Modeling Brain Diseases with Nonlinear Dynamical Systems to Optimize Medical Treatments

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"30th Summer School – Conference "Dynamical Systems and Complexity"
Calandra University Camping, Halkidiki, 28/8/2024 – 6/9/2024

Happy 70th anniversary Marko





Outline

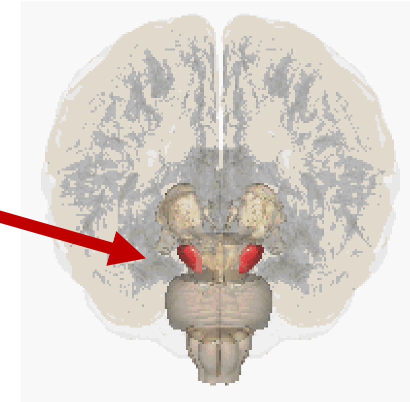
"Modeling Brain Diseases with Nonlinear Dynamical Systems to Optimize Medical Treatments"

- **Mathematical modeling** is a crucial tool for understanding the **fundamental mechanisms** of the human & animal brain.
- Models based on **ordinary differential equations** can capture and describe the **dynamic interactions** between **neurons** within specific brain regions or across different brain areas.
- We present recent studies demonstrating the usefulness of these **models in computationally understanding** and **mitigating** symptoms of two brain diseases:
  - **Parkinson's disease** (**Part I**) and
  - **Epilepsy** (**Part II**)

Part I - Parkinson’s disease

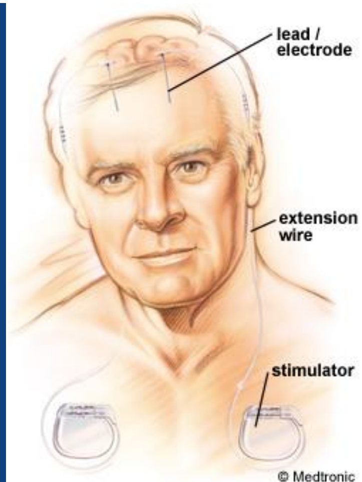
Clinical motivation

Parkinson's disease (loss of neurons → dopamine):
Neurodegenerative disease of the **substantia nigra** that results in a characteristic tremor at rest and a general paucity of movement.



pathological neuronal synchrony

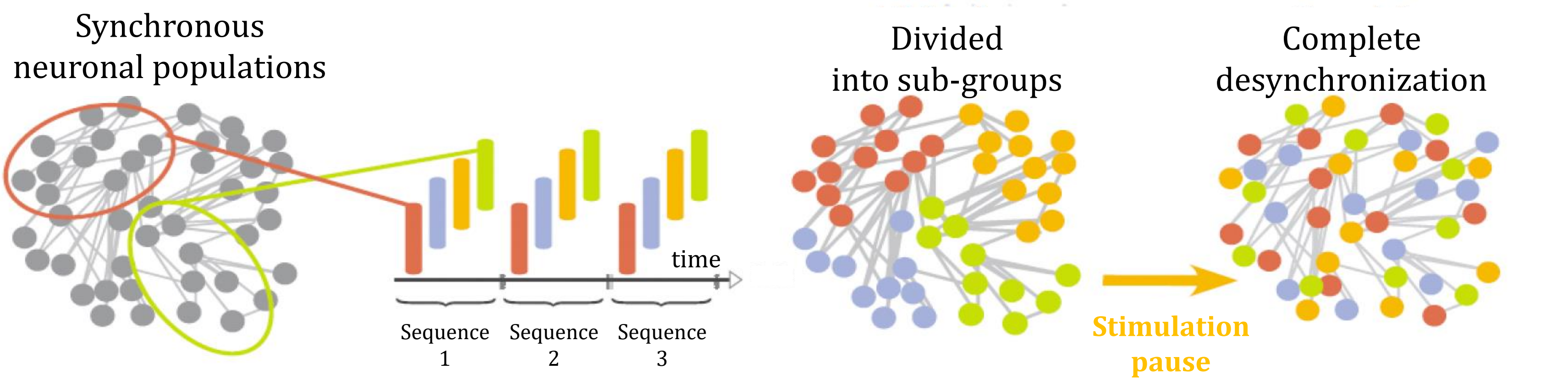
PD patient, 48ys tremor right hand



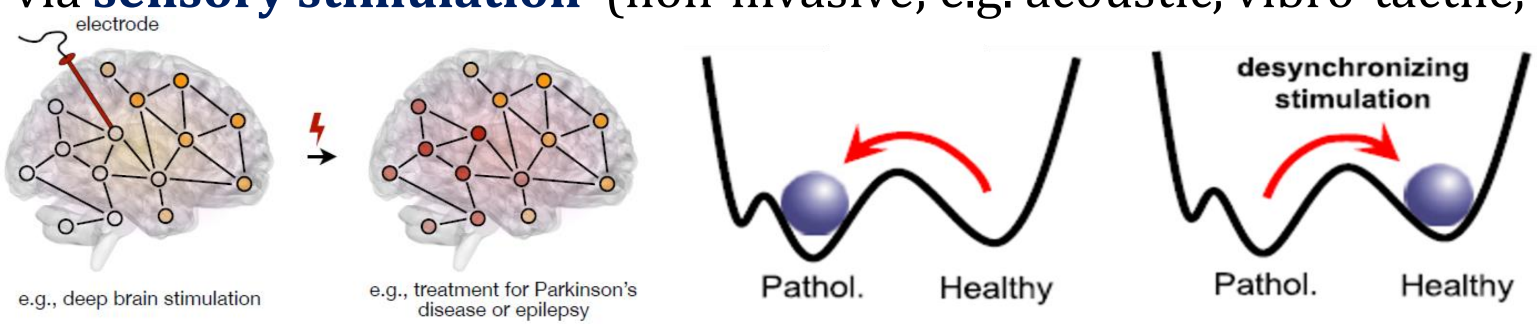
post-operative, directly before CR stimulation

Treatment with Neuromodulation

- **Coordinated Reset (CR) neuromodulation** means to: consecutively deliver brief **pulses to different locations** of the brain to sequentially **reset the phases** of the different stimulated subpopulations.



- **CR neuromodulation** intends to induce a **desynchronization** which starts a process of **unlearning** of both pathological **neuronal synchrony** and pathological **synaptic connectivity**.
- **CR neuromodulation** can be applied via **electrical stimulation** (invasive; e.g. DBS) or via **sensory stimulation** (non-invasive; e.g. acoustic, vibro-tactile, visual).

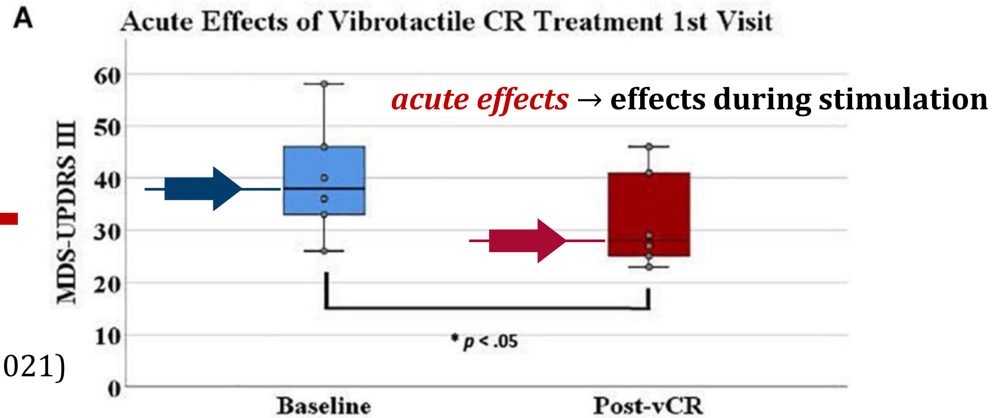


Tass PA, *Biol. Cybern.* 89:81 (2003) / Tass PA, *Prog. Theor. Phys. Suppl.* 150:281 (2003)

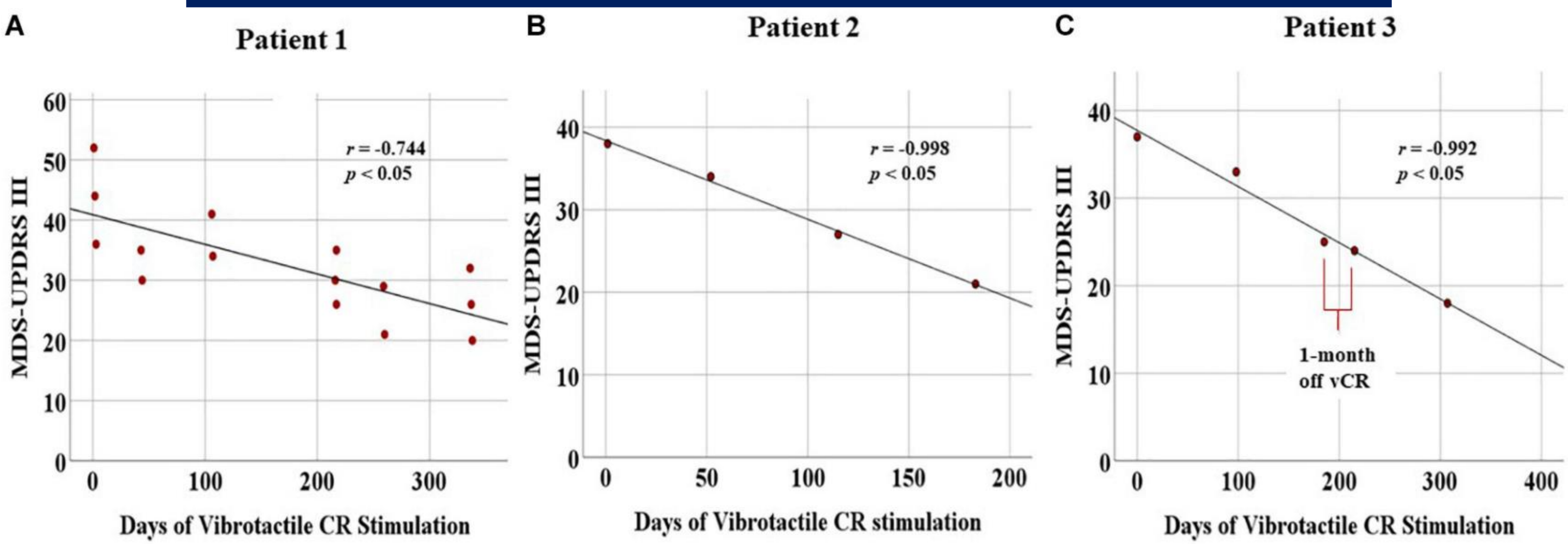
Vibrotactile Coordinated Reset Stimulation Induces <u>Sustained Cumulative</u> Benefits in Parkinson's Disease

Movement **D**isorders **S**ociety-**U**nified **P**arkinson's **D**isease **R**ating **S**cale **III**

Pfeifer et al. *Front. Physiol.*, 12:200 (2021)

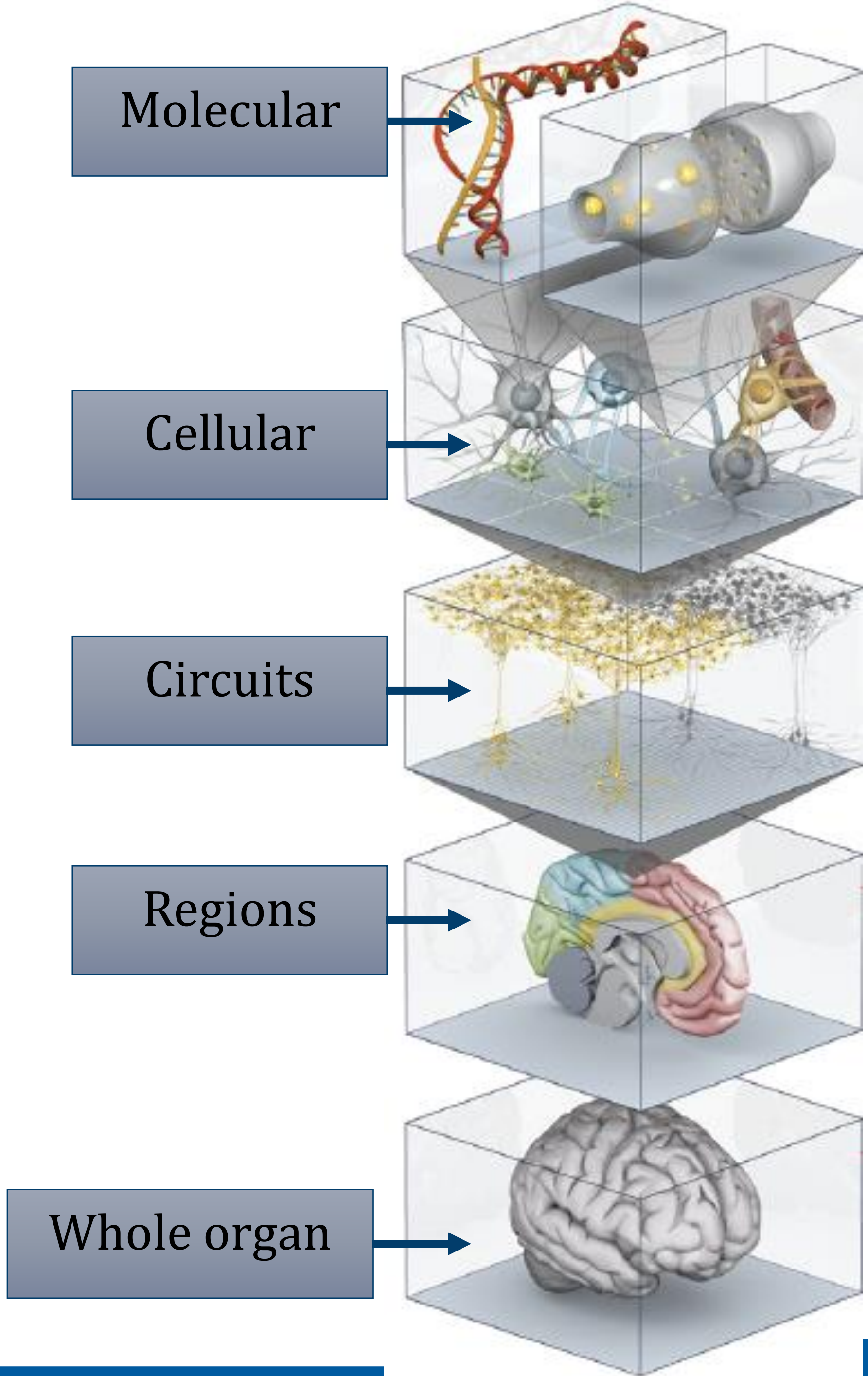


Cumulative chronic, **months-long effects** of vCR treatment



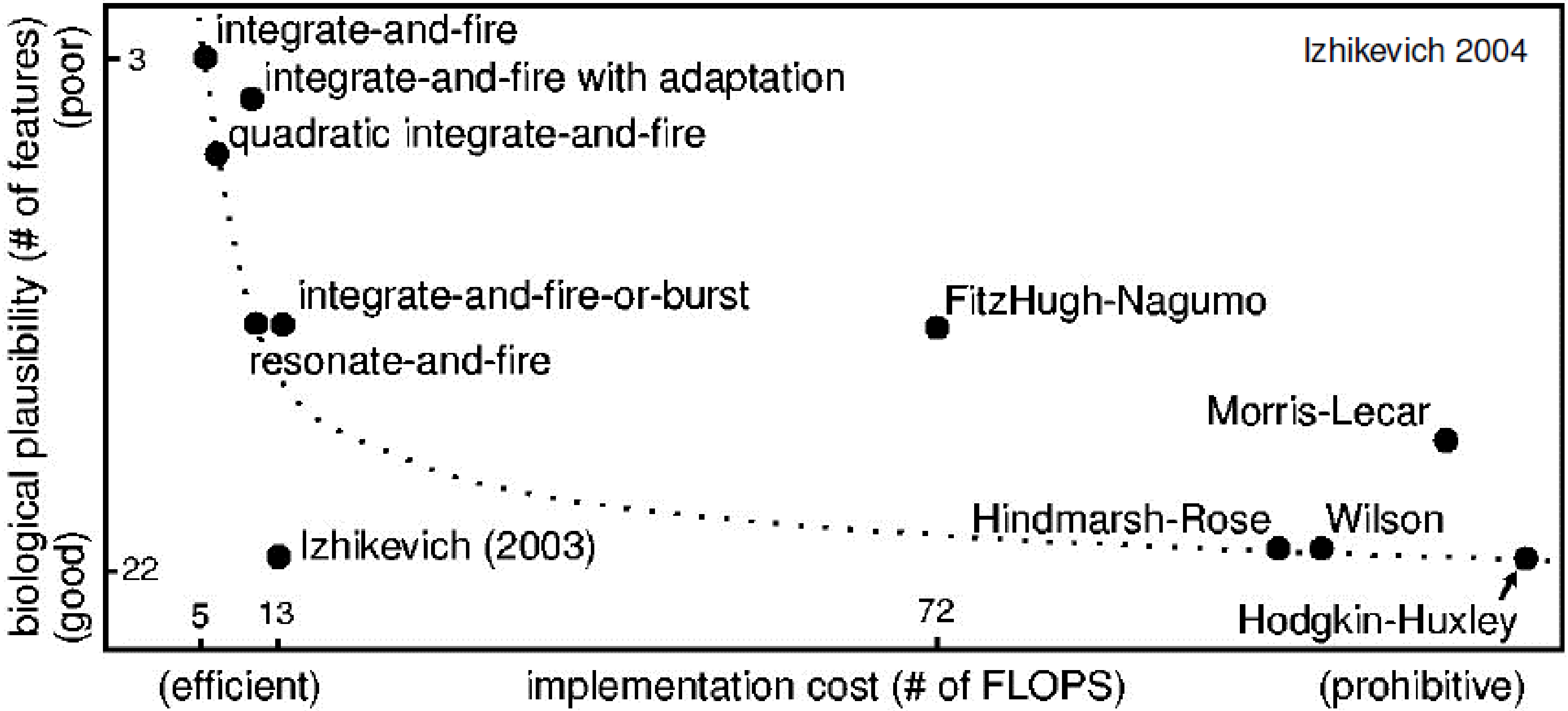
Hypothesis: Taking into account **structural plasticity** reveals **memory-type effects** of the network's treatment susceptibility.

Brain scales



Which neuron model to choose?

A brief comparison of the neuro-computational properties of spiking and bursting models

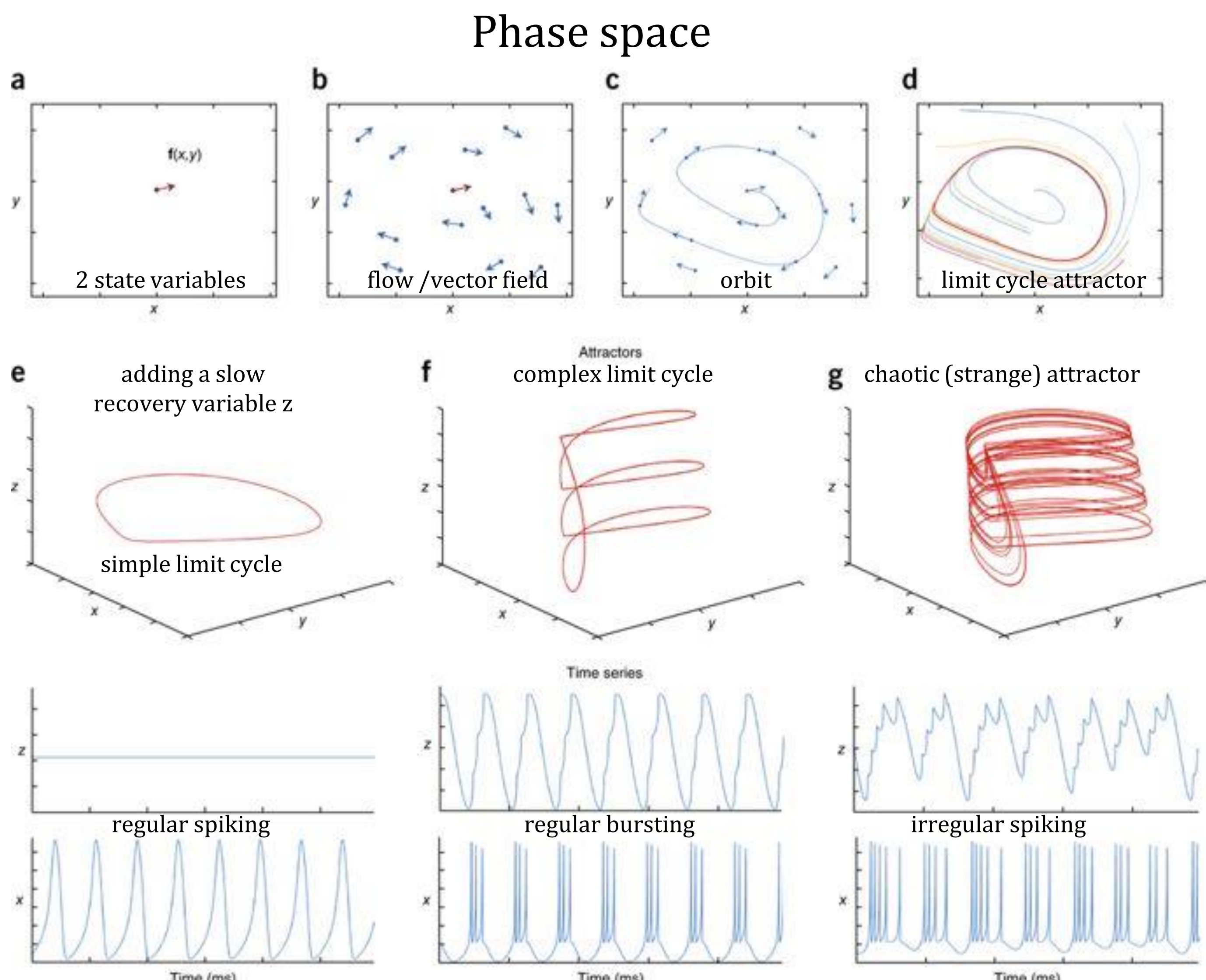


FLoating-point **O**perations **P**er **S**econd: a measure of computer performance

Phase space

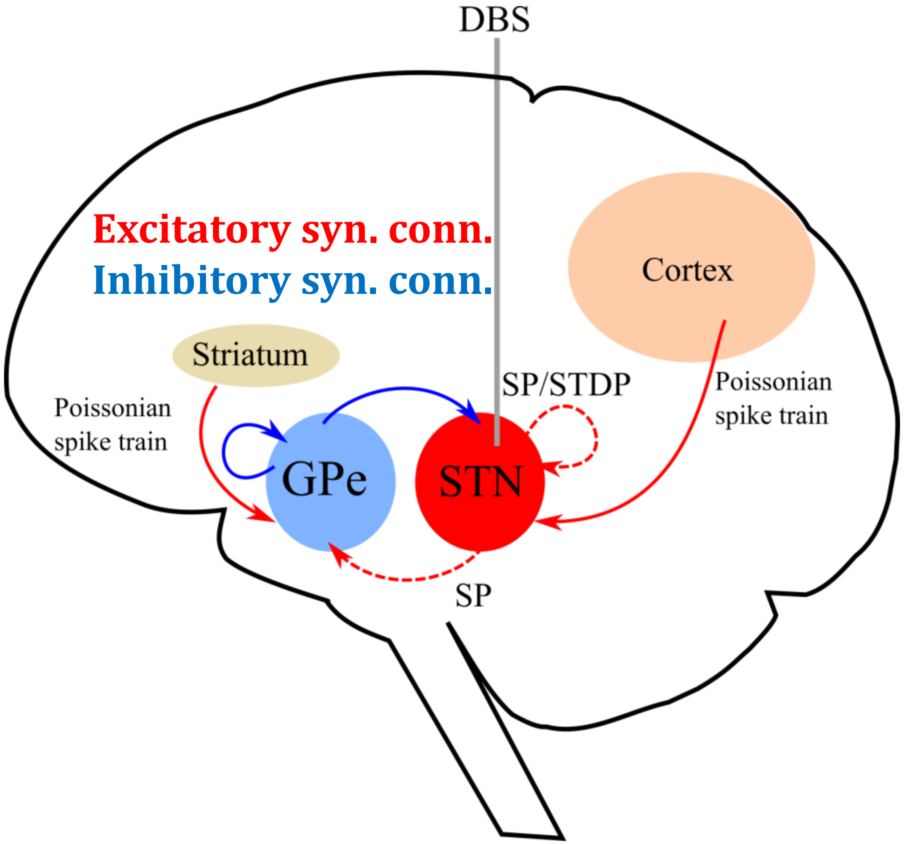
Dynamical system:
$$\dot{x} = f(x)$$

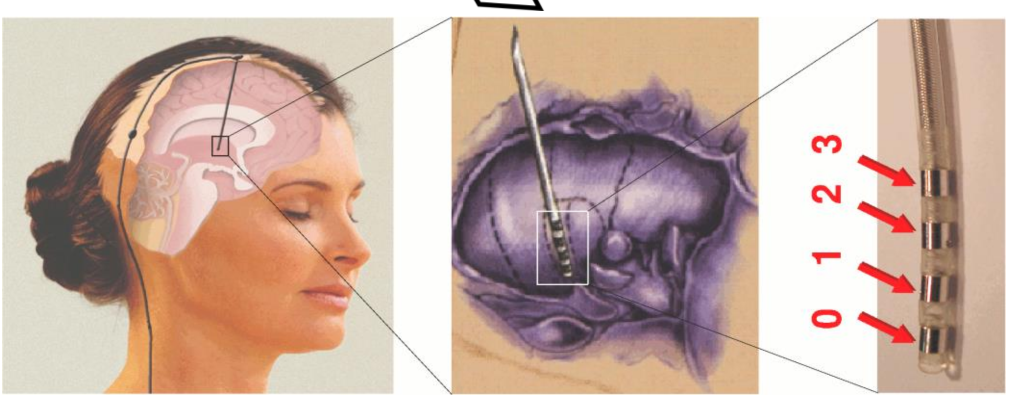
Attractors capture all the characteristics of the activity of the system: **steady state**, **periodic**, **quasiperiodic** and **chaotic**.



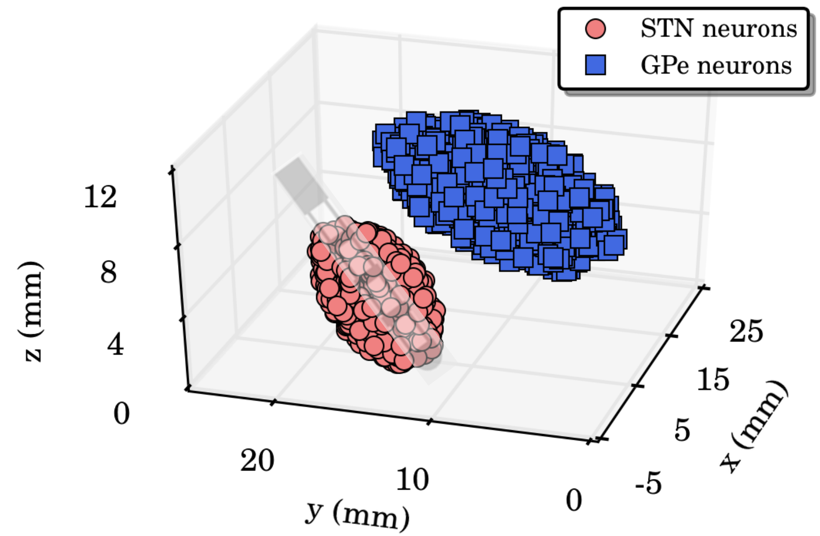
A model for Deep Brain Stimulation

Neural network structure



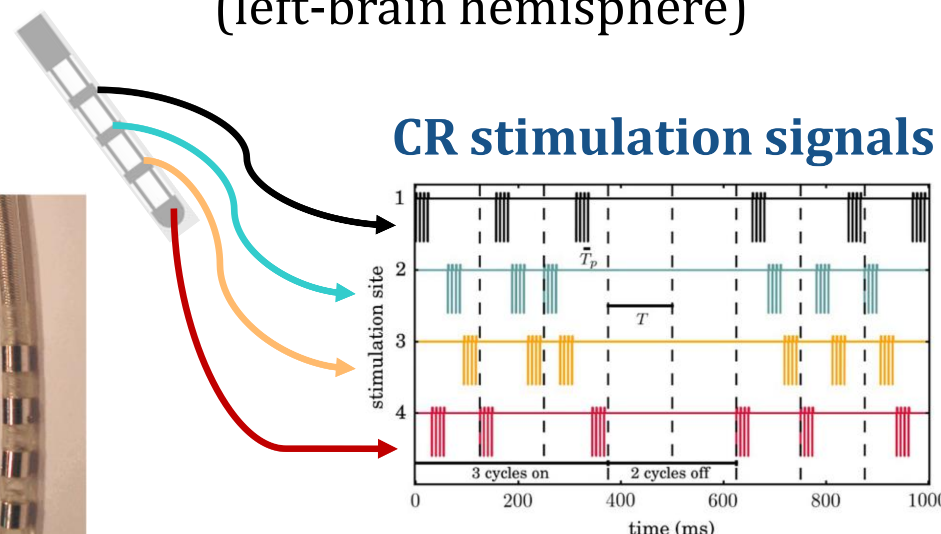


3D spatial neuron configuration



Coordinates → MRI before DBS surgery (left-brain hemisphere)

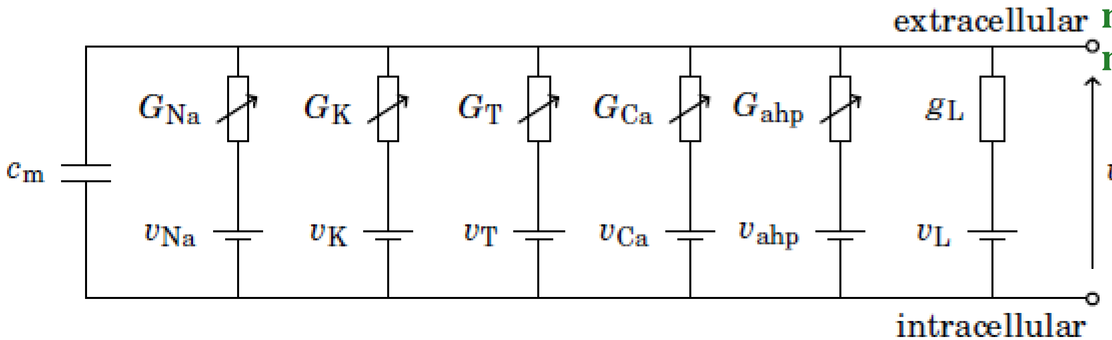
CR stimulation signals



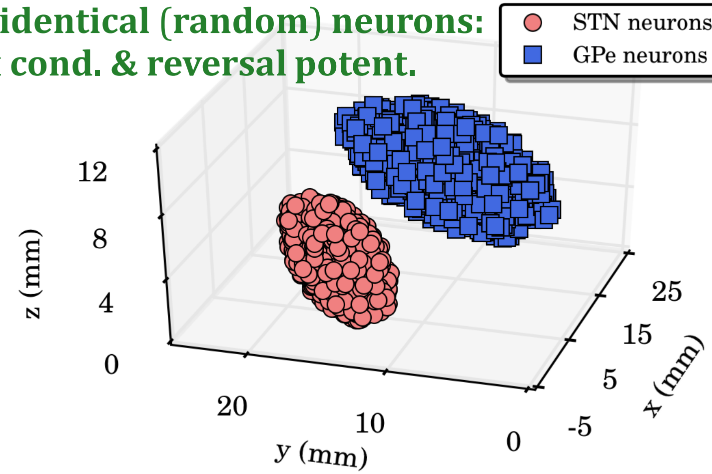
short biphasic current pulses

MT, Diaz-Pier S, Tass PA, *Front. Physiol.* 12:716556 (2021)

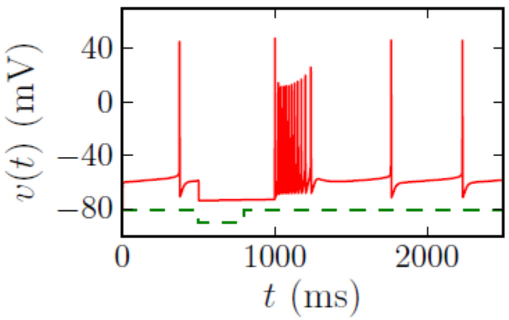
STN/GPe network - Terman-Rubin model



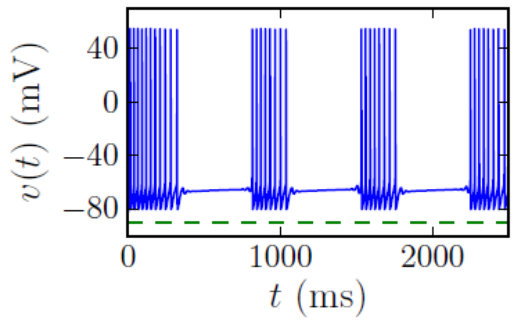
not-identical (random) neurons: max cond. & reversal potent.



$$C_m \frac{dv}{dt} = -I_L - I_K - I_{Na} - I_{Ca} - I_T - I_{AHP} - I_{syn} + I_{DBS}$$



STN



GPe

$$I_L = g_L [v - v_L]$$

$$I_K = g_K n^4 [v - v_K]$$

$$I_{Na} = g_{Na} m_\infty^3 (v) h [v - v_{Na}]$$

$$I_T = g_T a_\infty^3 (v) b_\infty^2 (v) [v - v_{Ca}]$$

$$I_T = g_T a_\infty^3 (v) r [v - v_{Ca}]$$

$$I_{Ca} = g_{Ca} s_\infty^2 (v) h [v - v_{Ca}]$$

$$I_{ahp} = g_{ahp} [v - v_K] \frac{[Ca]}{[Ca] + k_1}$$

$$\frac{d[Ca]}{dt} = \Gamma (-I_{Ca} - I_T - k_{Ca} [Ca])$$

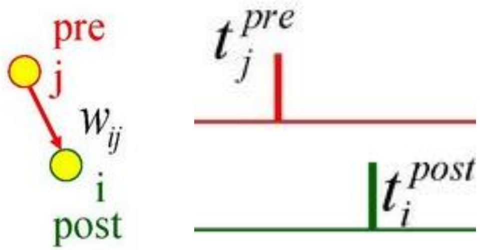
Terman D, Rubin JE, Yew AC, Wilson CJ, *J. Neurosci.* 7:2963 (2002)
Rubin JE, Terman D, *J. Comput. Neurosci*. 16:211 (2004)
Ebert M, Hauptmann C, Tass PA, *Front Comput Neurosci.* 8:154 (2014)
MT, Diaz-Pier S, Tass PA, *Front. Physiol*. 12:716556 (2021)

Spike timing-dependent plasticity (STDP)

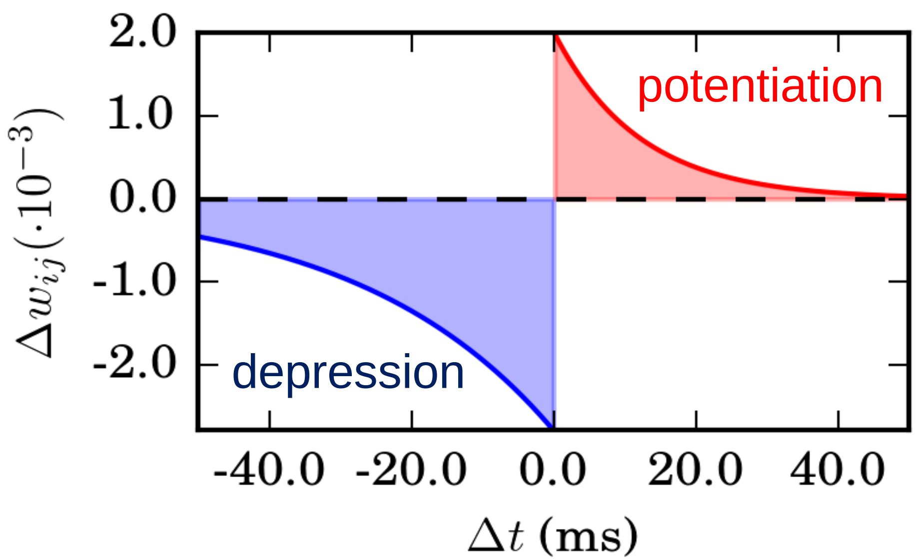
Synaptic plasticity: the ability of synapses to **strengthen** or **weaken** over time, in response to increases (↑) or decreases (↓) in their activity.

The **synaptic weights** w_{ij} are **dynamical variables** that depend on the time difference $\left(\Delta t_{ij} = t_j^f - t_i^f\right)$ between the firing (onset) of the ***post- and pre-synaptic spikes*** (t_i^f & t_j^f).

"Cells that fire together → wire together"



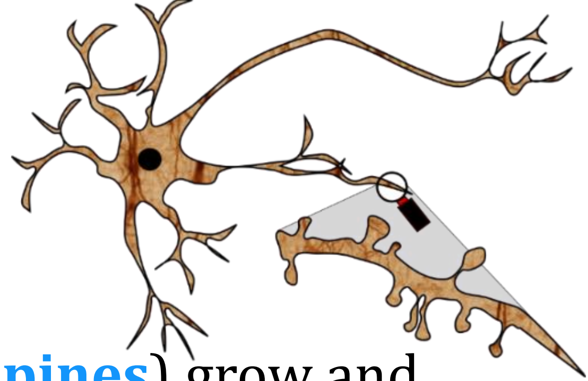
$$\Delta w_{ij}(\Delta t_{ij}) = \begin{cases} \lambda e^{-\frac{|\Delta t_{ij}|}{\tau_+}}, & \Delta t_{ij} > 0 \\ -\lambda \gamma e^{-\frac{|\Delta t_{ij}|}{\tau_-}}, & \Delta t_{ij} \leq 0 \end{cases}$$



- We restrict the synaptic weights (within the STN neurons) on the interval, **avoiding** in this way a **non-physiological unbounded** increase or decrease.
- The (de)synchronized dynamics are **stable** with the above rule and parameter values resulting in **multistability** (→ multiple stable equilibrium points).

Bi GQ, Poo MM, *J Neurosci.* 18, 10464-10472 (1998)

Structural plasticity



Physical creation/deletion of synapses (during **brain development**, **learning** and **recovery after lesions**).

Synaptic elements (**axonal boutons** and **dendritic spines**) grow and recede following **homeostatic rules** based on the **mean electrical activity/firing rate** (FR) of the neuron:

$$\frac{d\mathrm{FR}}{dt} = \begin{cases} -\frac{\mathrm{FR}(t)}{\tau_{\mathrm{SP}}} + \beta, & \text{if the neuron fires} \\ -\frac{\mathrm{FR}(t)}{\tau_{\mathrm{SP}}}, & \text{otherwise} \end{cases}$$

β: calcium intake const.

τ_{SP}: [Ca] decay time const.

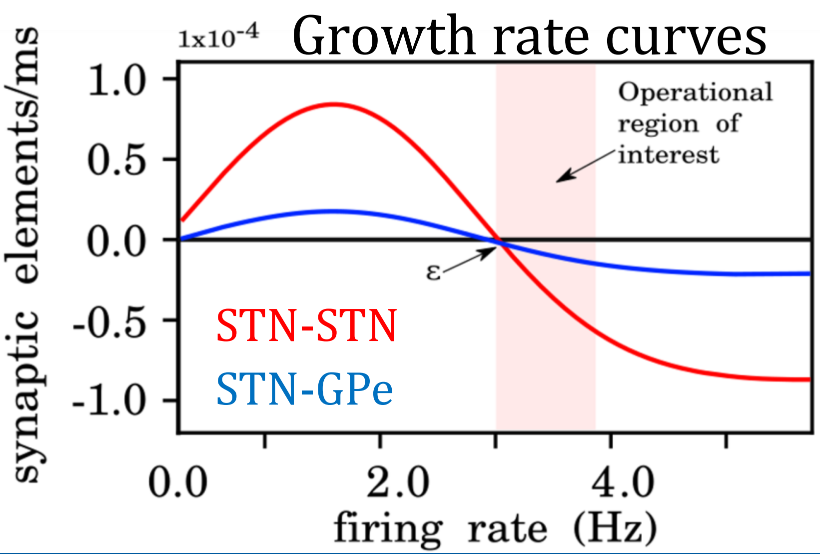
Gaussian growth rate:

$$\frac{dz}{dt} = \nu_{\mathrm{SP}} \left[2e^{-\left(\frac{\mathrm{FR}(t)-\xi}{\zeta}\right)^2} - 1 \right]$$

z: number of synaptic elements

ν_{SP}: max. amplitude of the growth rate

$\zeta = \frac{\varepsilon - \eta}{2\sqrt{\ln 2}}, \quad \xi = (\varepsilon + \eta)/2$



The global connectivity is updated on a **<u>much slower timescale</u>** than changes in electrical activity.

Butz M, van Ooyen A, *PLoS Comput. Biol.* 9:e1003259 (2013)
Diaz-Pier S et al., *Frontiers in Neuroanatomy*, 10(57):1662 (2016)

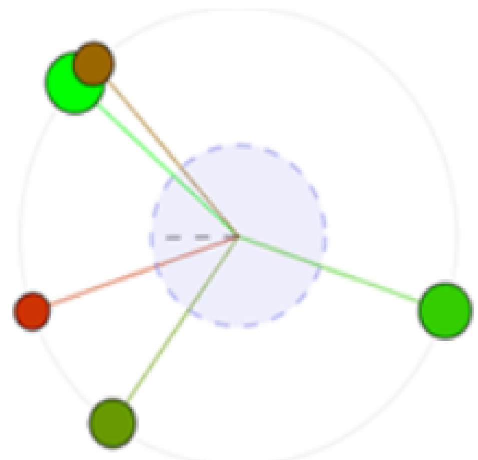
The Kuramoto order parameter

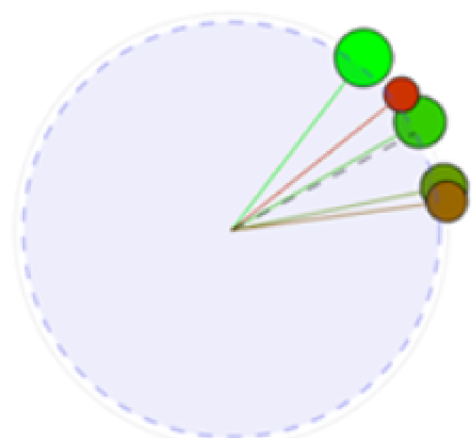
- One measure of synchrony is the **Kuramoto order parameter** (R) that indicates the **level of synchrony** of a **collection of phase oscillators**.

- We define the order parameters simply by **averaging** the ***complex numbers that represent the phase of the oscillators on the unit circle***.

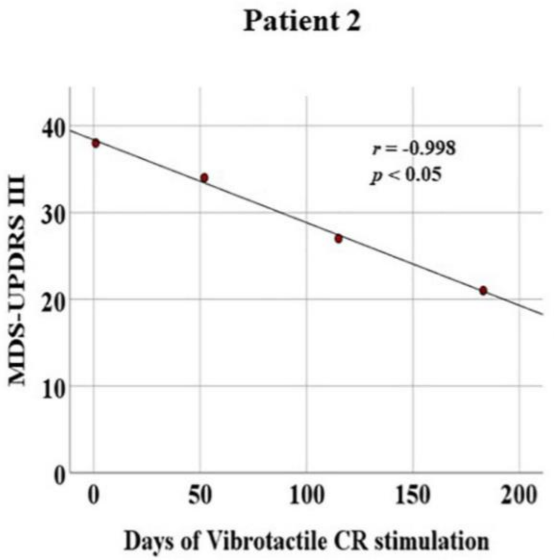
- Given a collection of N phase oscillators with phases θ_j for $j = 1,2, \dots N$, the positions of the oscillators on the unit circle are represented by the complex numbers $e^{i\theta_j}$, we define the **Kuramoto order parameter** as:

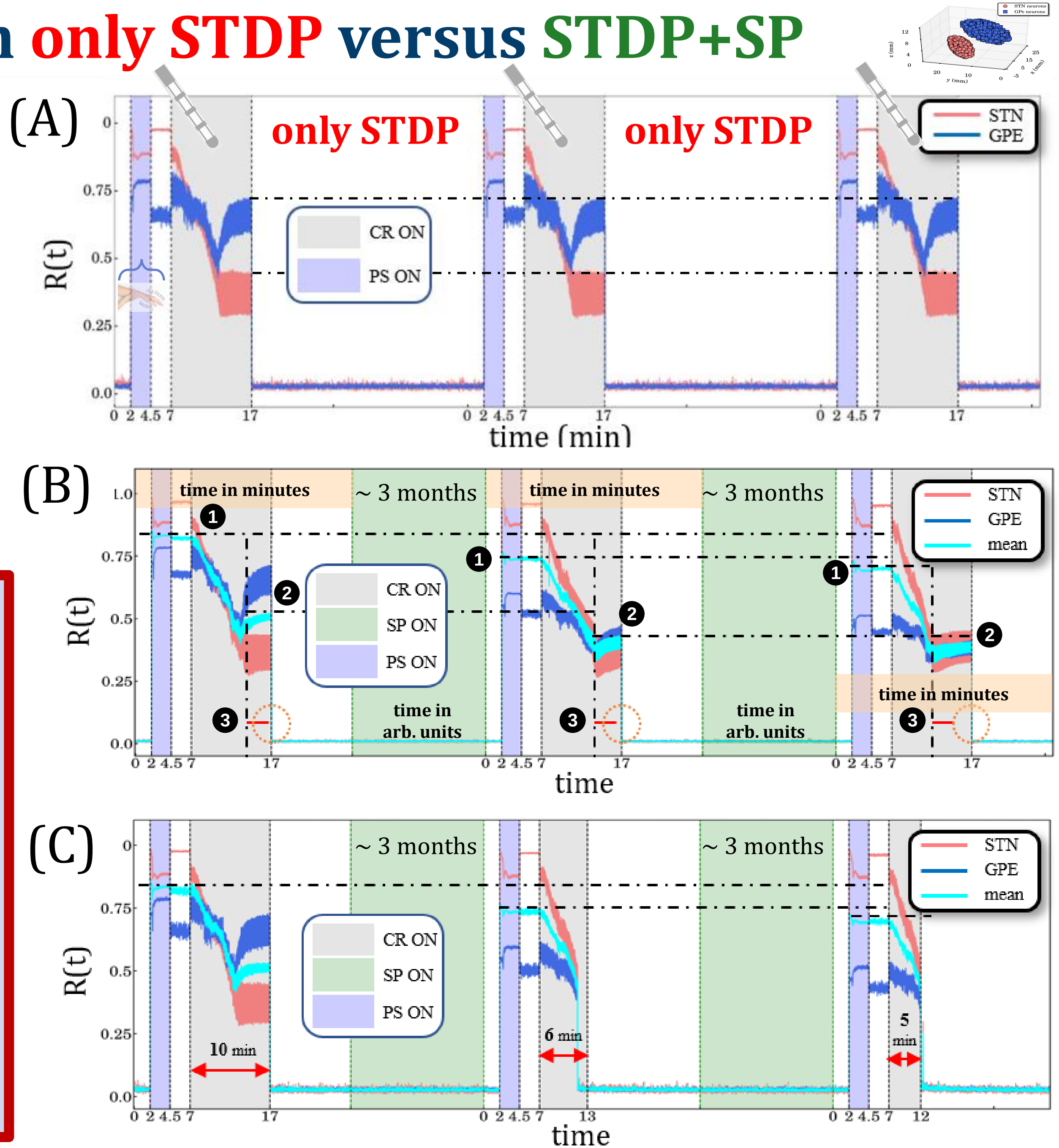
$$R(t) = \frac{1}{N}\left|\sum_{j=1}^{N} e^{i\theta_j}\right|$$





CR sequences with only STDP versus STDP+SP





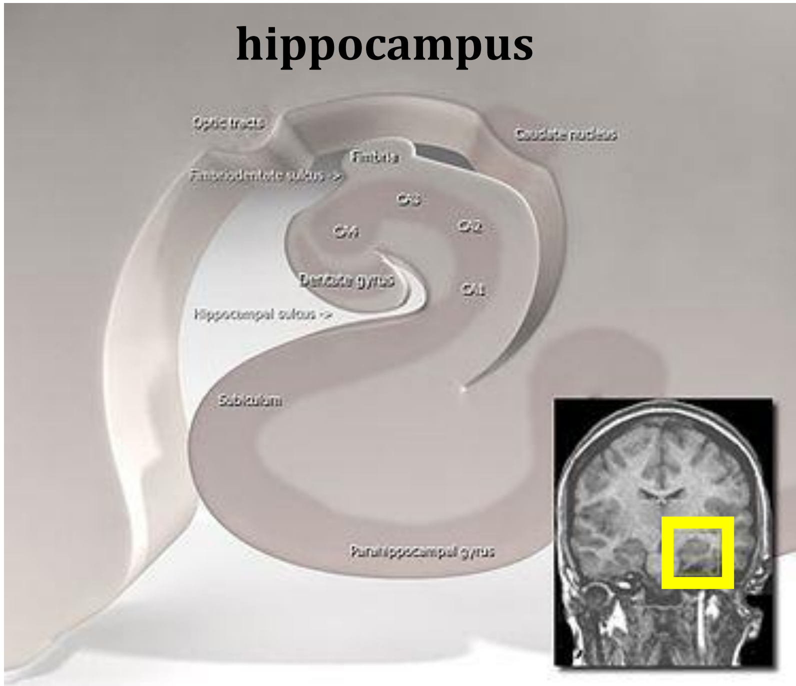
By combining **STDP+SP**, we increased the plasticity potential of the system to explore <u>different connectivity configurations</u>, allowing **long-term structural changes** and **short-term learning** in the **same simulation**.

MT, Diaz-Pier S, Tass PA, *Front. Physiol.* 12:716556 (2021)

Part II - Epilepsy

Epilepsy

- ❑ Common neurological disorder.
- ❑ **Epileptic seizures**:
  → Excessive electrical discharges.
- ❑ **Epileptic seizures** arise from an **imbalance** in the regulation of **excitation** and **inhibition**.
- ❑ **Symptoms**: language troubles, motor troubles, loss of consciousness etc.



CA: Cornu Ammonis (an earlier name of the hippocampus)
DG: Dentate Gyrus

- ❑ 30-40% of the patients are drug resistant: resective surgery. Resection of the entire **Epileptogenic Zone** (EZ).
- ❑ **Challenge** → **optimization of the resection.**
- ❑ Anti-seizure drugs → suppress epileptiform spikes and improve synaptic and cognitive function.
- ❑ Neuromodulation → manages seizure propagation.

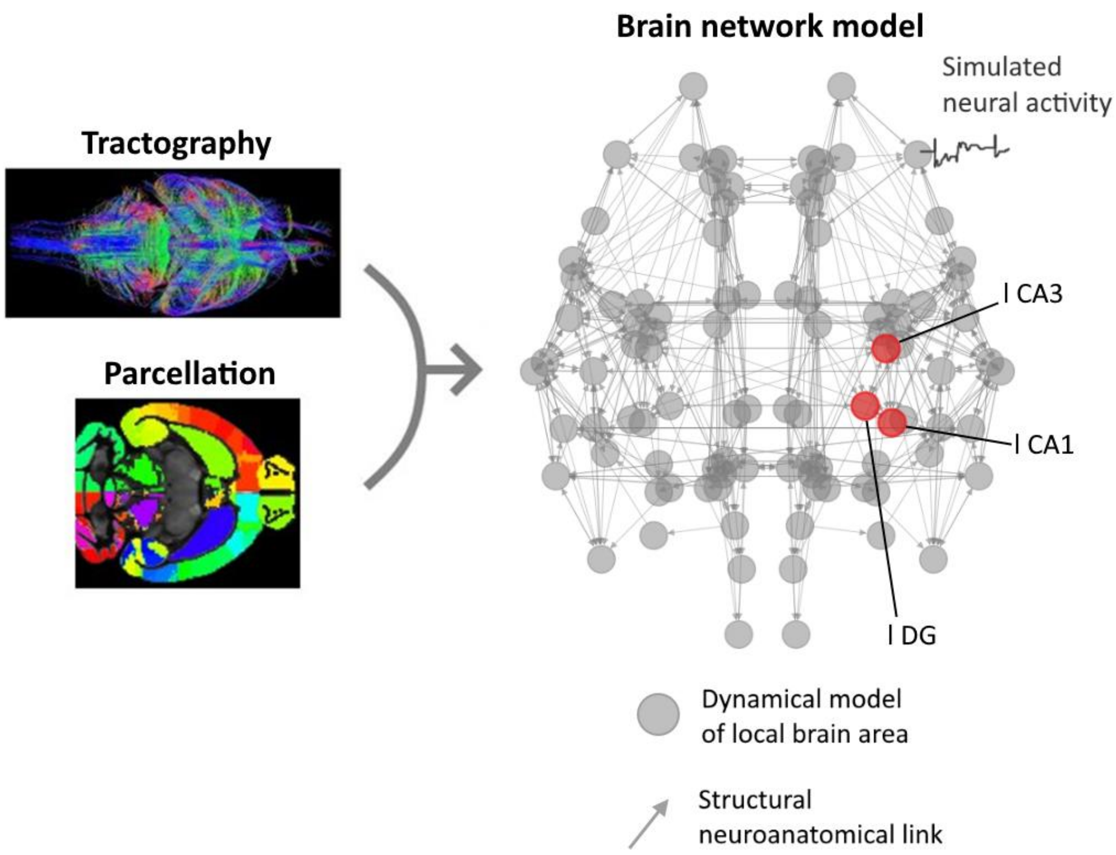
In this work:

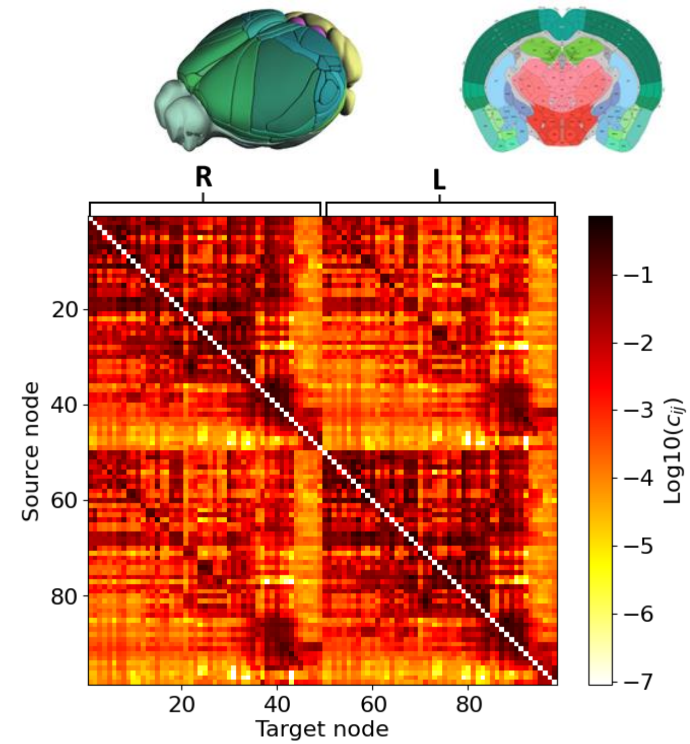
- We computationally study how the **location of an EZ area** and its **connectivity** relevance in the network are related to **widespread seizure propagation** in a mice brain.

- We search for strategies that can **confine widespread seizures** by either:
  - **removing the minimum amount of brain tissue** (by blocking certain connections in the network) or
  - **suppress the hyperexcitation** (loosely mimicking an anti-seizure drug or neuromodulation effect).

Large brain simulations

- ❖ Computational platform: **The Virtual Brain**
- ❖ Rodent species are often regarded as suitable analogues for humans due to the significant similarities in brain structure and connectivity between the two.
- ❖ Mice brain Structural Connectivity from the Allen Institute.





The Epileptor model

$$\dot{x}_{1,i} = y_{1,i} - f_1(x_{1,i}, x_{2,i}) - z_i + I_1, \qquad (1)$$

$$\dot{y}_{1,i} = 1 - 5x_{1,i}^2 - y_{1,i}, \qquad (2)$$

$$\dot{z}_i = \begin{cases} r(4(x_{1,i} - x_{0,i}) - z_i - 0.1z_i^7) + K\sum_j c_{ji}(x_{1,i} - x_{1,j}) & \text{if } z_i < 0, \\ r(4(x_{1,i} - x_{0,i}) - z_i) + K\sum_j c_{ji}(x_{1,i} - x_{1,j}) & \text{if } z_i \geq 0, \end{cases} \qquad (3)$$

$$\dot{x}_{2,i} = -y_{2,i} + x_{2,i} - x_{2,i}^3 + I_2 + 0.002g(x_{1,i}) - 0.3(z_i - 3.5), \qquad (4)$$

$$\dot{y}_{2,i} = \frac{1}{\tau}(-y_{2,i} + f_2(x_{2,i})), \qquad (5)$$

$$\dot{g}(x_{1,i}) = -0.01(g(x_{1,j}) - 0.1x_{1,i}), \qquad (6)$$

where

$$f_1(x_{1,i}, x_{2,i}) = \begin{cases} 3x_{1,i}^3 - x_{1,i}^2 & \text{if } x_{1,i} < 0, \\ (x_{2,i} - 0.6(z_i - 4)^2)x_{1,i} & \text{if } x_{1,i} \geq 0, \end{cases} \qquad (7)$$

and

$$f_2(x_{2,i}) = \begin{cases} 0 & \text{if } x_{2,i} < -0.25, \\ 6(x_2 + 0.25) & \text{if } x_2 \geq -0.25. \end{cases} \qquad (8)$$

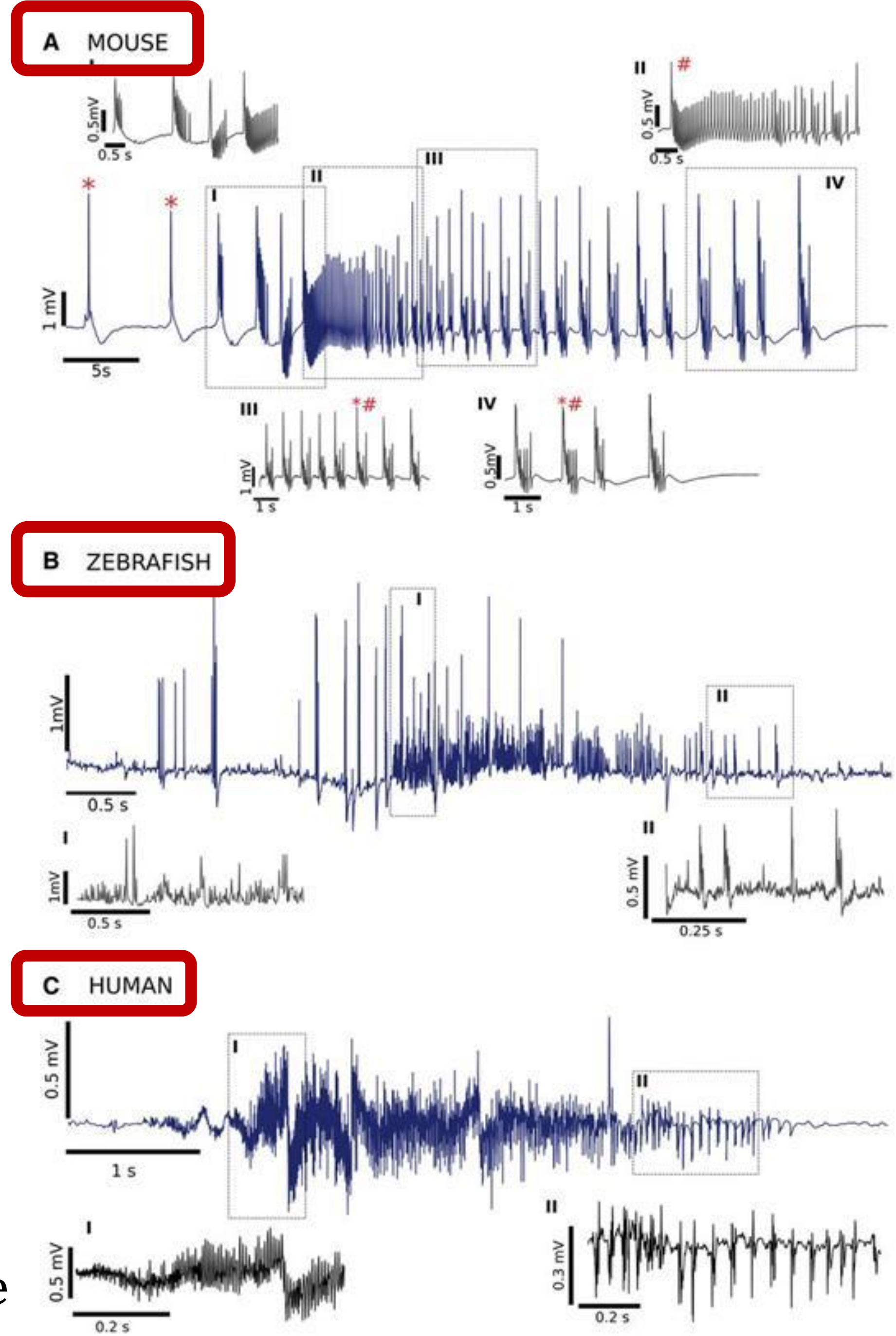
Phenomenological model:

$(x_{1,i}, y_{1,i}, z_i)$ **bursting neuron** (fast)

$(x_{2,i}, y_{2,i})$ **spiking neuron** (slow)

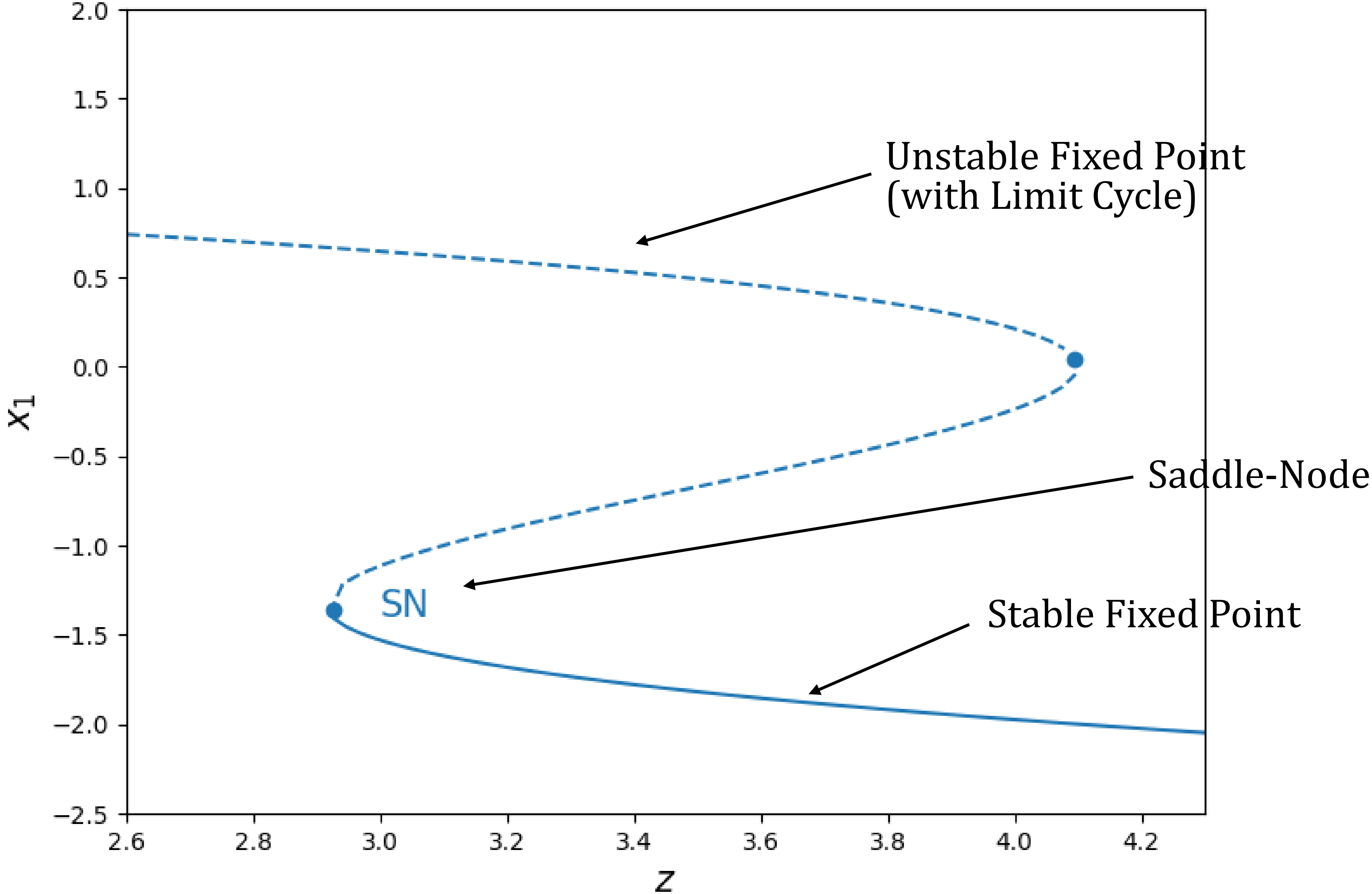
x_2-x_1: mimics the membrane potential

z: slow permittivity (dictates how close the system is to the seizure threshold)



Jirsa et al. *Brain* 137, 2210–2230 (2014)

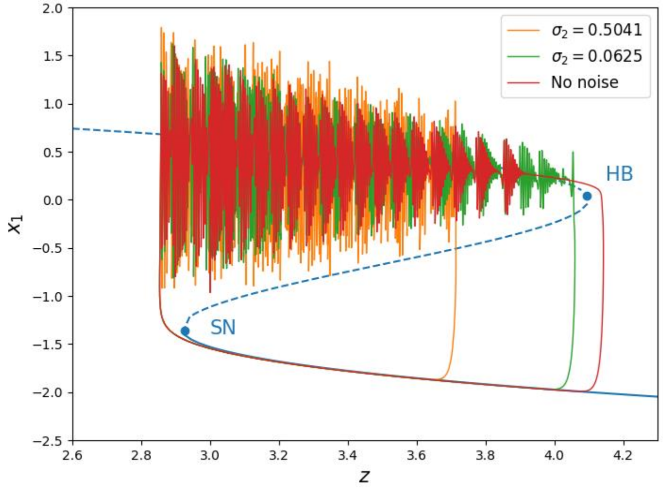
The Epileptor model: bifurcation diagram



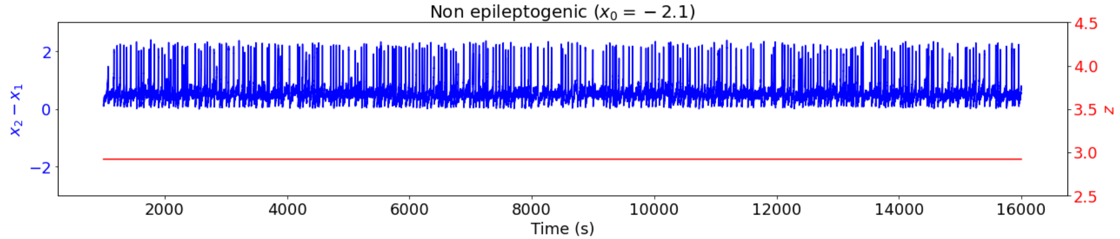
The Epileptor model: Epileptogenic Zone (EZ)

- **Epileptogenicity x_0** defines the distance to SN bifurcation.
- **Propagation Zone (PZ)** $(x_0 < -2.06)$: healthy brain areas.
- **Epileptogenic Zone (EZ)** $(x_0 > -2.06)$: spontaneous seizures.

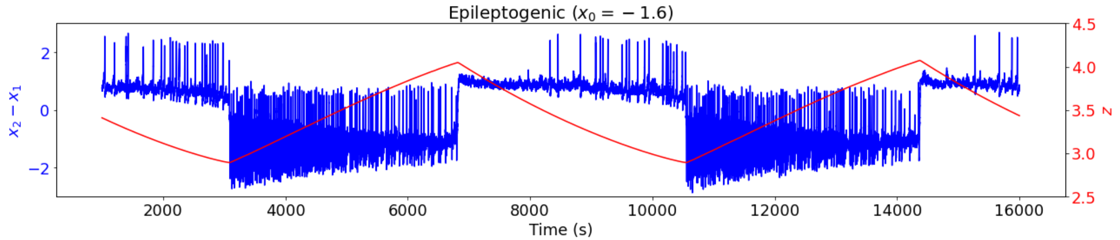
$(x_{1,i}, y_{1,i}, z_i)$ **bursting neuron** (fast)
$(x_{2,i}, y_{2,i})$ **spiking neuron** (slow)
x_2-x_1: mimics the membrane potential
z: slow permittivity



Propagation Zone (PZ)



Epileptogenic Zone (EZ)

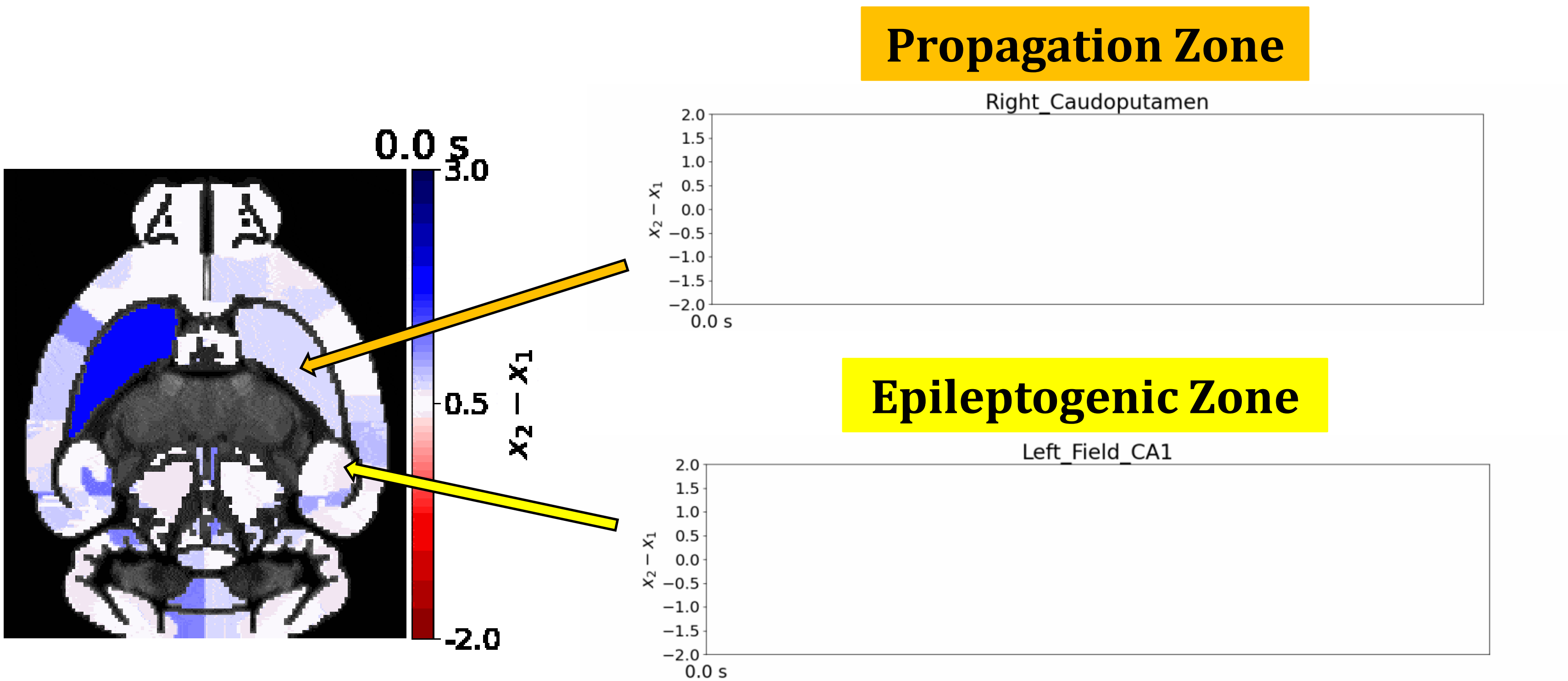


Seizures are generated by either a **localized** production of excessive discharges occurring in **one area or hemisphere** (***focal***), or simultaneously in both **hemispheres** (***generalized***), that can **either remain localized or propagate in the brain network** (**widespread seizure**).

Seizure propagation: widespread seizure

- Network of coupled Epileptors
- Epileptogenic Zone: left field **CA1**

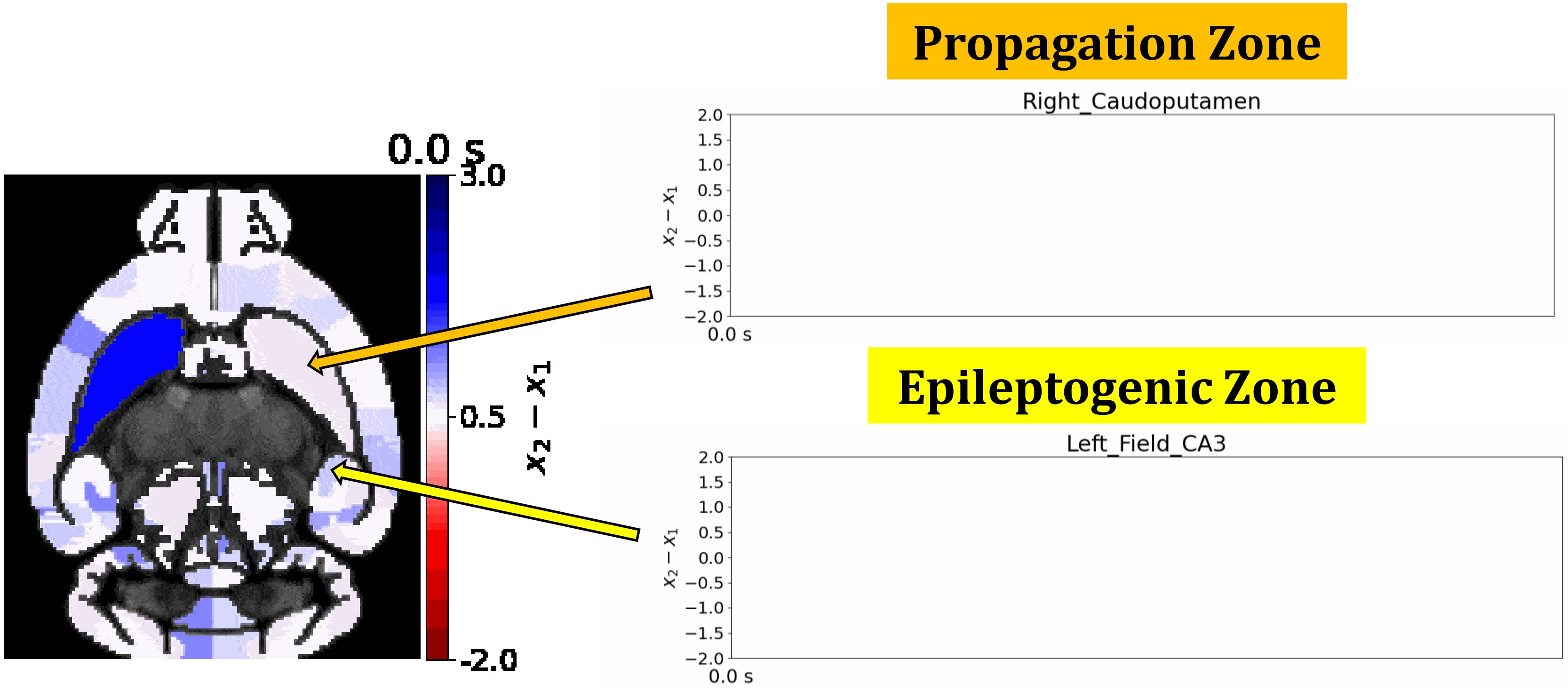
focal seizures: seizures that start in **one** brain area and **may or may not remain localized**



Courson, Quoy, Timofeeva, **MT** *Front. Comput. Neurosci.* 18:1360009, 2024

Seizure propagation: localized seizure

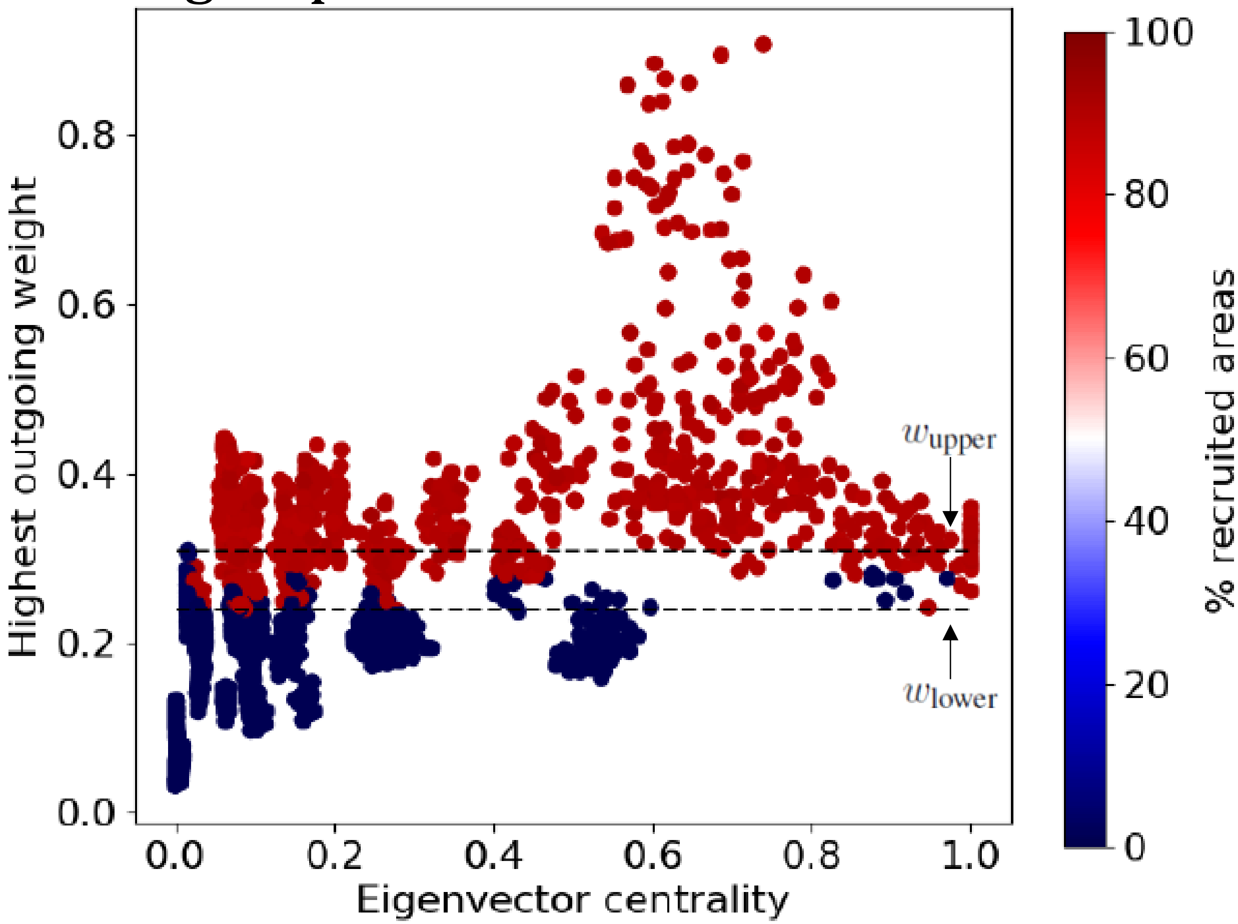
- Network of coupled Epileptors
- Epileptogenic Zone: left field **CA3**

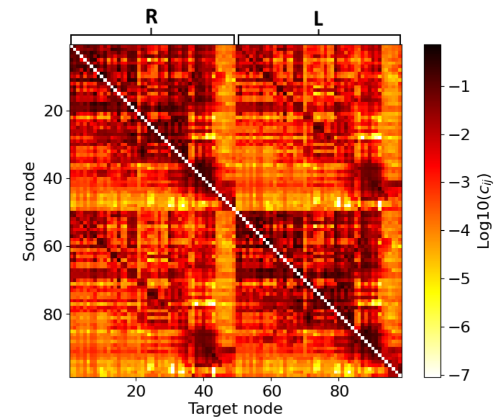


Courson, Quoy, Timofeeva, **MT** *Front. Comput. Neurosci.* 18:1360009, 2024

Connectivity properties of the EZs

- Testing all possible EZ of the Allen SC + 20 varied connectomes





$c_{ji}^{\text{new}}: N(c_{ji}, 0.1c_{ji})$

If $c_{ji}^{\text{new}} < 0 \rightarrow c_{ji}^{\text{new}} = c_{ji}$

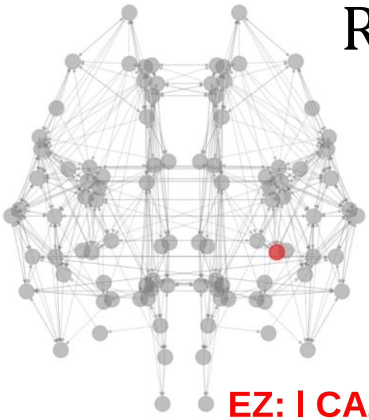
Eigenvector centrality (measure of influence) of node *v* with $A=(a_{i,j})$ the adjacency matrix, λ its highest eigenvalue:

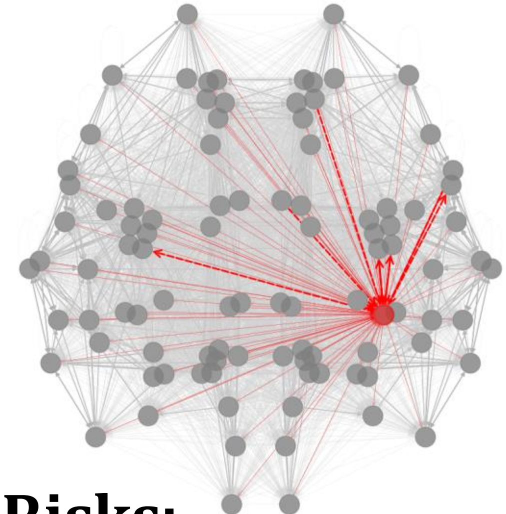
$$x_v = \frac{1}{\lambda} \sum_{t \in V} a_{v,t} x_t$$

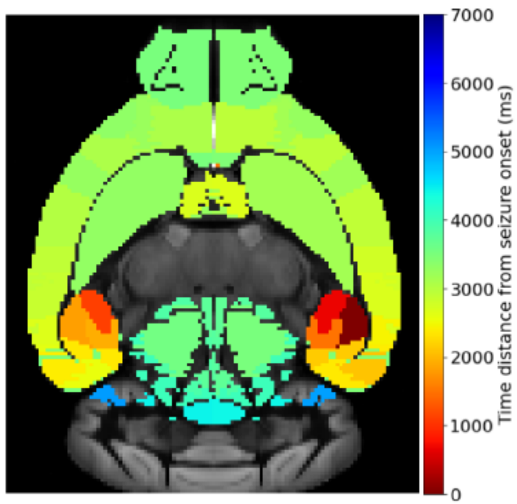
Courson, Quoy, Timofeeva, **MT** Front. *Comput. Neurosci.* 18:1360009, 2024

Widespread seizure prevention

Standard resection strategy:
Removal of a small portion of the brain.



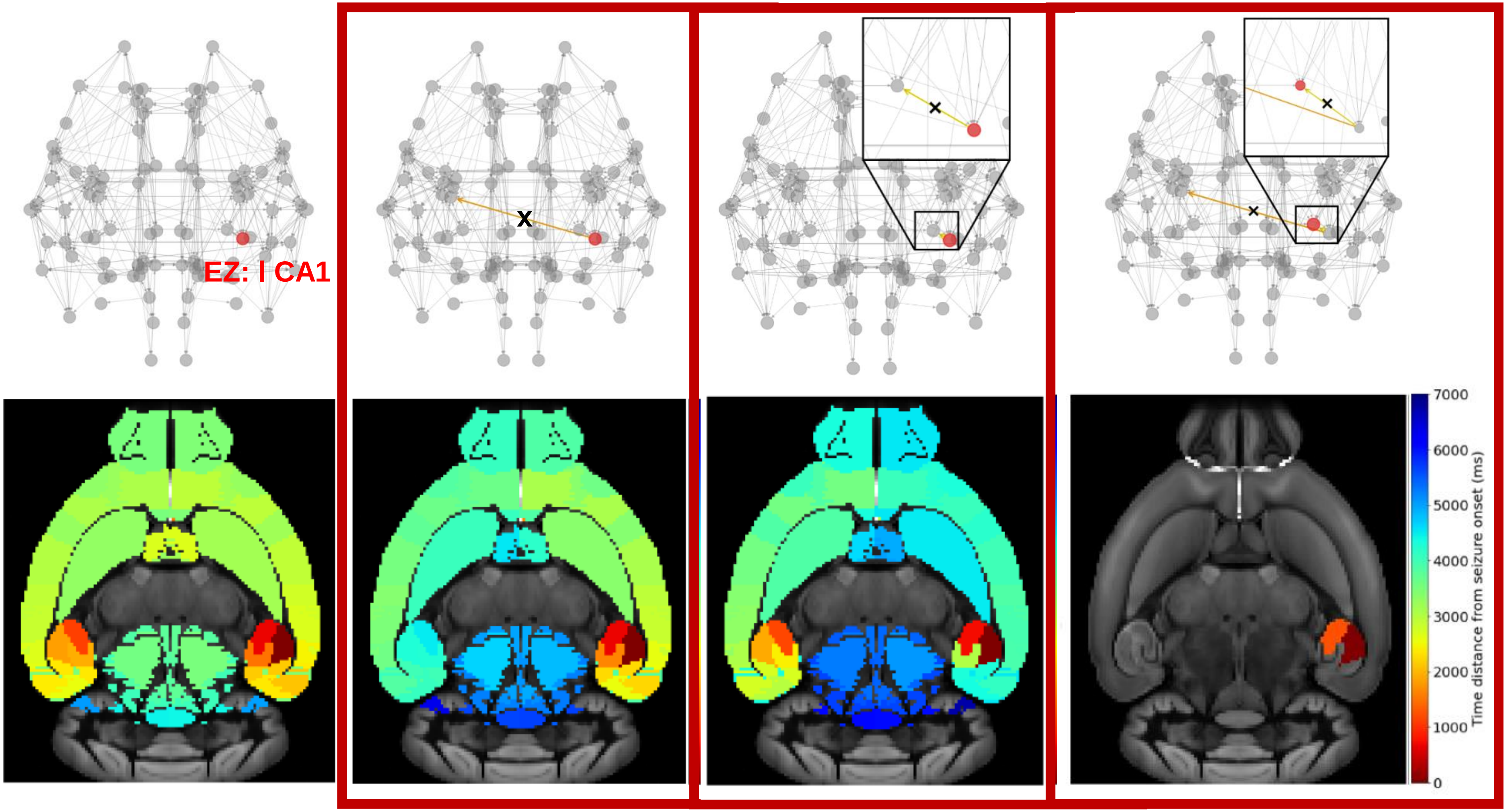




Risks:
- Memory and language
- Visual impairment
- Depression/mood changes
- Headache
- Stroke

Our strategies:
Minimal modification of the brain structure:
- **<u>Selective</u> edge resection** (milder surgical approach)
- **EZ outgoing weight reduction** (neuromodulation approach)

Widespread seizure prevention



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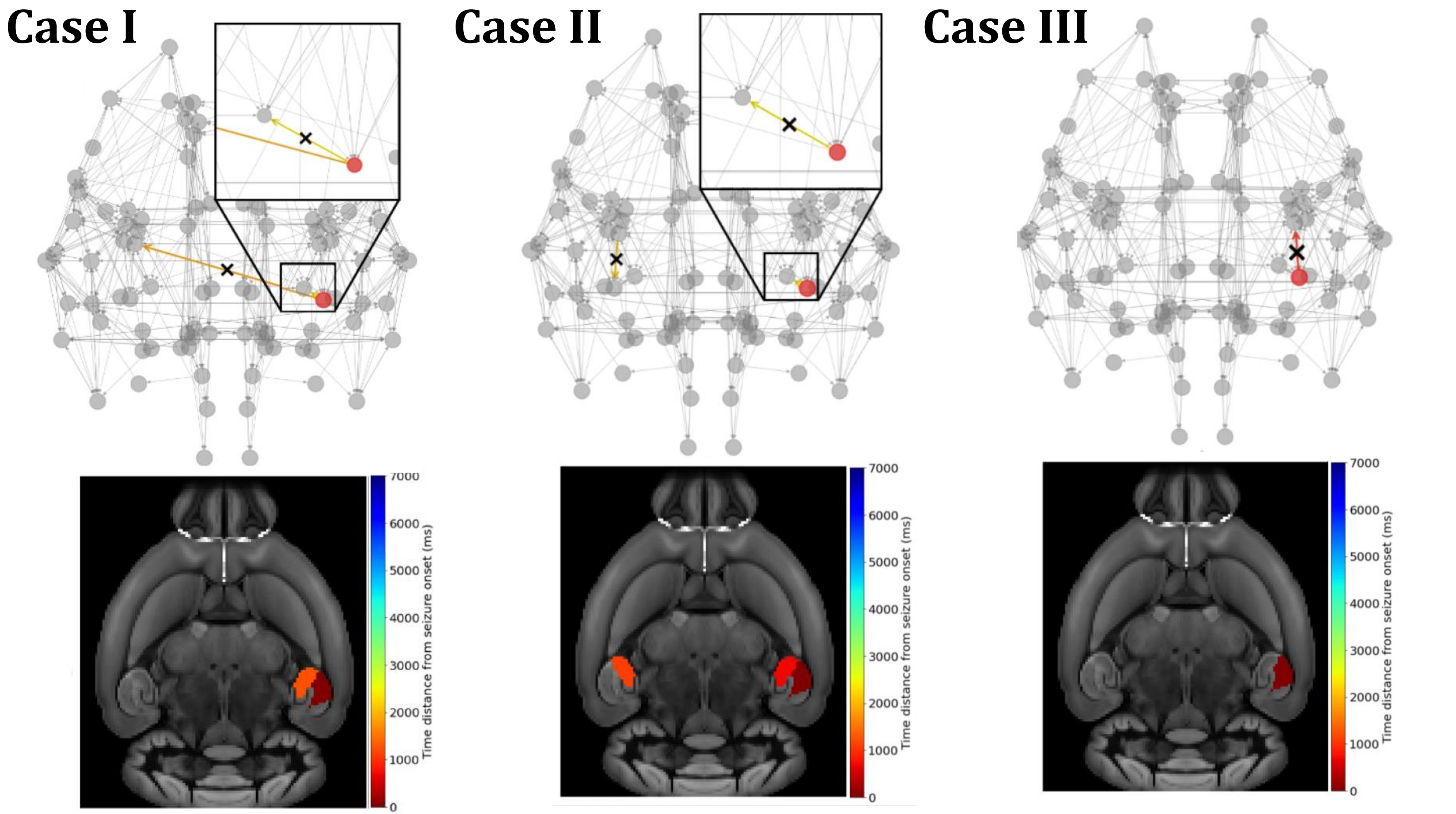
Widespread seizure prevention with edge removal

Resection strategies:

- Blocking pathways in both hemispheres
- Removing the strongest connection



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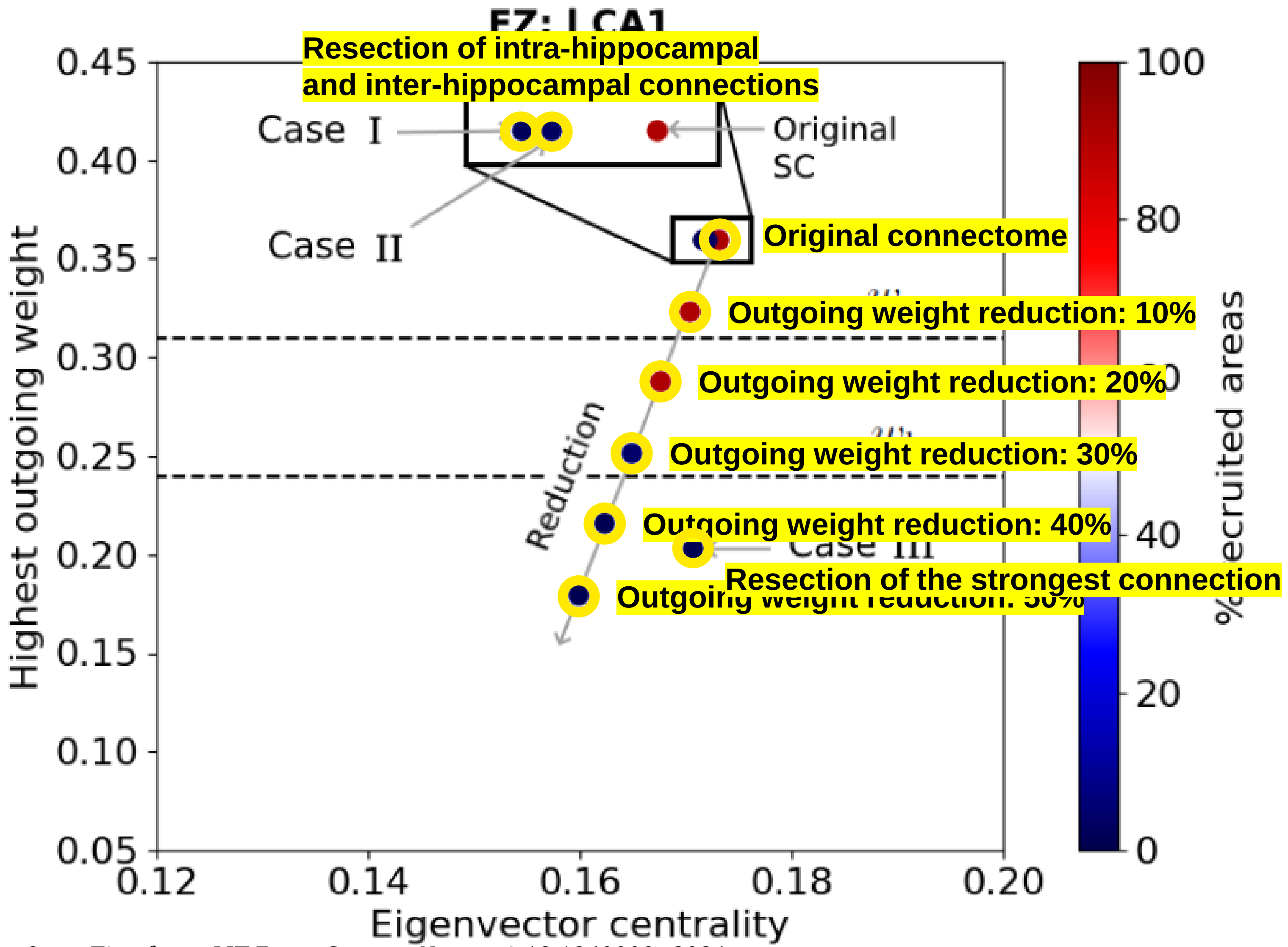
EZ connectivity after edge resection and outgoing weight reduction – CA1



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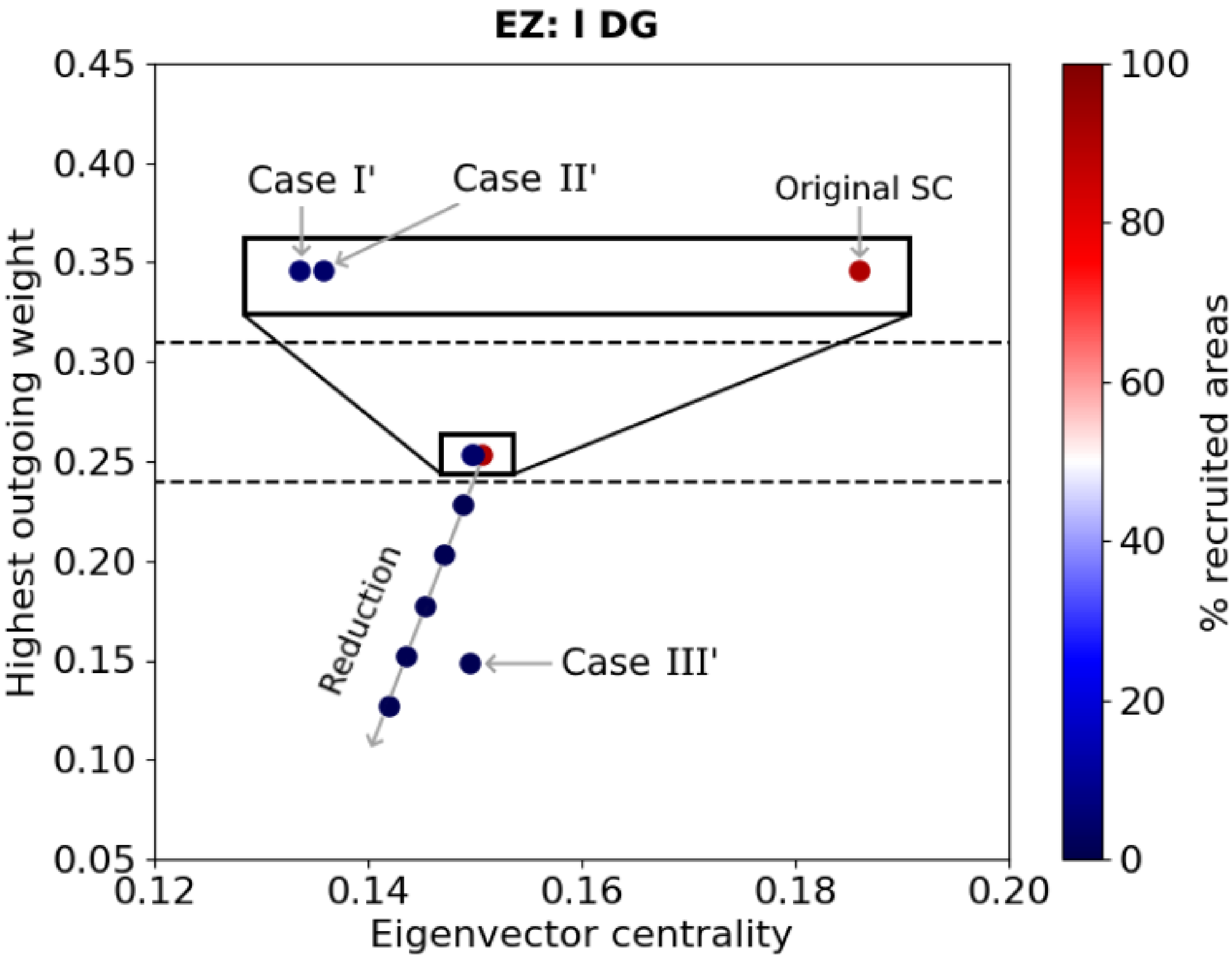
EZ connectivity after edge resection and outgoing weight reduction - DG



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Take home messages

Nonlinear Dynamical Systems can model brain healthy and diseased brain activity and be used to optimize medical treatments

Part I (Parkinson's Disease)

- Therapy and rehabilitation can employ structural plasticity to counteract maladaptive plastic changes and ultimately restore brain function.
- Structural plasticity reveals memory-type effects of the network's treatment susceptibility and predict dosage-dependent phenomena relevant for clinical studies.

Part II (Epilepsy)

- Seizures can be kept constrained around the EZ region → selectively removing (blocking) specific connections informed by the structural connectome and graph network measurements or by locally reducing outgoing connection weights of EZ areas.
- Such approaches may help in minimizing surgical or medical intervention while simultaneously preserving the original structural connectivity and maximizing brain functionality.

Collaborators

Parkinson's study

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Epilepsy study

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Articles

- **Manos T.**, Diaz-Pier S., Tass P.A. Front. Physiol. 12:716556, 2021
- Courson J, Quoy M., Timofeeva Y., **Manos T.** Front. Comput. Neurosci. 18:1360009, 2024

Acknowledgments & Funding

- ❑ **Helmholtz Association** - Helmholtz Portfolio Theme "Supercomputing and Modeling for the Human Brain"
- ❑ **European Union's Horizon 2020** - 720270 (HBP SGA1) and 785907 (HBP SGA2)
- ❑ **Labex MME DII** (ANR-11-LBX-0023-01, ANR-11-LBX-410 0023-01)
- ❑ **CNRS** (research semester in the IPAL Lab in Singapore)
- ❑ **UKRI MRC Project Grant** MR/T002786/1

Our computations were performed at Forschungszentrum Jülich: **Juwels/Jureca** supercomputers & **Osaka cluster** (CY).

Thank you for your attention!