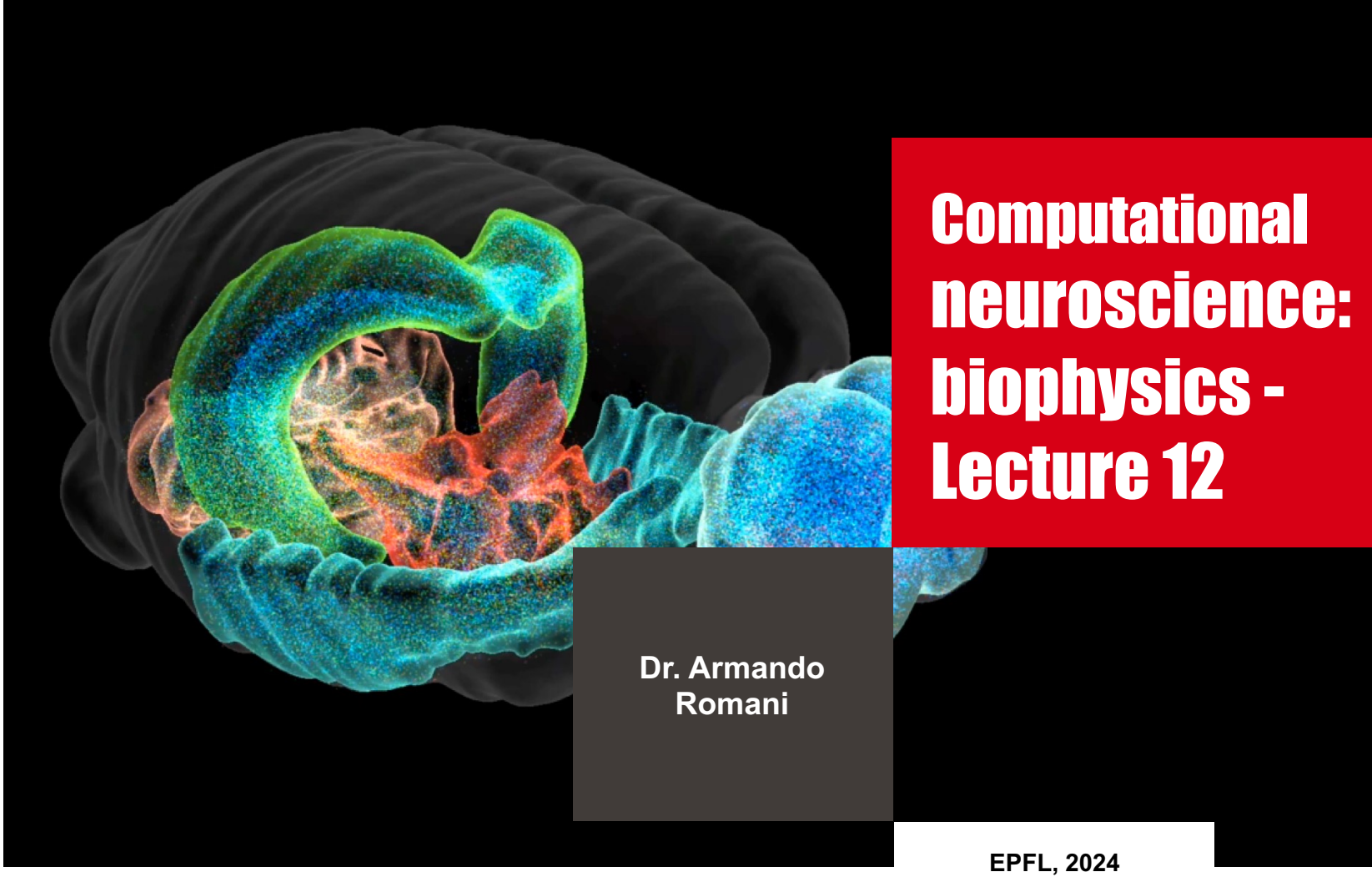


Computational neuroscience: biophysics - Lecture 12

Dr. Armando Romani

EPFL, 2024

Networks 3
Part 1 – Hippocampus

Part 1 Overview

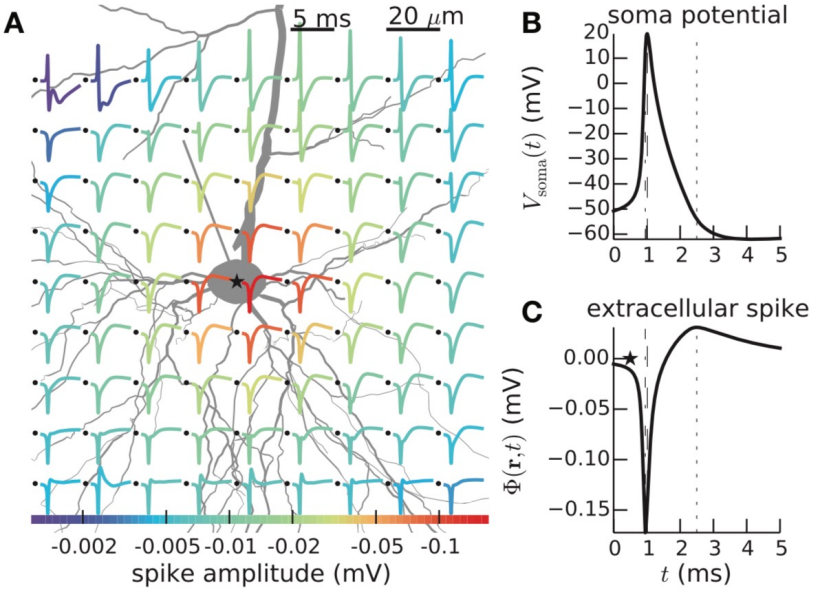
- Biological background
- Implementation

Part 1 Overview

- **Biological background**
- Implementation

Local-field potential (LFP)

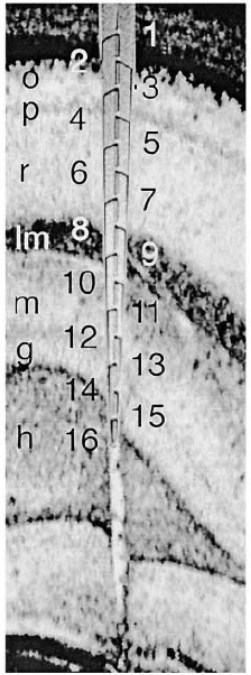
- The local field potential (LFP) refers to the electric potential in the extracellular space around neurons.
- The LFP gives information about population activity.
- Several methods are available to estimate LFP from model simulations (Reimann et al. 2013; Linden et al., 2014).

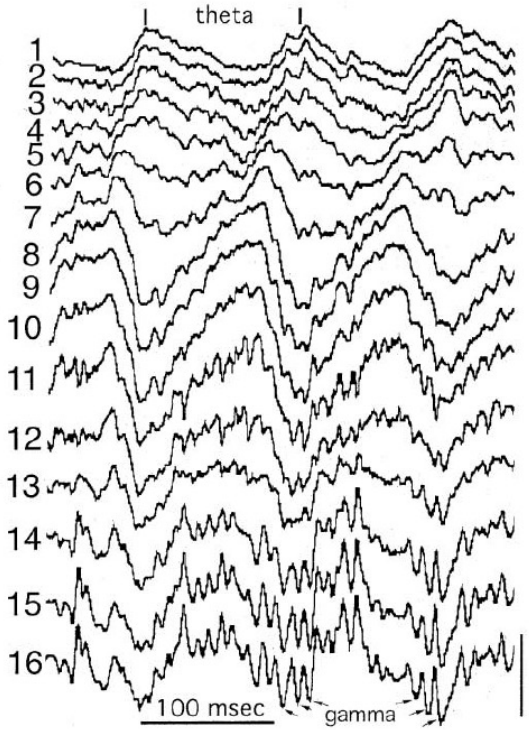


Linden et al., 2014

Oscillations

- Population activity can show a certain degree of synchrony and the LFP shows oscillations.
- The figure shows a 16-site silicon probe in the CA1-dentate gyrus axis.
- Gamma oscillations (30-80 Hz) are nested in theta oscillations (4-10 Hz).

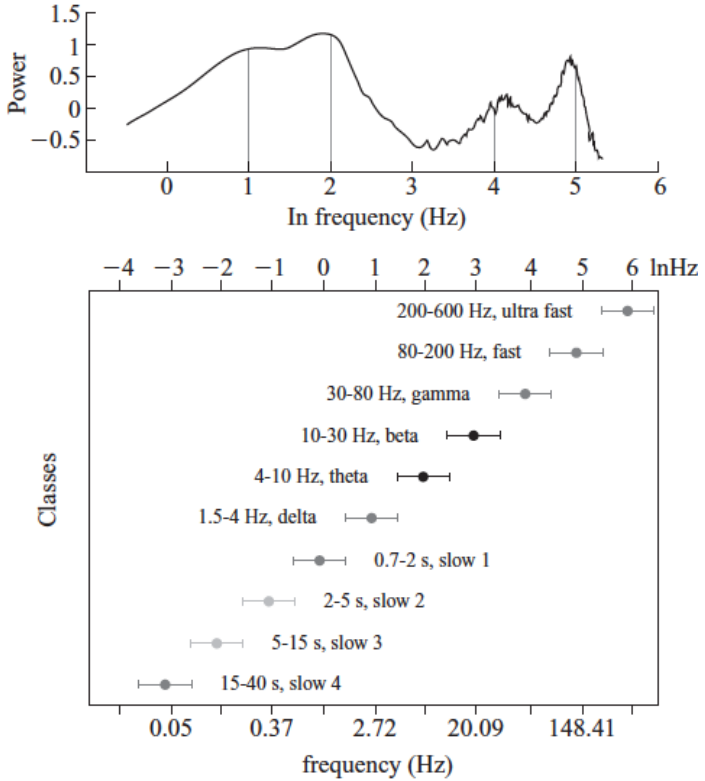




Buzsáki, 2002

Oscillations

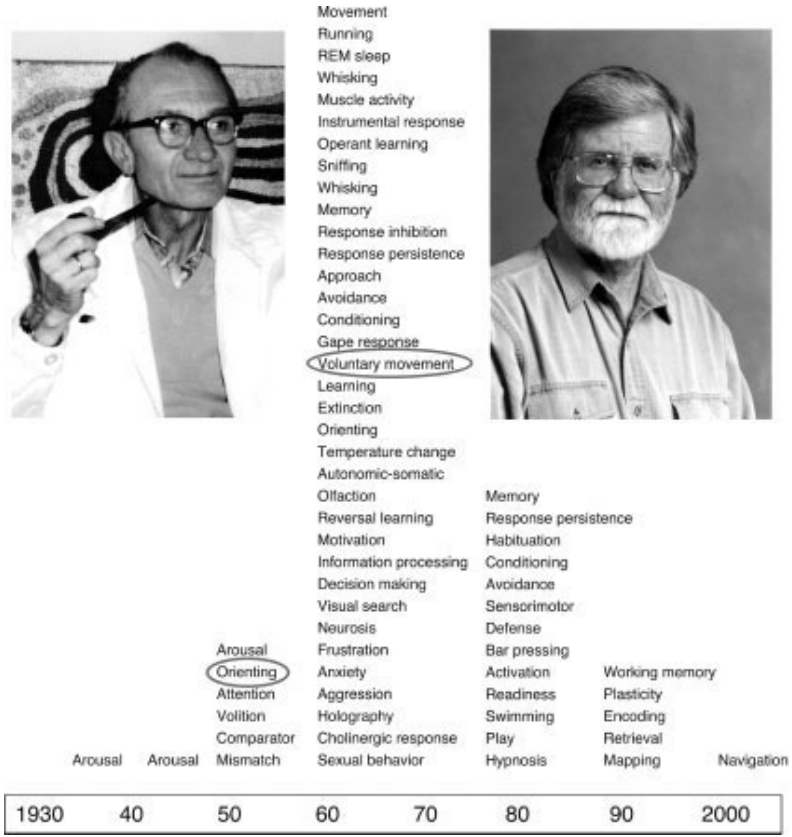
- LFP is a time series (time domain)
- The LFP can be decomposed into a series of sine and cosine of different frequencies thanks to Fourier transform.
- A way to represent how different frequencies contribute to the signal (i.e., LFP) is the power spectrum (frequency domain).
- Different frequencies are called in different ways.



Buzsáki, 2006

Theta rhythm

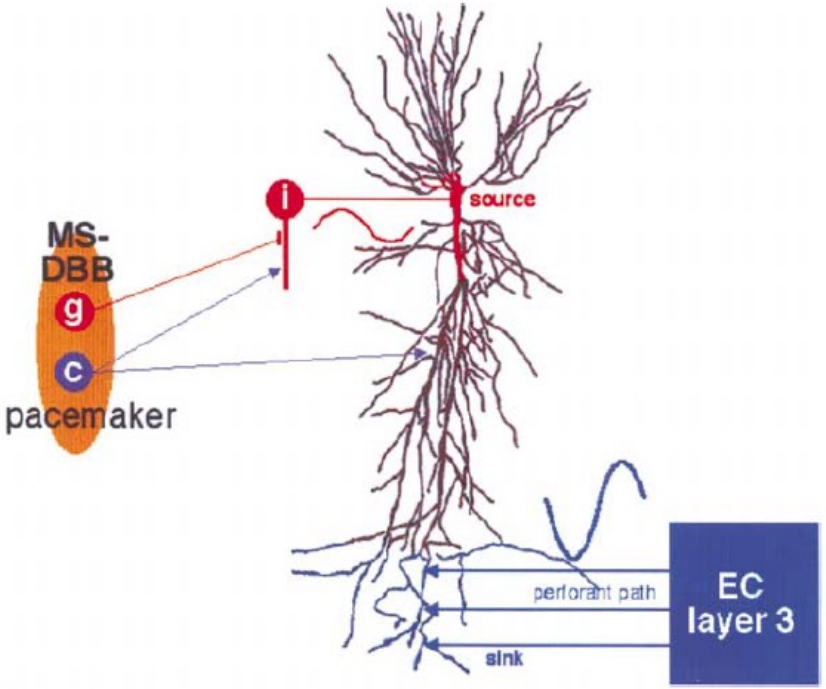
- Theta oscillations (4-10 Hz) has been correlated with many brain functions.
- In particular, theta seems to be associated with memory.



Buzsáki, 2005

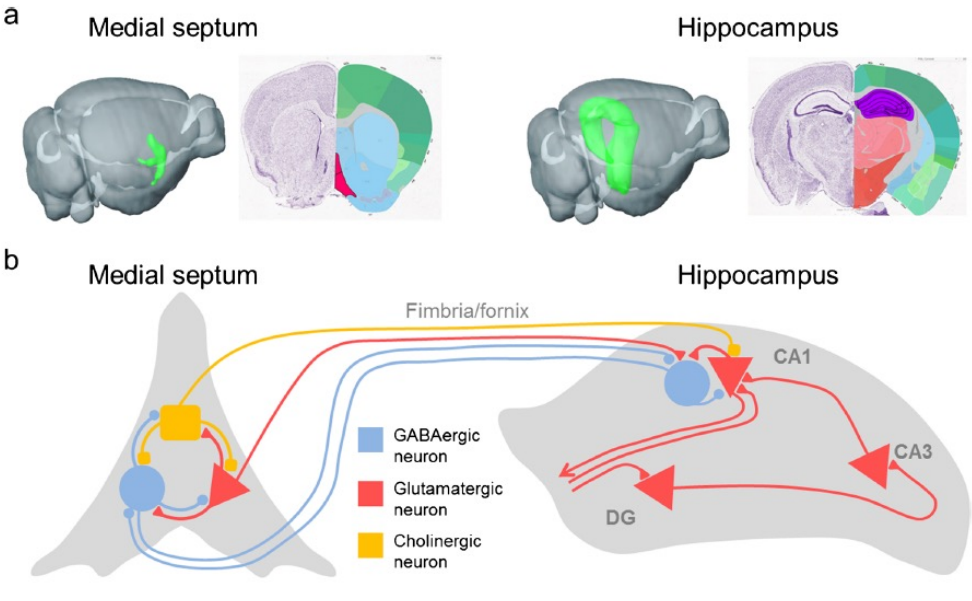
Theta initiation and maintenance

- The generation of theta oscillations in the CA1 is due to MS pacemaker cells.
- A type of theta oscillations is blocked by atropine suggesting a role of Acetylcholine (ACh).
- Depolarizing inputs may come from different sources: CA3, EC, MS, Sub (Sun et al., 2014), sub cortical regions (Vertes et al., 2004)



Buzsáki, 2002

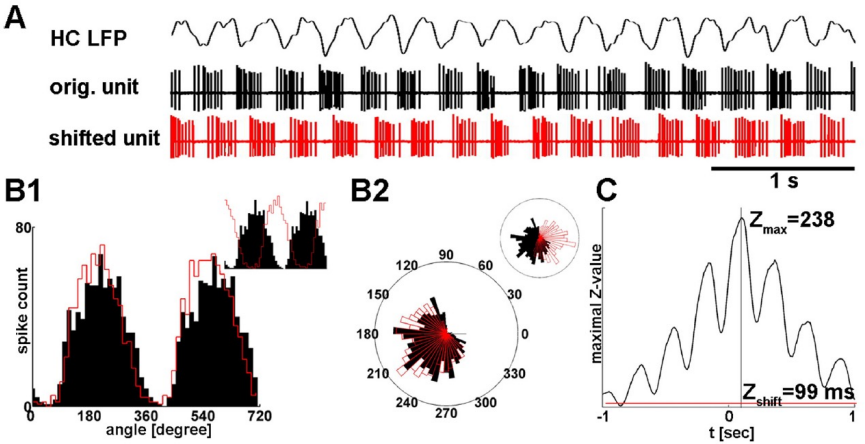
Medial septum



Müller and Remy, 2018

MS pacemaker cells

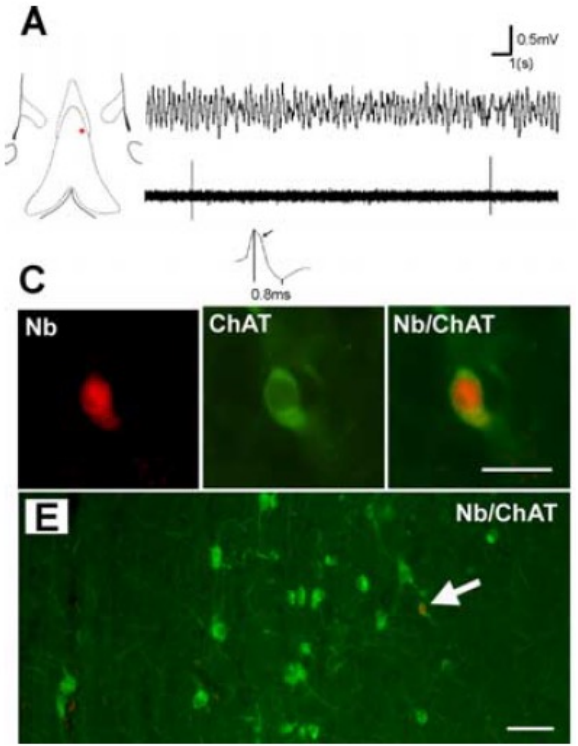
- MS pacemaker cells are GABAergic neurons which express hyperpolarization-activated and cyclic nucleotide-gated nonselective cation channels (HCN channels).
- They emit bursts at theta frequency.



Hangya et al., 2009

MS cholinergic neurons

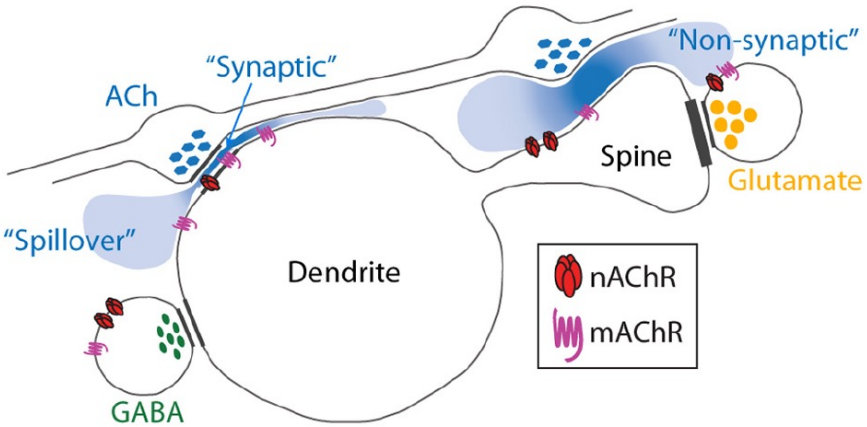
- MS cholinergic neurons fire with a low rate.
- They are neuromodulator neurons that release ACh in CA1.
- Neuromodulators as ACh have wider (in space and time) effects on the networks.



Simon et al., 2006

Acetylcholine

- Several types of transmission
- Effect on cells and synapses depending on receptors
- Nicotinic receptors (nAChR) are ionotropic and normally excitatory
- Muscarinic receptors (mAChR) are metabotropic. In general, M1 and M3 are excitatory, M2 and M4 and inhibitory.



Disney and Higley, 2020

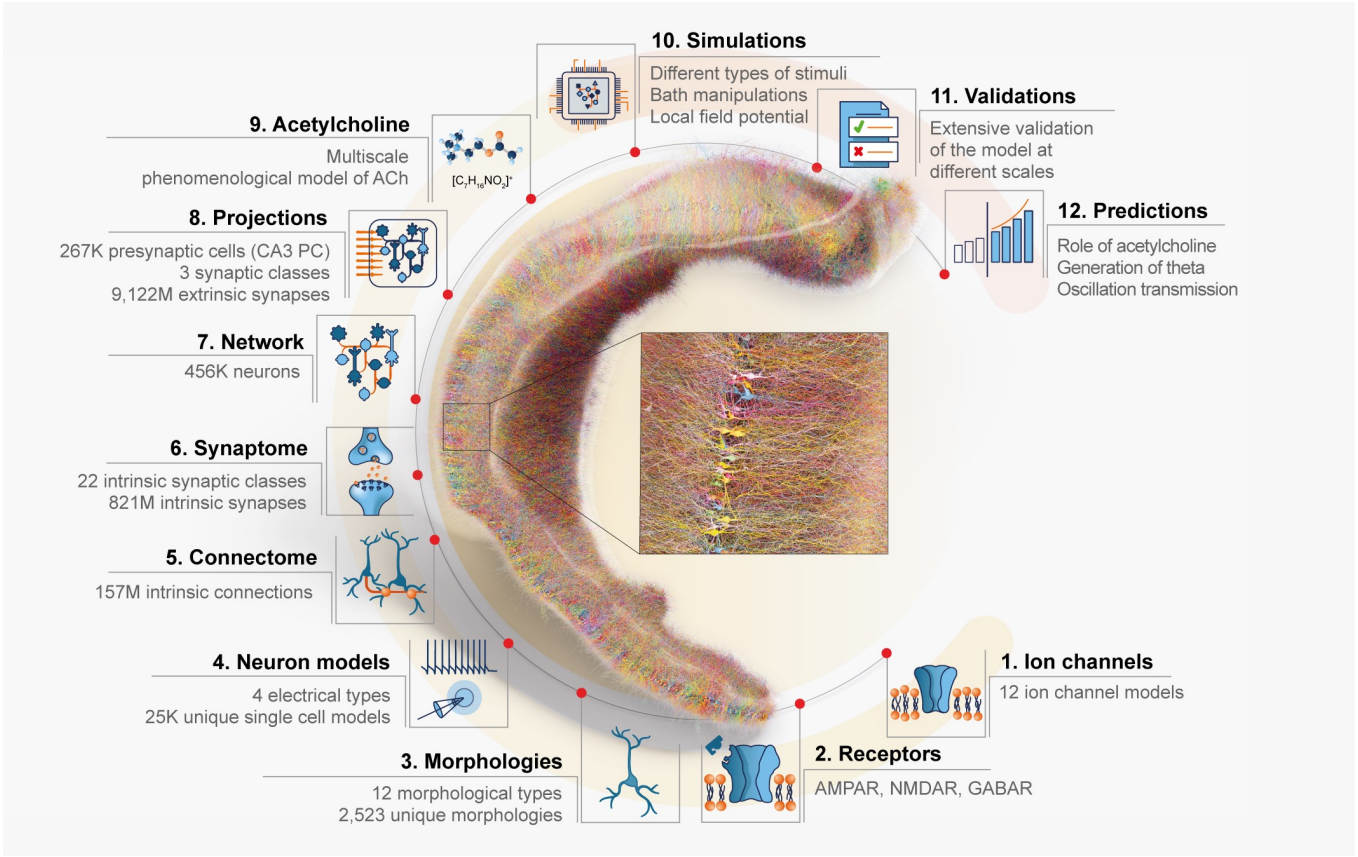
Summary 1.1

- Theta oscillations are generated by MS GABAergic neurons.
- MS cholinergic neurons seems to be also implicated at least in some forms of theta.
- Background excitation from different source could be also needed.

Part 1 Overview

- Biological background
- **Implementation**

CA1 model



Romani et al., 2024

MS pacemaker cells

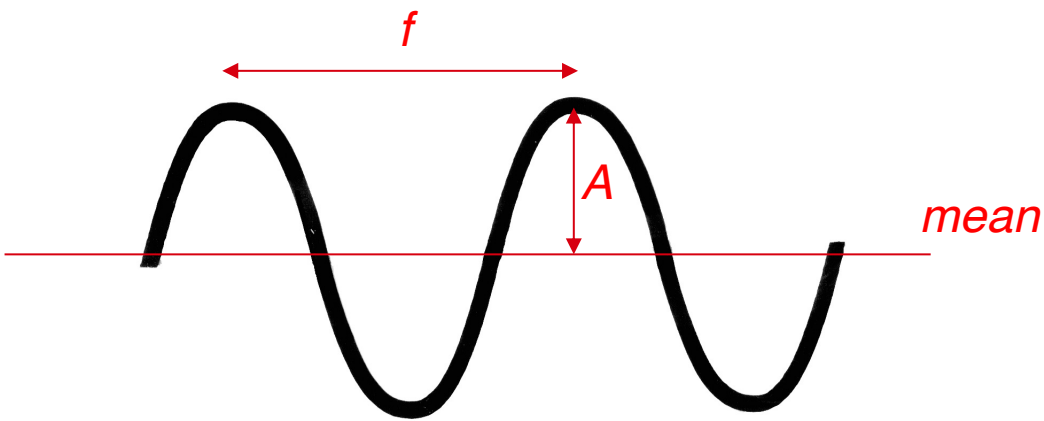
- GABAergic MS neurons target principally INT than PC in CA1 (Sun et al., 2014)
- MS INTs predominately target PV+ INT in CA1 (Müller and Remy, 2018; Sun et al., 2014)
- PV+ INT seems to play a major role compared to SOM+ INT (Amilhon et al., 2015)
- For simplicity, we can assume that they target only PV+ INT

MS pacemaker cells

- It is not clear how many MS cells are activate at the same time,
- how many cells converge on the same PV+INT,
- how strong are the IPSPs.
- We cannot model the MS INT innervation precisely, and we have to use a more phenomenological model.
- We can inject a hyperpolarizing current into the PV+INT somas.
- The size of this current is unknown and it will be a free parameter in the model.

MS pacemaker cells

- In particular, we have to define mean value, amplitude and frequency (*mean, A, f*) of the hyperpolarizing current to be injected in PV+INT.
- We can set *mean* = -*A* to reduce the parameter space. This is equivalent to say that the pacemaker cells are silent only around the peaks.



Background excitation

- The CA1 network is almost silent without an excitatory input.
- Background excitation is necessary to make the cells reach the spike threshold.
- It is not clear what is the source and intensity of this current.
- We use a phenomenological model and inject a depolarizing current into the cells.
- For the sake of simplicity, we treat all the cells in the same manner
- The size of this current is unknown and it will be a free parameter in the model.

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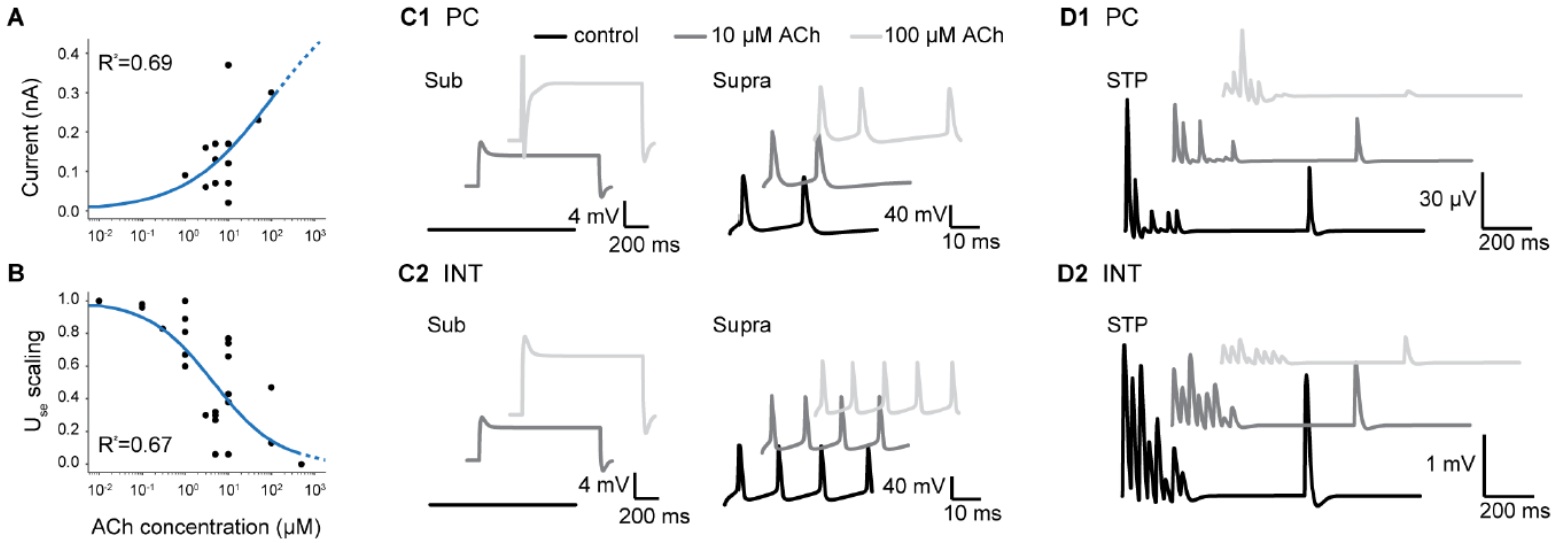
Acetylcholine

- The sparse available data suggest that ACh increases the neuron excitability (= depolarize the neurons) and reduces the PSPs.
- The data is not sufficient to discriminate between cell types and different pathways.
- For neuron excitability, we can compute an equivalent net current due to ACh (*in vitro* bath application) and fit a dose-effect curve.
- For PSP, we assume that the ACh acts mainly at the level of synaptic probability (i.e., term *U* of the Tsodyks-Markram model) and fit a dose-effect curve.
- The amount of ACh released during theta oscillations is unknown and it will be a free parameter in the model.

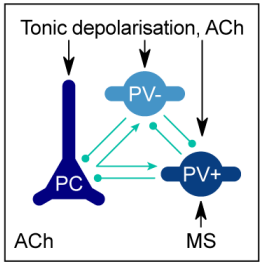
Acetylcholine

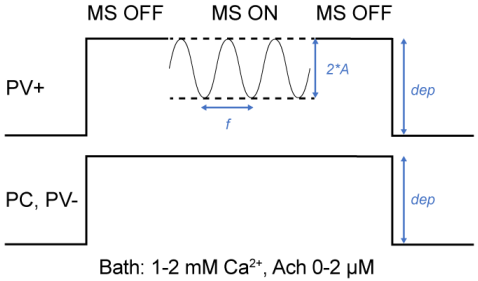


Romani et al., 2024

In summary…

- All the neurons receive a depolarizing current *dep.*
- *dep* needs to be from 100% (threshold) to ~130%. Afterwards, we observe non-physiological behaviors of the cells.
- PV+INT receive a hyperpolarizing current of amplitude *A* and frequency *f.*
- We tested *A* in a range that produces physiological hyperpolarization (0.1-0.5 nA).
- We tested *f* = 8 Hz, a mid frequency in the theta range, to reduce parameter space.

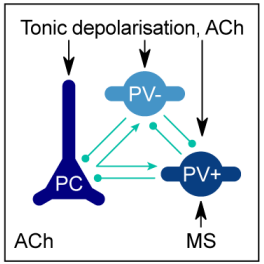


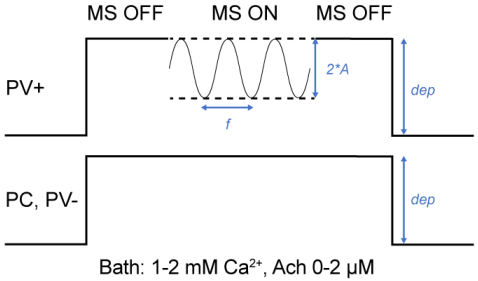


Romani et al., 2024

In summary…

- ACh affects all the neurons and synapses. It has a concentration *ACh*.
- We tested concentrations of 0-2 *μ*M, which are biological plausible
- Simulations are run at *in vitro* (2 mM) and *in vivo* (1 mM) calcium concentration.

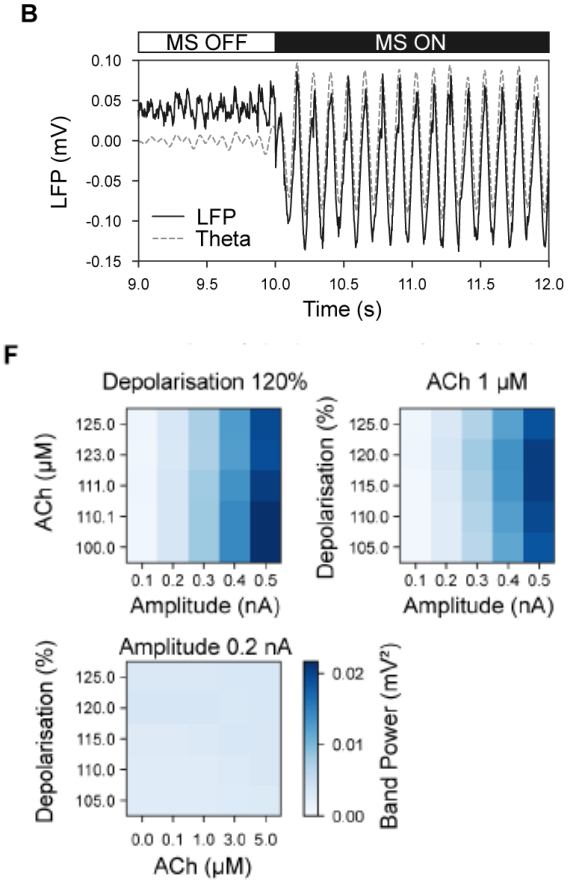




Romani et al., 2024

Results

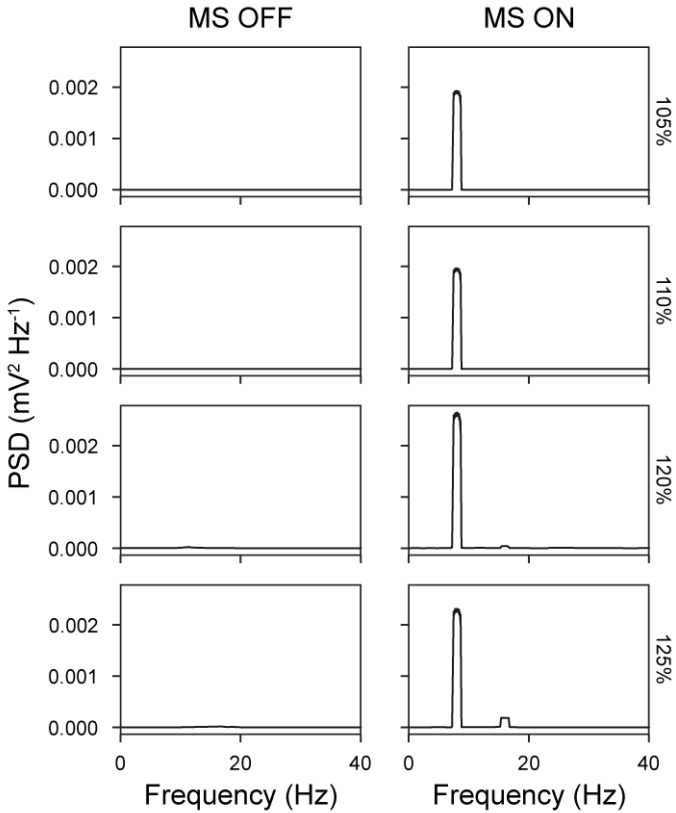
- Given the complexity of the simulations, we simulated only a portion of the entire circuit.
- When MS pacemaker cells are activated, we can record a strong theta oscillations in CA1
- We scanned a 4D space of parameters.
- Let's focus on *in vivo* calcium simulations.
- MS pacemaker cells are the major contributor to the theta.



Romani et al., 2024

Results

- When MS pacemaker cells oscillate at 8 Hz, we observe an 8 Hz oscillation in CA1.
- In the image, we can see the power spectrum at different depolarization levels with and without pacemaker cells.



Romani et al., 2024

Discussion

What is the role of background excitation, ACh, and low calcium?

- Both background excitation and ACh depolarize the cells. Both ACh and low calcium decrease synaptic release probability.
- We can speculate that background excitation and ACh cooperate to bring the cells to a sufficient activity, and both ACh and low calcium cooperate to uncouple the cells.
- The latter seems important to create an asynchronous activity necessary to be entrained by the pacemaker cells.
- Interestingly, in high calcium, background excitation and ACh bring the cells to an high activity that cannot be easily entrained by the pacemaker cells

Summary 1.2

- The network model is used to integrate available data.
- We combined the biophysical model with other models more phenomenological (disinhibition, ACh, excitation).
- The network was not “tuned” to obtain the result.
- The model supports the role of the MS pacemaker cells to generate theta and provides additional predictions.

Networks 3
Part 2 – Sustainability

Part 2 Overview

- Introduction
- Computational neuroscience
- Conclusions

Part 2 Overview

- **Introduction**
- Computational neuroscience
- Conclusions

Definition

« Sustainable development is development that meets the needs of the present without compromising the ability of future generations to meet their own needs. […] a concern for social equity between generations, a concern that must logically be extended to equity within each generation. »

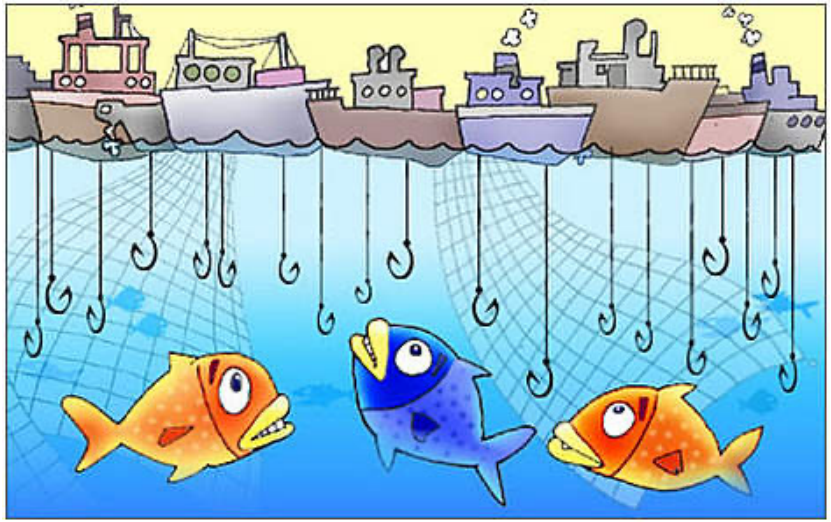
Our common future, Bruntland report, United Nations, 1987

«possibility that humans and other life will flourish on the Earth forever»

John Ehrenfeld, 2008

An example: overfishing

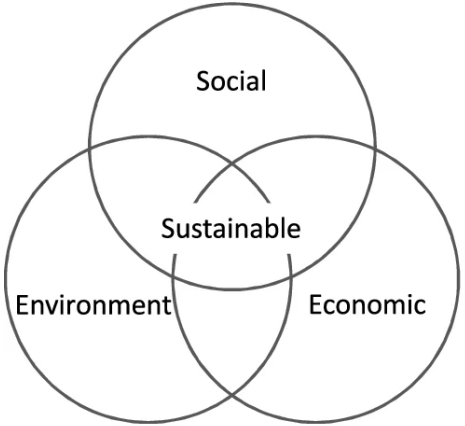
- Fishing more than necessary
- Fishing with a rate (consumption rate) that is higher than the reproduction (replacement rate)
- Risk of species extinction
- New generations will not have enough fishes

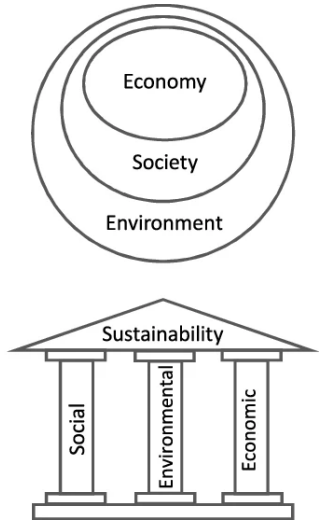


wwf.panda.org

Weak vs. strong sustainability

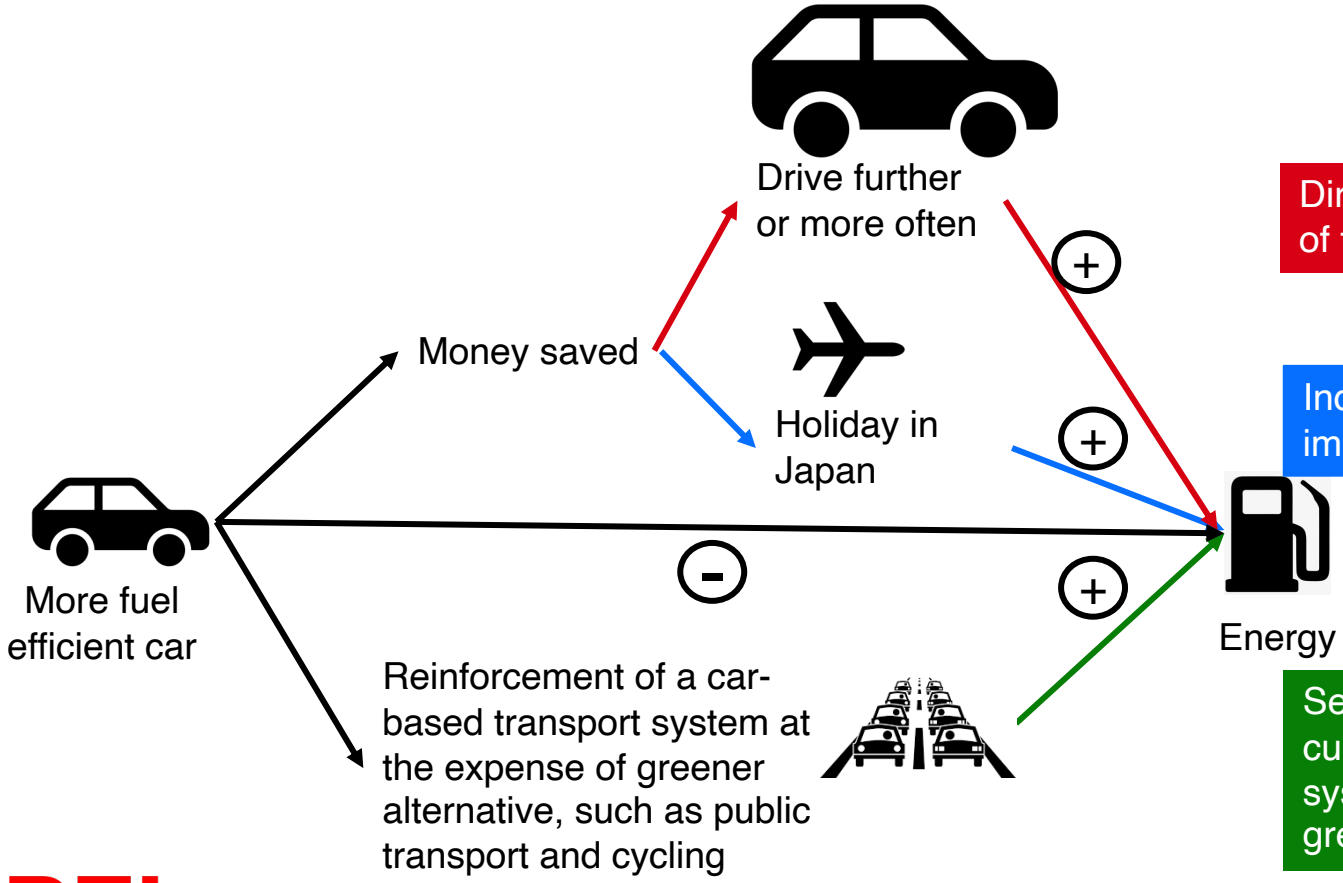
- Sustainability is based on 3 pillars: social (or equity), economic, environment
- In weak sustainability we have to compromise between them
- In strong sustainability we have a hierarchy where environment is higher in the hierarchy





wikipedia

Rebound effect



Direct rebound effect: more of the same consumption

Indirect rebound effect: other impactful consumption

Secondary effect: reinforce current socio technical system at the expense of greener alternative

Sorrell et al, 2018

Sustainability at EPFL

Sustainability

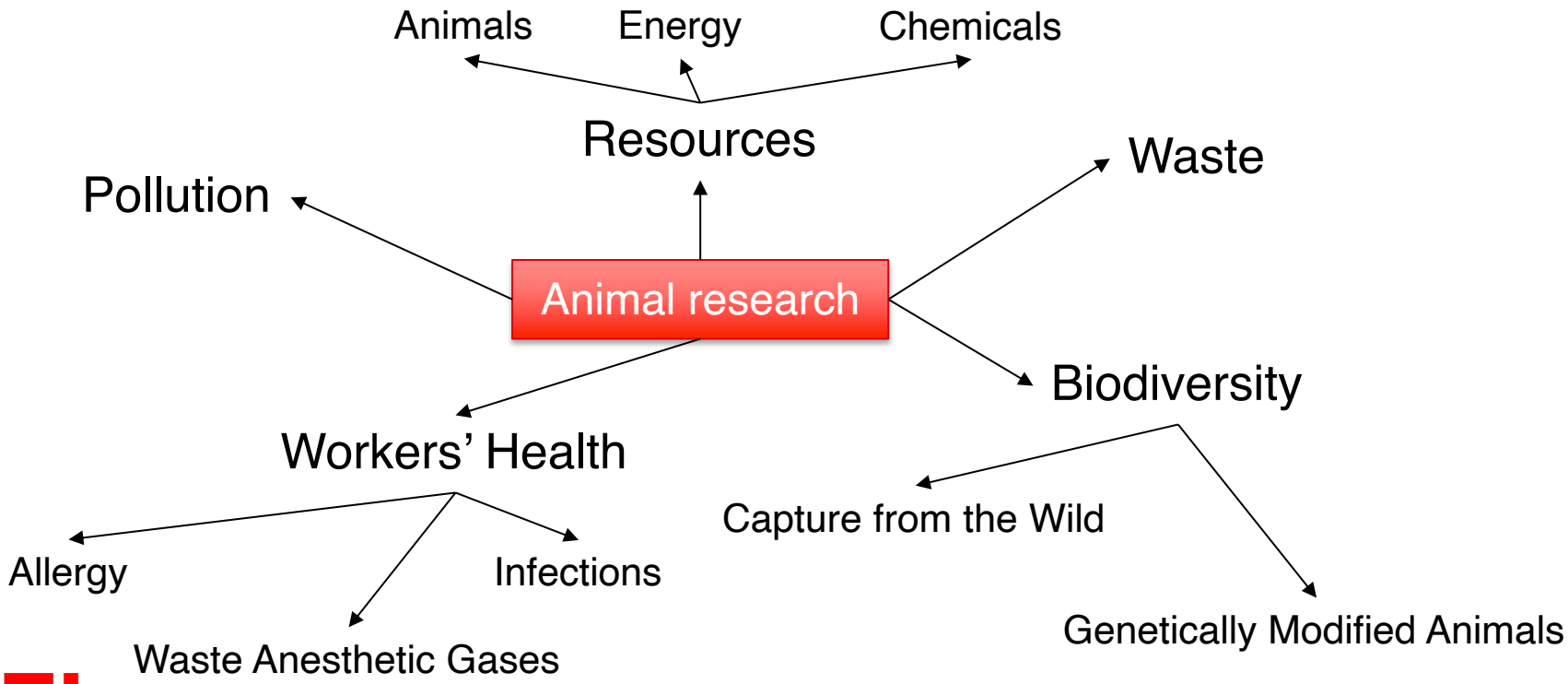
Sustainability is one of our strategic focus areas, and we're committed to incorporating it into our operations – across all our campuses – as we pursue our missions of education, research and innovation.

Part 2 Overview

- Introduction
- **Computational neuroscience**
- Conclusions

EPFL

Wet-lab experiments



Minimise wet-lab experiments

In addition to the previous points, we can consider other reasons to do so:

- Ethical reasons
- Animals as models to study human brains. Are they really good models?
- We cannot measure everything. Use model-based predictions
- We could design drugs and reduce testing phases

Computer models can help to reduce wet-lab experiments and use of animals.

Impact of computer simulations

We can estimate the complexity of a simulation by estimating the number of ODEs to be solved.

We can assume that each compartment has roughly 3 channels, and each one solves 1-2 ODE. So, let's say, we solve roughly 5 ODEs per compartment.

Total num ODEs = (ODEs for channels) + (ODEs for voltage) + (ODEs for synapses)

ODEs for channels = (N neurons) * (avg num compartments per neuron) * (ballpark num ODEs per channel)

ODEs for voltage = (N neurons) * (avg num compartments per neuron)

ODEs for synapses = (N neurons) * (avg num synapses per neuron) * (ODEs per synapse) = (total number of synapses) * (ODEs per synapse)

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Impact of computer simulations

For a network of 800k neurons (older version of the rat CA1 model, Romani et al.):

ODEs for channels = (N neurons) * (avg num compartments per neuron) * (ballpark num ODEs per channel)

ODEs for channels = 800000 * 1000 * 5 = $4 * 10^9$

ODEs for voltage = (N neurons) * (avg num compartments per neuron)

ODEs for voltage = 800000 * 1000 = $8 * 10^8$

ODEs for synapses = (N neurons) * (avg num synapses per neuron) * (ODEs per synapse) = (total number of synapses) * (ODEs per synapse)

ODEs for voltage = $(0.6 * 10^9) * 4 = 2.4 * 10^9$

Total num ODEs = (ODEs for channels) + (ODEs for voltage) + (ODEs for synapses)

Total num ODEs = $4 * 10^9 + 0.8 * 10^9 + 2.4 * 10^9 = 7.2 * 10^9$

Impact of computer simulations

The BBP uses a supercomputer roughly capable of 2 × 10^3 TFLOPS, with 400 TB of memory and 200 TB/s of memory bandwidth. The energy use for 720 processors involved in this simulation is around 400 kW. A simulation of 10 million neurons [i.e., the entire neocortex] *in a cortical circuit requires approximately 1,460 TFLOPS and 270 kW to simulate 1 s of biological time and took more than 8 h of processing time* […]. *If we convert power (W or J/s) to energy (J) units, 270 kW (for 8 h) is 7,776,000,000 J of energy to compute 1 s of mouse cortical activity.*

When extrapolating to the entire mouse brain with 10^8 neurons, a simulation would require 2.7 MW. Extrapolating again to a human brain with 10^3 times as many neurons as a mouse brain, the power requirement would be 2.7 GW.

Stiefel and Coggan, 2023

Impact of computer simulations

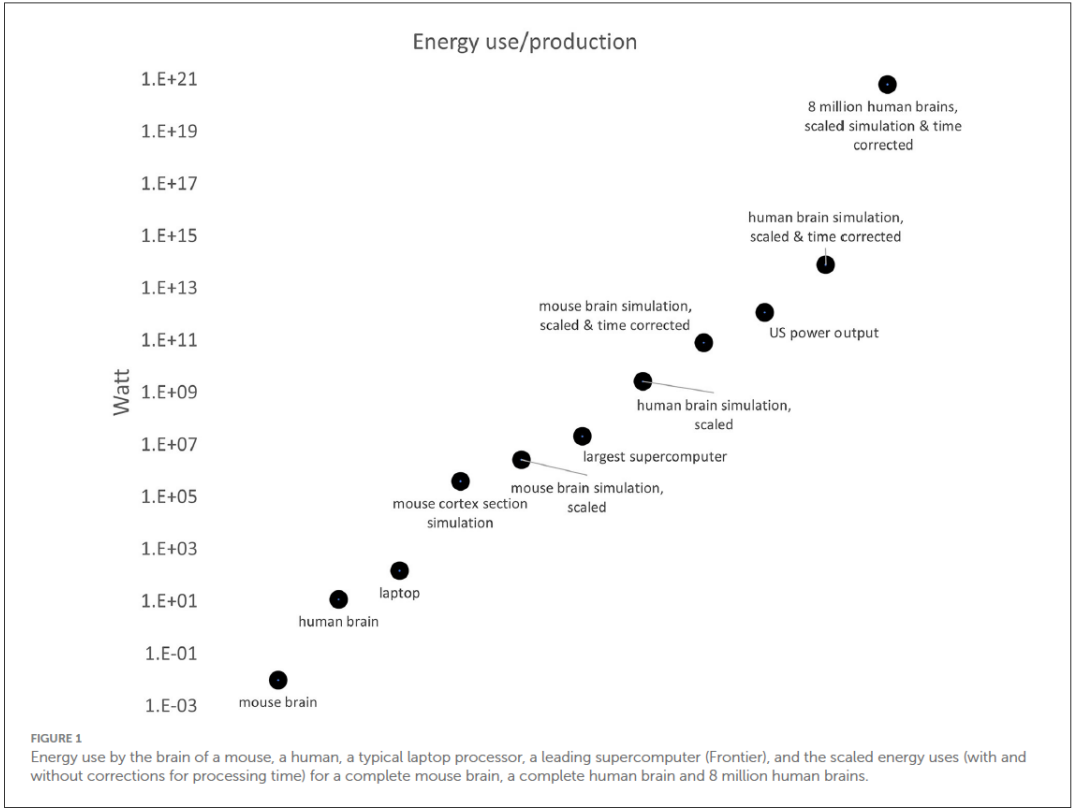
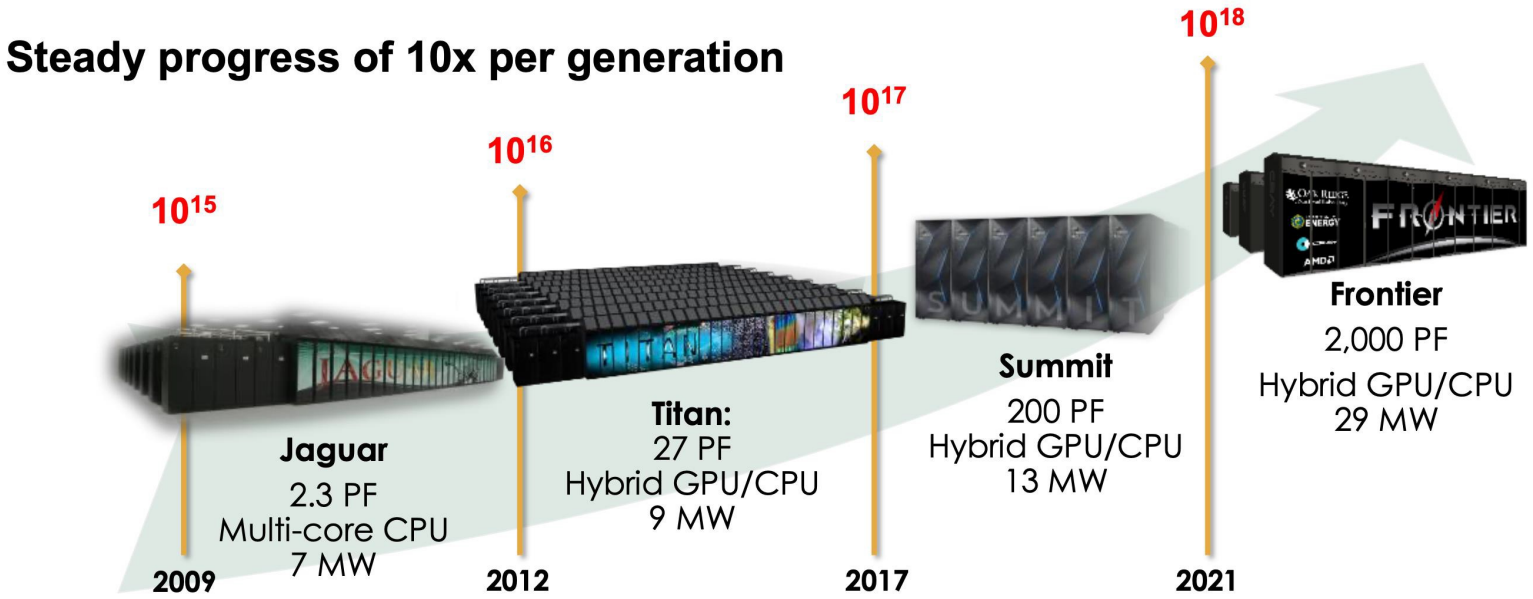


FIGURE 1
Energy use by the brain of a mouse, a human, a typical laptop processor, a leading supercomputer (Frontier), and the scaled energy uses (with and without corrections for processing time) for a complete mouse brain, a complete human brain and 8 million human brains.

Stiefel and Coggan, 2023

Impact of computer simulations

Mission: Providing world-class computational resources and specialized services for the most computationally intensive global challenges	Vision: Deliver transforming discoveries in energy technologies, materials, biology, environment, health, etc.

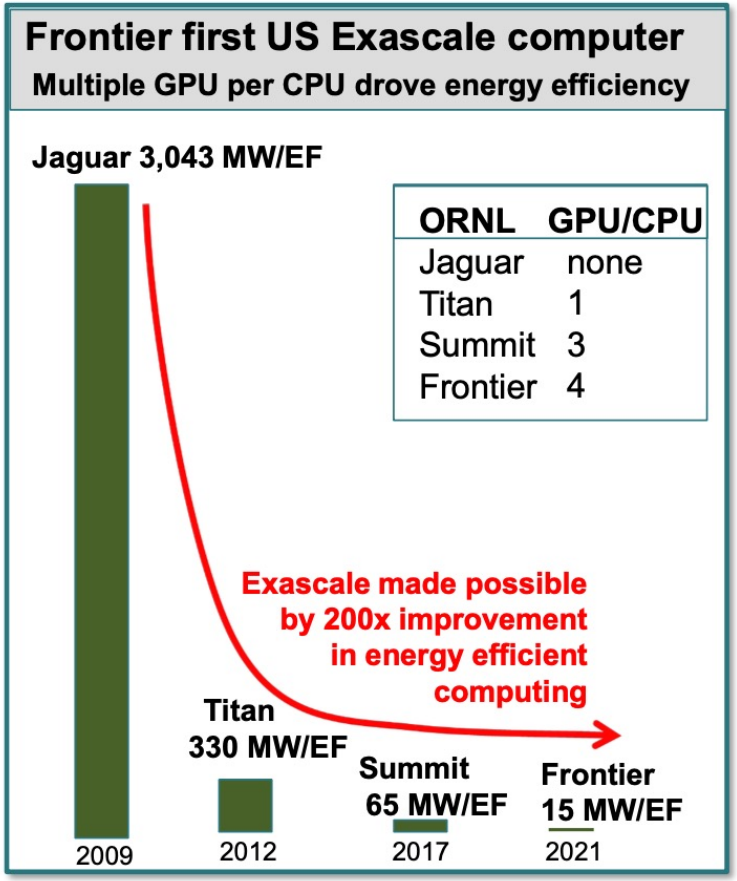


Oak Ridge Leadership Computing Facility (OLCF)

More efficient computers

1 MegaWatt (MW) power could cost ~

1 million dollar per year



Oak Ridge Leadership Computing Facility (OLCF)

More efficient simulators

frontiers in Neuroinformatics

TECHNOLOGY REPORT
published: 19 September 2019
doi: 10.3389/fninf.2019.00063

Check for updates

CoreNEURON : An Optimized Compute Engine for the NEURON Simulator

*Pramod Kumbhar[1], Michael Hines[2], Jeremy Fouriaux[1], Aleksandr Ovcharenko[1], James King[1], Fabien Delalondre[1] and Felix Schürmann[1]**

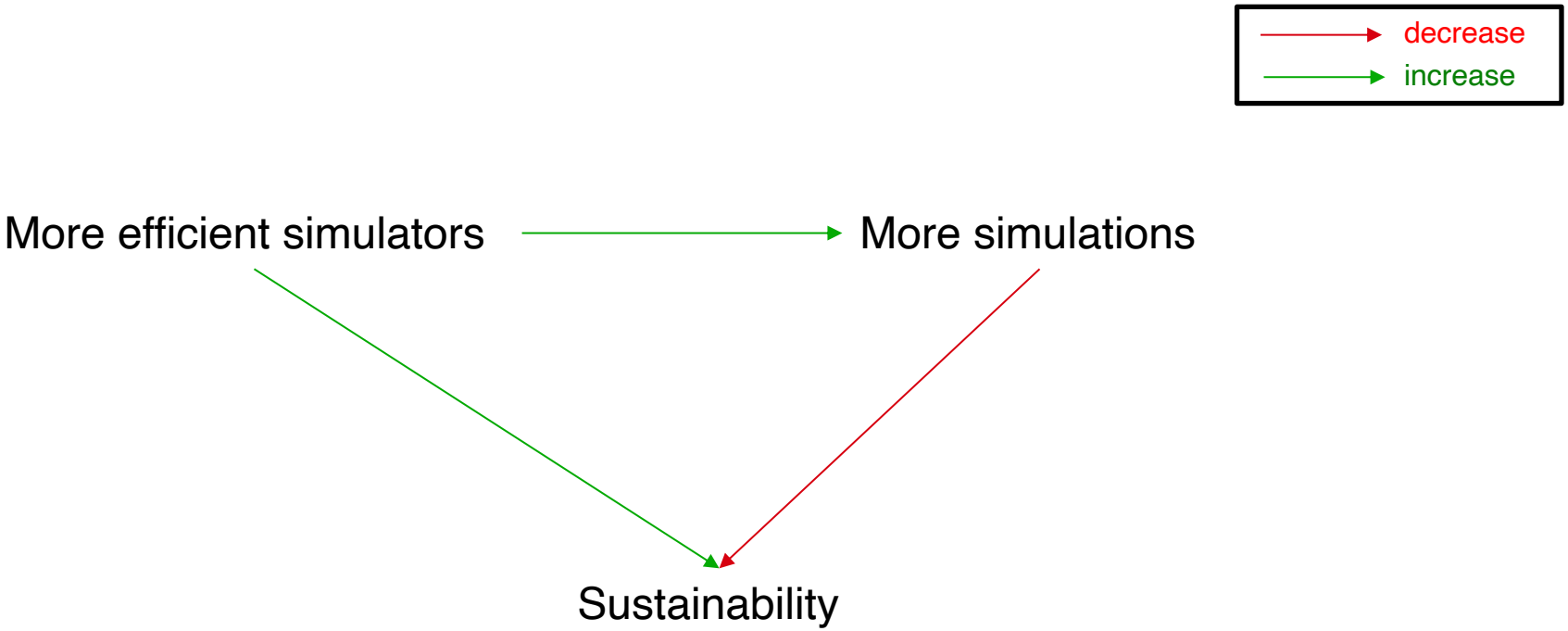
[1] Blue Brain Project, École Polytechnique Fédérale de Lausanne (EPFL), Geneva, Switzerland, [2] Department of Neuroscience, Yale University, New Haven, CT, United States

4–7x less memory usage and 2–7x less execution time

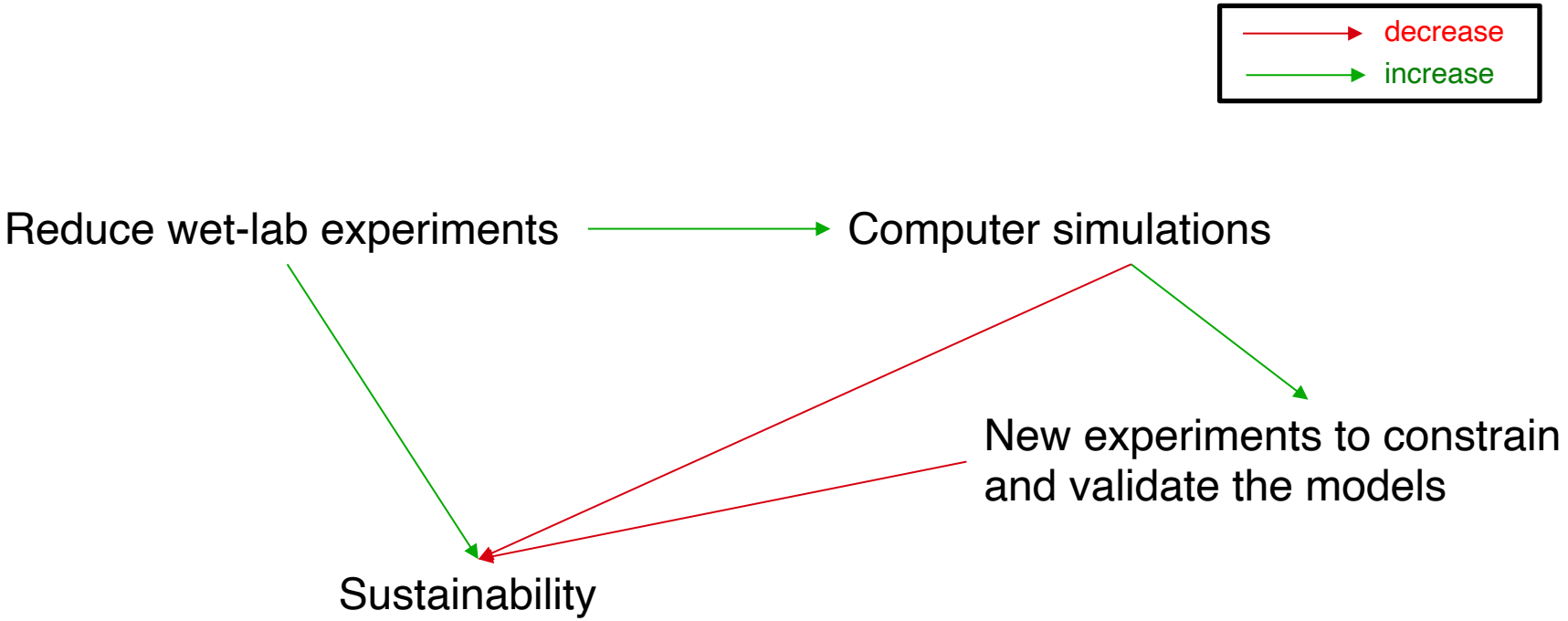
More efficient simulations

- Design a simulation campaign that minimizes the core-hours. Example, the cylinder is a good proxy of the full model. We extensively scan parameters with cylinder, and then run few test simulations with the full-scale model.
- Scan parameters to reduce the number of animals. From models back to experiments.
- Reuse existing results. Reuse the models, experimental data… Identify the gaps and ask the community to do only certain experiments.
- Better model but bigger environmental impact. Adding granularity or not?

Rebound effect



Rebound effect



Part 2 Overview

- Introduction
- Computational neuroscience
- **Conclusions**

Summary 2

- Computer models are complementary to animal experiments, and in some cases a valid alternative
- Also computer models have a significant impact on the environment
- Improving computer and software efficiency reduce this impact, but we have rebound effects
- It is clear that there are complex relationships between science, society, economics, and environment
- First important thing is to be aware of the problem and implications, and try to do our best to be more sustainable.

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What you have learnt

- Example of a more sophisticated simulation experiment
- Sustainability. Definitions. Different types.
- Impact of computer simulations, wet-lab experiments
- Rebound effect