Journal of Neuroscience, December 1, 2010 • 30(48):16332–16342

Cellular/Molecular

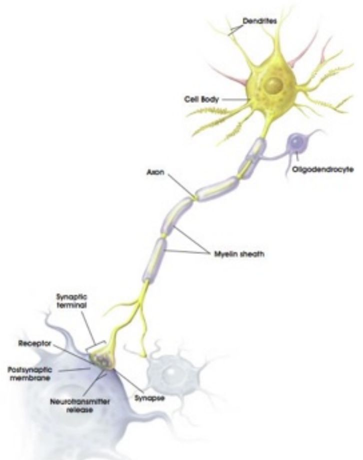
Dynamics of Excitability over Extended Timescales in Cultured Cortical Neurons

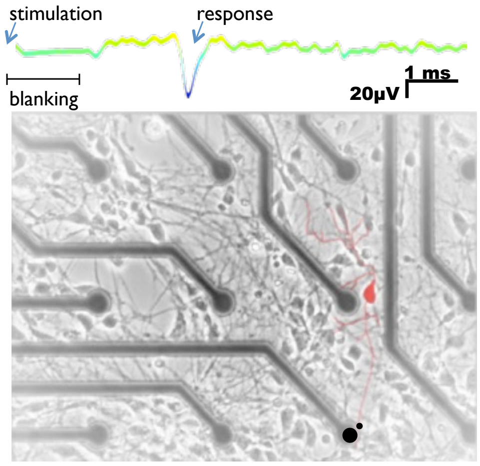
Asaf Gal,[1,4] Danny Eytan,[1,5] Avner Wallach,[1,2] Maya Sandler,[3] Jackie Schiller,[3] and Shimon Marom[1,3]
[1]Network Biology Research Laboratories, Lorry Lokey Interdisciplinary Center for Life Sciences and Engineering, [2]Faculty of Electrical Engineering, and [3]Department of Physiology, Faculty of Medicine, Technion, Haifa 32000, Israel, [4]The Interdisciplinary Center for Neural Computation, The Hebrew University, Jerusalem 91904, Israel, and [5]Rambam Medical Center, Haifa 31096, Israel



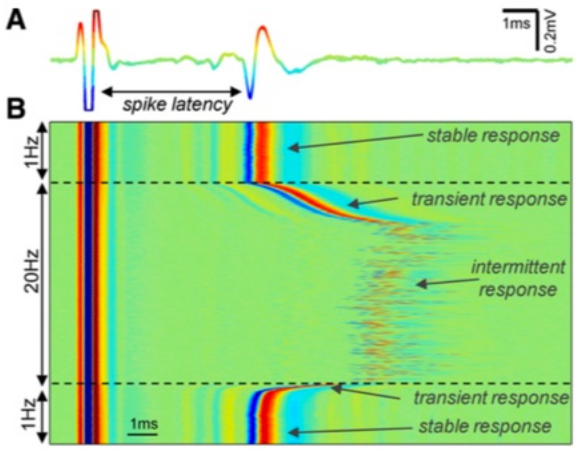
Is HH enough for single neurons?
(Is a typical experiment enough?)

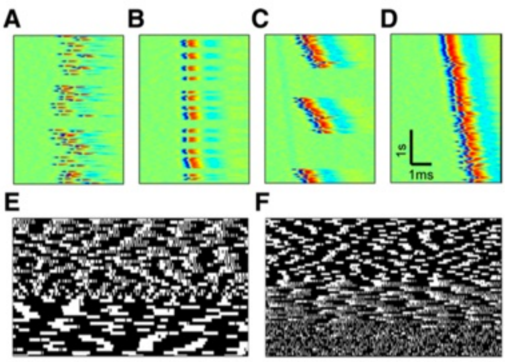
The “problem” of extended time-scales of excitability

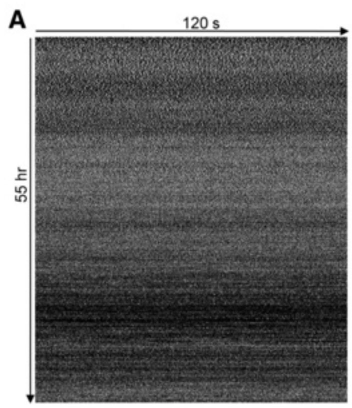




Gal et al., J Neurosci, 2010







Gal et al., J Neurosci, 2010

Is HH enough for single neurons?
(Is a typical experiment enough?)

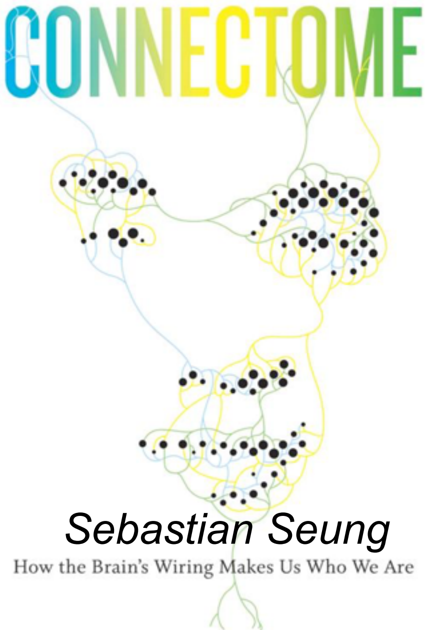
Probably not.

Intracellular (biochemical) pathways, their deep inter-dependencies and links to ion channel dynamics/regulation/expression, **makes *excitability* <u>complex</u>**
(at cell- and synaptic-levels).

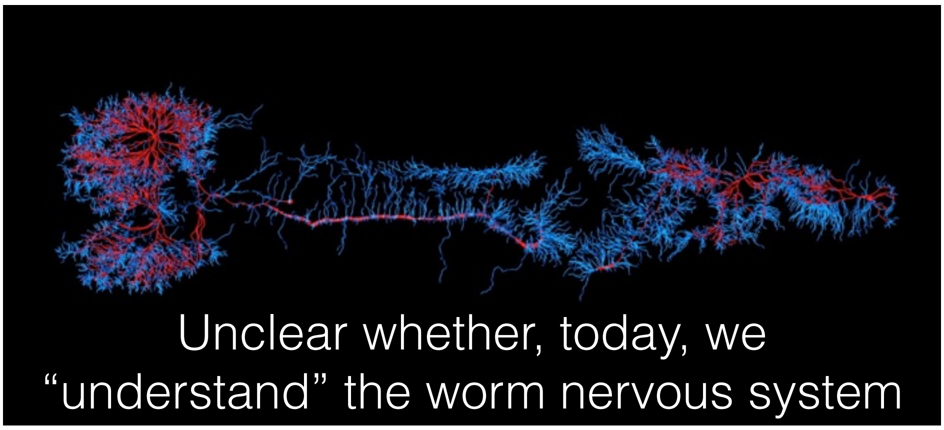
Extended models of (sub)cellular dynamics of ion channel opening and inactivation are needed but **identifying their parameters is extremely difficult in conventional (short) experiments.**

- What is genome/*genomics*?
- What is proteome/*proteomics*?
- What is connectome/*connectomics*?

Is the *connectome* enough?



(TED talk & book)
https://youtu.be/HA7GwKXfJB0



Is the *connectome* enough?

Probably not.

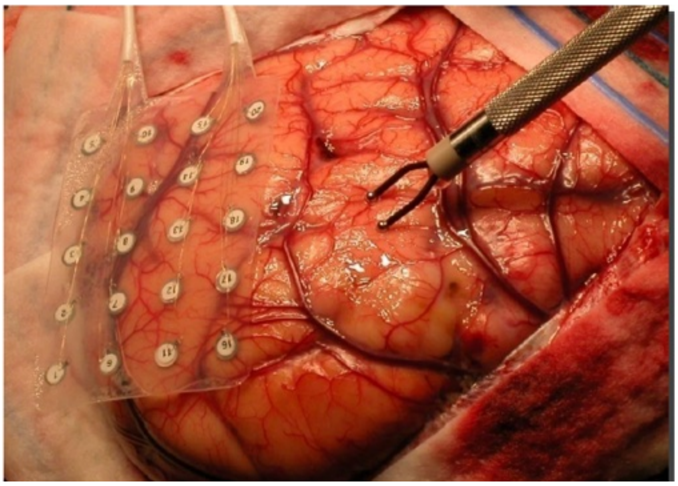
Current digital reconstructions are (based on)
- a temporal *snapshot*, at the EM-level, or
- a statistical/morphol. recreation of typical connectivity
- **and do not include neuromodulation (yet).**

Redundancy might exists
(*principles at work* versus *exquisite detailed replica*)

Is "translation" to human brains from rodent models *mature*?

The data and approach described so far is **based on experimental data collected over decades in rodents**.

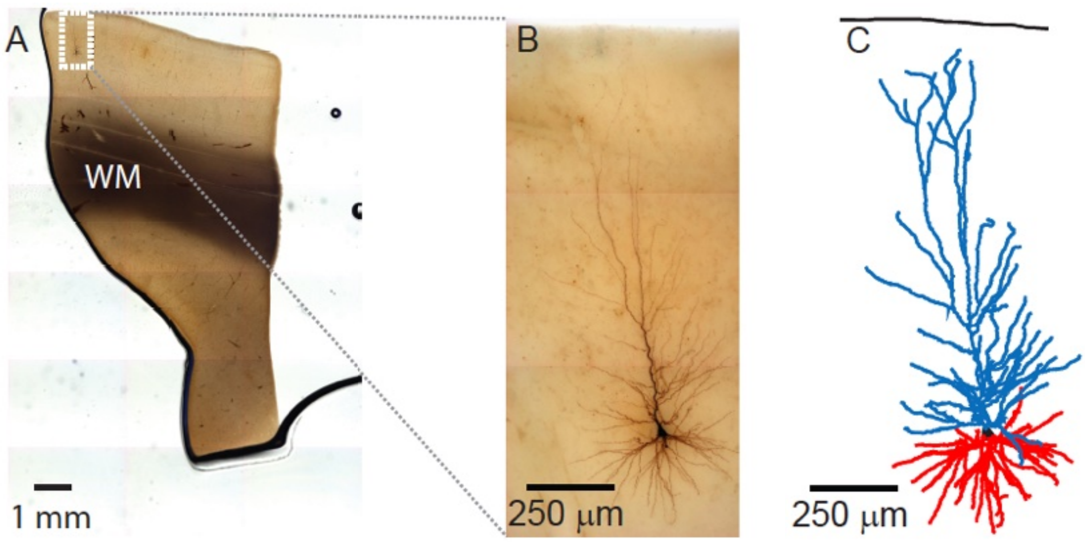
Getting living adult human neurons in the lab



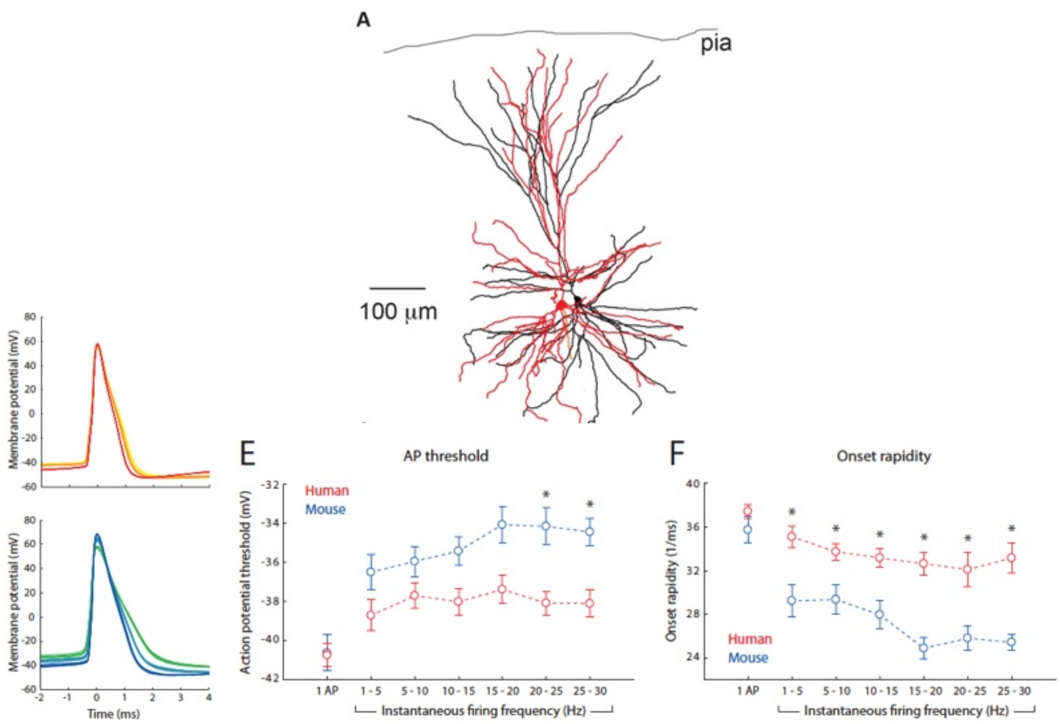
Hans Baayen, MD, Neurosurgery, VUmc Amsterdam

Testa-Silva, et al., Front Syn Neurosci 2010
Testa-Silva, et al., PLoS Biology 2014

Recording and reconstructing human neurons



Thijs Verhoog
Natalia Goriounova
Guilherme Testa-Silva
Christiaan de Kock



Testa-Silva et al., PLoS Biology, 2014

Is “translation” to human brains from rodent models *mature*?

No

Preliminary experiments suggest **fundamental quantitative** differences:

synaptic transmission & AP generation are “high-bandwidth”, compared to rodents.

Valuable to understand by **synthesis**, not enumeration/classification

- Simulate to uncover **missing data**
- Simulate as a “live”, digital, **database of knowledge**

Holism (or Reductionism?):

- theories should be as simple as possible (*but not simpler*)
- where is the theory in a brute-force simulation?? (1-to-1 map)
- difficulty for falsifying highly detailed models

Are 1-to-1 maps: useful?

On Exactitude in Science
Jorge Luis Borges, *Collected Fictions*, translated by Andrew Hurley.

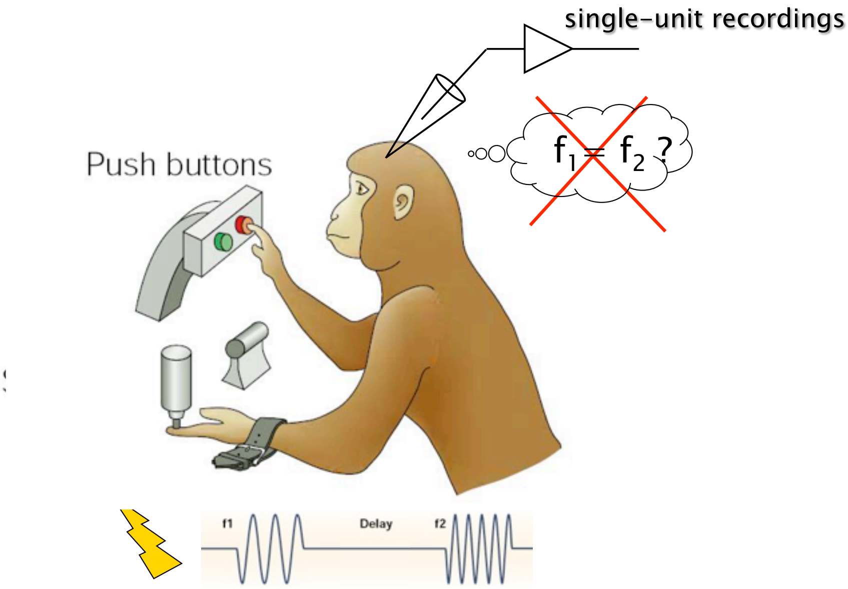
…In that Empire, the Art of Cartography attained such Perfection that the map of a single Province occupied the entirety of a City, and the map of the Empire, the entirety of a Province. In time, those Unconscionable Maps no longer satisfied, and the Cartographers Guilds struck a Map of the Empire whose size was that of the Empire, and which coincided point for point with it. The following Generations, who were not so fond of the Study of Cartography as their Forebears had been, saw that that vast Map was Useless, and not without some Pitilessness was it, that they delivered it up to the Inclemencies of Sun and Winters. In the Deserts of the West, still today, there are Tattered Ruins of that Map, inhabited by Animals and Beggars; in all the Land there is no other Relic of the Disciplines of Geography.

—Suarez Miranda, *Viajes de varones prudentes*, Libro IV, Cap. XLV, Lerida, 1658

One (experimental) example we will try to model

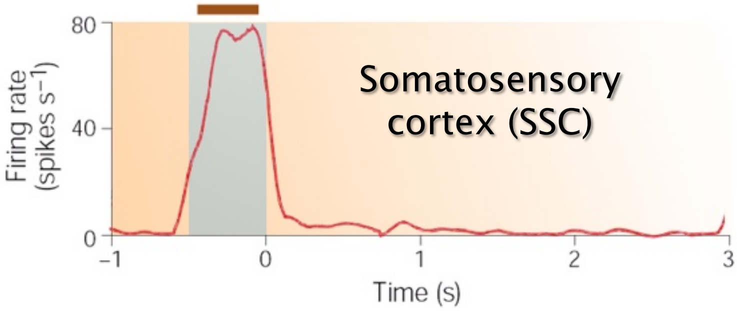
Working memory, decision making, metastability, persistent activity

In vivo: Delay Match-to-Sample Task



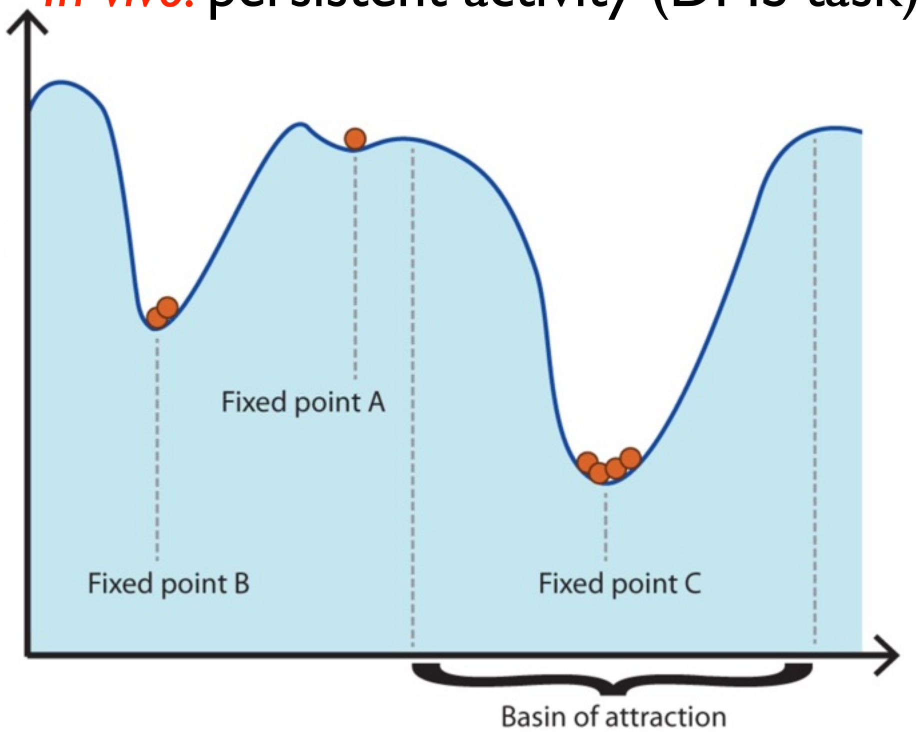
Romo and Salinas, 2003

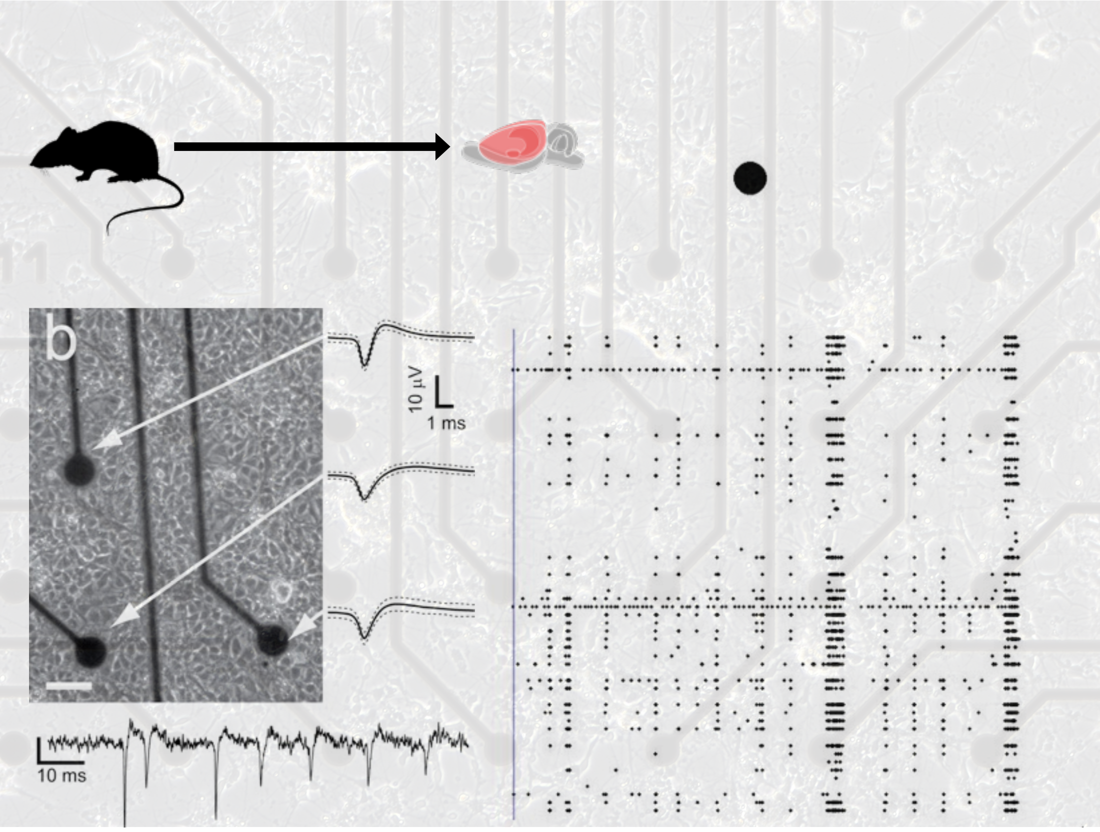
In vivo: persistent activity (DMS task)



Romo and Salinas, 2003

In vivo: persistent activity (DMS task)





Simulations and/or analysis of a mathematical model

Use a model:

- to find its most important parameters/features
- to investigate the situations unattainable in real systems
- to predict and guide future experiments in physiology
- *to understand information processing*