



Intelligent Closed-Loop Neurostimulation with Spatiotemporal Complexity for Neurological Disorders

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ELLIIT Seminar Series

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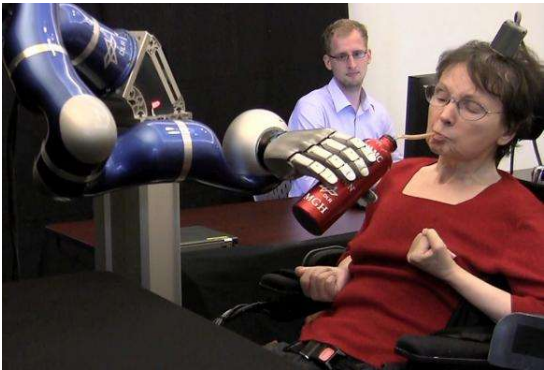




A summary to guide us

1. A bit about neuroengineering and its complexities
2. Our efforts in to overcome challenges dealing with refractory epilepsy (**NPS**)
3. Intelligent closed-loop control of seizures
4. Proposals

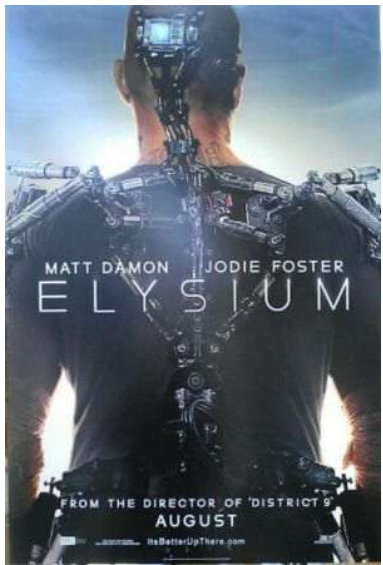




BrainGate 2 - 2012
Brown university
Harvard Med. School



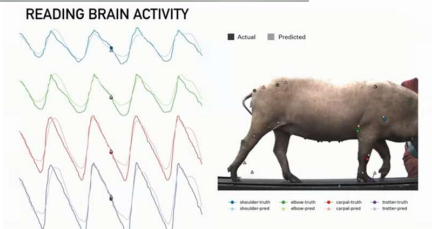
Benabid's lab – Univ Grenoble
2016 - 2019



Ghost in the shell

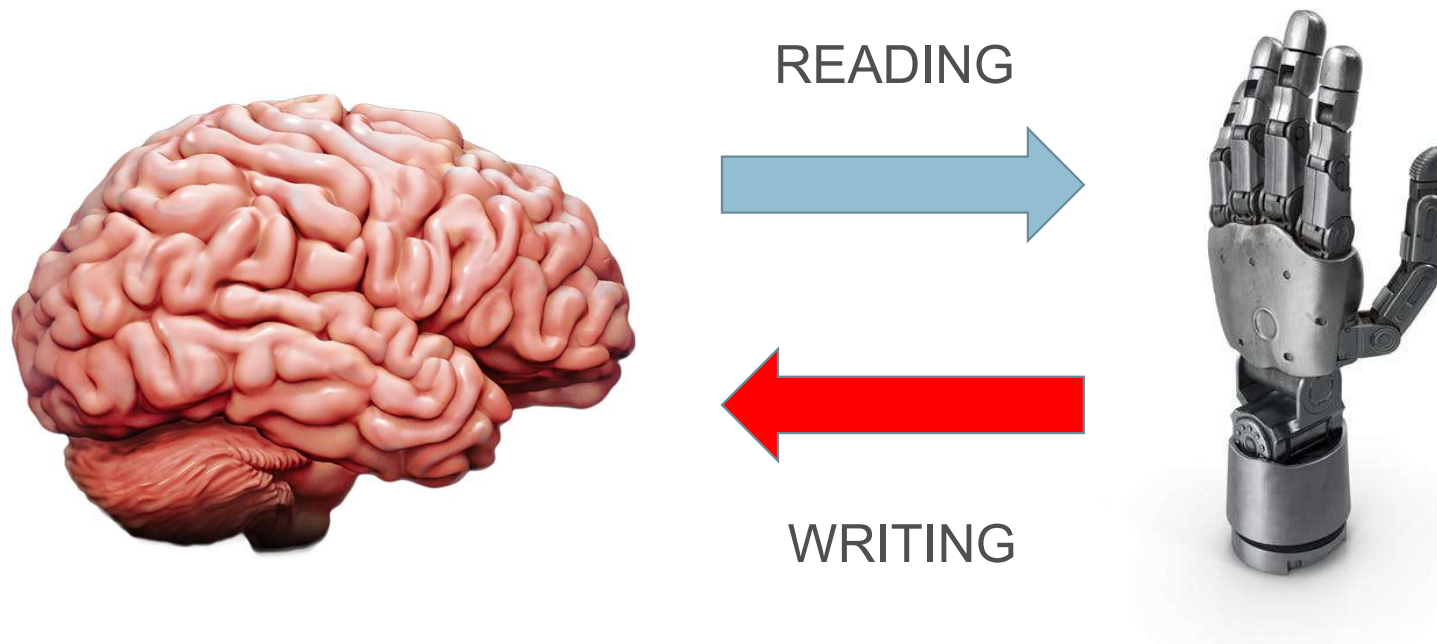


Nicolelis' lab
BR World Cup-14



Elon Musk's Neuralink, 2018

A bi-directional (electronic) link with the brain



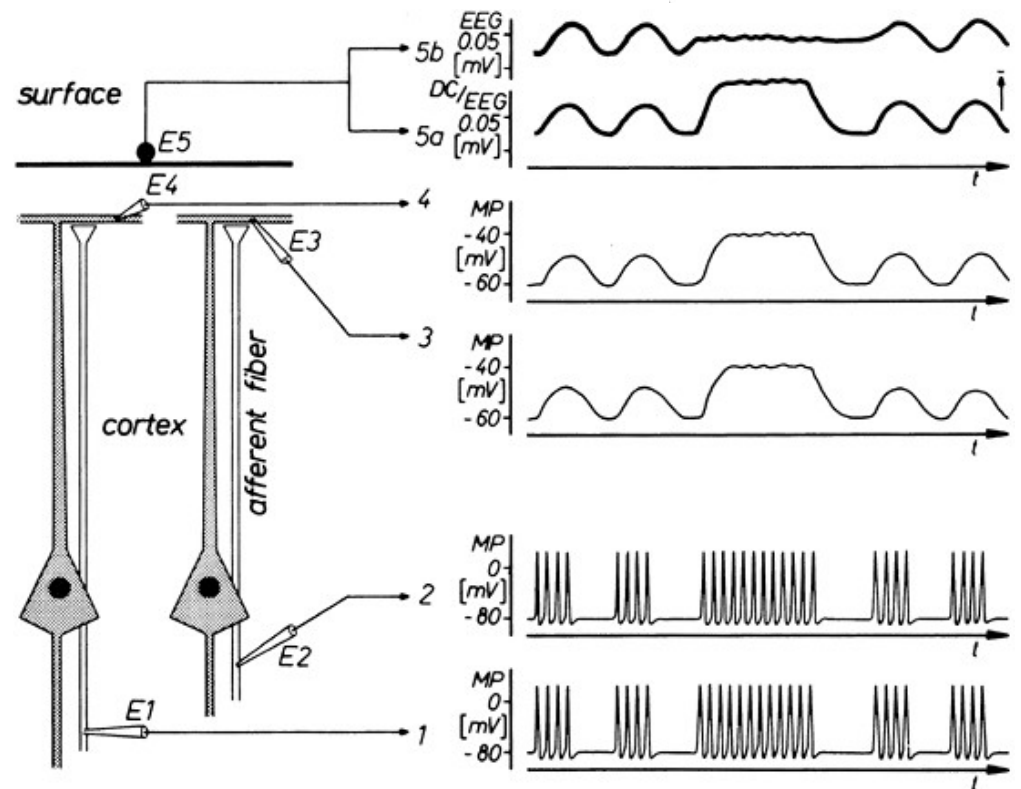
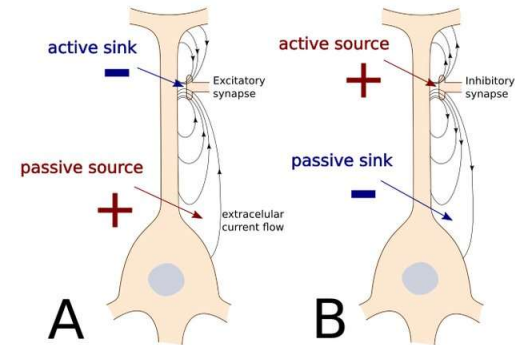
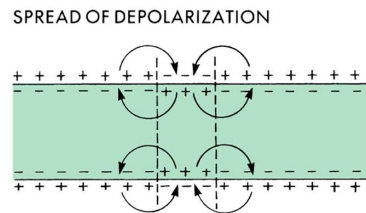
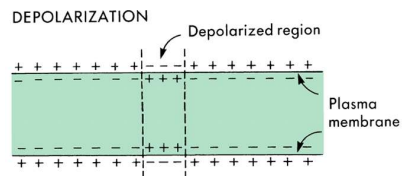
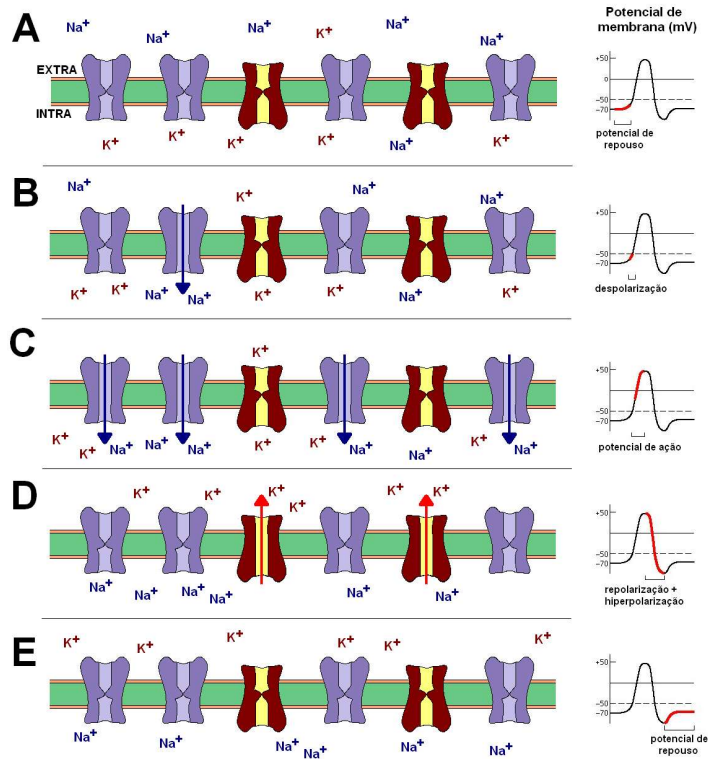
Neuroengineering is the science and practice of such technologies

The neuron and the brain are electrochemical machines

A red, rectangular stamp with a distressed, ink-like texture. The word "DISCLAIMER" is written in bold, uppercase letters inside the stamp, which is tilted slightly upwards to the right.

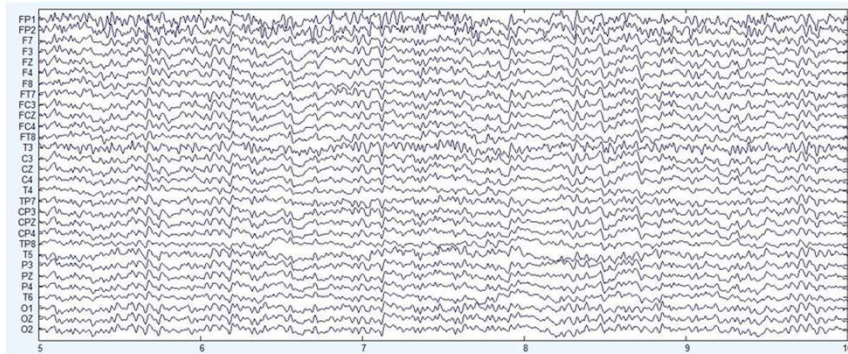
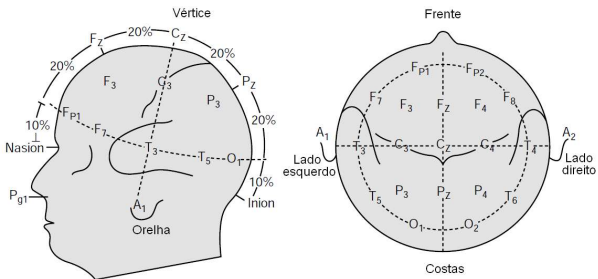
Sometimes, the term “neuron” means the biological thing...

The neuron and the brain are electrochemical machines

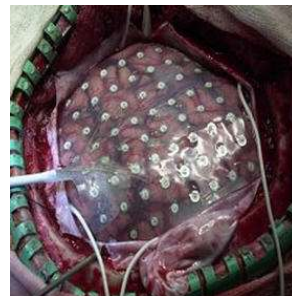


Neural biopotentials: electrophysiology

Electroencephalogram (EEG)

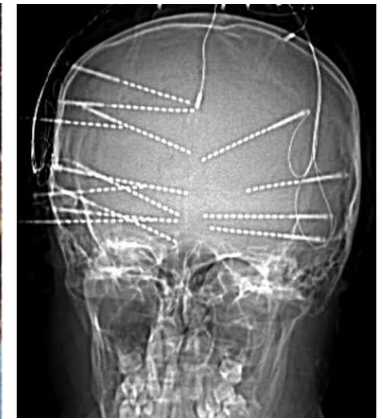


HD-EEG

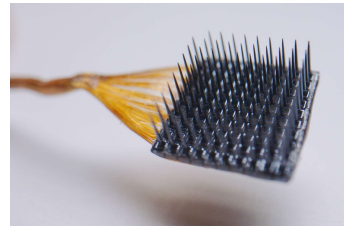


ECoG

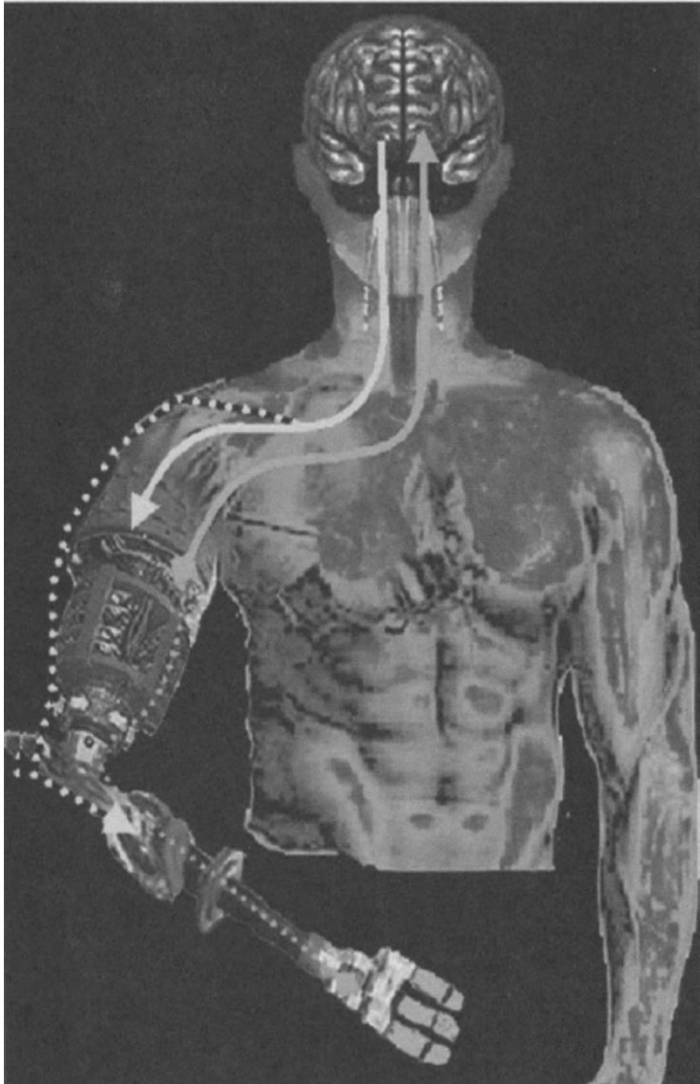
Stereo EEG IC-EEG



Multi-unit activity recordings

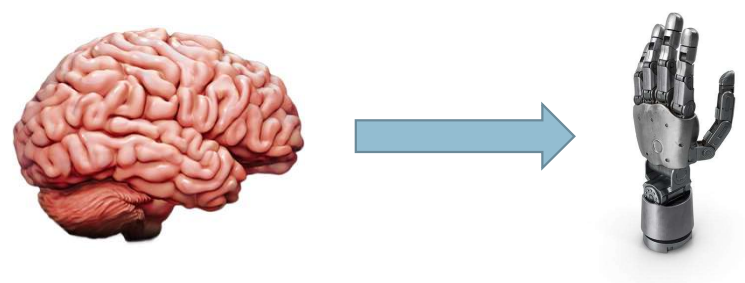


And many other experimental methods

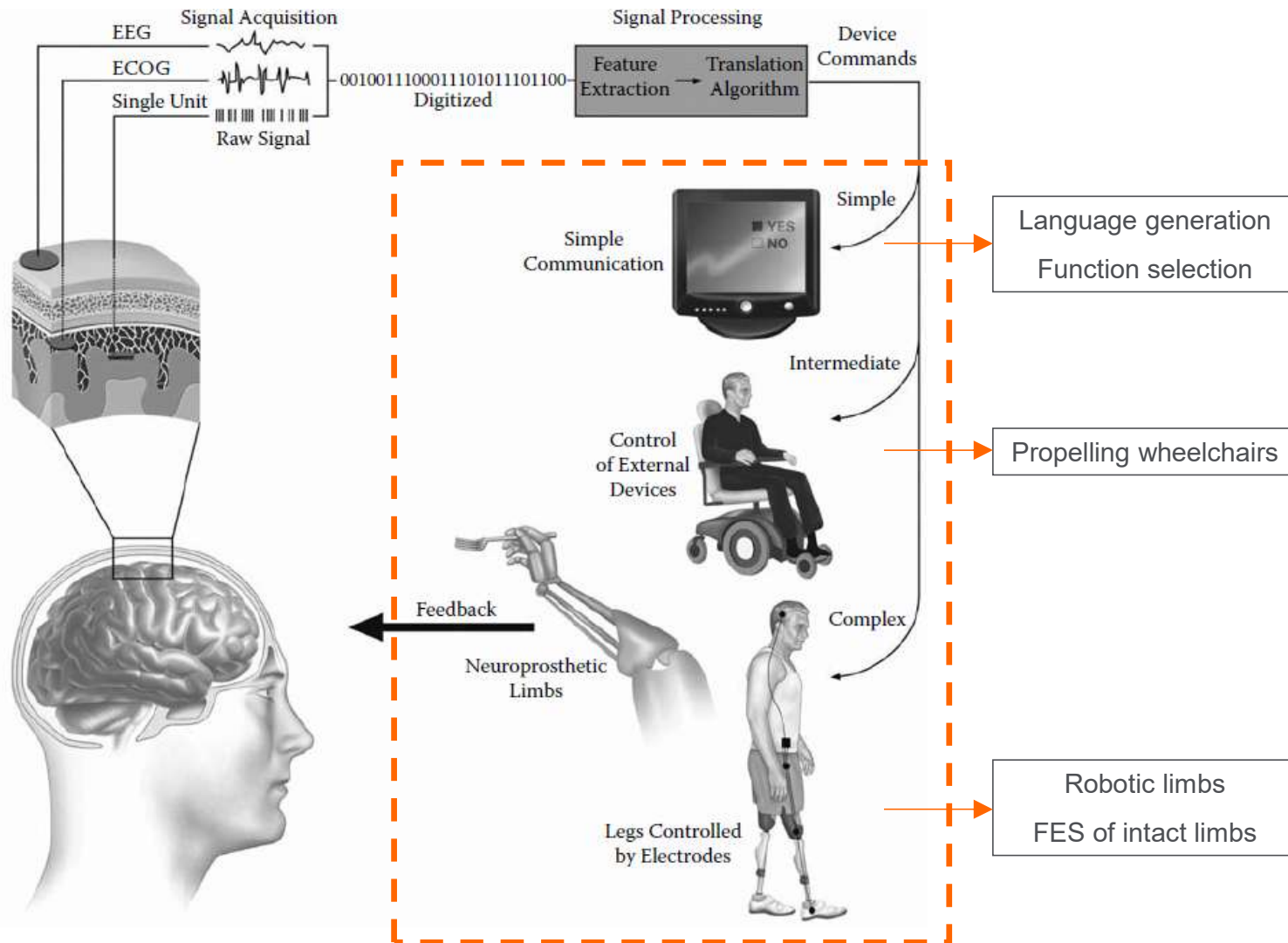


Brain computer interfaces

*Reading from the brain
to restore motor function*

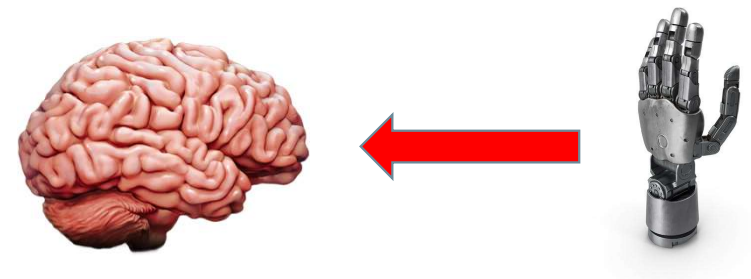


Fonte: Di Lorenzo 2008



Sensory prosthesis

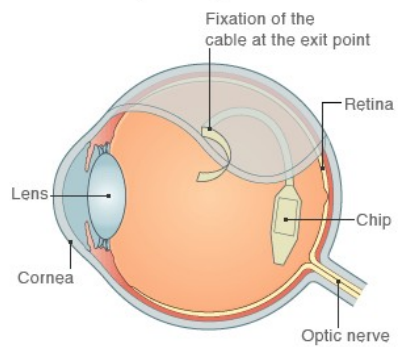
*Writing into the brain inputs
to restore sensory function*



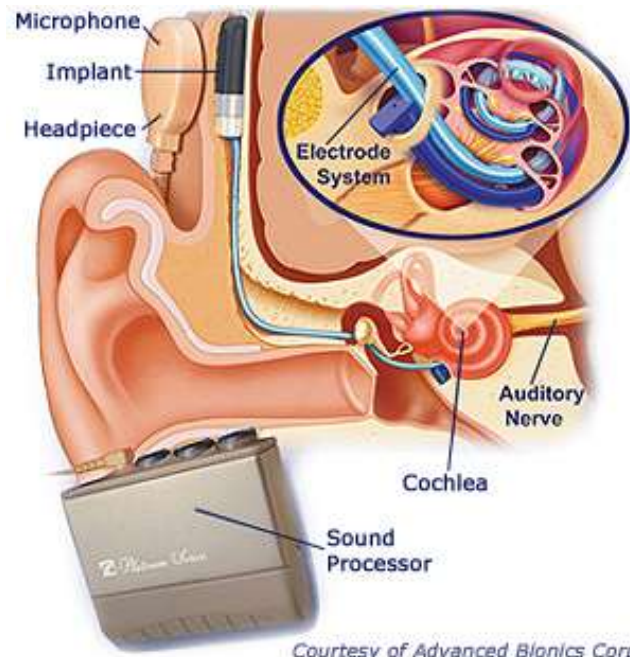
Sensorial prosthesis

- Cochlear implant
- Visual implant

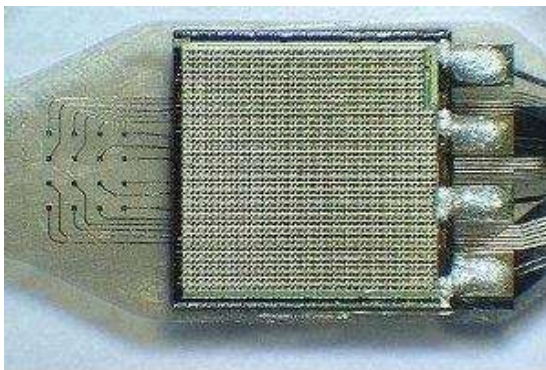
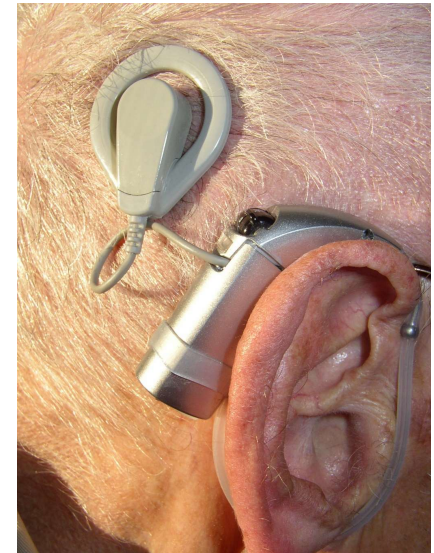
Where the implant is placed



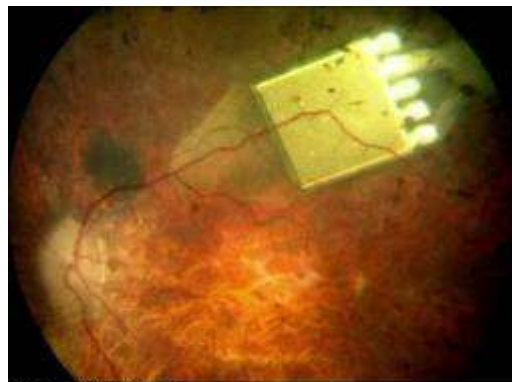
Source: Retina Implant AG



Courtesy of Advanced Bionics Corp.



3dnews.ru→novostey.com

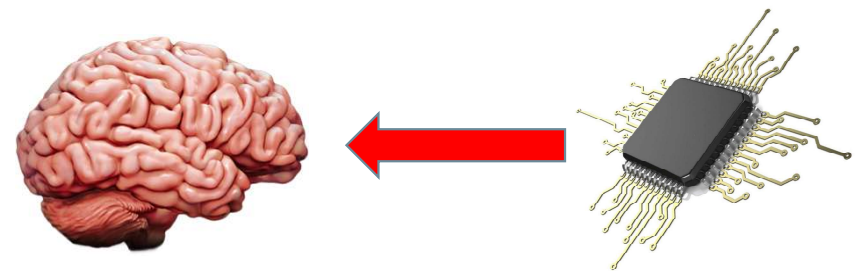


3dnews.ru→novostey.com

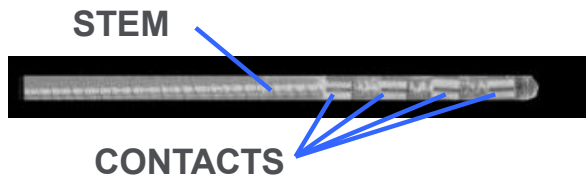


Neuromodulation or Neurostimulation

*Writing into the brain
to treat neurological disorders*



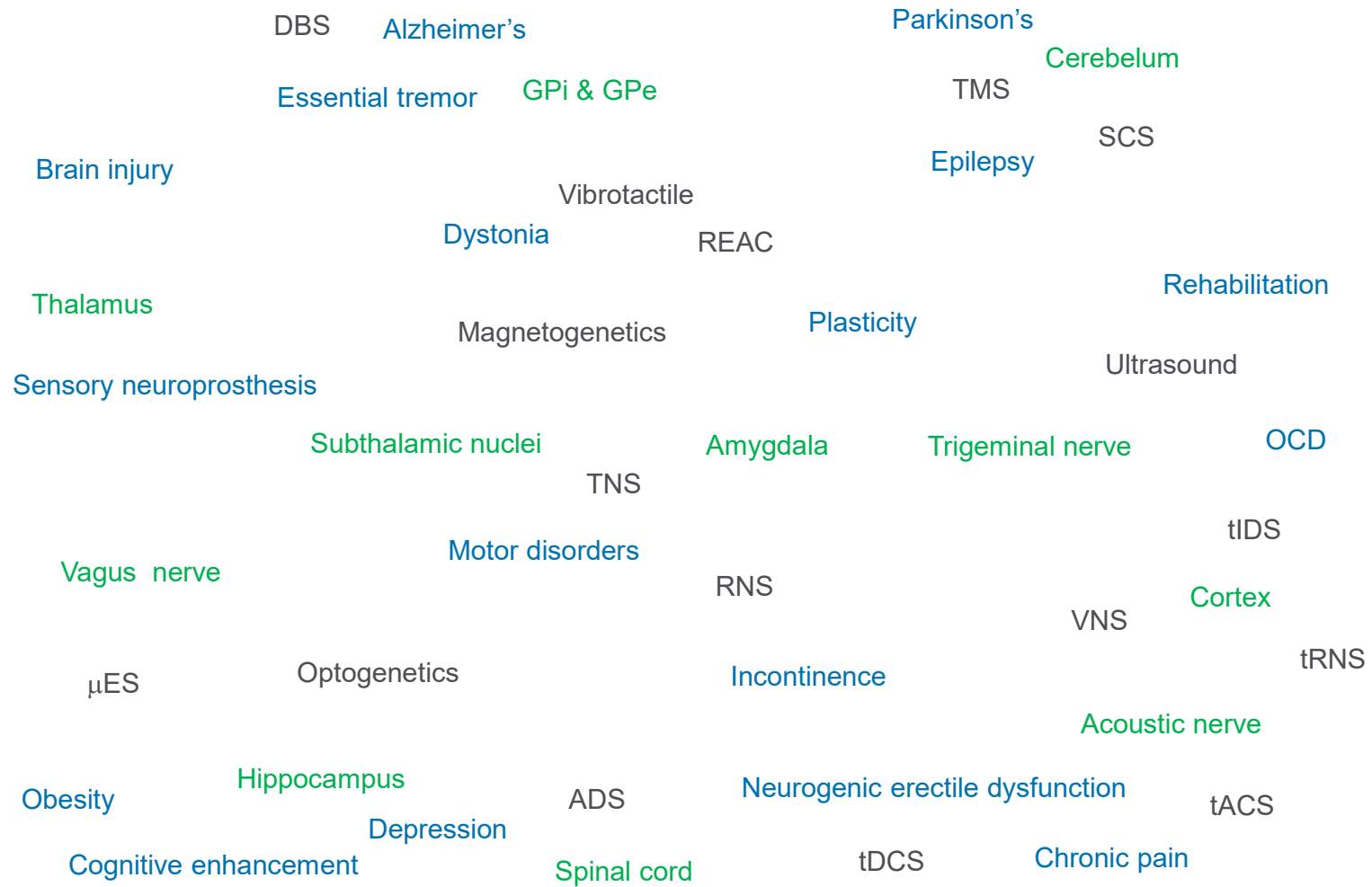
Deep Brain Stimulation - DBS



Stimulation parameters

- Monopolar cathodic pulses
- Charge balanced
- Amplitude: 1 a 5 V
- Width: 60 a 200 μ s
- Frequency: 90 a 180 Hz

NEUROMODULATION ZOO



Why don't we see people...

...connecting to the Matrix?

...directly connecting the mind to information databases?

...walking with robotic exoskeletons controlled by the brain?

...with electronic vision, hearing, etc.?

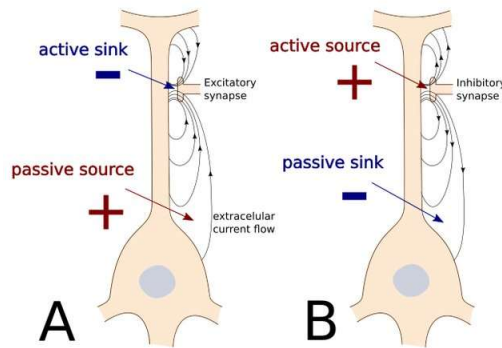
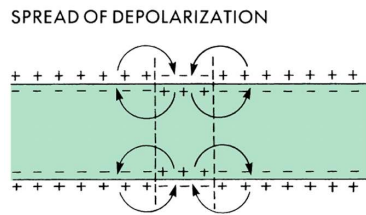
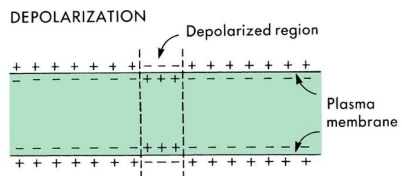
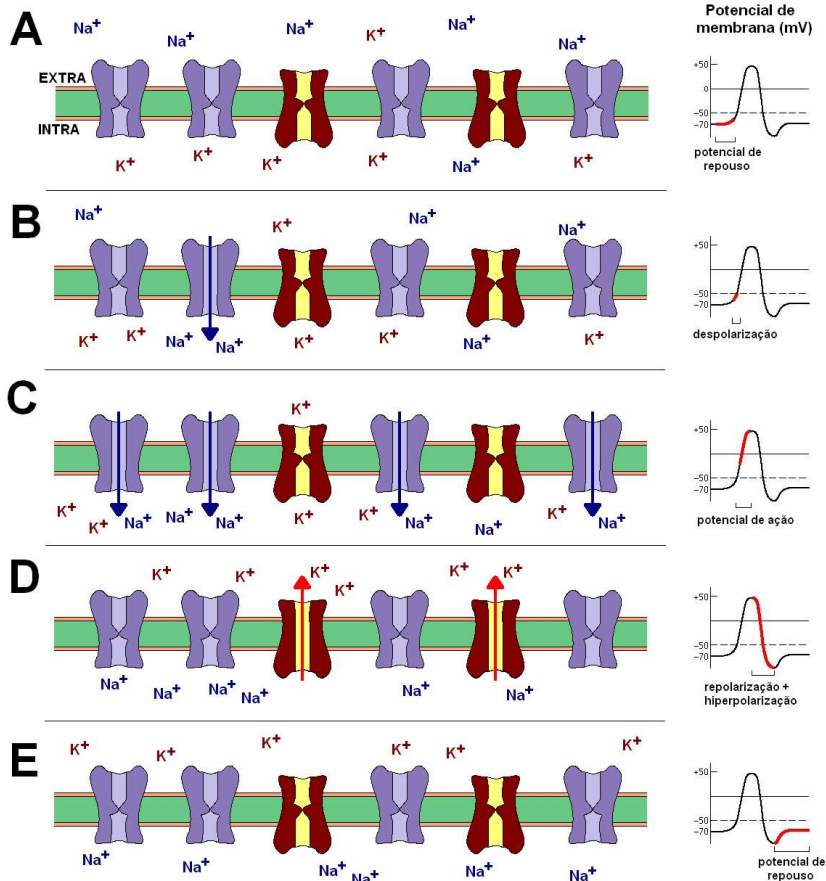
Why do we see...

...so much suffering from neurological disorders?

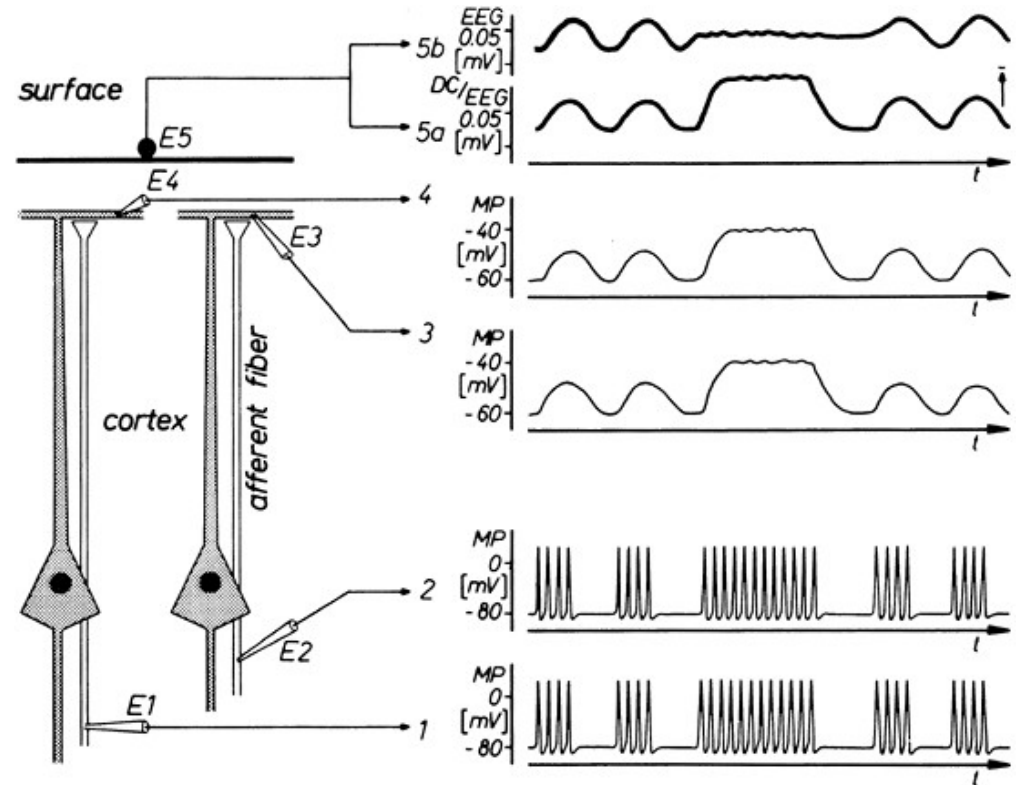
Interactions between the nervous system and electro-electronic devices by means of electromagnetic fields are a tremendously complex issue



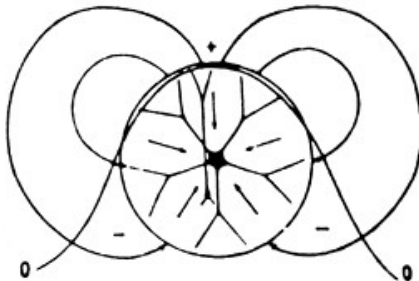
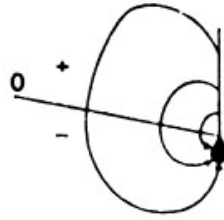
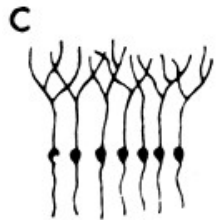
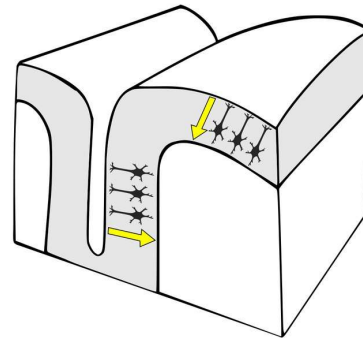
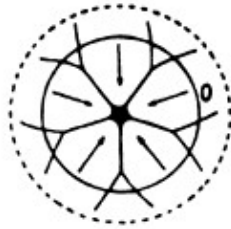
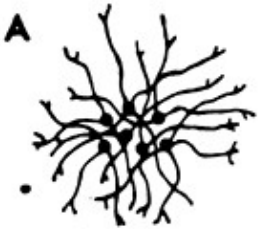
**The complexity of neurophysics
underlying brain signals
and response to external stimuli**



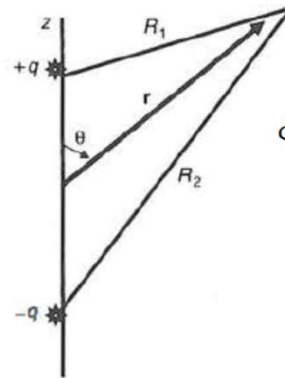
*These are channels and cells...
What about the brain?*



Generation and propagation of electromagnetic fields across the head



Fonte: Novel algorithmic approaches for the forward and inverse M/EEG problems Kostia Maksymenko, 2019 (tese)



$$\Phi(\mathbf{r}) = \frac{1}{4\pi\epsilon_0} \sum_{n=1}^N \frac{q_n}{R_n}$$

$$\Phi(\mathbf{r}) \cong \frac{qd \cos \theta}{4\pi\epsilon_0 r^2}$$

$$\Phi(\mathbf{r}) = \frac{q}{4\pi\epsilon_0} \left(\frac{1}{R_1} - \frac{1}{R_2} \right)$$

Conservation of charge: $\nabla \cdot \mathbf{J} + \frac{\partial \rho}{\partial t} = 0$

Gauss' law: $\nabla \cdot \mathbf{D} = \rho$

Ohm's constitutive law for linear conductors: $\mathbf{J} = \sigma \mathbf{E}$

Constitutive law for linear dielectrics: $\mathbf{D} = \epsilon \mathbf{E}$

Defines scalar potential for low-frequency (quasi-static) fields: $\mathbf{E} = -\nabla \Phi$

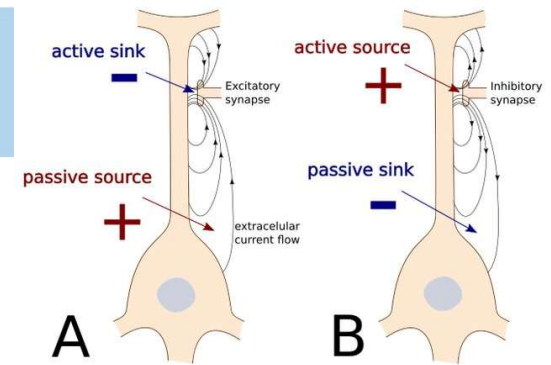
Table 4-1 Typical resistivity of several materials and tissues

Material	Resistivity ($\Omega \text{ cm}$)
Copper	2×10^{-6}
Seawater	20
CSF	64
Blood	150
Spinal cord (longitudinal)	180
Cortex (5 kHz)	230
Cortex (5 Hz)	350
White matter (average)	650
Spinal cord (transverse)	1200
Bone (100 Hz)	8,000–16,000
Pure water	$\times 10^7$
Active membrane	$\times 10^7$
Passive membrane (squid axon)	10^9

ANISOTROPIES!

Fonte: Schomer e Lopes da Silva, 2011
Niedermeyer's Electroencephalography book

An useful analogy



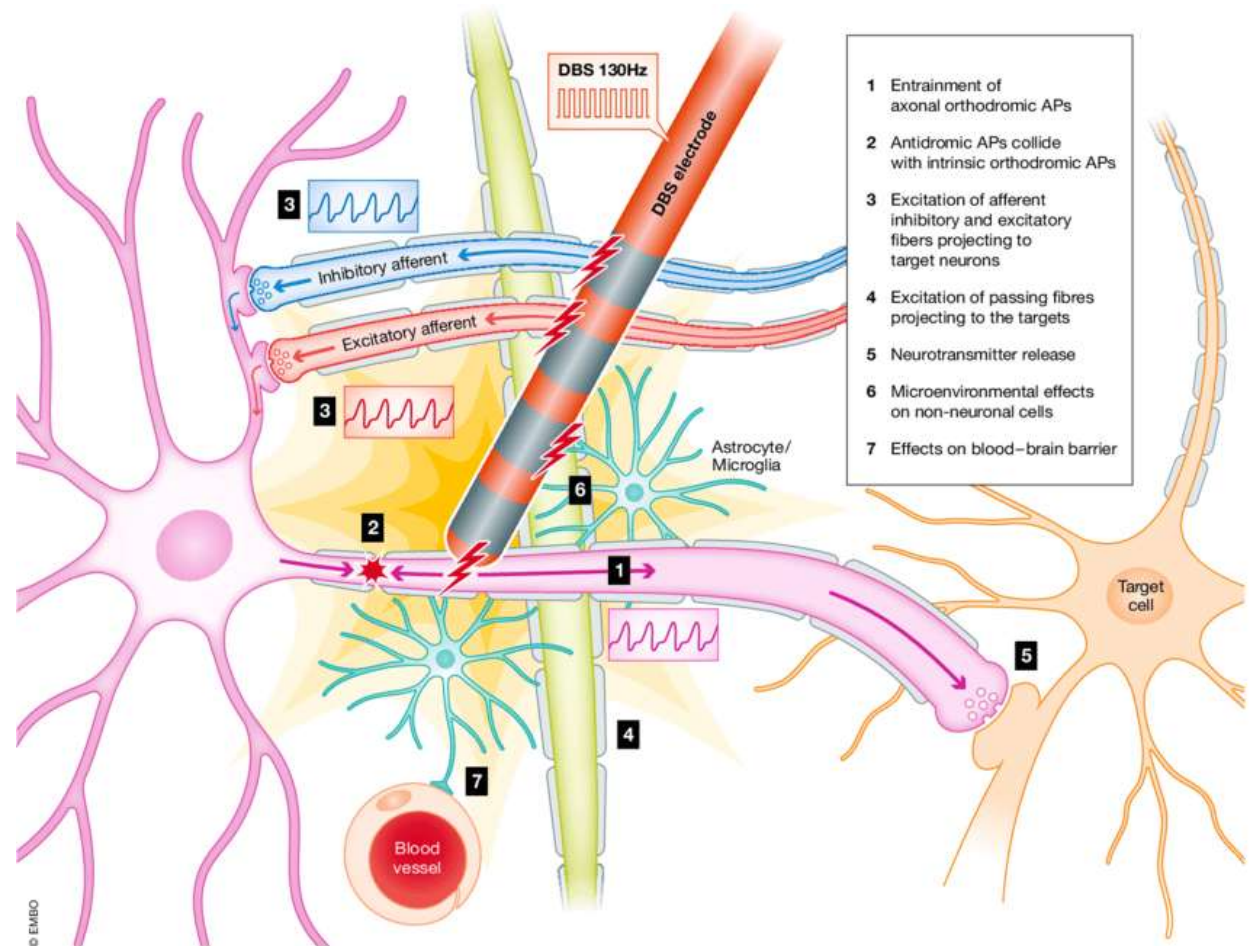
Reality



EEG signals are (very) hard to interpret

Neurophysics of electrical stimulation

- Cellular architecture
- Dendrite
- Soma
- Axon
- Passing fibers
- Blood vases!
- Electrode characteristics



*Jakobs et al., 2019
EMBO Molecular Medicine*

THE BRAIN

"You wish..."



"I'm a neuroengineer"

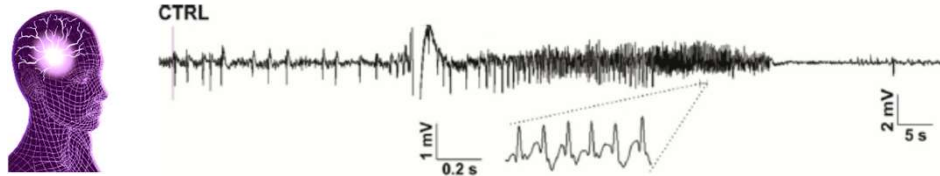
How to tackle such complexity?

1. ENGINEERED neuroengineering: spatiotemporal complexity

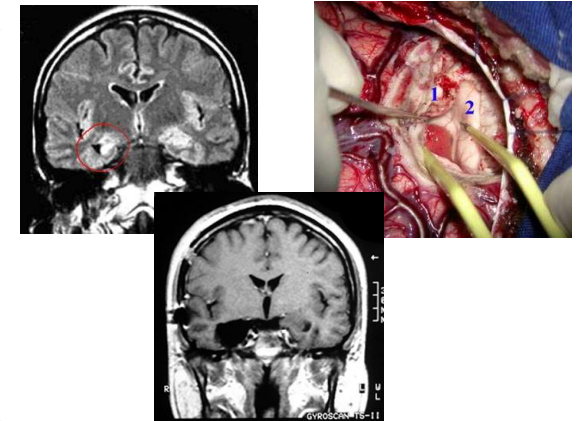
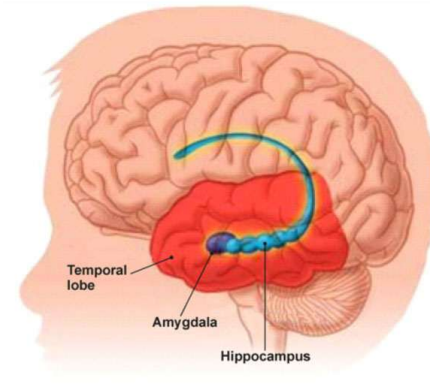
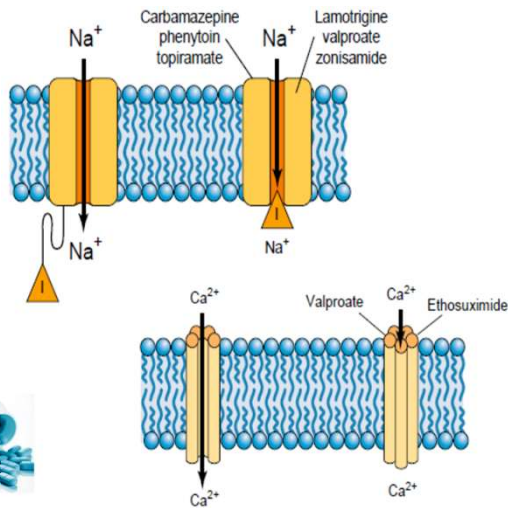
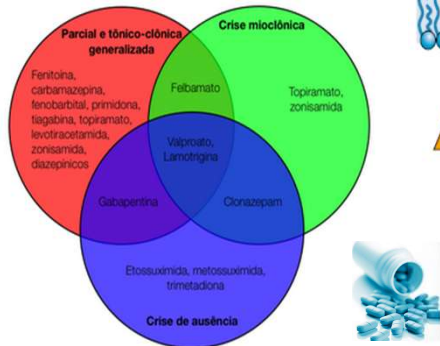
EPILEPSY

- Chronic neurological disorder
- Spontaneous and recurrent episodes of aberrant synchronous activity
- Expression: seizures
- Neurobiological hallmark: hyperexcitability

- Great prevalence worldwide (1 to 2%)
- Seizures:
 - Jeopardize physical activity (ILAE 1997)
 - Professional restrictions (Borges 2000)
 - Daily activities (e.g. driving) (Devereux 2002)
- Stigma / prejudice
- Impairment in the quality of life



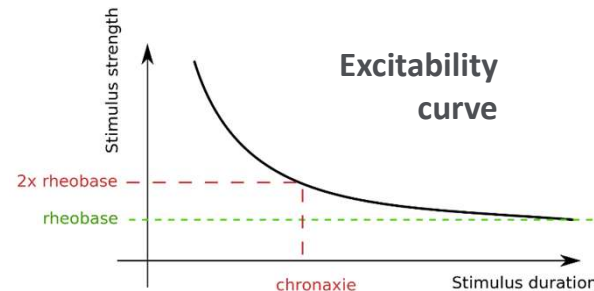
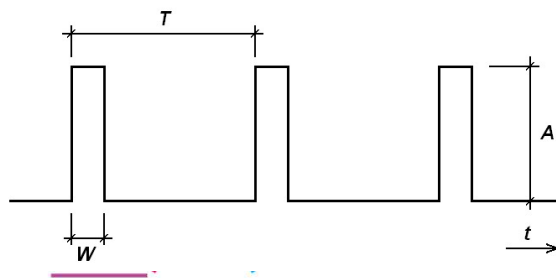
Pharmacological Excitation vs Inhibition



~30% patients do not obtain control of seizures w/ AED
½ is not eligible to surgery

AN ALTERNATIVE: THERAPEUTIC NEUROMODULATION

Brain injury DBS Alzheimer's Parkinson's
 μES Thalamus Essential tremor GPi & GPe Cerebellum TMS
 Sensory neuroprosthesis Epilepsy Vibratatile Dystonia SCS
 tRNS Vagus nerve Magnetogenetics Rehabilitation
 Cognitive enhancement Subthalamic nuclei REAC Ultrasound
 Depression Optogenetics Motor disorders Amygdala tIDS Plasticity
 Hippocampus Incontinence RNS Trigeminal nerve OCD
 Neurogenic erectile dysfunction VNS
 Spinal cord ADS Acoustic nerve Cortex tACS
 tDCS Chronic pain



Parameters of pulsatile stimulation

Amplitude

Duration

Polarity

Number of phases

Frequency

Target substrate

Multi-site regimen

NEURONAL RESPONSE

Neurophysics

$$I_{th} = I_{rh} \left(1 + \frac{T_{ch}}{W}\right) \quad I_{th} = I_r + Kr^2$$



ACTIVATION AND INHIBITION OF CIRCUITS AND RHYTHMS

Neurobiology

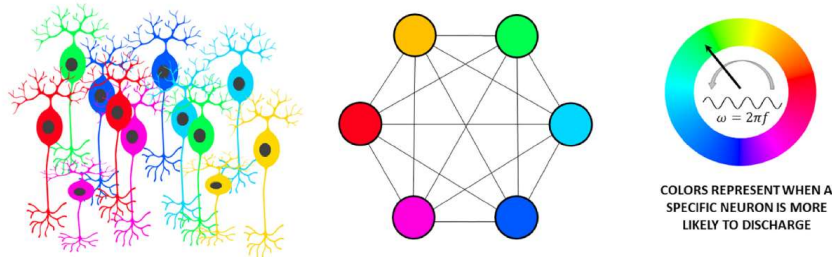


THERAPEUTIC EFFICACY AND SAFETY

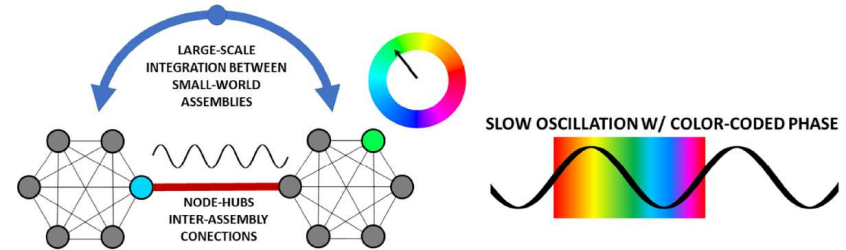
Neurology

Time to search for more mechanistic insight: computing of information in time

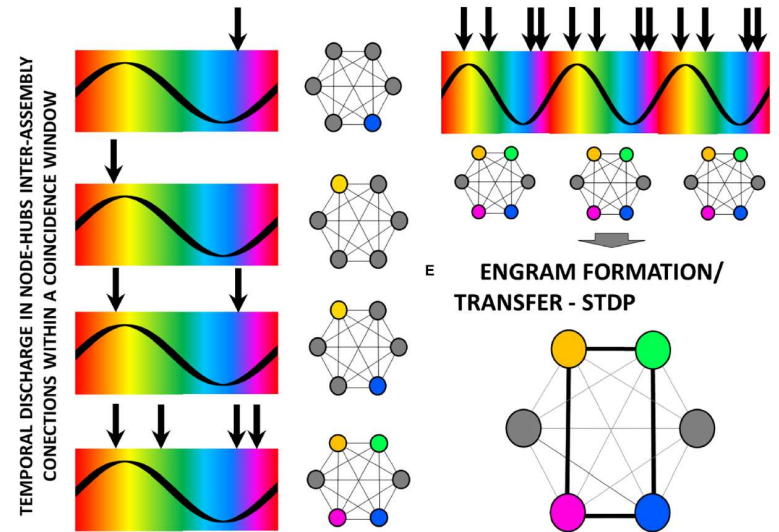
A NEURAL ASSEMBLIES AS SMALL-WORLD NETWORKS



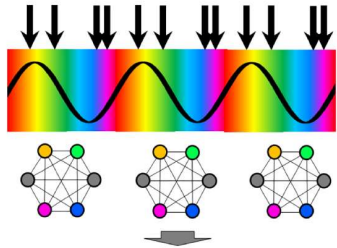
B NEURAL ASSEMBLIES BINDED BY SLOW OSCILLATION



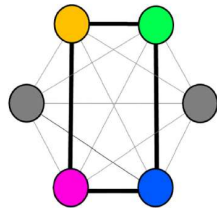
C COINCIDENCE DETECTION



D SAME PATTERN – SAME CIRCUIT

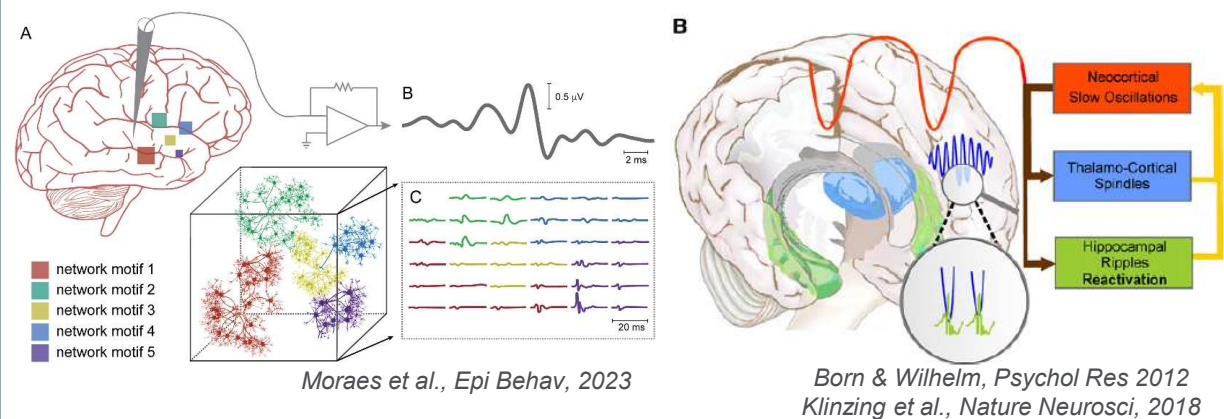


E ENGRAM FORMATION/ TRANSFER - STDP



Cota et al., Front Neuroinfo, 2023

FROM CONNECTIVITY TO RHYTHMICITY



NEURAL SYNCHRONIZATION

A temporal coincidence framework in neurosciences

Neurological disorders and treatment could benefit from the same perspective...

DISTURBANCES IN
CONNECTIVITY / NETWORK



ABERRANT
SYNCHRONISM



NEURAL
DYSFUNCTION

Uhlhaas & Singer, Neuron, 2006



EPILEPSY

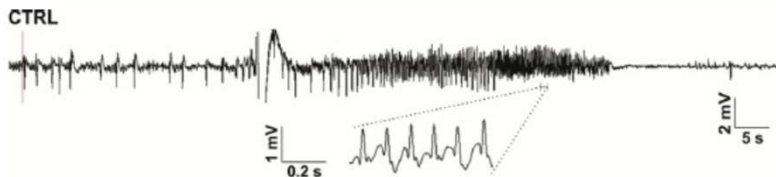
Hallmark: hyperexcitability

HYPERSYNCHRONISM

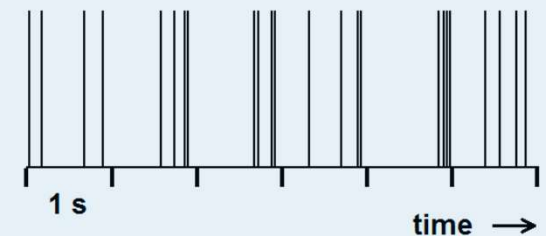
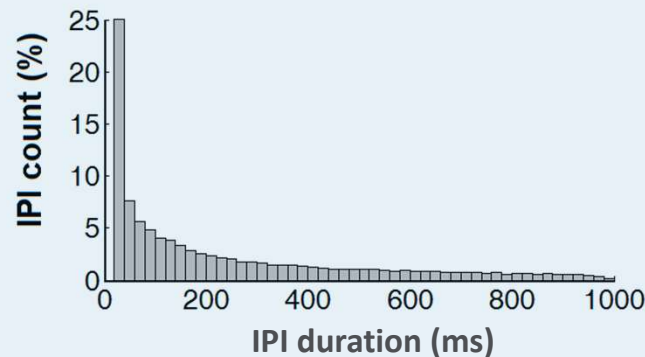
EPILEPTIC PHENOMENA:

Ictogenesis

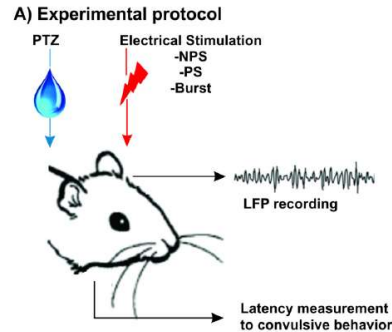
Epileptogenesis



Temporally complex stimulation
Non-periodic stimulation (NPS)
Low energy temporally randomized pulsatile stimulus

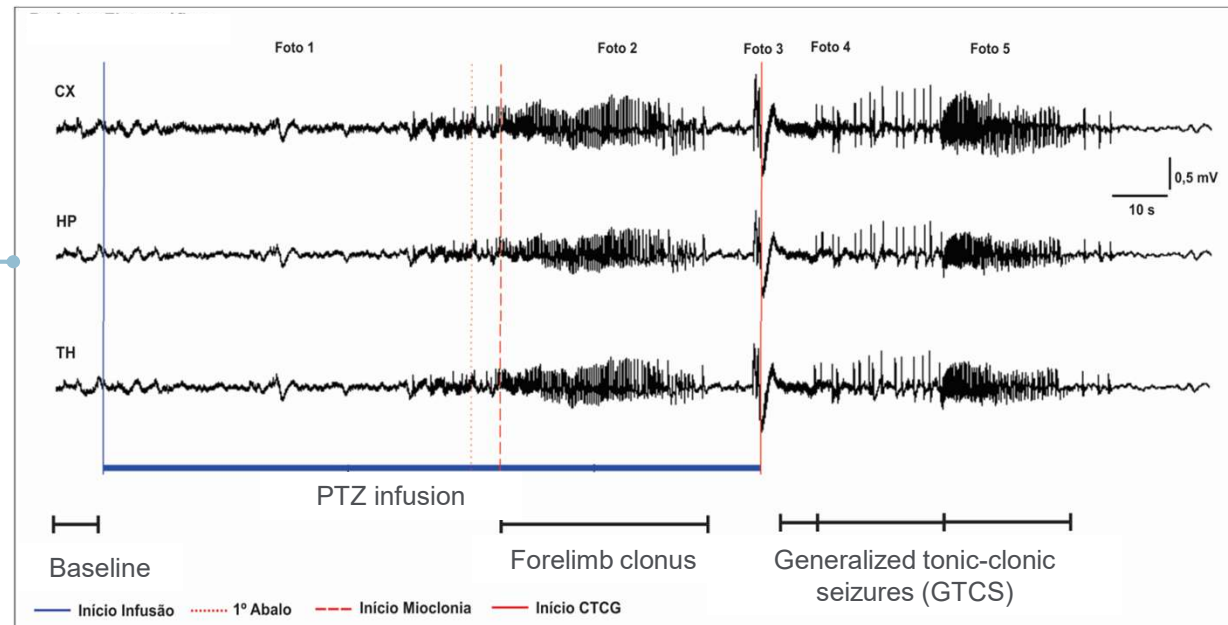


Protocols and methods



- **Animal models of epileptic phenomena**
 - Acute ictogenesis: Pentylentetrazole (PTZ)
 - Chronic ictogenesis: Pilocarpine (PILO)
 - Epileptogenesis: PILO and amygdalar kindling
- **Behavioral assesement**
 - Occurrence and latency to convulsive behavior
 - Motor test (open field)
 - Anxiety levels (open field + elevated plus-maze)
 - Social interaction
 - Mnemonic function (object recognition)
- **Electrophysiology**
 - Electrical stimulation
 - Basolateral amygdala
 - Recordings of Local Field Potential (LFP) and Multi-unit activity (MUA)
- Non invasive imaging
- Computational neuroscience

Controlled infusion of PTZ (10 mg/ml/min) – Video-EEG (LFP)



Cota et al., Epi Behav, 2023

After a long series of experiments...

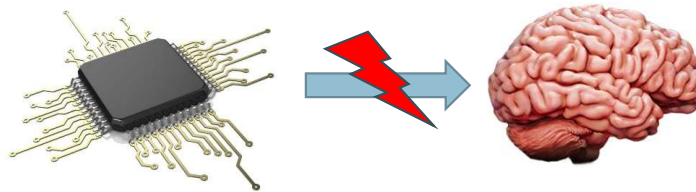
- NPS is anticonvulsant
 - Even with dysfunctional hyperexcitable tissue
- Most efficacious when bilateral and asynchronous
- Mechanisms point to a rectification of synchronism coordination
 - Local versus global
- NPS has no significant impact on:
 - Neural functions
 - Global forebrain neurodynamics (sleep)
- Results are better explained under the temporal coincidence framework

How to tackle such complexity?

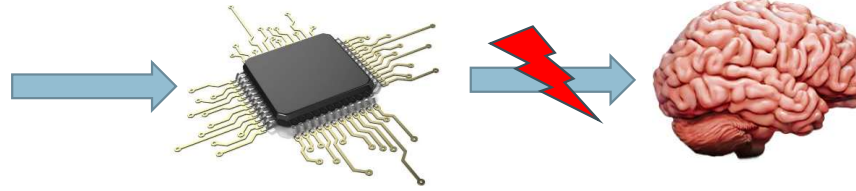
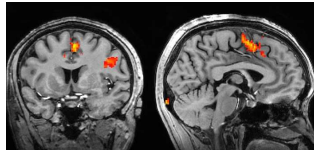
1. ENGINEERED neuroengineering: spatiotemporal complexity
2. Personalized, precision neuroengineering: closing the loop

Different modes of neurostimulation

OPEN LOOP

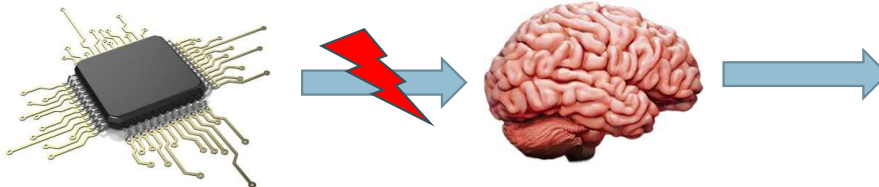


Fixed set of parameters
Empirically derived



Adjustable set of parameters
Asynchronously informed
Personalized neurostimulation

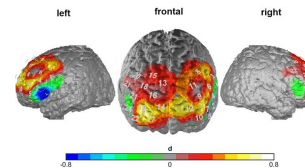
CLOSED LOOP



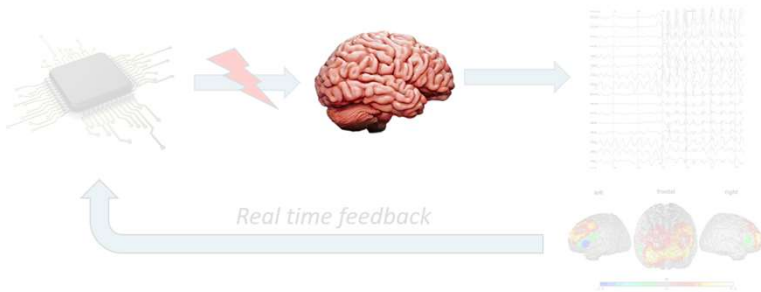
Real time assessment of brain
Tracks neurodynamics
Synchronously informed

Improved:
efficiency, efficacy, safety
autonomy

Real time feedback



A platform in computational models: Izhikevich model of neurons



$$\begin{cases} v' = 0.04v^2 + 5v + 140 - u + I \\ u' = a(bv - u) \end{cases}$$

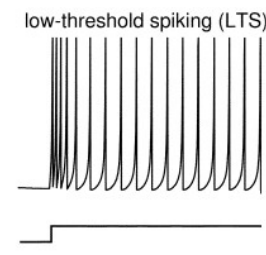
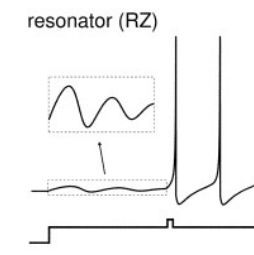
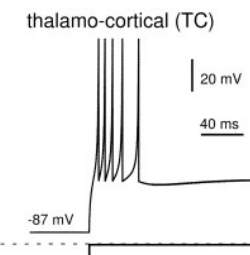
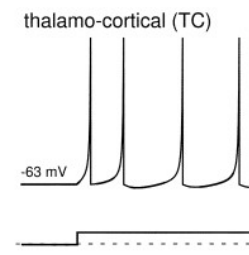
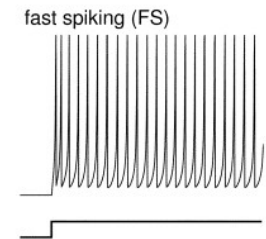
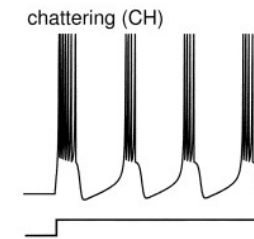
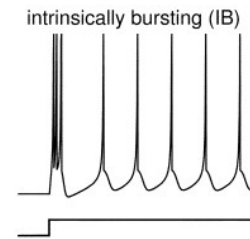
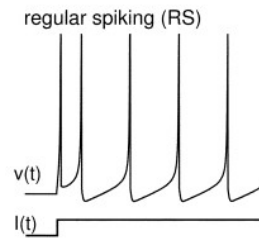
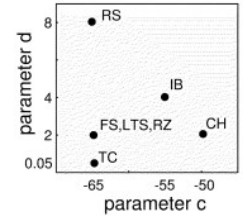
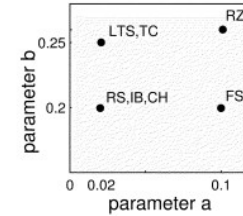
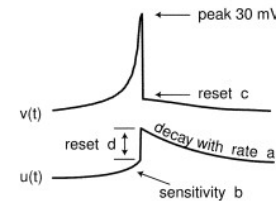
$$\text{if } v \geq 30 \text{ mV, then } \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases}$$

Quadratic integrate and fire model
Low computational cost
Reproduces neuronal firing patterns



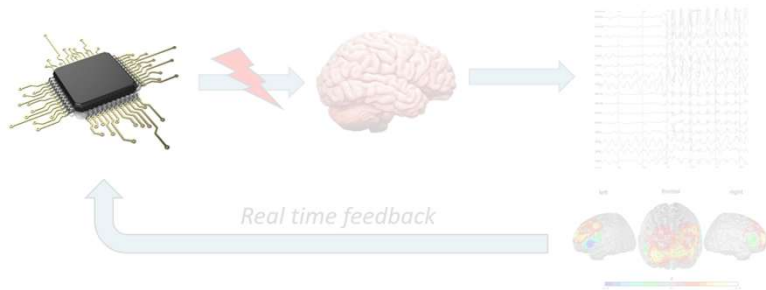
$$\begin{aligned} v' &= 0.04v^2 + 5v + 140 - u + I \\ u' &= a(bv - u) \end{aligned}$$

if $v = 30 \text{ mV}$,
then $v \leftarrow c$, $u \leftarrow u + d$



Izhikevich, IEEE Tran Neu Networks, 2003

A strategy for closing the loop: intelligent control



In Silico Application of the Epsilon-Greedy Algorithm for Frequency Optimization of Electrical Neurostimulation for Hypersynchronous Disorders



Gabriel da Silva Lima^{1,3} , Vinícius Rosa Cota²⁽⁾ ,
and Wallace Moreira Bessa³

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IEEE TRANSACTIONS ON NEURAL SYSTEMS AND REHABILITATION ENGINEERING, VOL. 33, 2025



Intelligent Control to Suppress Epileptic Seizures in the Amygdala: In Silico Investigation Using a Network of Izhikevich Neurons

Gabriel da Silva Lima¹ , Member, IEEE, Vinícius Rosa Cota² ,
and Wallace Moreira Bessa³ , Senior Member, IEEE

Embedded Implementation of an Intelligent Closed-Loop Controller for Pulsatile Seizure Suppression

Leila Alhabib, *MSc in Robotics and Embedded AI, Maynooth University*, leila.alhabib.2026@mumail.ie, and
Dr. Vinícius Cota, *Supervisor*

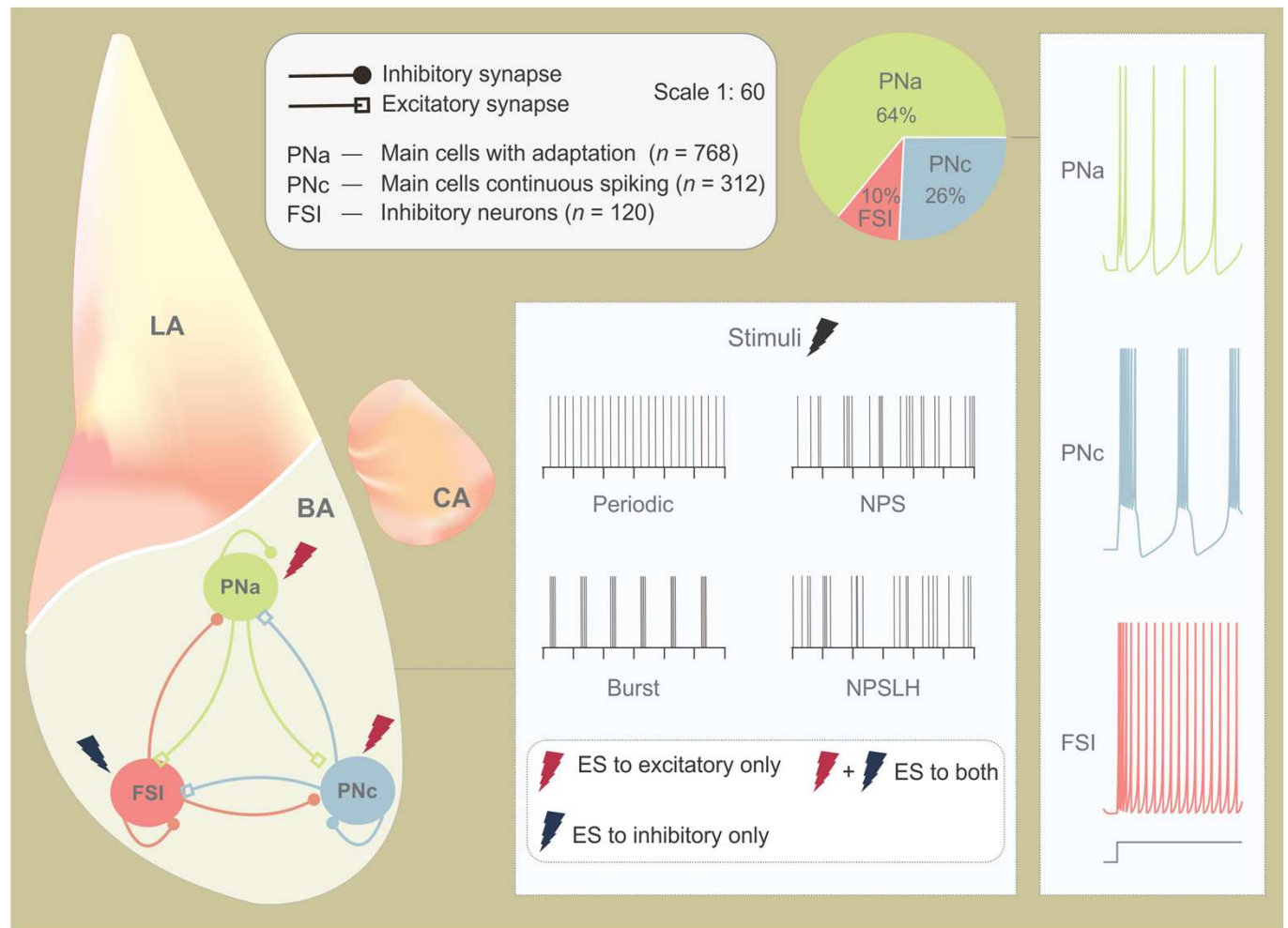
In preparation, 2026



A network of Izhikevich neurons to model the amygdala

1200 neurons
All to all connectivity
 Uniformly distributed
 synaptic weights

**Anatomically and functionally
 informed connectivity (BLA)**



Ictogenesis, LFP characterization, and stimulation

Ictogenesis

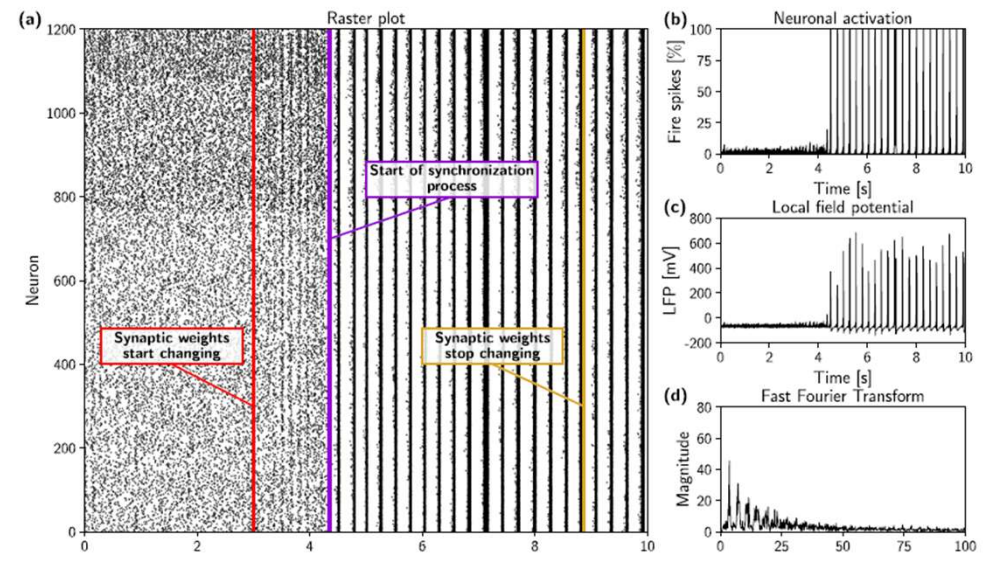
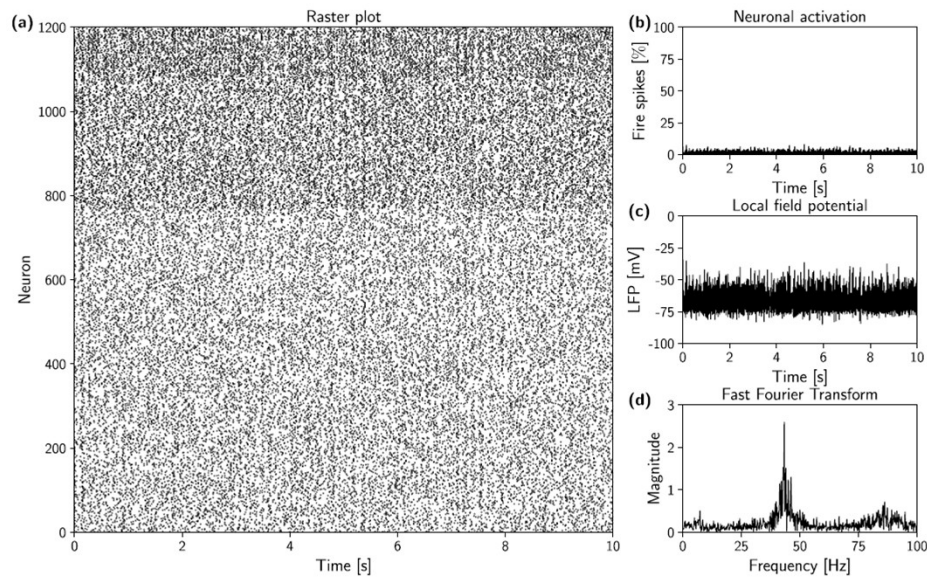
Development of a seizure
Modification of synaptic weights
Increase of excitatory neurons
Decrease of inhibitory neurons

LFP characterization

Simple sum of voltages
Weighted by v_k
Calculation of FFT (300 ms)
to characterize excitability

Application of stimulation “anatomically weighted”

$$J_k = \nu_k \bar{J} \max\{0, \text{sgn}[\cos(2\pi t f) - \cos(\pi d f)]\}$$



A Lyapunov-based non-linear controller (adaptive ANN)

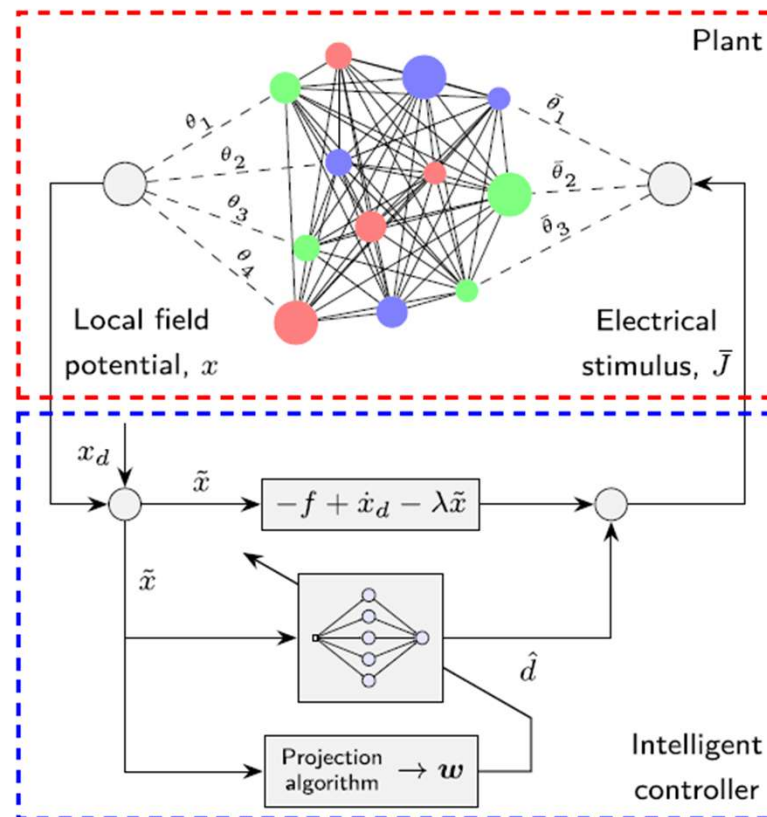
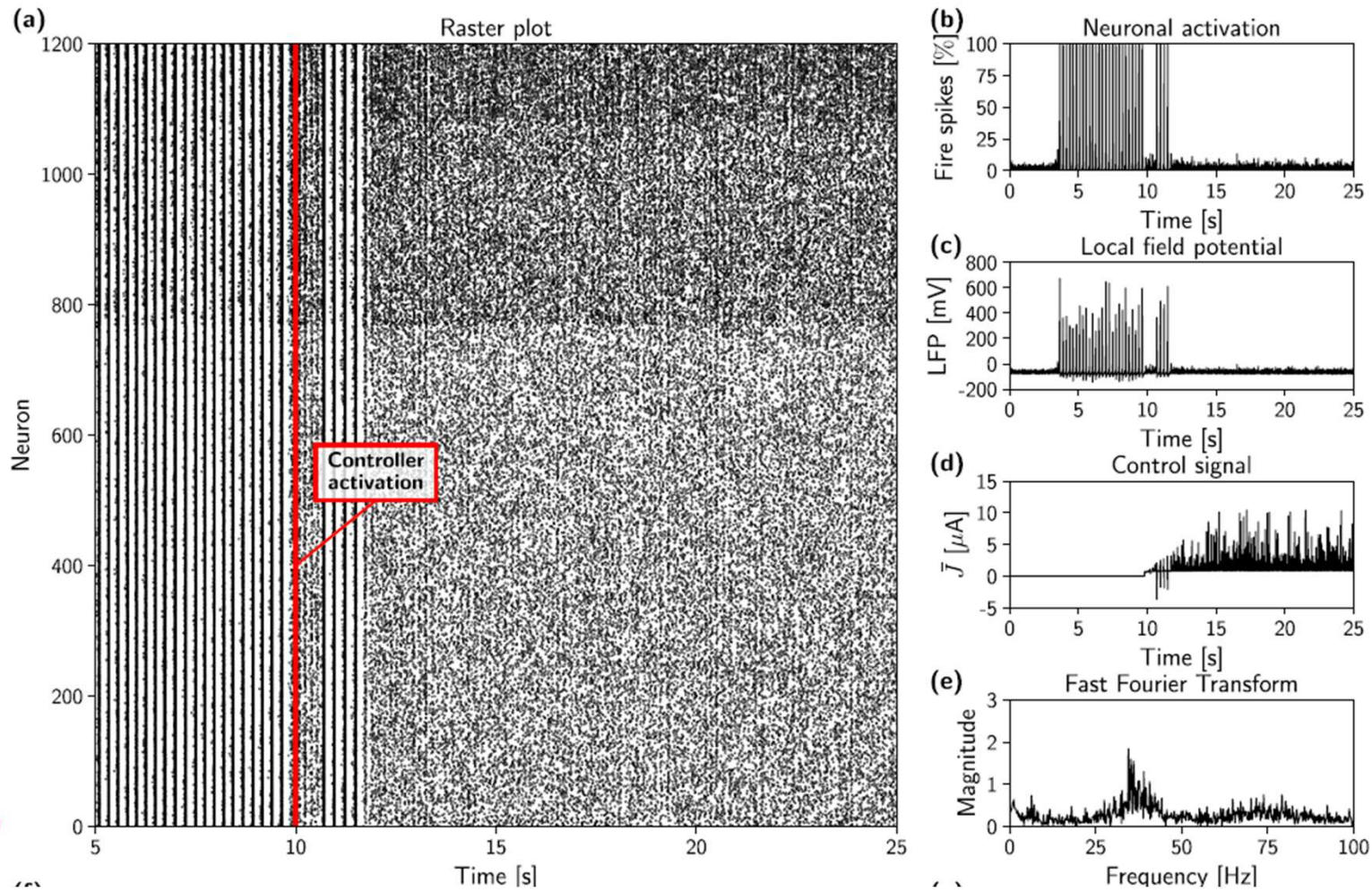
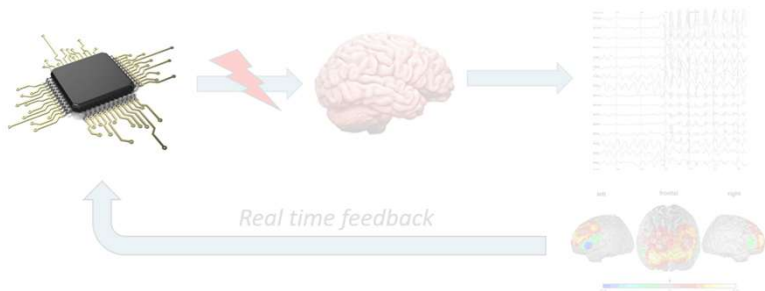


Fig. 7. Controller framework with the representation of how the computed electrical stimulus is applied to the Izhikevich network (the indices are for illustrative purposes).

Results





Intelligent control on hardware

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FireBeetle 2 ESP32-E IoT Microcontroller (32M / 512KB, Supports Wi-Fi & Bluetooth)

\$8.90

SKU: DFF

- 1 +

Volume Discou

The ESP32-E controller board supports WiFi, Bluetooth, Arduino, and w soon support Scratch and MicroPython. It's ideal for IoT applications.



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ESP32

\$8.90

Stage 2 — Pulsatile Stimulation

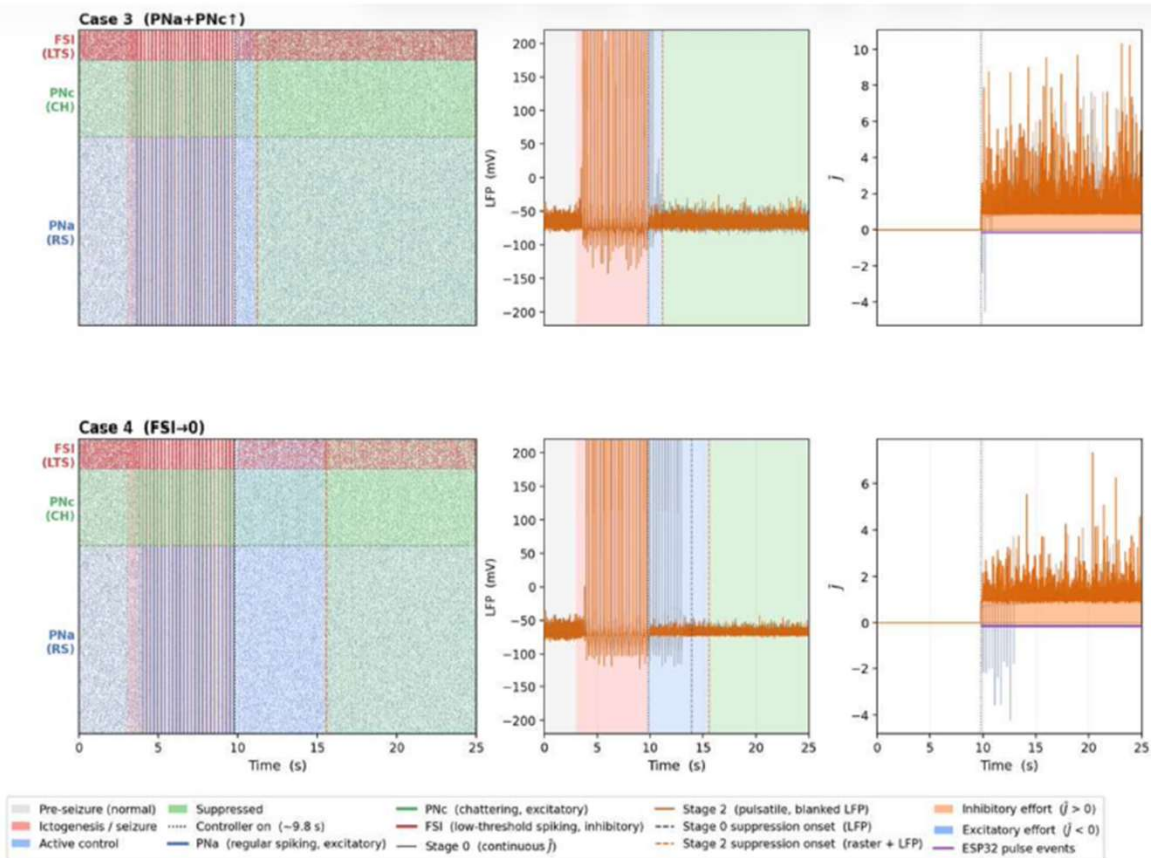


Figure 4. Stage 2 (orange) vs Stage 0 (grey), Cases 3 (PNa+PNc↑) and 4 (FSI→0). Left: raster coloured by population. Centre: LFP. Right: control effort J. Suppression onset marked by dashed lines; ESP32 pulse events shown in purple.



WHY PULSATILE

Continuous DC current risks tissue damage. Real devices use charge-balanced pulse trains.

PULSE ENCODING

```
N = |stim_fbl| // pulses / 5 ms window Width = 100
μs · Amplitude = 5.0
```

CASE	STAGE 0 DELAY	STAGE 2 DELAY	EXTRA DELAY
1 (PNa↑)	1.0 s	2.4 s	+1.4 s
2 (PNc↑)	0.9 s	1.4 s	+0.5 s
3 (PNa+PNc↑)	1.4 s	1.4 s	0.0 s
4 (FSI→0)	4.1 s	5.8 s	+1.7 s

Perspectives

- The strategy seems promising
- Improve the model
 - Larger biological networks (higher level of abstraction)
 - Better neurophysics (both LFP generation and response to stimuli)
 - More realistic neurostimulation
- Test closed-loop systems in animals (planned with MU collaborator)

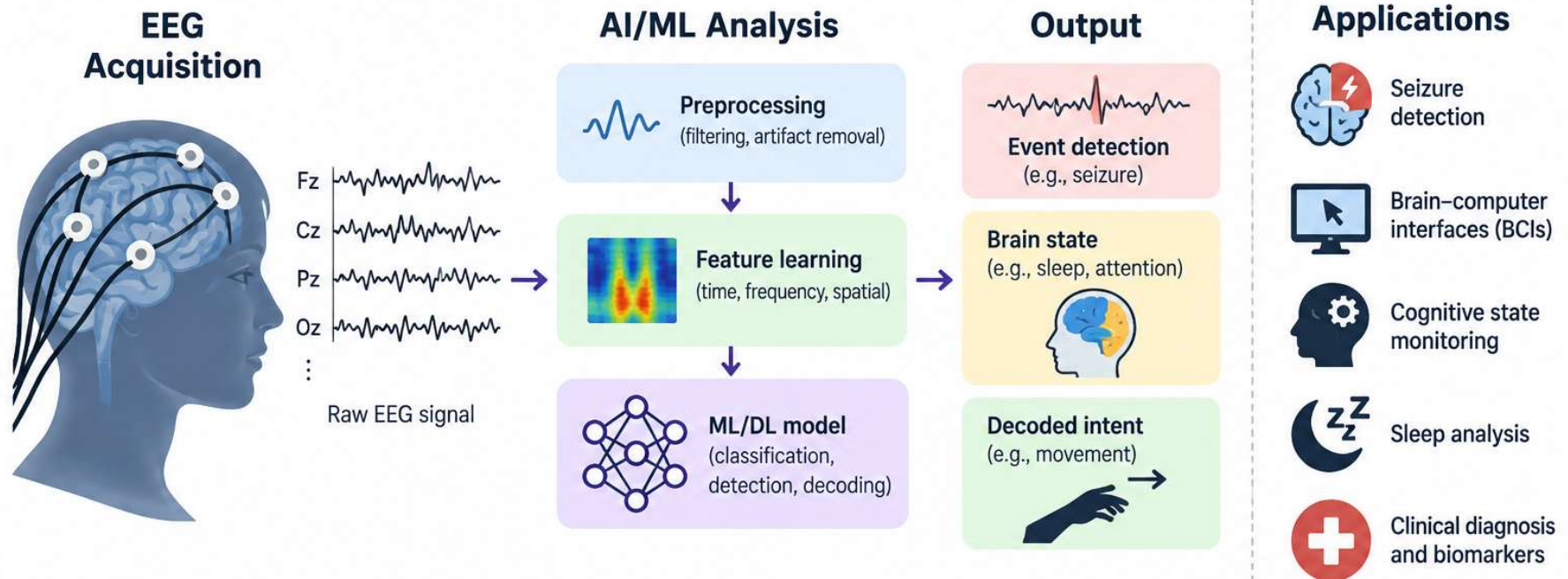
How to tackle such complexity?

1. ENGINEERED neuroengineering: spatiotemporal complexity
2. Personalized, precision neuroengineering: closing the loop
3. AI/ML for brain decoding

AI/ML for brain decoding

Definition

AI/ML learns patterns from EEG and other neural signals to automatically detect events, classify brain states, and decode neural information.



Efficient Sleep–Wake Cycle Staging via Phase–Amplitude Coupling Pattern Classification

Vinicius Rosa Cota ^{1,*} , Simone Del Corso ², Gianluca Federici ², Gabriele Arnulfo ² 
and Michela Chiappalone ^{1,2,*} 

Modulation index

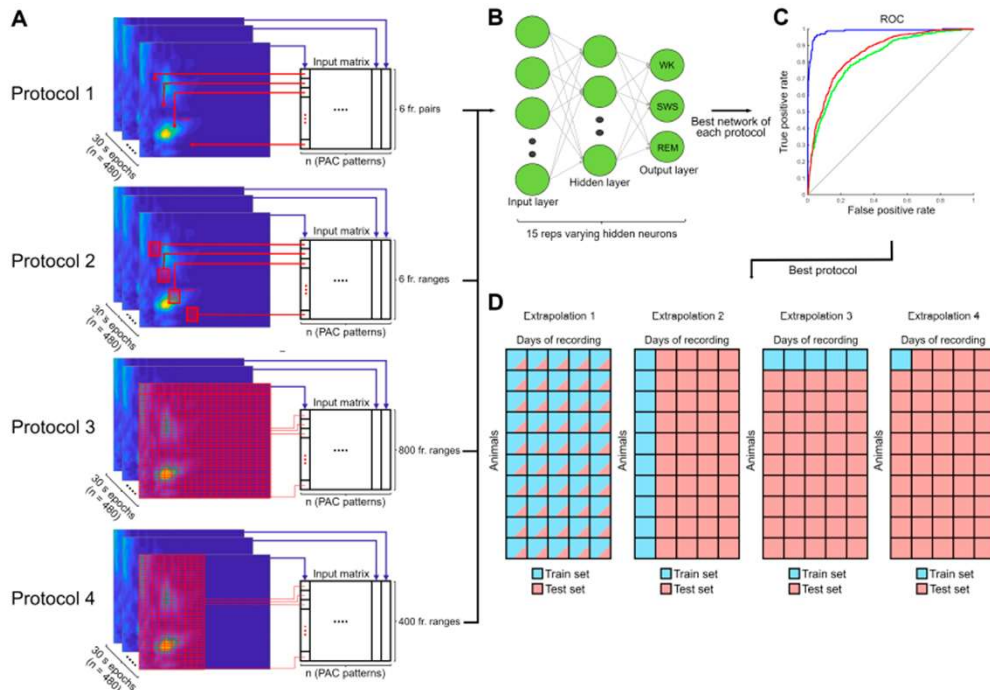
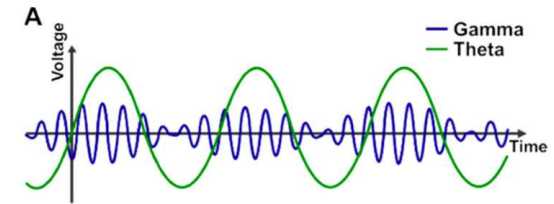
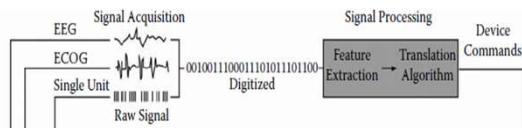
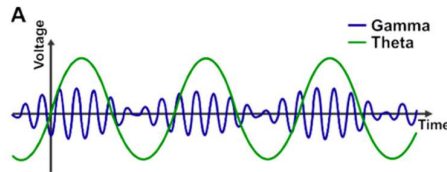
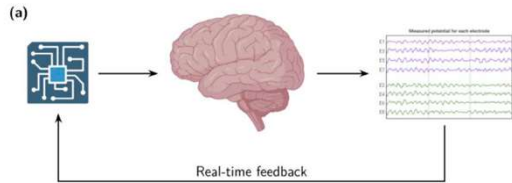


Table 5. F1-score values for all extrapolation strategies.

	WK	SWS	REM
Strategy 1	0.877	0.943	0.926
Strategy 2	0.883	0.940	0.916
Strategy 3	0.845	0.932	0.853
Strategy 4—best	0.846	0.913	0.775
Strategy 4—worst	0.784	0.924	0.772

Proposals for ELLIIT / collaborations



1. AI/ML strategies for closed-loop neuromodulation

2. A framework for the dichotomy AI vs. signal processing

3. Robust AI-based brain-wave decoding

4. Robust AI-based seizure anticipation / prediction

Thanks! Questions?



"That's amazing—I was just thinking the same thing."