

# 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

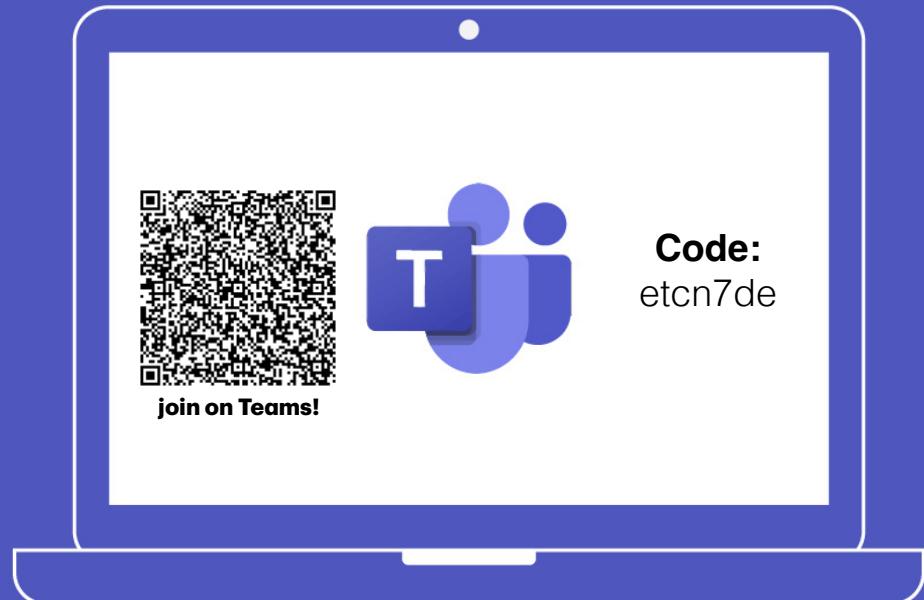


Download for Android



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

# Teams - Instant messaging



Announcements; Forum/Q&A for all !

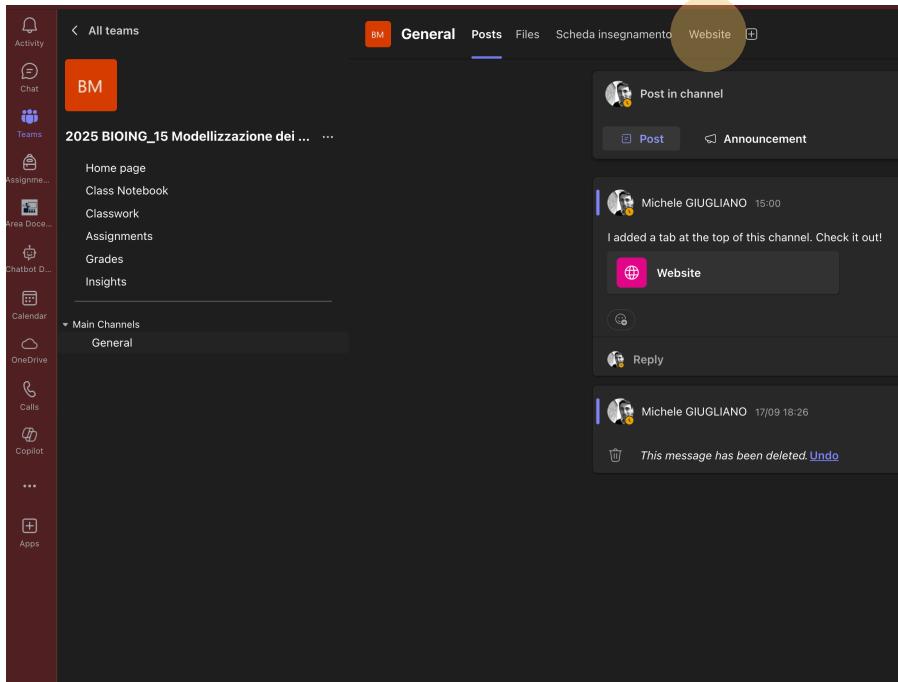
## Website and GitHub repository

<https://mgiugliano.github.io/ModellingNeuralSystems>



<https://github.com/mgiugliano/>  
ModellingNeuralSystems

# Website and GitHub repository



Lectures: recorded (not streamed!)  
Posted (with delay / without guarantees) on



[https://www.youtube.com/@Michele\\_GIUGLIANO](https://www.youtube.com/@Michele_GIUGLIANO)

**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>
- QR code:
- “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 **jupyter** on your device - **ask**

# Evaluation and Exam(s)

- **this** 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

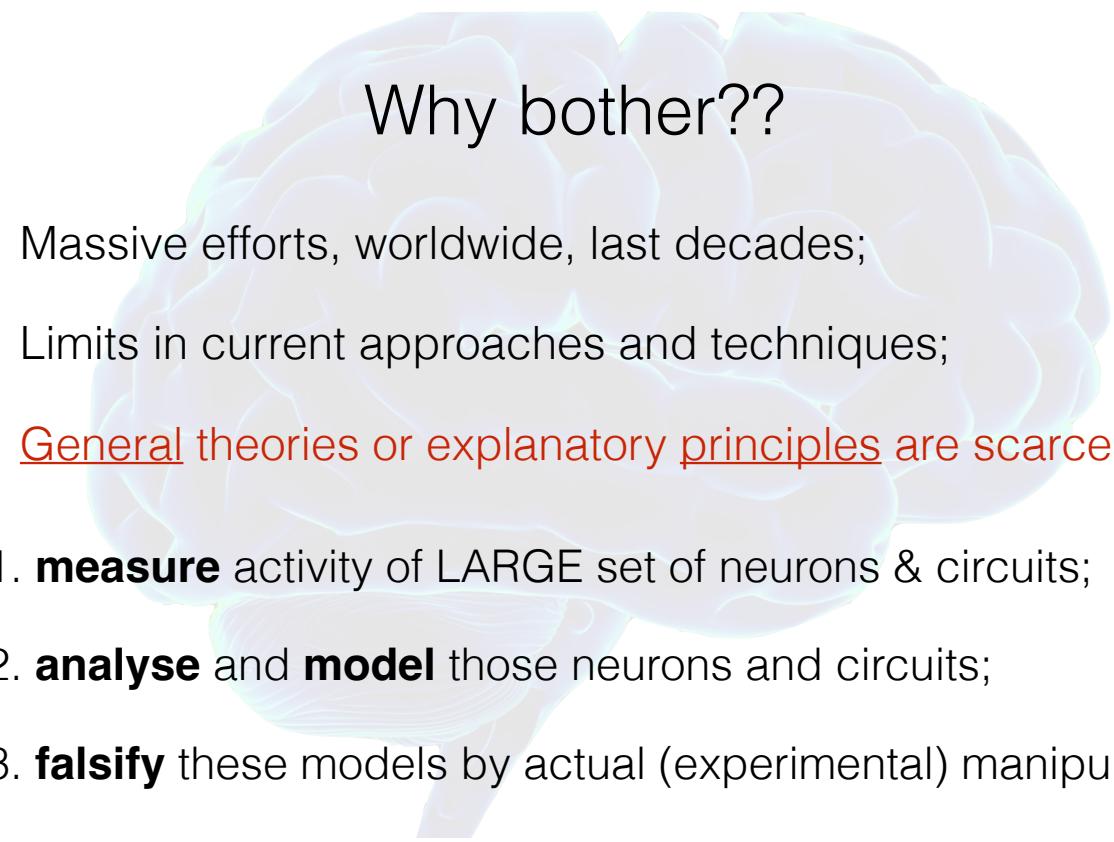
- Jan 2026: 14th, 21st, 28th      16-19,      4 slots/day
- Feb 2026: 4th, 18th, 25th      16-19,      4 slots/day
- 1-2 sessions in June, TBA
- 1-2 sessions in July, TBA
- exceptionally: on appointment (1-2 slots/day)

# 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/extracellular
  - “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 SCIENCES 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*

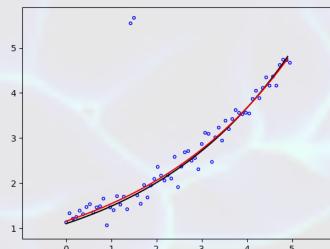
## Computational/Theoretical Neuroscience

**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:

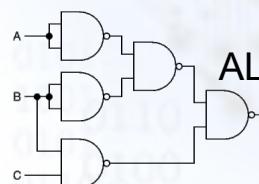
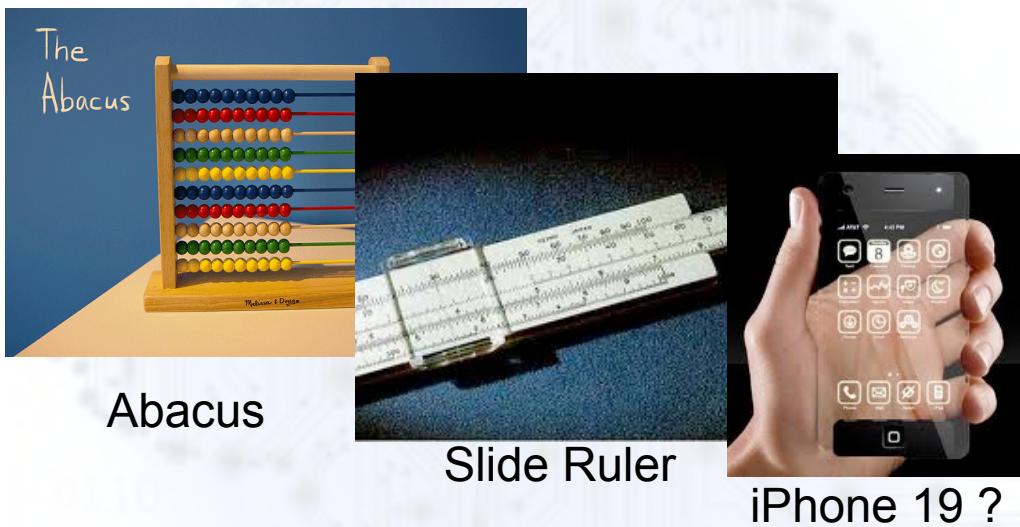
**using computers to support the study the brain**

*manage huge data set, data analysis and interpretation*

*simulate mathematical models that are too complex for*

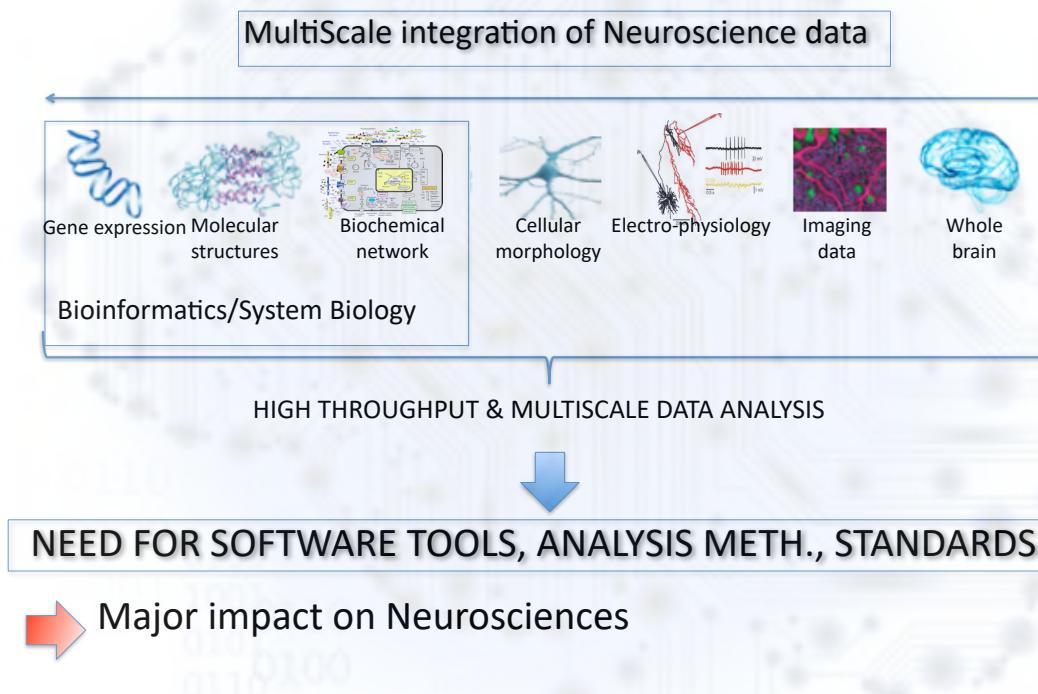
*being approached by “paper-and-pen”*

*computation = representation + dynamics*



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

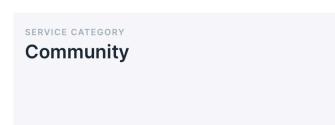
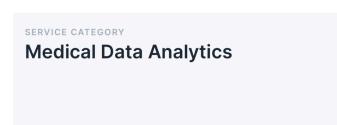
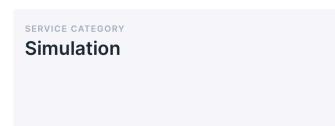
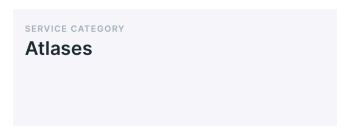
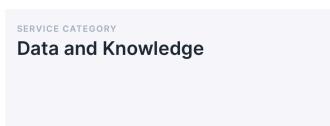
# Manage & Analyze data : Neuroinformatics



<https://ebrains.eu>



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



## What is EBRAINS

### A key enabler to advance brain science

EBRAINS is a new digital research infrastructure, created by the EU-funded Human Brain Project, that gathers an extensive range of data and tools for brain-related research. EBRAINS will capitalize on the work performed by the Human Brain Project teams in digital neuroscience, brain medicine, and brain-inspired technology and will take it to the next level. Read more and discover EBRAINS in our introduction document.

## 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?

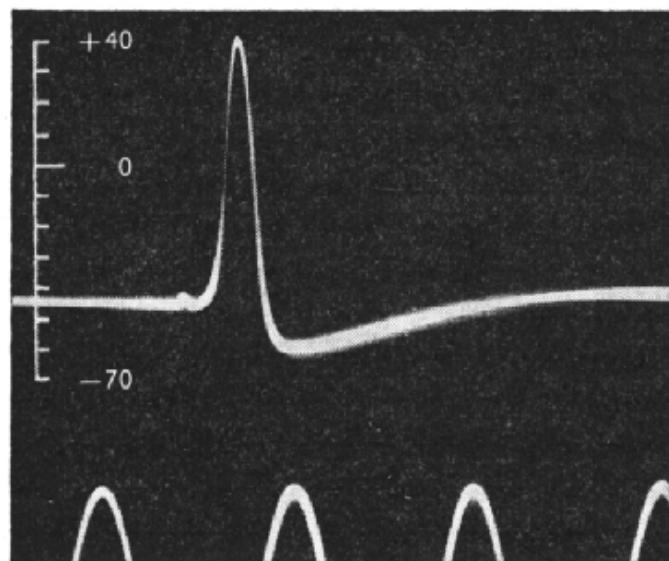
What are the mechanisms underlying oscillations in health/disease?

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?

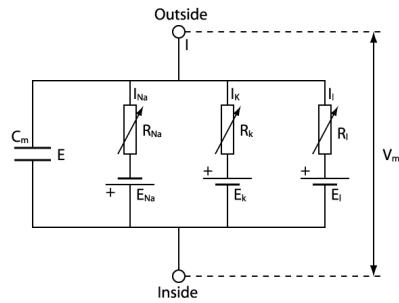
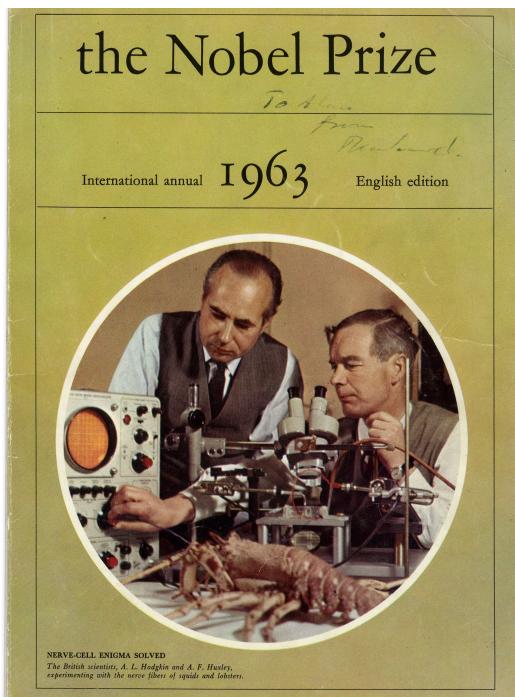
The most successful **theory** in Neuroscience (so far)



Alan Hodgkin and Andrew Huxley  
1952

The nerve impulse, or Action Potential

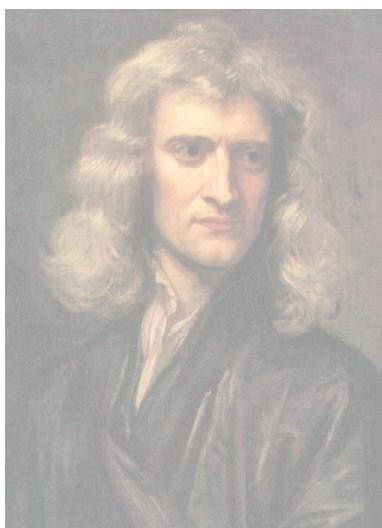
## Nerve-cell enigma solved



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

## Understanding by modelling

## Astronomical & terrestrial motion enigma solved

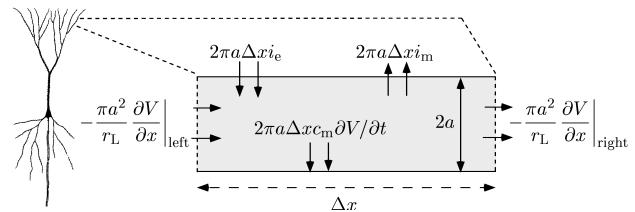
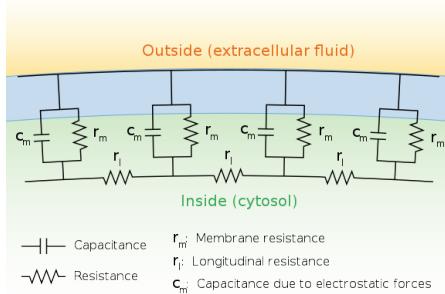


The three laws of motion and the universal gravitation law explain

- 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



Ramon Cajal



Camillo Golgi

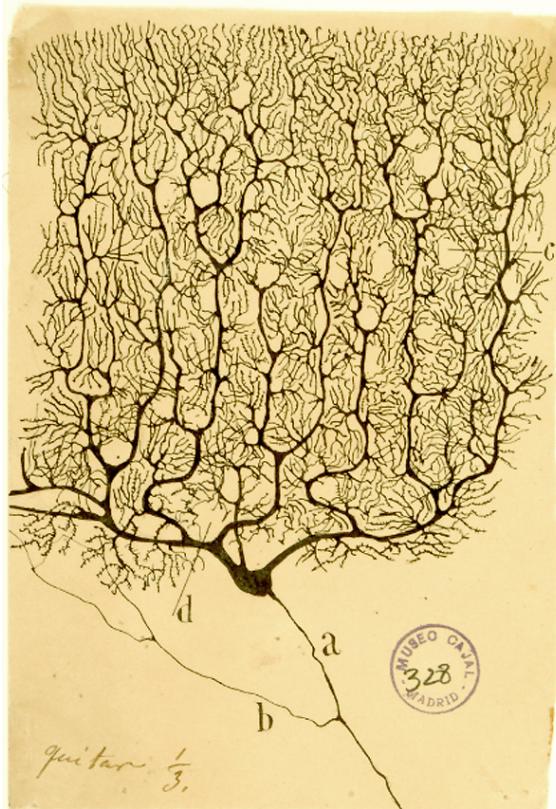
Nobel prize for medicine (1906)

*G. Ramon Cajal*

*Prof Camillo Golgi*

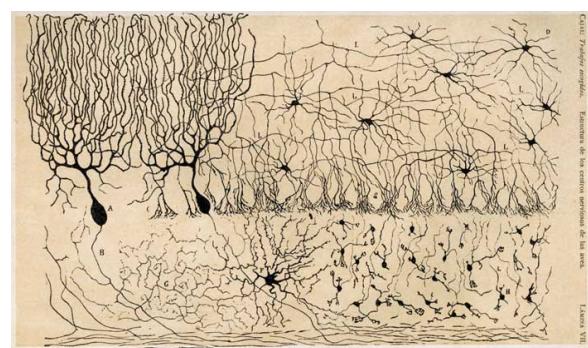
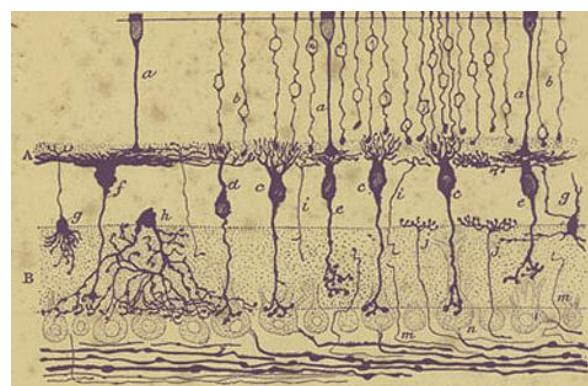
Ramon Cajal

*G. Ramon Cajal*

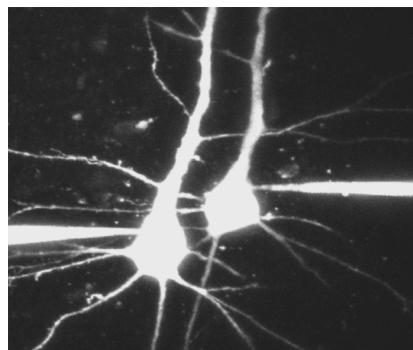
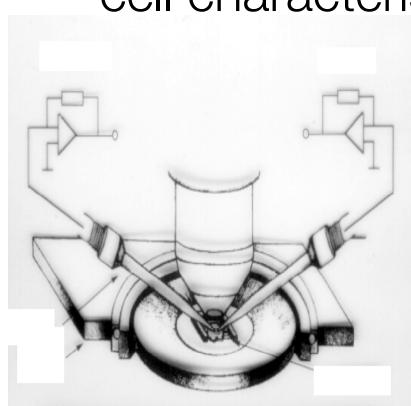




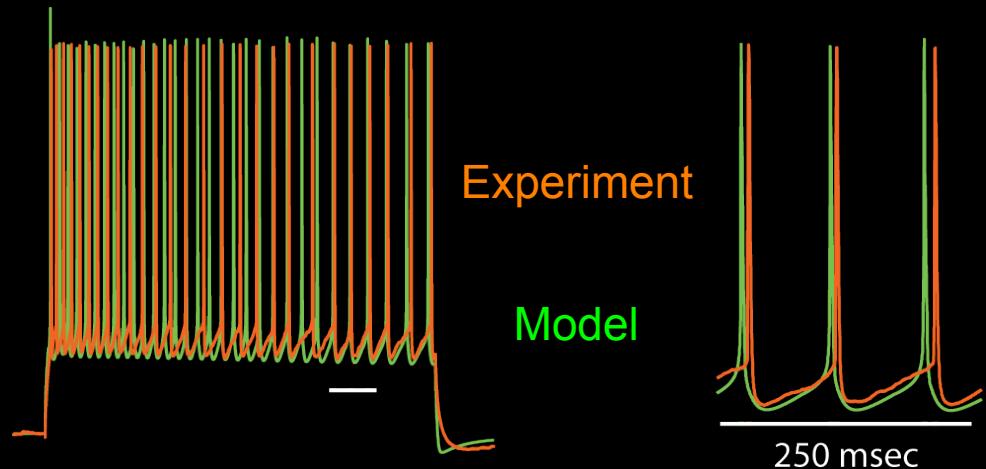
Ramon Cajal



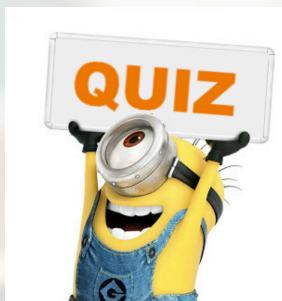
## Simultaneous Morphological & Electrical cell characterisation/digitization



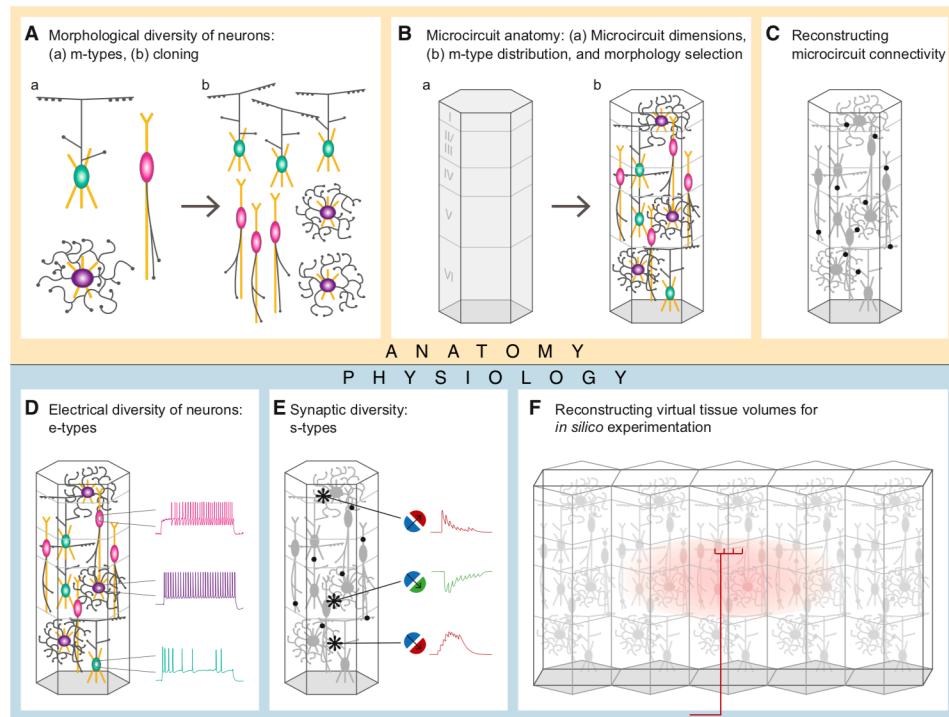
Quantitative recreation of  
single-neuron electrical response:  
bring to life a mathematical description of the cells



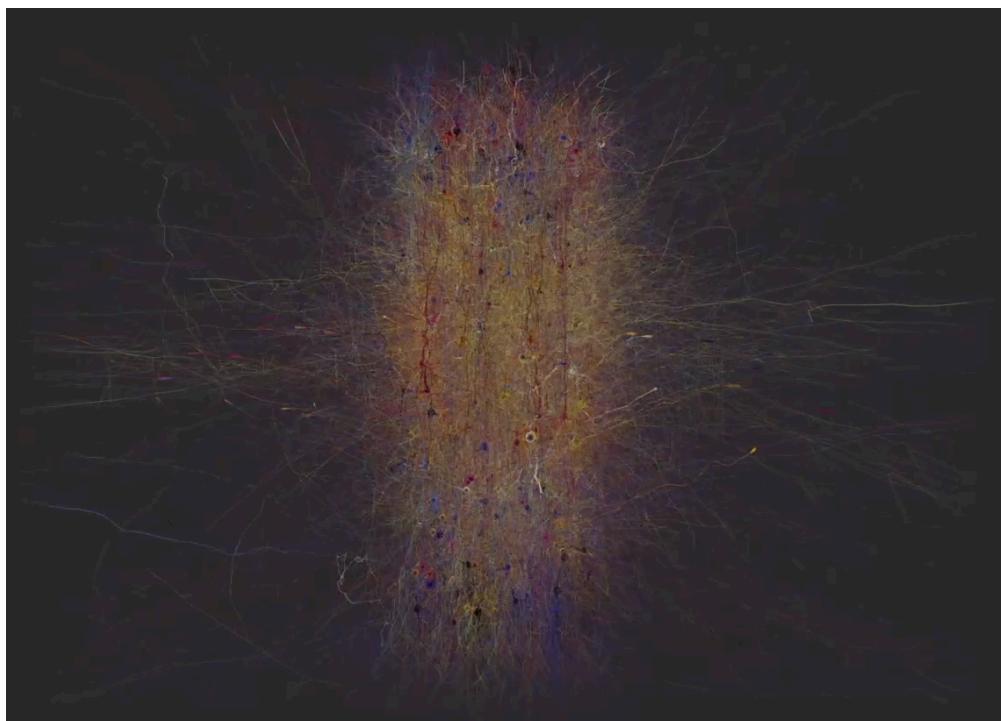
- Are you impressed by the quality of the “fit”, comparing real data and simulated data?
- What would convince you that the model captures the (bio)physical phenomenon correctly?



# 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,<sup>1,2,19</sup> Elif Müller,<sup>1,19</sup> Srikanth Ramaswamy,<sup>1,19</sup> Michael W. Reimann,<sup>1,19</sup> Marwan Abdellah,<sup>1</sup> Carlos Aguirre,<sup>1,20</sup> Sander Antilus,<sup>1,19</sup> Leticia Arisco-Nicolares,<sup>2</sup> Nicolas Antille,<sup>1</sup> Sella Arsover,<sup>1</sup> Guy Audebert,<sup>1</sup> Alessandro Arshavsky,<sup>1</sup> Thomas Attwells,<sup>1</sup> Antonio Bilezikci,<sup>1</sup> Giuseppe Chindemi,<sup>1</sup> Jean-Denis Courcoult,<sup>1</sup> Fabien Delalondre,<sup>1</sup> Vincent Delpire,<sup>1</sup> Shaul Druckmann,<sup>1</sup> Raphaël Dumusc,<sup>1</sup> James Dynes,<sup>1</sup> Stefan Eilemann,<sup>1</sup> Eyal Gal,<sup>1</sup> Michael Emil Gevaert,<sup>1</sup> Jean-Pierre Ghozzi,<sup>2</sup> Albert Gidon,<sup>1</sup> Joe W. Graham,<sup>1</sup> Anirudh Gupta,<sup>1</sup> Valentin Haenel,<sup>1</sup> Etay Hay,<sup>1</sup> Thomas Heins,<sup>1,19,21</sup> Juan B. Hernando,<sup>1,2</sup> Michael Hines,<sup>1</sup> Lida Hanania,<sup>1</sup> Daniel Kelsch,<sup>1</sup> John Kirov,<sup>1</sup> Georges Komaromy,<sup>1</sup> Koen Koenig,<sup>1</sup> Zohar Krasnayay,<sup>1</sup> Prasad Krishnamoorthy,<sup>1</sup> Sébastien Lasserre,<sup>1</sup> Yves Le Feuvre,<sup>1</sup> Vincent Le Be,<sup>1</sup> Bruno R.C. Maccioni,<sup>1</sup> Angel Merchán-Pérez,<sup>1,2</sup> Julie Meyste,<sup>1</sup> Benjamin Roy Morrice,<sup>1</sup> Jeffrey Muller,<sup>1</sup> Alberto Muñoz-Cáspedes,<sup>1,2</sup> Shiru Muradilov,<sup>1</sup> Keerthi Muthurasa,<sup>1</sup> Daniel Nachbaur,<sup>1</sup> Taylor H. Newton,<sup>1</sup> Max Nolte,<sup>1</sup> Aleksandr Ovcharenko,<sup>1</sup> Juan Palacios,<sup>1</sup> Luis Pastor,<sup>1</sup> Rodrigo Perin,<sup>1</sup> Raphaël Pfeifer,<sup>1</sup> David Pucci,<sup>1</sup> José-Rafael Rodríguez,<sup>1</sup> Silke Silberberg,<sup>1,2</sup> Ricardo Silva,<sup>1</sup> Farhad Tahvildari,<sup>1,19</sup> Martin Telefont,<sup>1</sup> María Toledo-Rodríguez,<sup>1</sup> Thomas Tränkler,<sup>1</sup> Werner Van Geit,<sup>1</sup> Jafet Villafranca Diaz,<sup>1</sup> Richard Walker,<sup>1</sup> Yun Wang,<sup>1,19</sup> Stefano M. Zaninetta,<sup>1</sup> Javier DuFelipe,<sup>1,20</sup> Sean L. Hill,<sup>1,20</sup> Idan Segev,<sup>3,4,20</sup> and Felix Schürmann,<sup>1,20</sup>

<sup>1</sup>EPFL, EPFL, Ecole polytechnique fédérale de Lausanne, EPFL Biotech Campus, 1023 Geneva, Switzerland  
<sup>2</sup>Laboratory of Neurobiology, Brain Mind Institute, EPFL, 1015 Lausanne, Switzerland  
<sup>3</sup>Department of Neurobiology, Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel  
<sup>4</sup>The Edmond and Lily Safra Center for Brain Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel  
<sup>5</sup>Janelia Farm Research Campus, Howard Hughes Medical Institute, Ashburn, VA 20147, USA  
<sup>6</sup>UCLouvain, UCLouvain, Institut des Sciences Biomédicales, Université Polytechnique de Madrid, 28223 Madrid, Spain  
<sup>7</sup>Instituto Cajal (CSIC) and CIBERMED, 28002 Madrid, Spain  
<sup>8</sup>CeSVMa, Centro de Supercomputación y Visualización de Madrid, Universidad Politécnica de Madrid, 28223 Madrid, Spain  
<sup>9</sup>Modeling and Virtual Reality Group, Universidad Rey Juan Carlos, 28933 Móstoles, Madrid, Spain  
<sup>10</sup>Key Laboratory of Visual Science and National Ministry of Health, School of Optometry and Ophthalmology, 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

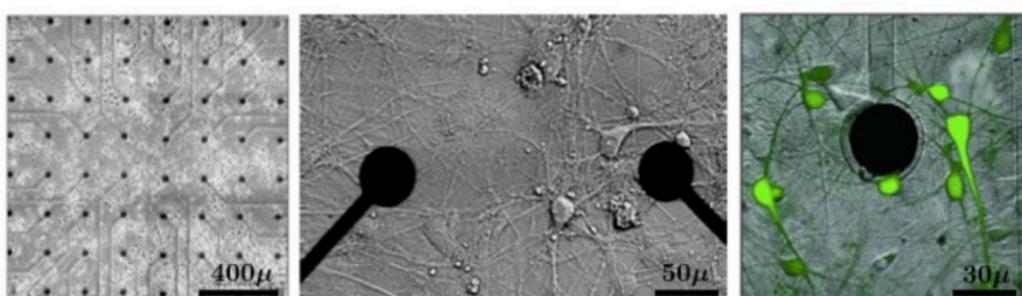
Cellular/Molecular

## Dynamics of Excitability over Extended Timescales in Cultured Cortical Neurons

Asaf Gal,<sup>1,4</sup> Danny Eytan,<sup>1,5</sup> Avner Wallach,<sup>1,2</sup> Maya Sandler,<sup>3</sup> Jackie Schiller,<sup>3</sup> and Shimon Marom<sup>1,3</sup>

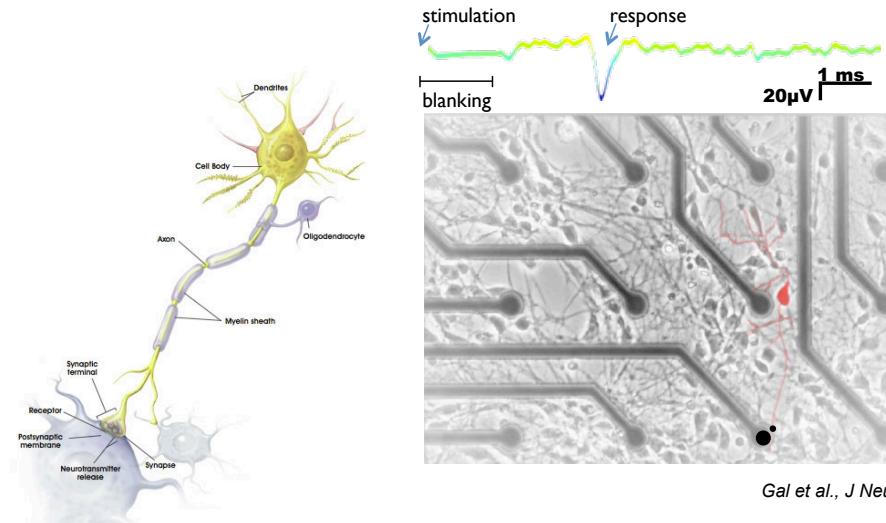
<sup>1</sup>Network Biology Research Laboratories, Lorry Lokey Interdisciplinary Center for Life Sciences and Engineering, <sup>2</sup>Faculty of Electrical Engineering, and

<sup>3</sup>Department of Physiology, Faculty of Medicine, Technion, Haifa 32000, Israel, <sup>4</sup>The Interdisciplinary Center for Neural Computation, The Hebrew University, Jerusalem 91904, Israel, and <sup>5</sup>Rambam Medical Center, Haifa 31096, Israel

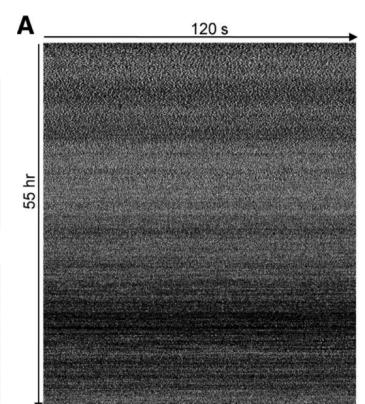
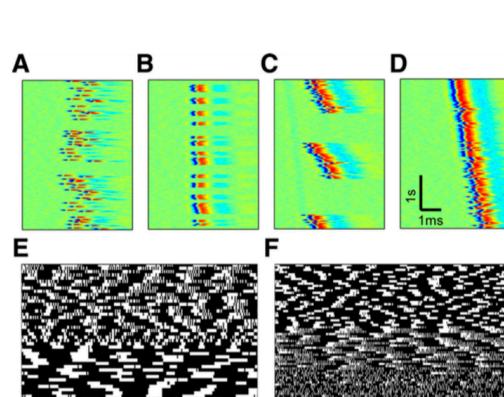
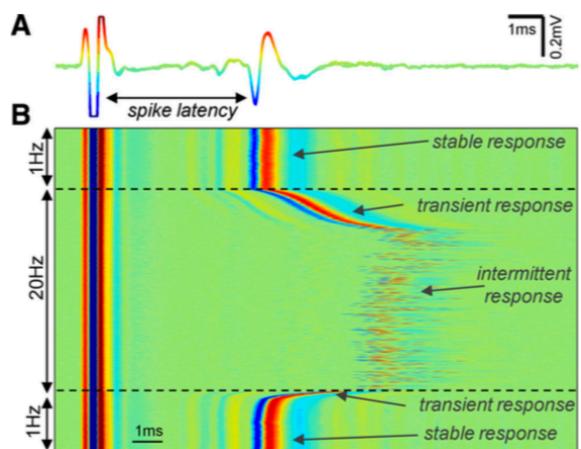


# Is HH enough for single neurons? (Is a typical experiment enough?)

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.

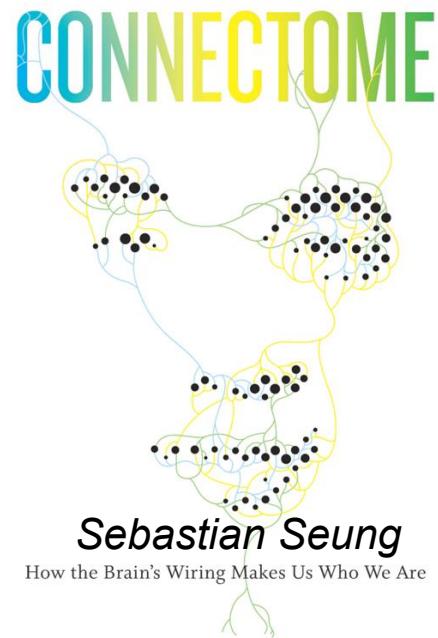
Intracellular (biochemical) pathways, their deep inter-dependencies and links to ion channel dynamics/regulation/expression, **makes excitability complex (at cell- and synaptic-levels).**

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.**

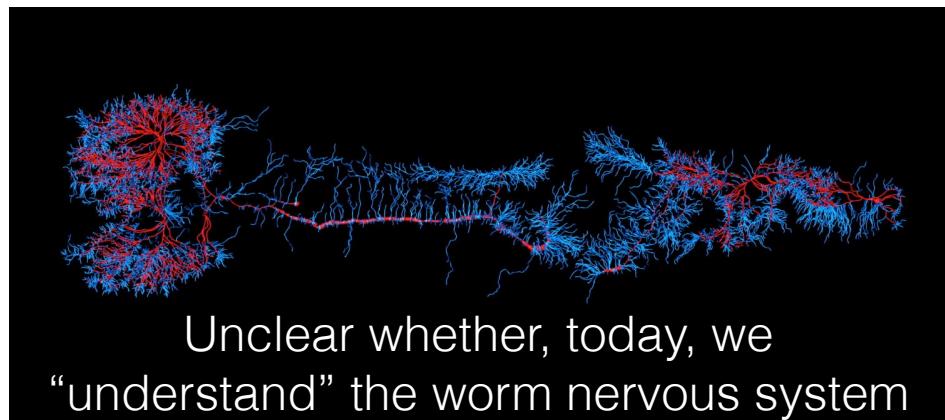
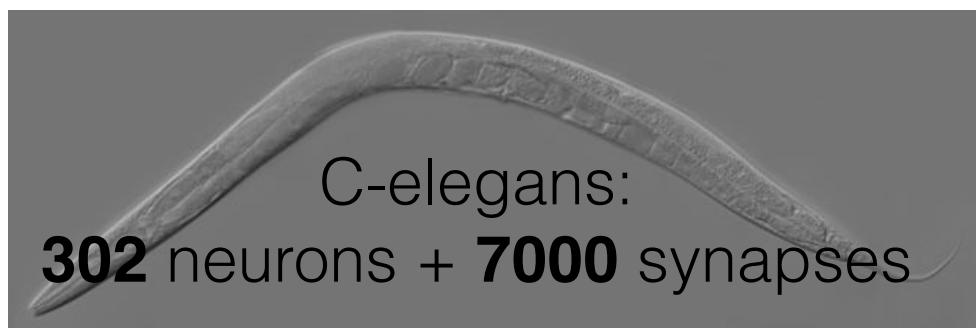
- What is genome/genomics?
- What is proteome/proteomics?
- What is connectome/connectomics?



Is the *connectome* enough?



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



Is the *connectome* enough?

Probably not.

Current digital reconstructions are (based on)

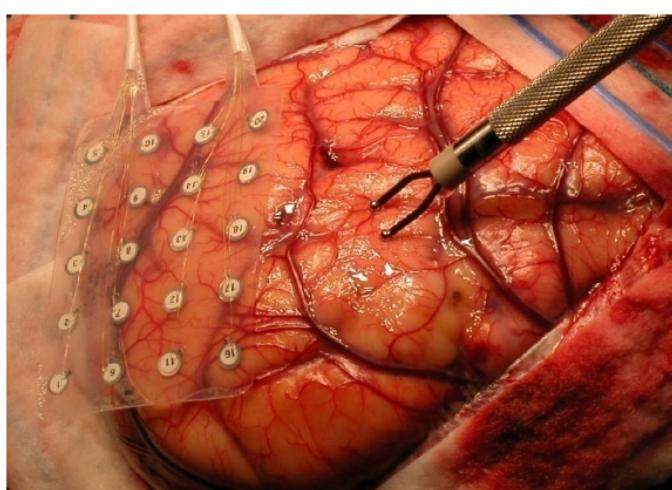
- a temporal *snapshot*, at the EM-level, or
- a statistical/morphol. recreation of typical connectivity
- and do not include neuromodulation (yet).**

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.**

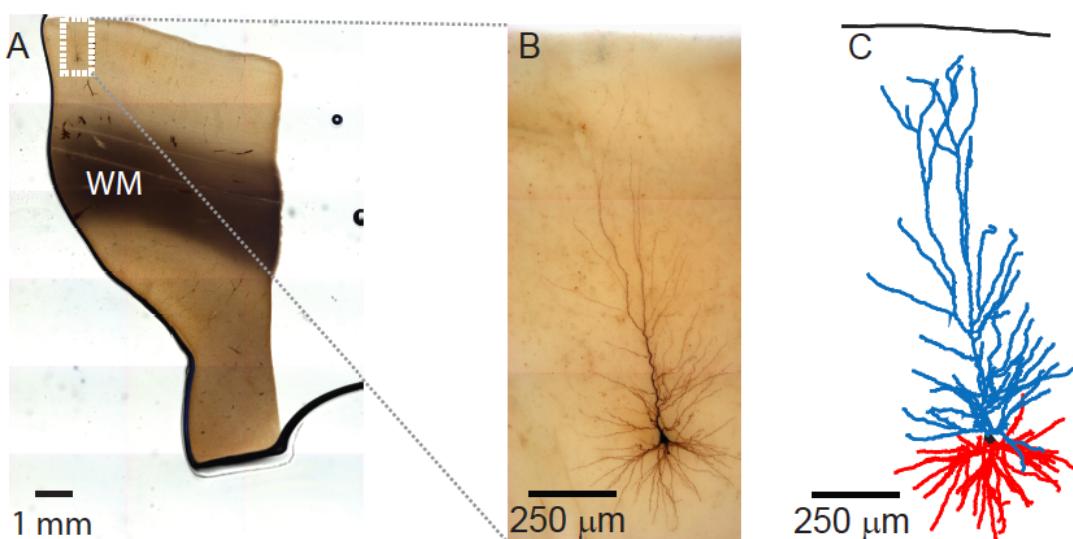
## Getting living adult human neurons in the lab



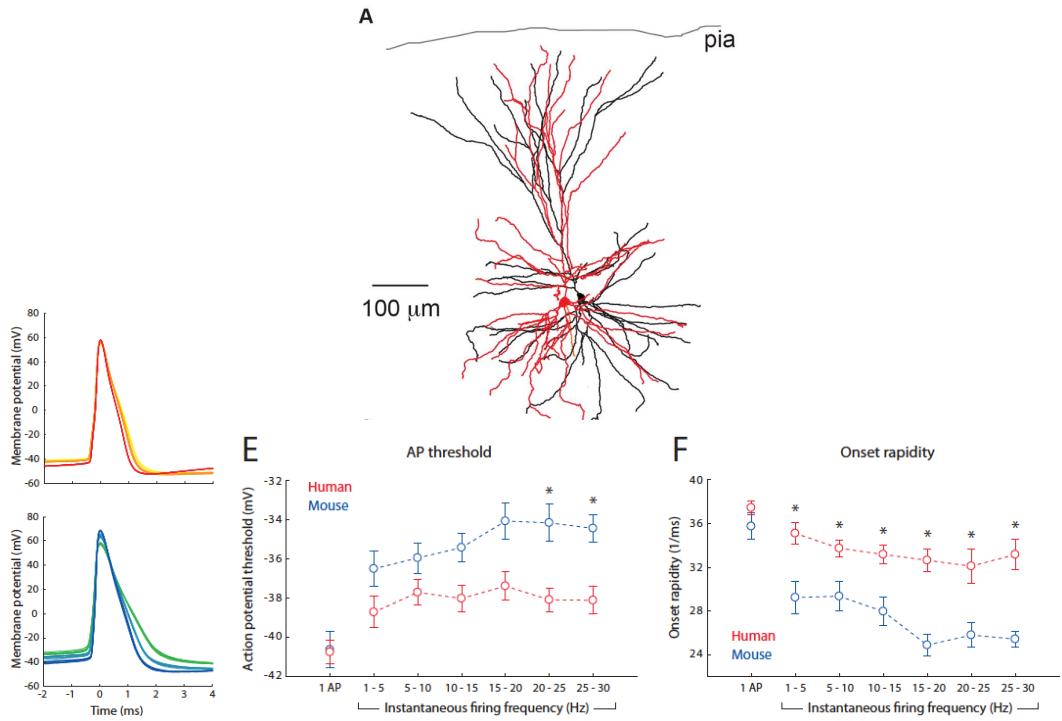
Hans Baayen, MD, Neurosurgery, VUmc Amsterdam

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.

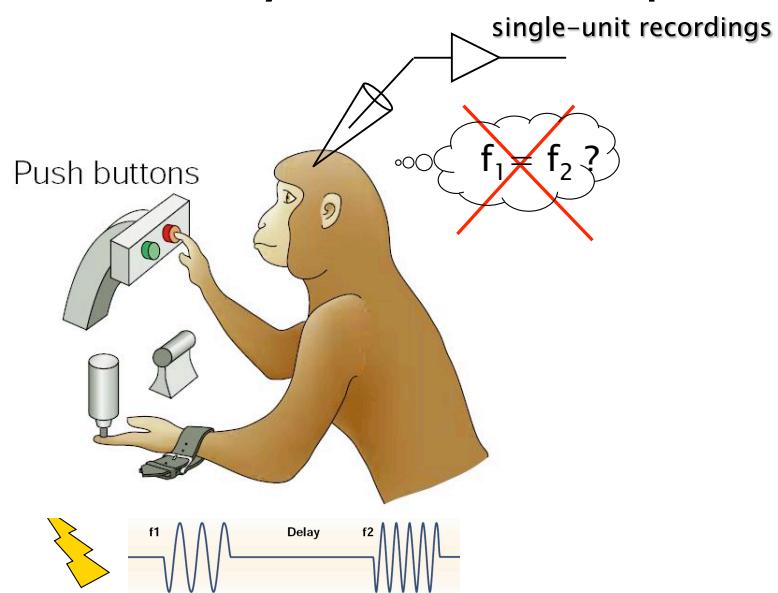
...In that Empire, the Art of Cartography attained such Perfection that the map of a single Province occupied the entirety of a City, and the map of the Empire, the entirety of a Province. In time, those Unconscionable Maps no longer satisfied, and the Cartographers Guilds struck a Map of the Empire 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

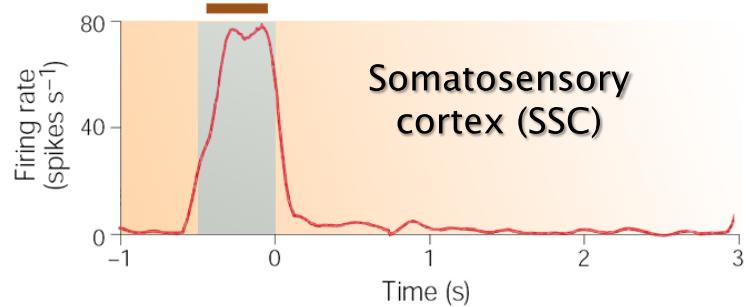
Working memory, decision making,  
metastability, persistent activity

## *In vivo:* Delay Match-to-Sample Task



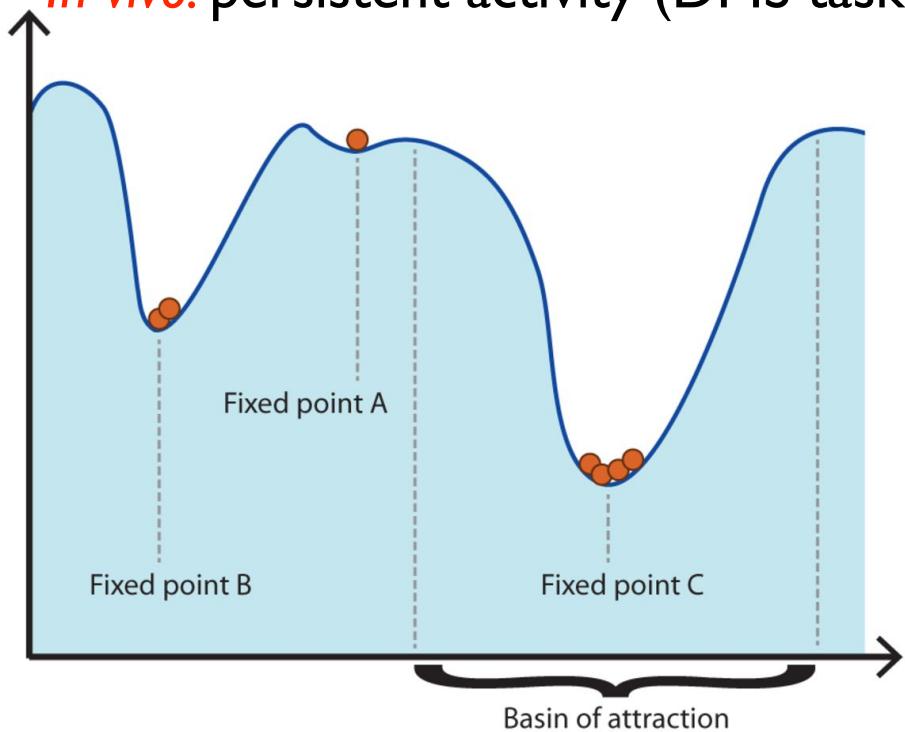
Romo and Salinas, 2003

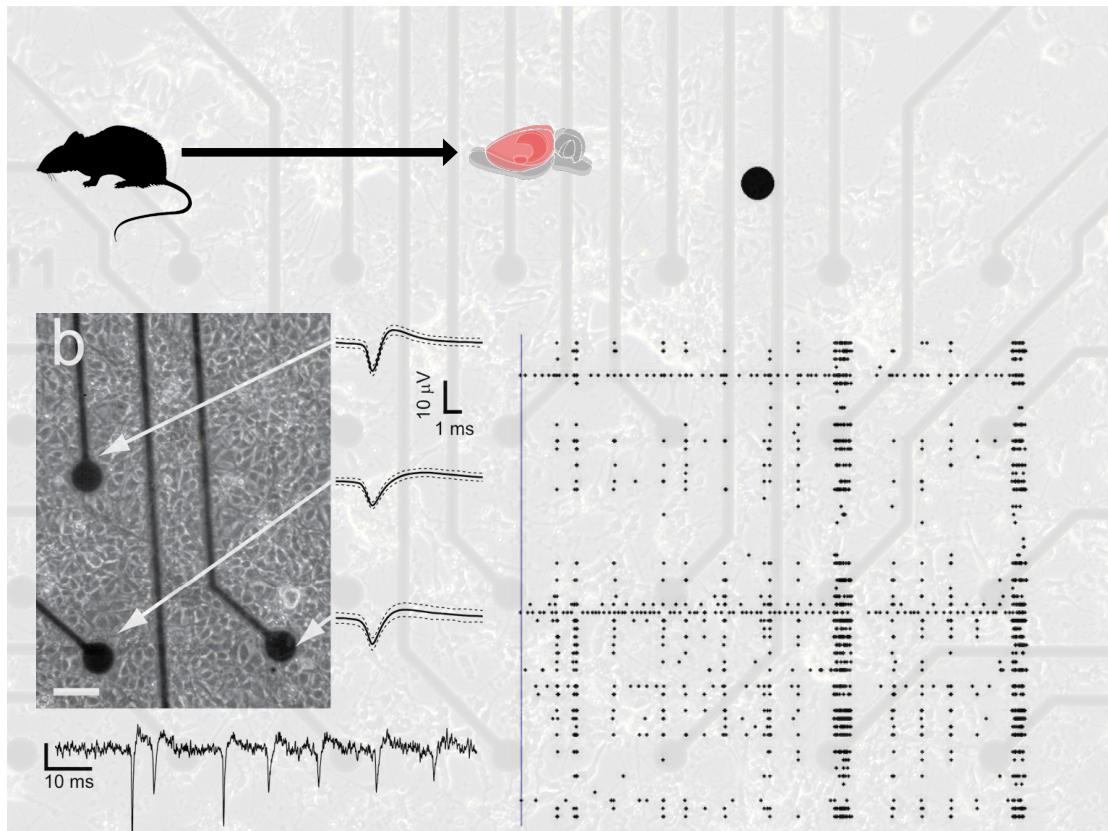
## *In vivo*: persistent activity (DMS task)



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*