Closed-loop approaches to deep brain stimulation for Parkinson's disease

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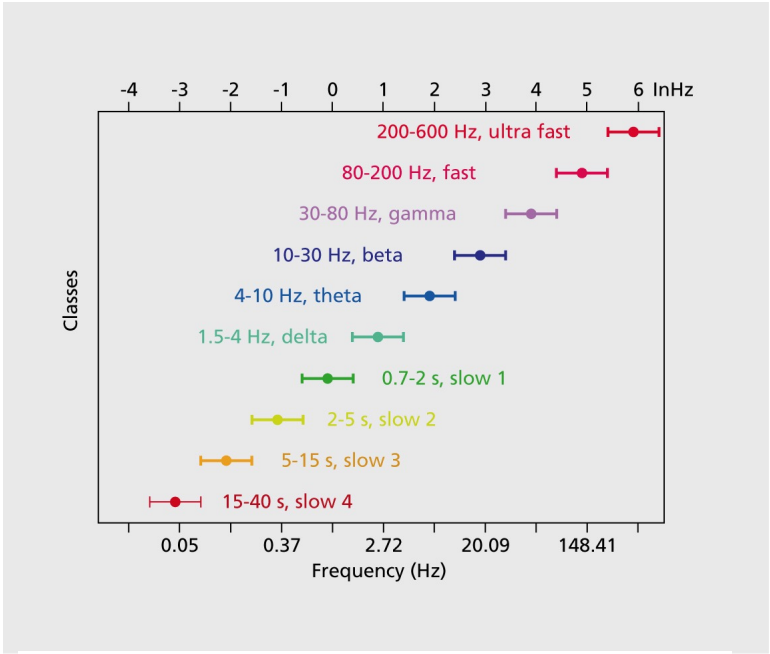
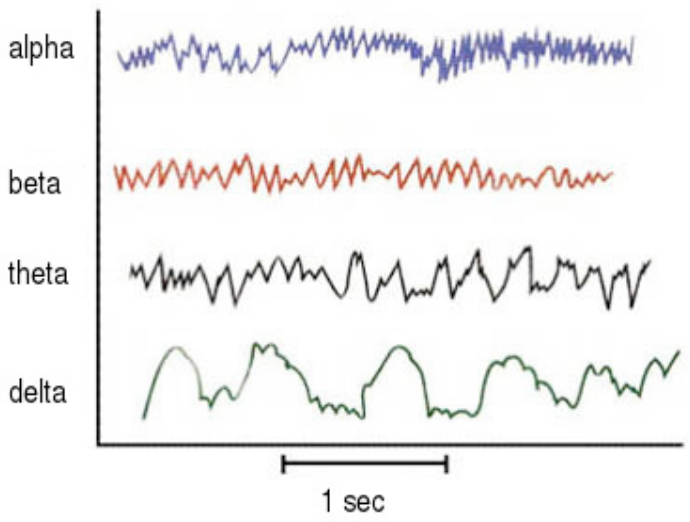
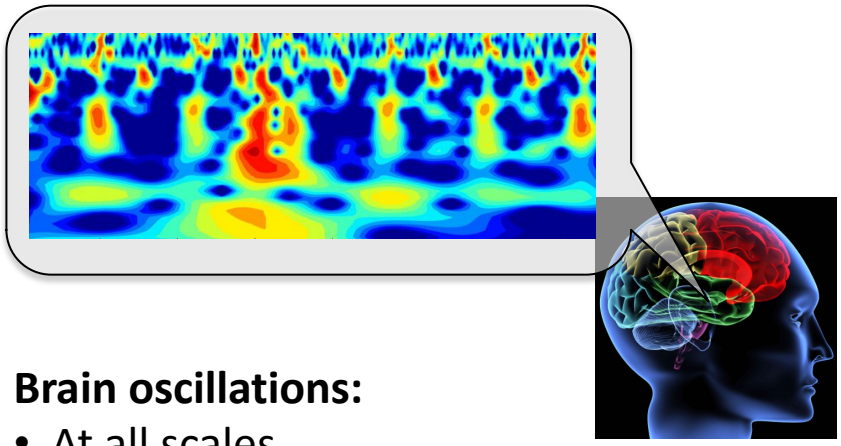
Brain oscillations



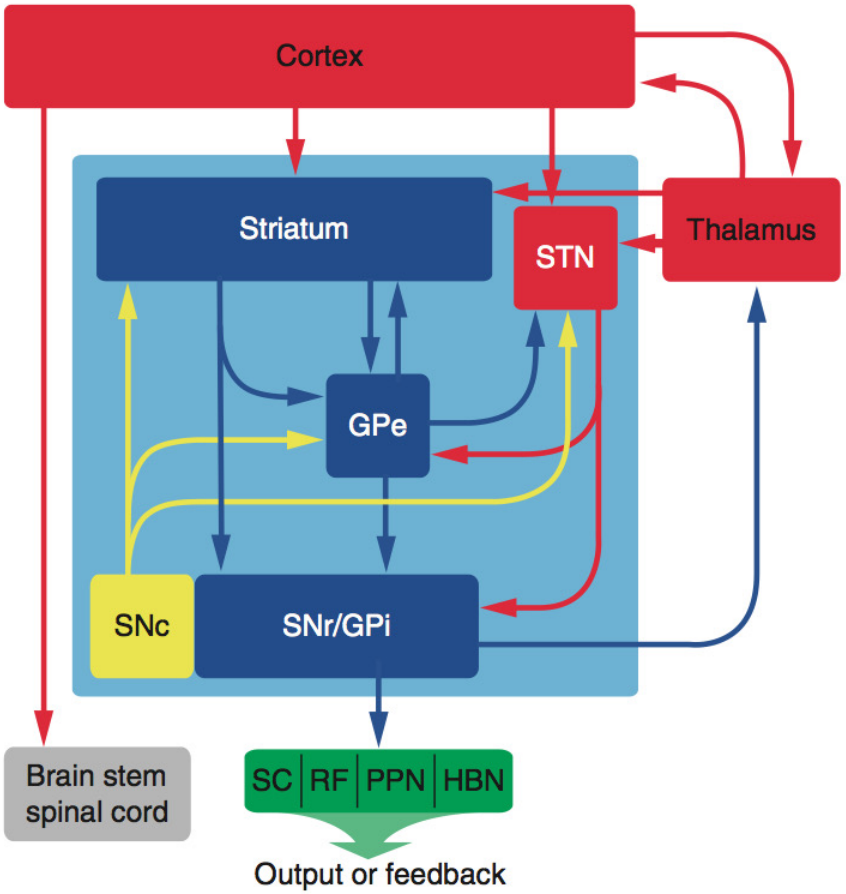




Brain oscillations:

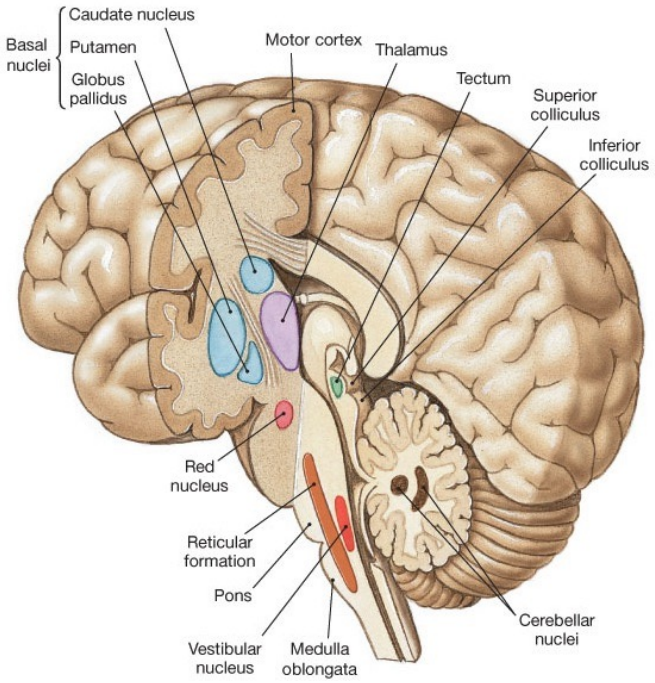
- At all scales
- Linked to most brain functions
- Not just an epiphenomenon: an orchestra conductor of the brain.

Parkinsonian brain oscillations

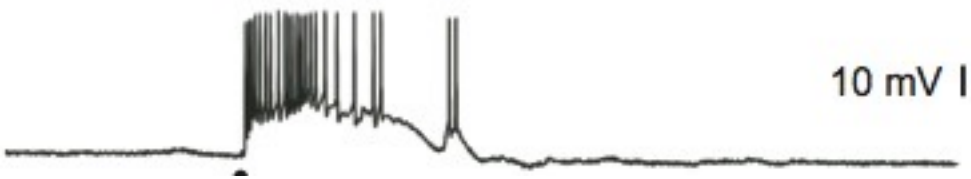


[Bolam et al. 2009]

- Basal ganglia: deep brain structures
- Involved in motor, cognitive and associative functions.

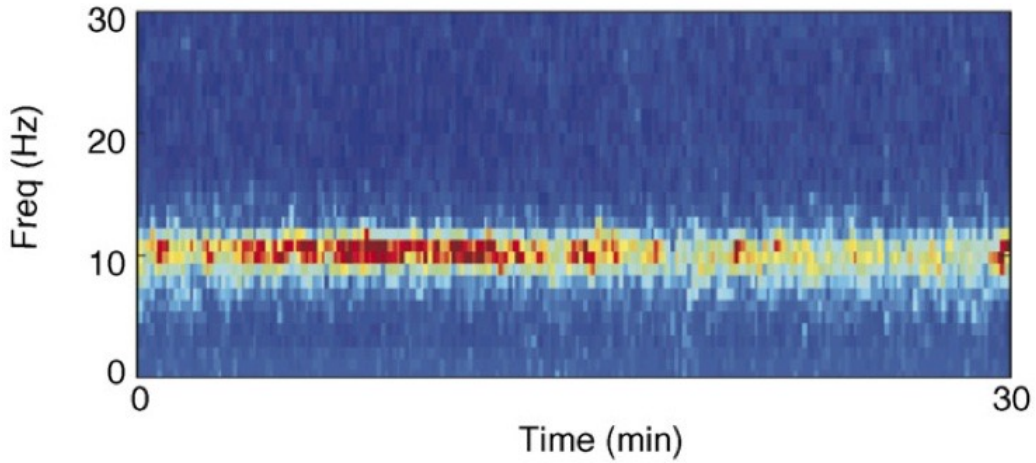


Parkinsonian brain oscillations



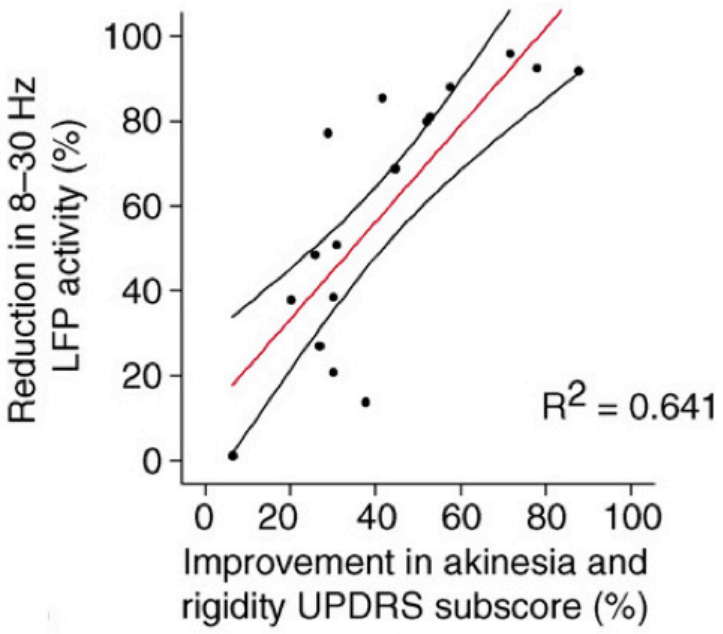
Bursting activity in STN
[Ammari et al. 2011]



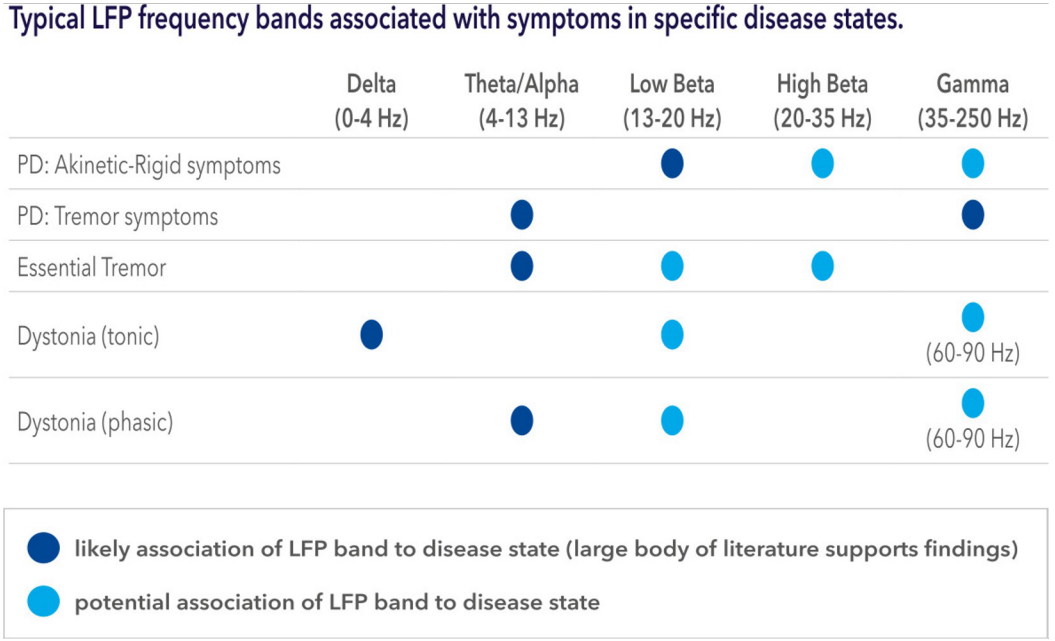


Sustained oscillations
in β band (13-30Hz)
[Hammond et al. 2007]

Parkinsonian brain oscillations

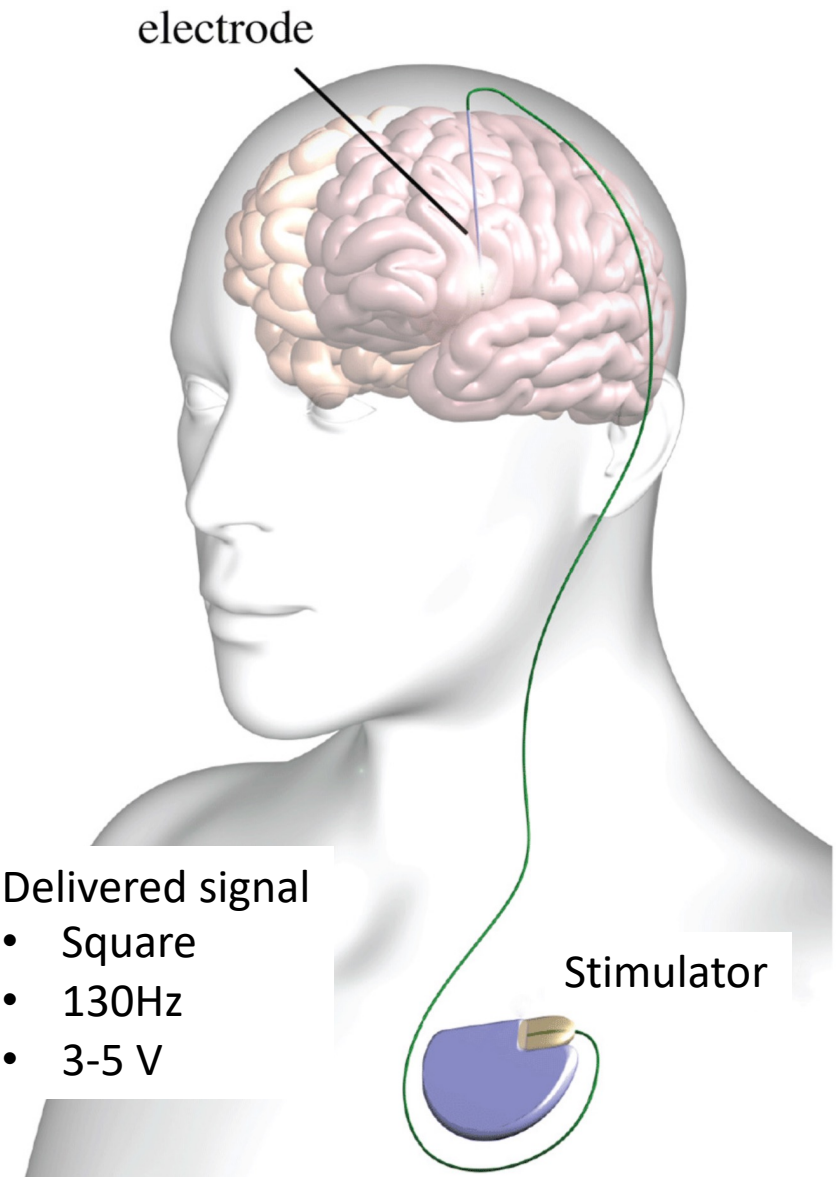


Reduction in β oscillations correlates with motor skills improvement
[Hammond et al. 2007]



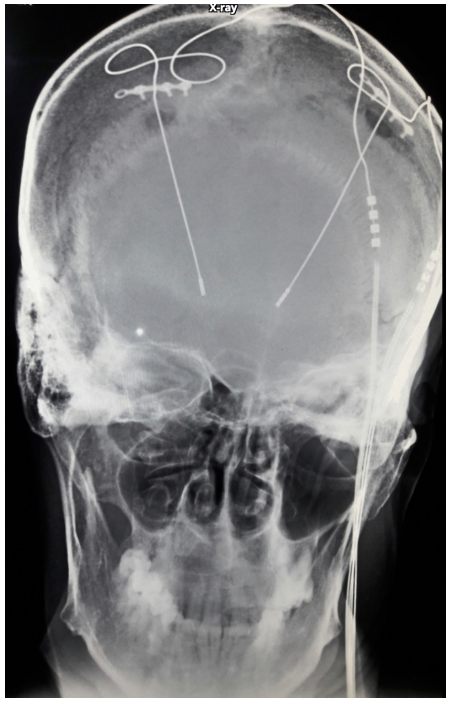
β oscillations correlate mainly with rigidity and akinesia. Different symptoms correlate with different brain oscillations.
[Medtronic 2023]

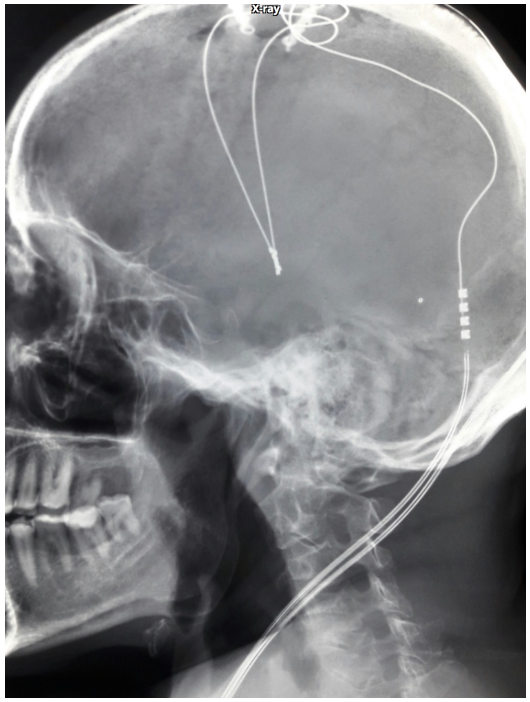
Deep brain stimulation



Delivered signal

- Square
- 130Hz
- 3-5 V





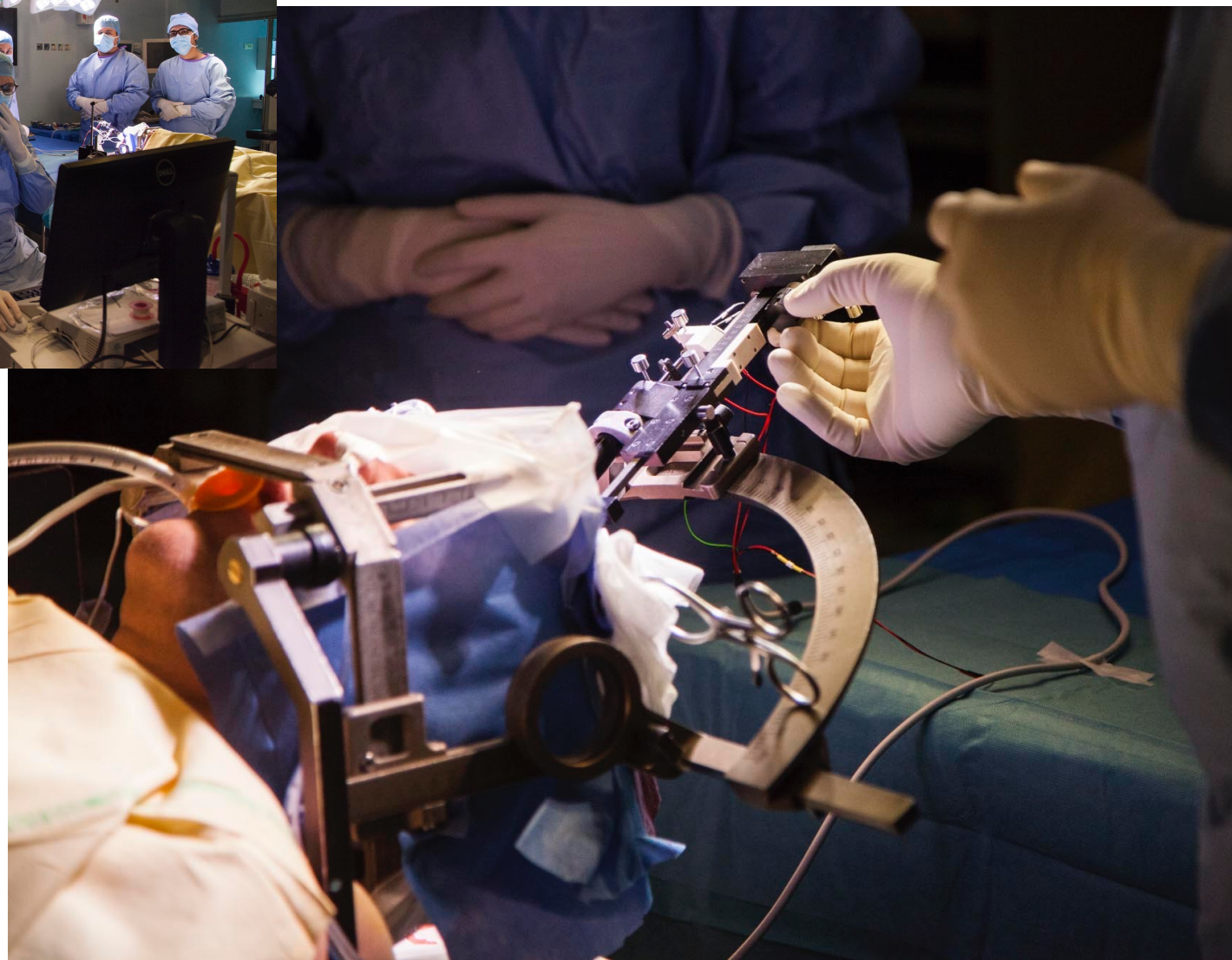




Deep brain stimulation



Neurosurgery department
H. Mondor hospital: S. Palfi & S. Senova



Parkinsonian STN-GPe loop

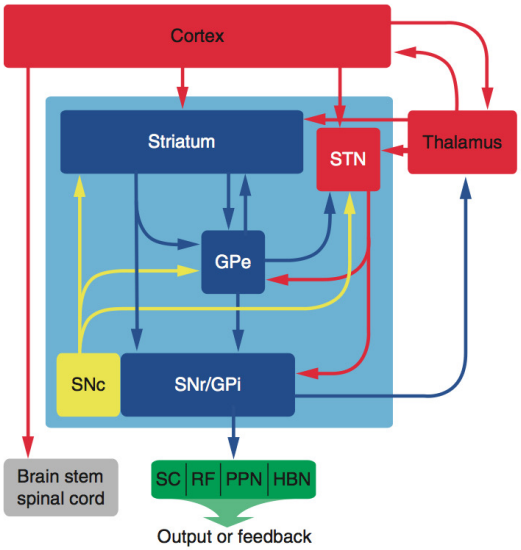
- Parkinson's disease:
  - Bradykinesia and rigity correlate with strong STN activity in beta band (13-30 Hz)

    [Hammond et al., 2007; Kühn et al., 2006; Little et al., 2012]
  - Tremor correlates with strong STN activity in gamma band (31-45Hz) [Beudel et al. 2015]

- Possible explanations:
  - STN-GPe as a pacemaker

    [Plenz and Kital 1999, Nambu & Tachibana, 2014]
  - Entrainment by other brain structures

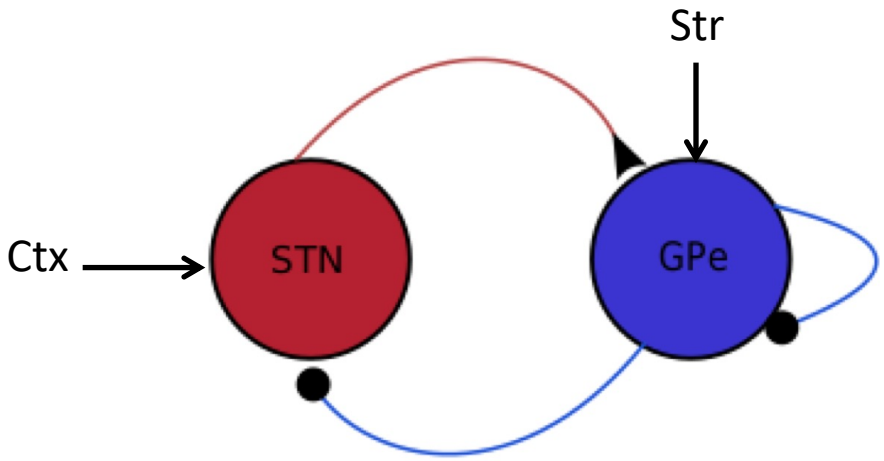
    [McCarthy et al. 2011]



The pacemaker hypothesis

Parkinsonian STN-GPe loop

- Subthalamic nucleus (STN):
  - Mainly excitatory
  - Receives inputs from cortex and projects on GPe
- External Globus pallidus (GPe):
  - Mainly inhibitory
  - Receives inputs from striatum and projects on STN
- Interconnection:
  - Synaptic gains
  - Axonal delays.



Modeling

- Mesoscopic perspective:
  - Focuses on populations rather than individual neurons
  - Allows for analytic results
  - Adequate for *in vivo* measurements.
- Spatiotemporel aspects:
  - Strong sensitivity to electrode positioning in DBS
  - Possible influence of spatial organization of neurons
  - Possible use of multi-plot electrodes.
- Delays:
  - Axonal propagation
  - Synaptic and dendritic delays.
- Nonlinearities due to activation functions.

Modeling

Chosen model: neural fields [Bressloff 2012; Coombes, 2005]

$$\tau_1 \frac{\partial z_1}{\partial t}(r,t) = -z_1(r,t) + S_1\left(\sum_{j=1}^{2}\int_{\Omega} w_{1j}(r,r')z_j(r',t-d_{1j}(r,r'))dr' + I_1^{\text{ext}}(r,t)\right)$$

$$\tau_2 \frac{\partial z_2}{\partial t}(r,t) = -z_2(r,t) + S_2\left(\sum_{j=1}^{2}\int_{\Omega} w_{2j}(r,r')z_j(r',t-d_{2j}(r,r'))dr' + I_2^{\text{ext}}(r,t)\right)$$

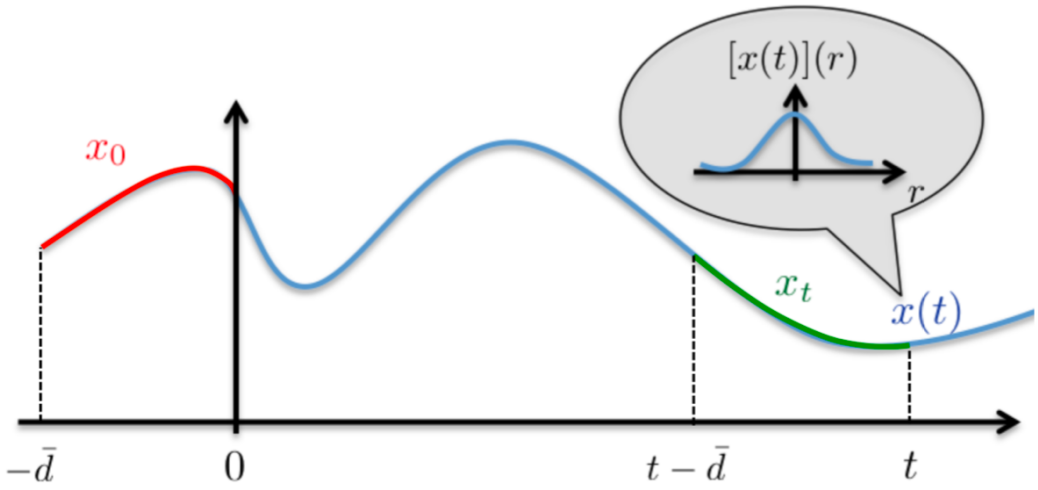
- $z_1(r,t),\ z_2(r,t)$: STN and GPe activity at position *r* and time *t*
- $\tau_1,\ \tau_2$: time constants
- $S_1,\ S_2$: activation functions (ex: sigmoïdal)
- w_{ij} : synaptic weights
- d_{ij} : axonal delays
- I_1^{ext} : cortical input, I_2^{ext} : striatal input.

Mathematical framework

System: $\dot{x}(t) = f(x_t, p(t))$

$\mathcal{F} := L^2(\Omega, \mathbb{R}^n)$

$\mathcal{C} := C([-\bar{d}; 0], \mathcal{F})$



- $f : \mathcal{C} \times \mathcal{U} \to \mathcal{F}$
- $x(t) \in \mathcal{F}$: at each fixed t, it is a *function* of the space variable
- $x_t \in \mathcal{C}$: state prehistory. For each $\theta \in [-\bar{d}; 0]$, $x_t(\theta) := x(t + \theta)$.
- $p \in \mathcal{U}$: exogenous input.

Associated norms [Faye & Faugeras 2010]:

- $\|x\|_{\mathcal{F}} := \sqrt{\int_\Omega |x(s)|^2 ds}$ for all $x \in \mathcal{F}$
- $\|x_t\|_{\mathcal{C}} := \sup_{\theta \in [-\bar{d}; 0]} \|x(t + \theta)\|_{\mathcal{F}}$ for all $x_t \in \mathcal{C}$.

Necessary condition for pacemaker effect

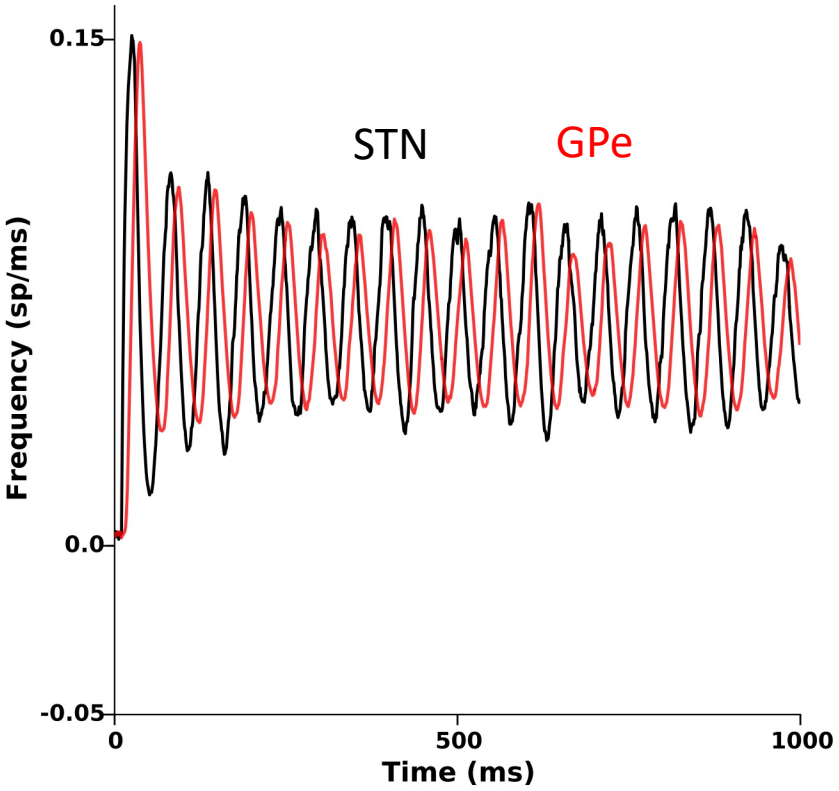
If S_1 and S_2 are Lipschitz with Lipschitz constant ℓ and the synaptic weights satisfy:

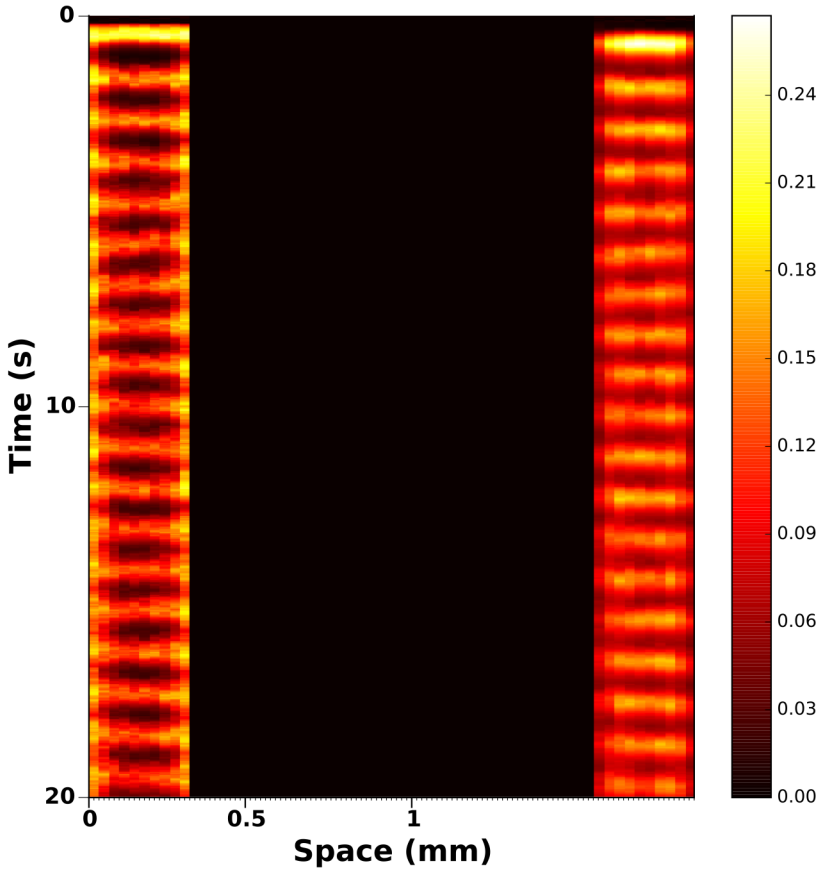
$$\ell \|w\|_{\mathcal{F}} < 1$$

then, for all constant inputs, there exists a unique equilibrium configuration which is globally asymptotically stable. [Faye & Faugeras 2010]

- If the synaptic coupling is weak enough, no pacemaker effect no matter the value of delays
- Trade-off between excitability and synaptic strength
- Robust condition: no precise knowledge of the parameters is needed.

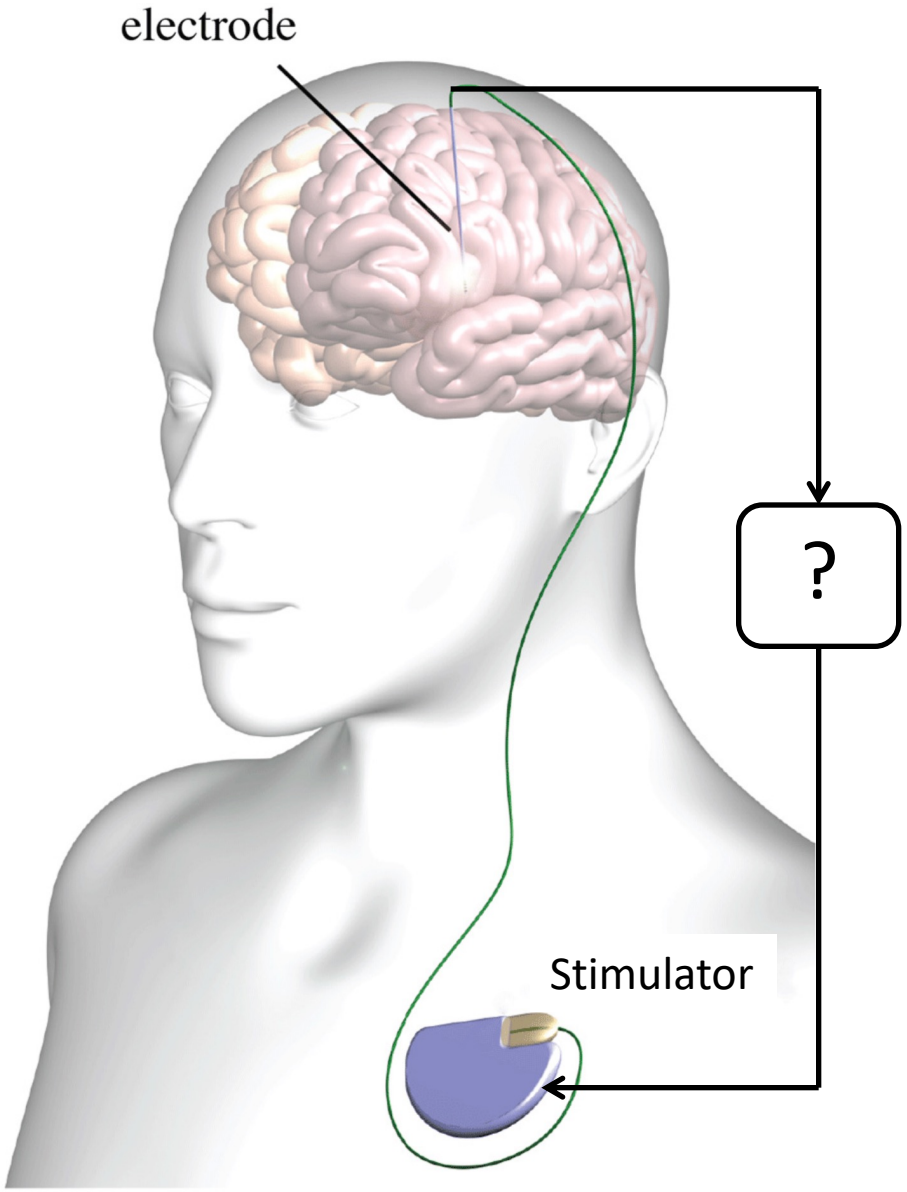
Pacemaker effect





The model reproduces beta oscillations when the stability condition is violated.

Closing the loop of DBS



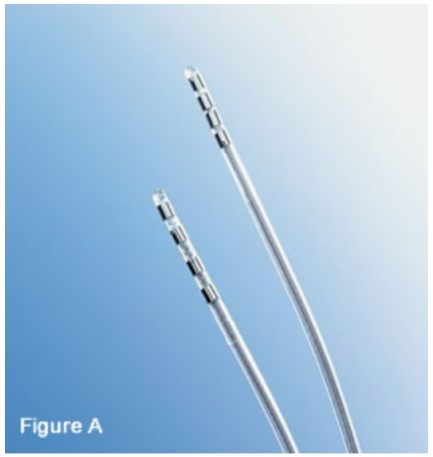
Current limitations of DBS:

- Parameter tuning: amplitude, frequency, impulse length
- Possible loss of efficiency with time
- Side effects reported
- Overuse of battery

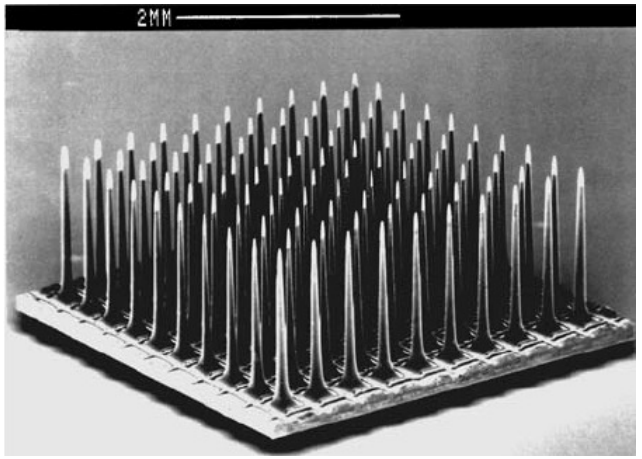
Possible solution:
Adapting DBS signal based on real-time brain measurements

Available sensors

- Preferred solution: invasive electrical recording

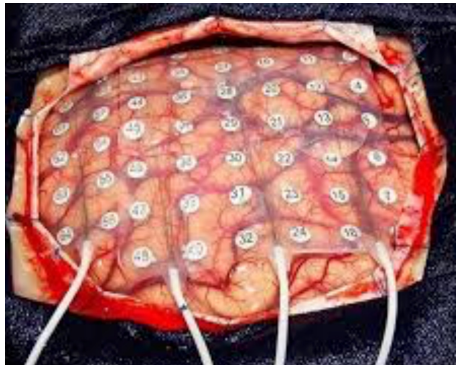


DBS electrodes

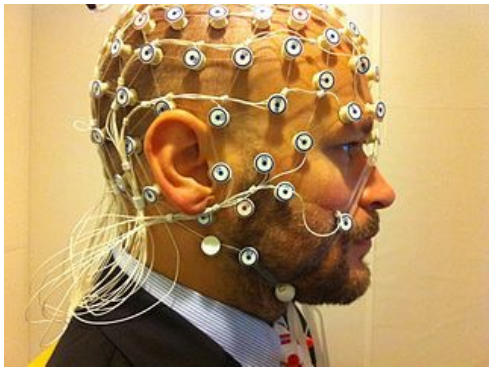


Electrode arrays

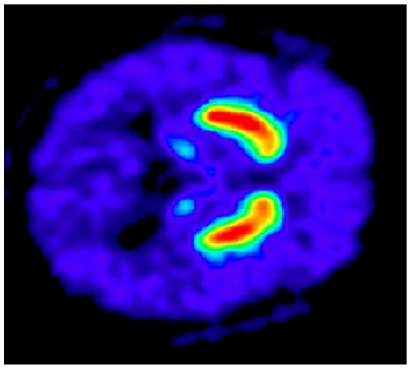
- Other means to measure brain activity:



ECoG



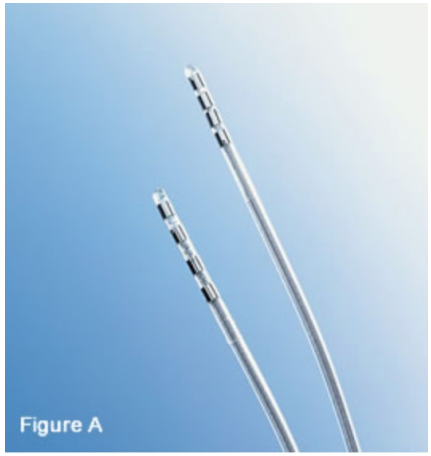
EEG



fMRI

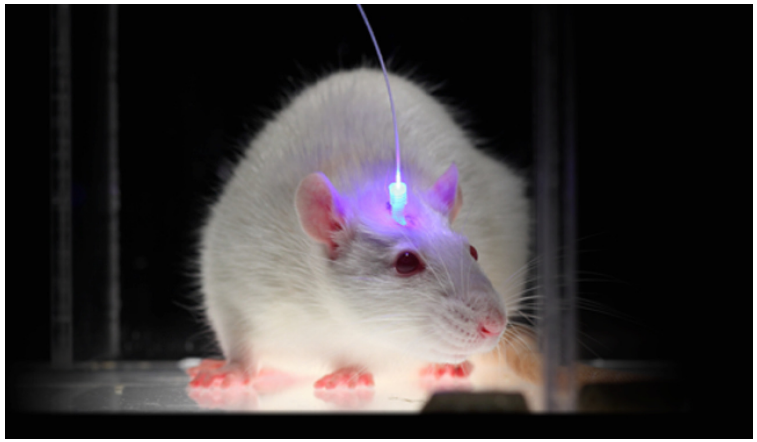
Available actuators

- Clinical solution:



DBS electrodes

- Experimental solution:



Optogenetics
[Boyden et al. 2005]

- Other options:
  - Accoustic neuromodulation
  - Sonogenetics
  - Magnetic stimulation
  - …

Proportional feedback on STN

- Make it simple: stimulate STN proportionally to its activity:

$$\tau_1 \frac{\partial z_1}{\partial t} = -z_1 + S_1 \left(\sum_{j=1}^{2} \int_{\Omega} w_{1j}(r,r') z_j(r', t - d_{1j}) dr' + I_1^{\text{ext}} - k_c \alpha(r) \big(z_1(r,t) - z_{ref}(r) \big) \right)$$

$$\tau_2 \frac{\partial z_2}{\partial t} = -z_2 + S_2 \left(\sum_{j=1}^{2} \int_{\Omega} w_{2j}(r,r') z_j(r', t - d_{2j}) dr' + I_2^{\text{ext}} \right)$$

  - k_c : tunable gain
  - $z_{ref}(r)$: chosen reference pattern
  - $\alpha(r)$: possible heterogeneity in stimulation impact
- Requires no GPe measurement or stimulation.

Equilibrium under proportional stimulation

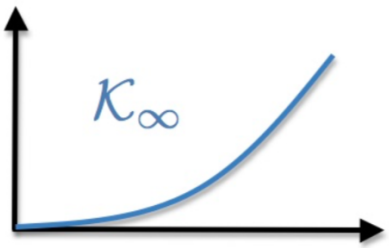
Consider constant inputs from other brain structures:

$$I_1^{\text{ext}}(r,t) = I_1^*(r), \qquad I_2^{\text{ext}}(r,t) = I_2^*(r)$$

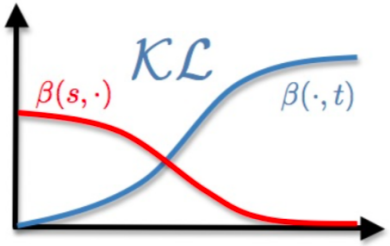
If S_1 and S_2 are continuous and bounded, $\alpha \in L^2(\Omega, \mathbb{R}_{\geq 0})$ and $I_1^*, I_2^*, z_{ref} \in L^2(\Omega, \mathbb{R})$ then the closed-loop system admits at least one equilibrium in $L^2(\Omega, \mathbb{R})^2$.

[Brivadis, Tamekue, Chaillet, Auriol 2023]

ISS for spatiotemporal delay dynamics



$$\dot{x}(t) = f(x_t, p(t))$$



Definition: Input-to-state stability

The system (2) is *ISS* if there exist $\nu \in \mathcal{K}_\infty$ and $\beta \in \mathcal{KL}$ such that, for any $x_0 \in \mathcal{C}$ and any $p \in \mathcal{U}$,

$$\|x(t)\|_{\mathcal{F}} \leq \beta(\|x_0\|_{\mathcal{C}}, t) + \nu\left(\sup_{\tau\in[0;t]} \|p(\tau)\|_{\mathcal{F}}\right), \quad \forall t \geq 0.$$

- Delayed spatio-temporal extension of ISS [Sontag]
- In line with ISS for delay systems: [Pepe & Jiang 2006, Mazenc et al. 2008]
- . . . and for infinite-dimensional systems: [Karafyllis & Jiang 2007, Dashkovskiy & Mironchenko 2012], [Mironchenko & Prieur 2020].

Lyapunov condition for ISS

$$\dot{x}(t) = f(x_t, p(t)) \tag{2}$$

Theorem: Lyapunov-Krasovskii function for ISS

Let $\underline{\alpha}, \overline{\alpha}, \alpha, \gamma \in \mathcal{K}_\infty$ and $V \in C(\mathcal{C}, \mathbb{R}_{\geq 0})$. Assume that, given any $x_0 \in \mathcal{C}$ and any $p \in \mathcal{U}$, solutions of (2) satisfy

$$\underline{\alpha}(\|x(t)\|_{\mathcal{F}}) \leq V(x_t) \leq \overline{\alpha}(\|x_t\|_{\mathcal{C}})$$
$$V(x_t) \geq \gamma(\|p(t)\|_{\mathcal{F}}) \quad \Rightarrow \quad \dot{V}|_{(2)} \leq -\alpha(V(x_t)).$$

Then the system (2) is ISS.

Proof similar to Sontag's original result.

Recentering the system

- For constant striatal and cortical inputs, consider an equilibrium configuration: $z^*(r)$
- Consider variations around this equilibrium:

$$x(r,t) := z(r,t) - z^*(r)$$

- With external perturbations, the system reads:

$$\tau_1 \frac{\partial x_1}{\partial t} = -x_1 + S_1 \left(\sum_{j=1}^{2} \int_\Omega w_{1j}(r,r') x_j(r', t - d_j(r,r')) dr' + \alpha(r) u(r,t) + p_1(r,t) \right)$$

$$\tau_2 \frac{\partial x_2}{\partial t} = -x_2 + S_2 \left(\sum_{j=1}^{2} \int_\Omega w_{2j}(r,r') x_j(r', t - d_j(r,r')) dr' + p_2(r,t) \right) .$$

ISS under proportional DBS

$$\tau_1 \frac{\partial x_1}{\partial t} = -x_1 + S_1\left(\sum_{j=1}^{2}\int_\Omega w_{1j}(r,r')x_j(r',t-d_j(r,r'))dr' + \alpha(r)u(r,t) + p_1(r,t)\right)$$

$$\tau_2 \frac{\partial x_2}{\partial t} = -x_2 + S_2\left(\sum_{j=1}^{2}\int_\Omega w_{2j}(r,r')x_j(r',t-d_j(r,r'))dr' + p_2(r,t)\right).$$

Theorem: ISS stabilization with partial measurement/actuation

Assume that S_i are nondecreasing and ℓ_i-Lipschitz. If

$$\int_\Omega\int_\Omega w_{22}(r,r')^2 dr'dr < \frac{1}{\ell_2} \tag{4}$$

then there exists $k^* > 0$ such that, for any $k \geq k^*$, the proportional feedback $u(r,t) = -kx_1(r,t)$ makes the coupled neural fields ISS.

- (4) imposes that oscillations are not endogenous to GPe (weak internal coupling: in line with neurophysiology literature)
- No precise knowledge of parameters required

Overview of the proof

1. Show that GPe is ISS under condition (4) with

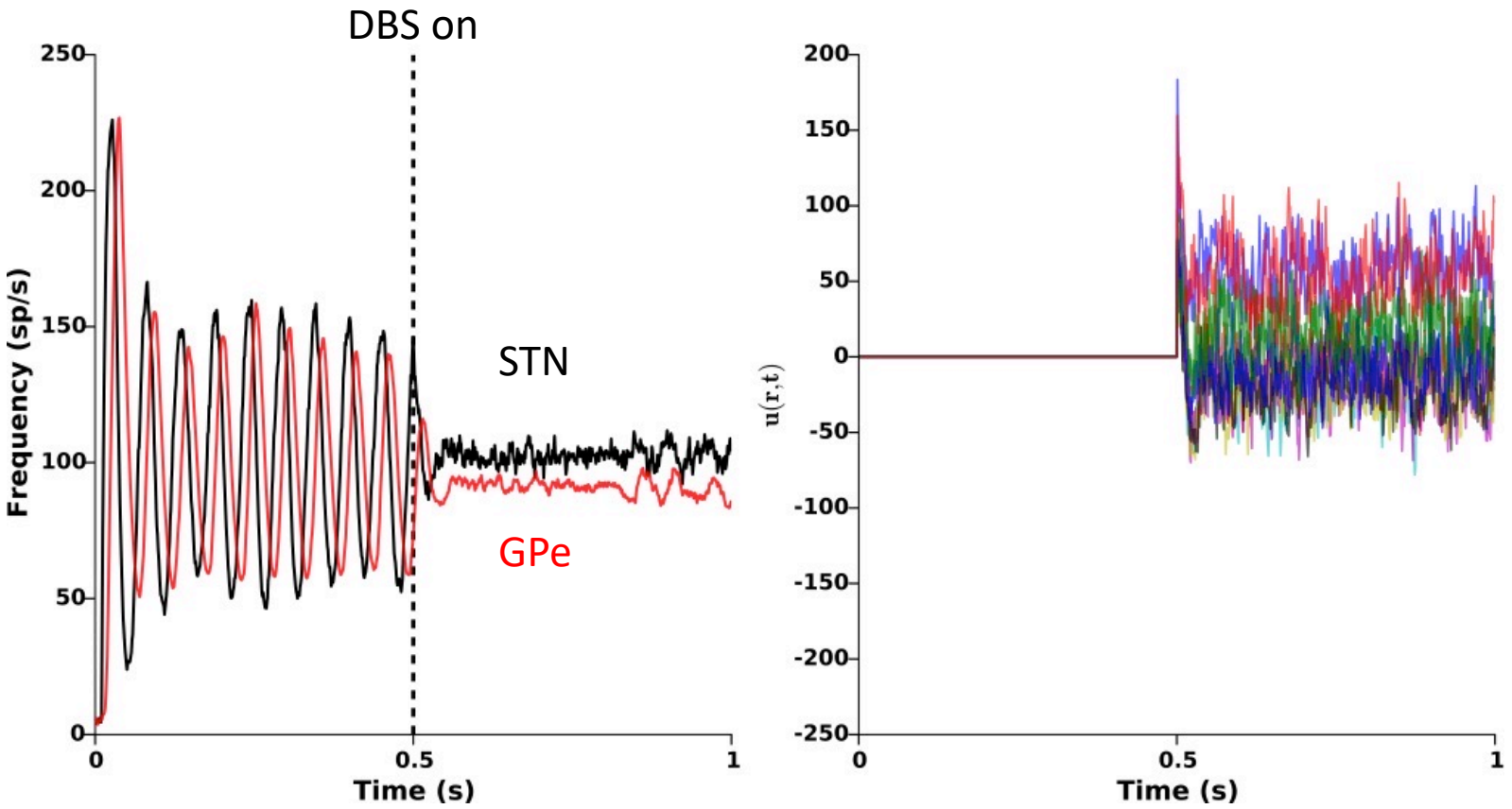
$$V_2(x_{2t}) := \frac{\tau_2}{2}\int_\Omega x_2(r,t)^2 dr + \int_\Omega \beta(r)\int_\Omega \int_{-d_2(r,r')}^{0} e^{c\theta} x_2(r',t+\theta)^2 d\theta dr' dr.$$

2. Show that, for k large enough, STN is ISS with arbitrarily small ISS-gain with

$$V_1(x_{1t}) := \frac{\tau_1}{2}\int_\Omega x_1(r,t)^2 dr + \frac{\tau_1}{2\#\Omega}\int_\Omega \int_\Omega \int_{-d_1(r,r')}^{0} e^{\theta} x_1(r',t+\theta)^2 d\theta dr' dr.$$

3. Invoke small-gain theorem.

Simulations: efficient oscillations disruption



For *k* large enough, oscillations are indeed attenuated.

Robustness to acquisition/processing delays

Estimation of STN activity requires acquisition and computation time:

$$u(r,t) = -kx_1(r, t - d_c(r)).$$

Proposition: Robustness to feedback delays

Under the same assumptions, consider any $k \geq k^*$ and assume that S_1 is bounded. Then there exists a function $\nu \in \mathcal{K}_\infty$ such that

$$\limsup_{t \to \infty} \|x(t)\|_{\mathcal{F}} \leq \nu \left(\sup_{r \in \Omega} d_c(r) \right).$$

- Magnitude of remaining oscillations "proportional" to acquisition/processing delays
- Does not provide much information for large feedback delays...
- Requires a bounded activation function on the STN.

Overview of the proof

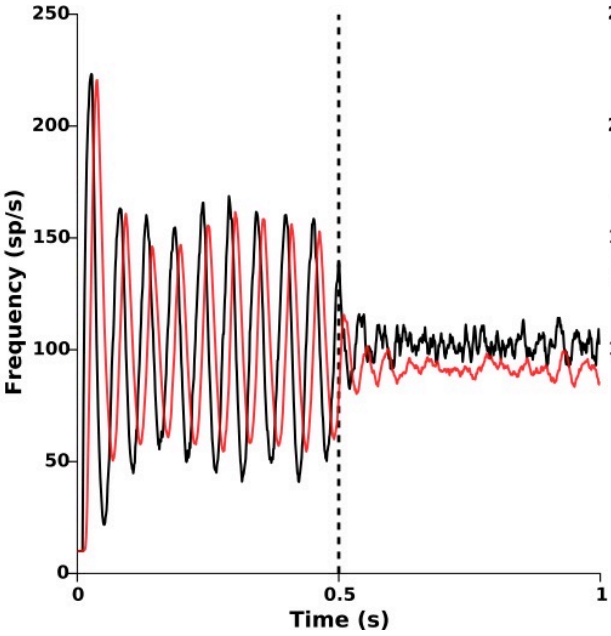
1. See the difference between the delayed and the non-delayed control inputs as a disturbance:

$$p_1(r,t) = -k\big(x_1(r, t - d_c(r)) - x_1(r,t)\big).$$

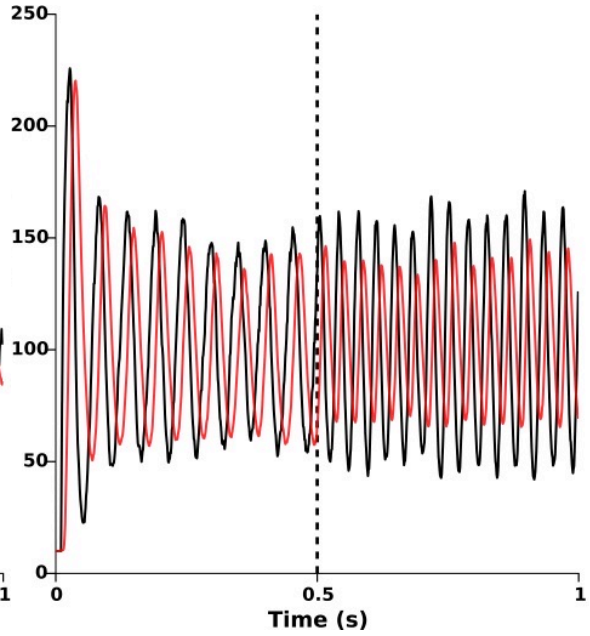
2. Show that this quantity is bounded by a linear function of d_c using boundedness of S_1

3. Exploit the "asymptotic gain property" induced by ISS.

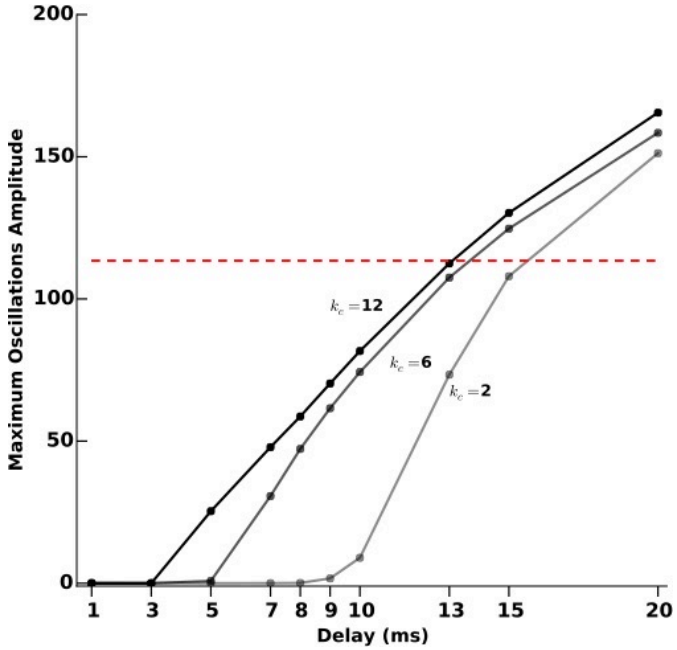
Robustness to acquisition/processing delays



6ms delay



13ms delay



Unique stimulation signal

In practice (e.g. optogenetics), the whole STN receives the same stimulation signal: $u(t) = -\int_\Omega \alpha'(r) x_1(r,t) dr$.

Measure of heterogeneity: $\mathcal{H}(q) := \sqrt{\int_\Omega \int_\Omega (q(r) - q(r'))^2 dr' dr}$.

Proposition: Practical stabilization by homogeneous feedback

Under the same assumptions, consider any $k \geq k^*$. Assume that the activation functions S_i are bounded and that the delay distributions d_i are homogeneous ($d_i(r,r') = d_i^*$). Then there exist $\nu_1, \nu_2 \in \mathcal{K}_\infty$ such that

$$\limsup_{t\to\infty} \|x(t)\|_{\mathcal{F}} \leq \nu_1 \left(\mathcal{H}(w_{11}) + \mathcal{H}(w_{12})\right) + \nu_2 \left(\mathcal{H}(\alpha)\right).$$

- Magnitude of remaining oscillations "proportional" to heterogeneity of STN synaptic weights and stimulation impact
- Requires space-independent delays.

Overview of the proof

1. Considering $W(x_1(t)) = \mathcal{H}_1(x_1(t))^2$, show that

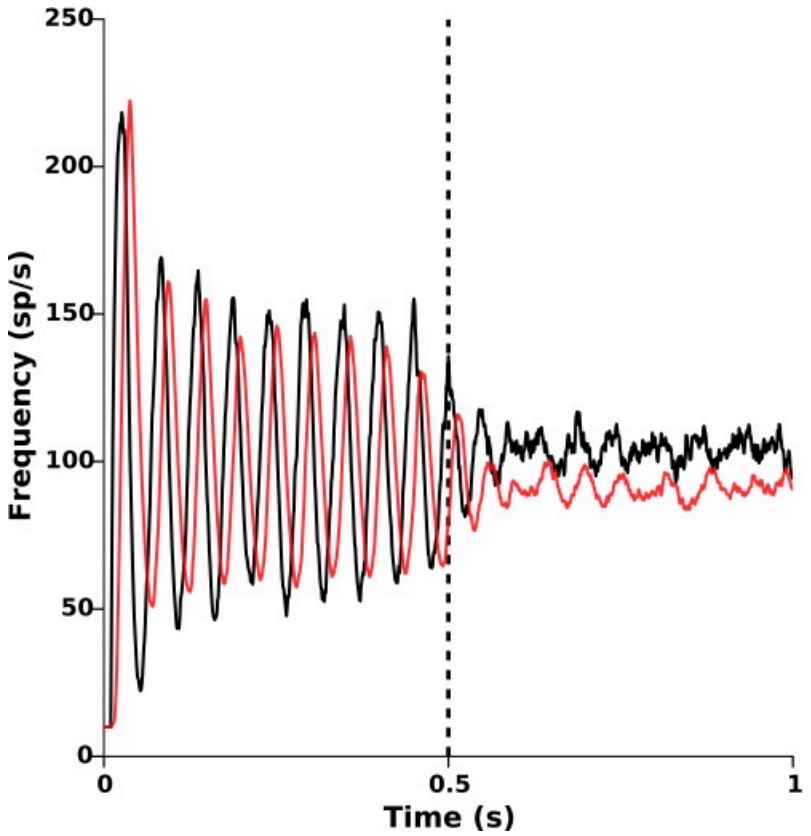
$$\mathcal{H}(x_1(t)) \leq \mathcal{H}(x_1(t_0))e^{-(t-t_0)/\tau_1^*} + c\left(\mathcal{H}(w_{11}) + \mathcal{H}(w_{12}) + \mathcal{H}(\alpha)\right).$$

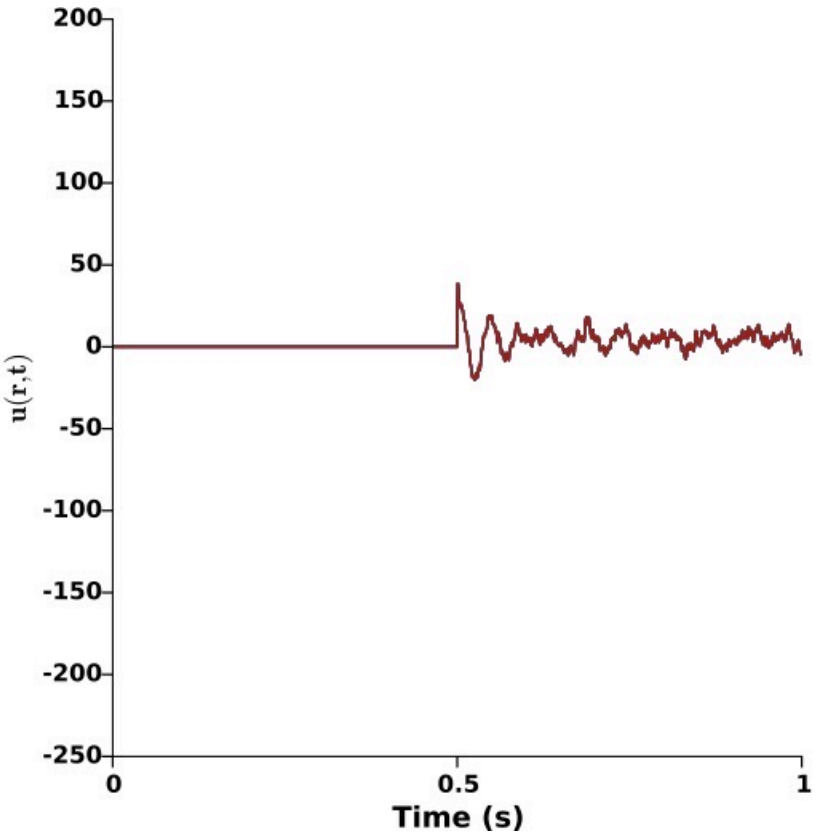
2. Evaluate the difference between the nominal and uniform control laws:

$$\int_\Omega \left(\int_\Omega \alpha'(r')x_1(t,r')dr' - x_1(t,r) \right)^2 dr \leq c\mathcal{H}(x_1(t))^2.$$

3. Exploit the "asymptotic gain property" induced by ISS.

Unique stimulation signal





$$u(r,t) = u(t) = -k_c \int_{\Omega_1} (z_1(r,t) - z_{ref}(r))\, dr.$$

Adaptive DBS

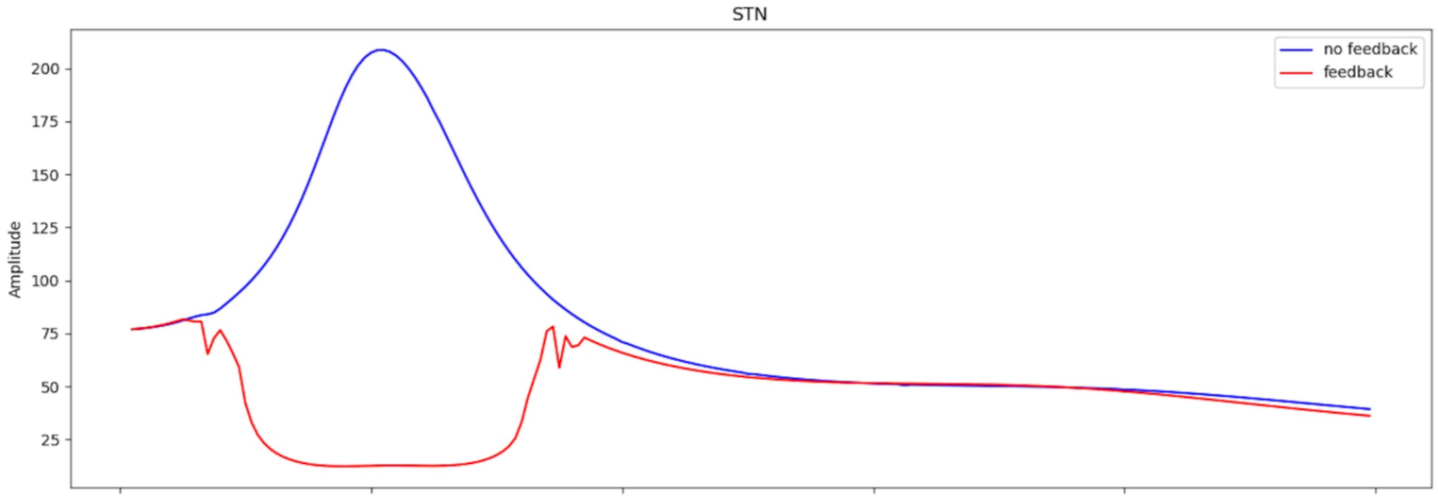
Self-tuning proportional gain

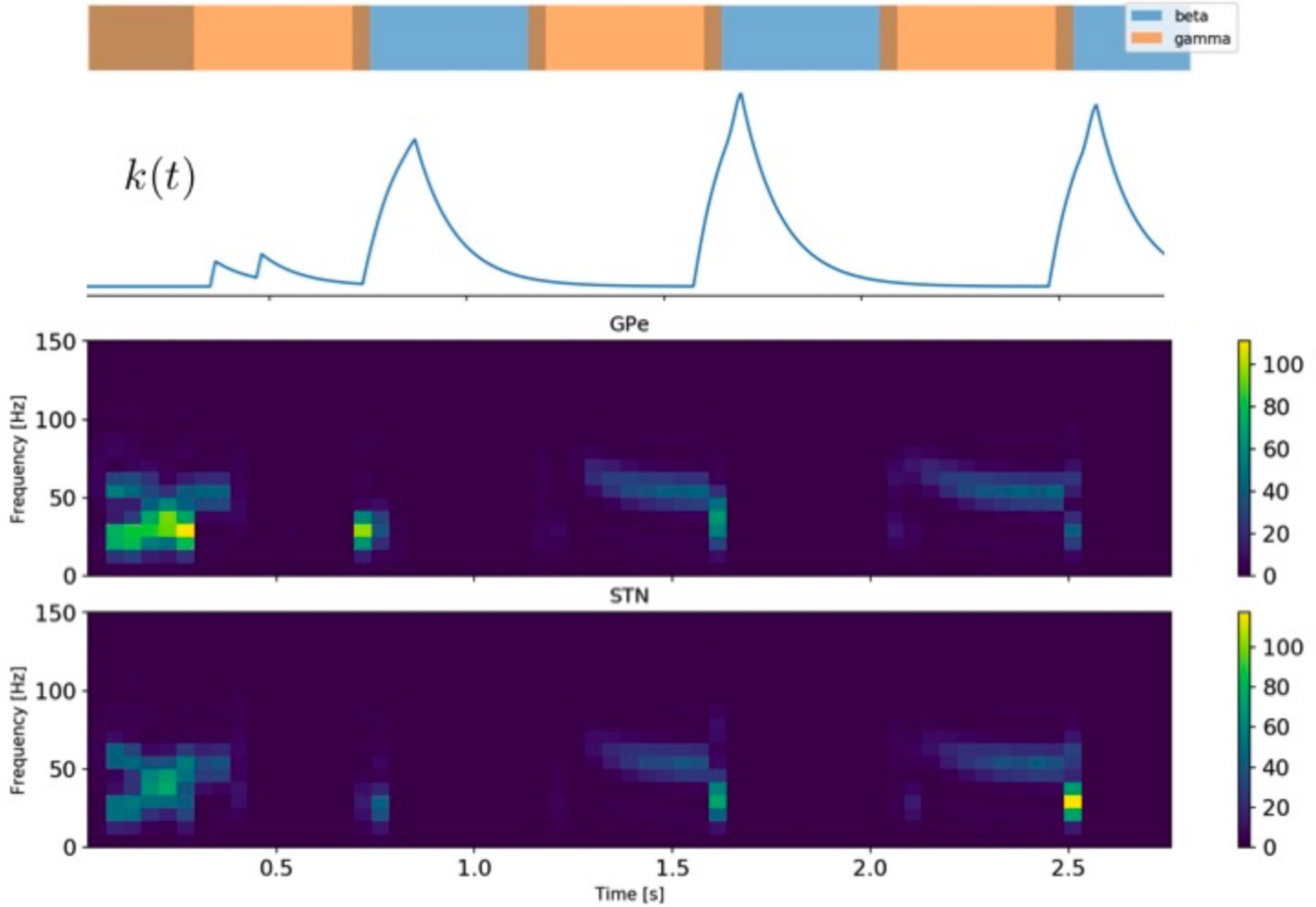
Modification of the stimulation law:

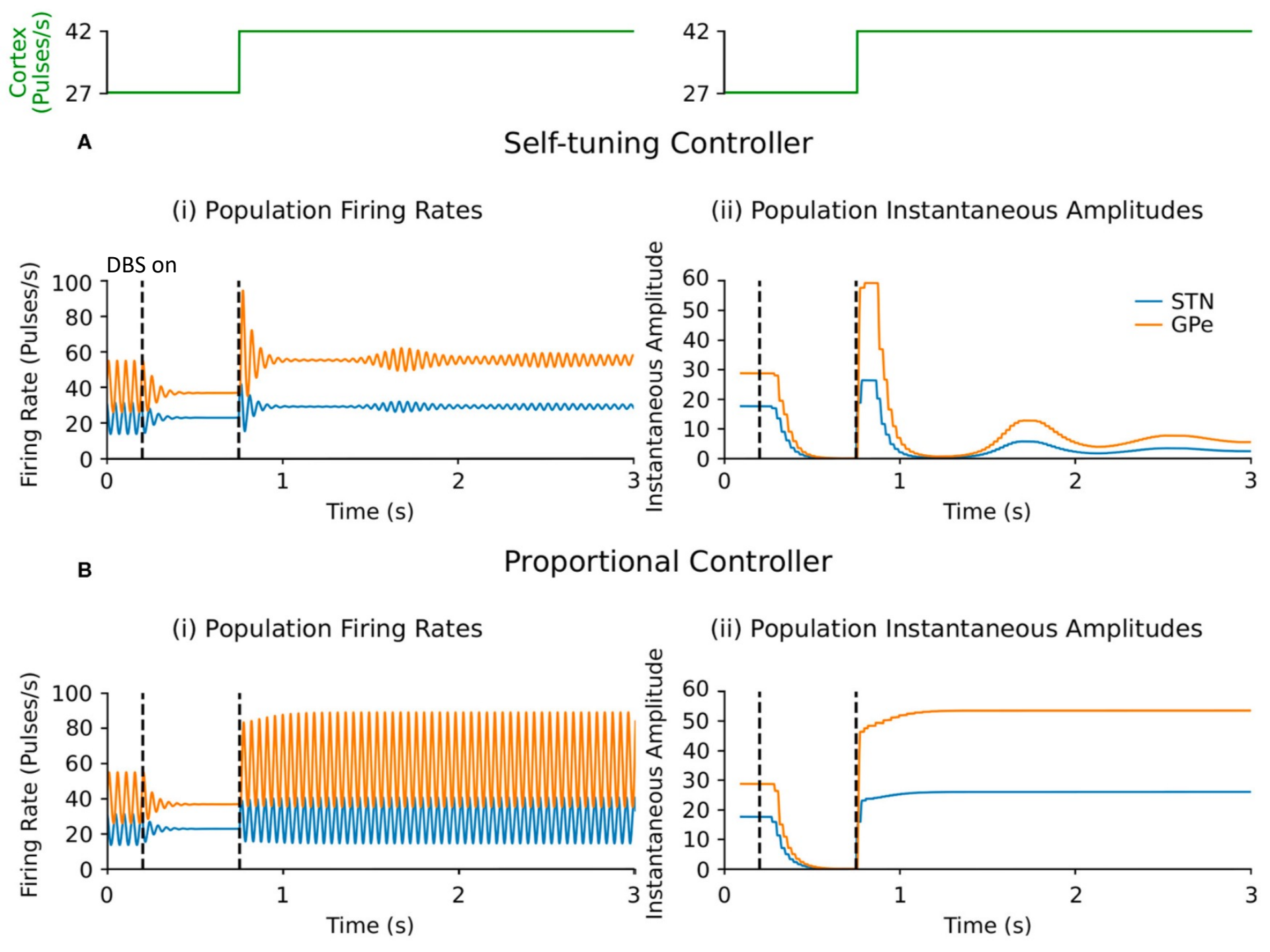
$$u = -kx_1$$
$$\tau \dot{k} = z - \sigma k.$$

"Sigma-modification" [Ioannou & Kokotovic 1984].

- z: intensity of STN activity in the β-band
- $\sigma > 0$: parameter inducing decrease of the gain k when opportune
- $\tau > 0$: time constant.

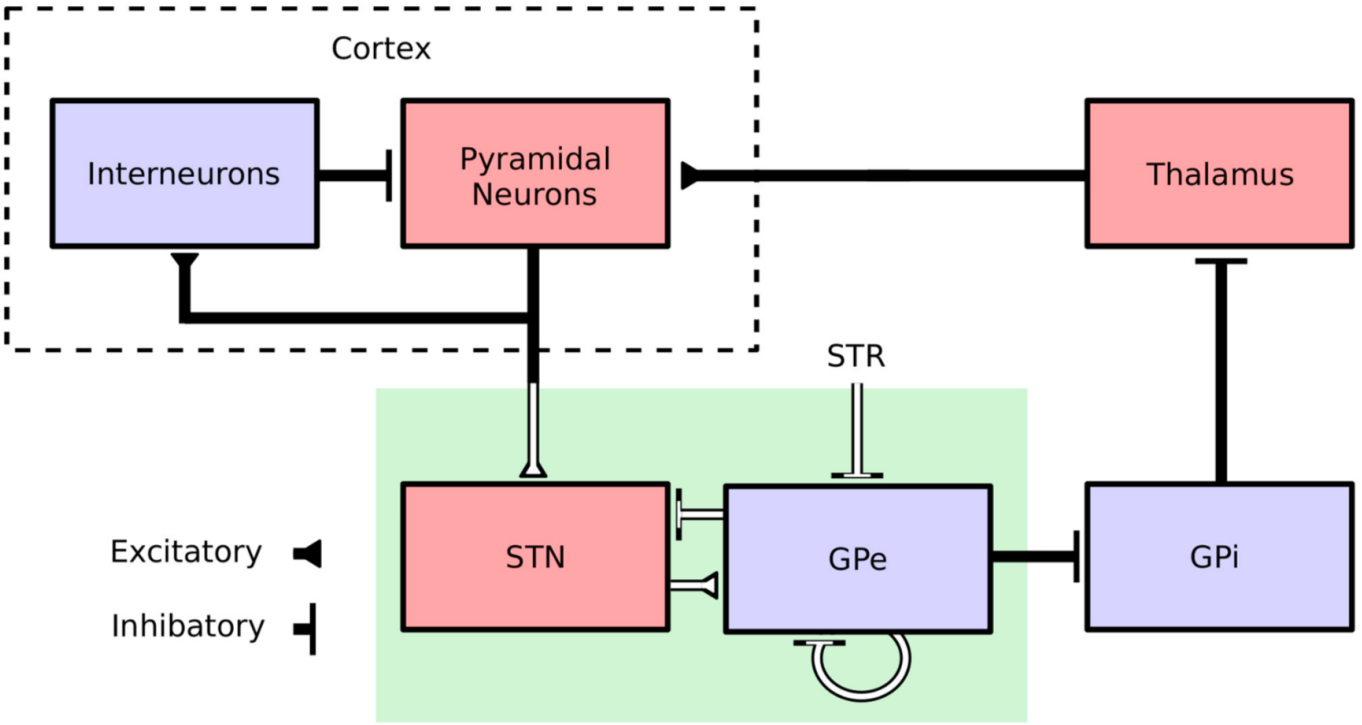



beta
gamma
$k(t)$
GPe
STN
Frequency [Hz]
150
100
50
0
0.5
1.0
1.5
2.0
2.5
Time [s]
100
80
60
40
20
0


Cortex (Pulses/s)
42
27
42
27
A
Self-tuning Controller
(i) Population Firing Rates
(ii) Population Instantaneous Amplitudes
DBS on
Firing Rate (Pulses/s)
Instantaneous Amplitude
STN
GPe
Time (s)
Time (s)
B
Proportional Controller
(i) Population Firing Rates
(ii) Population Instantaneous Amplitudes
Firing Rate (Pulses/s)
Instantaneous Amplitude
Time (s)
Time (s)

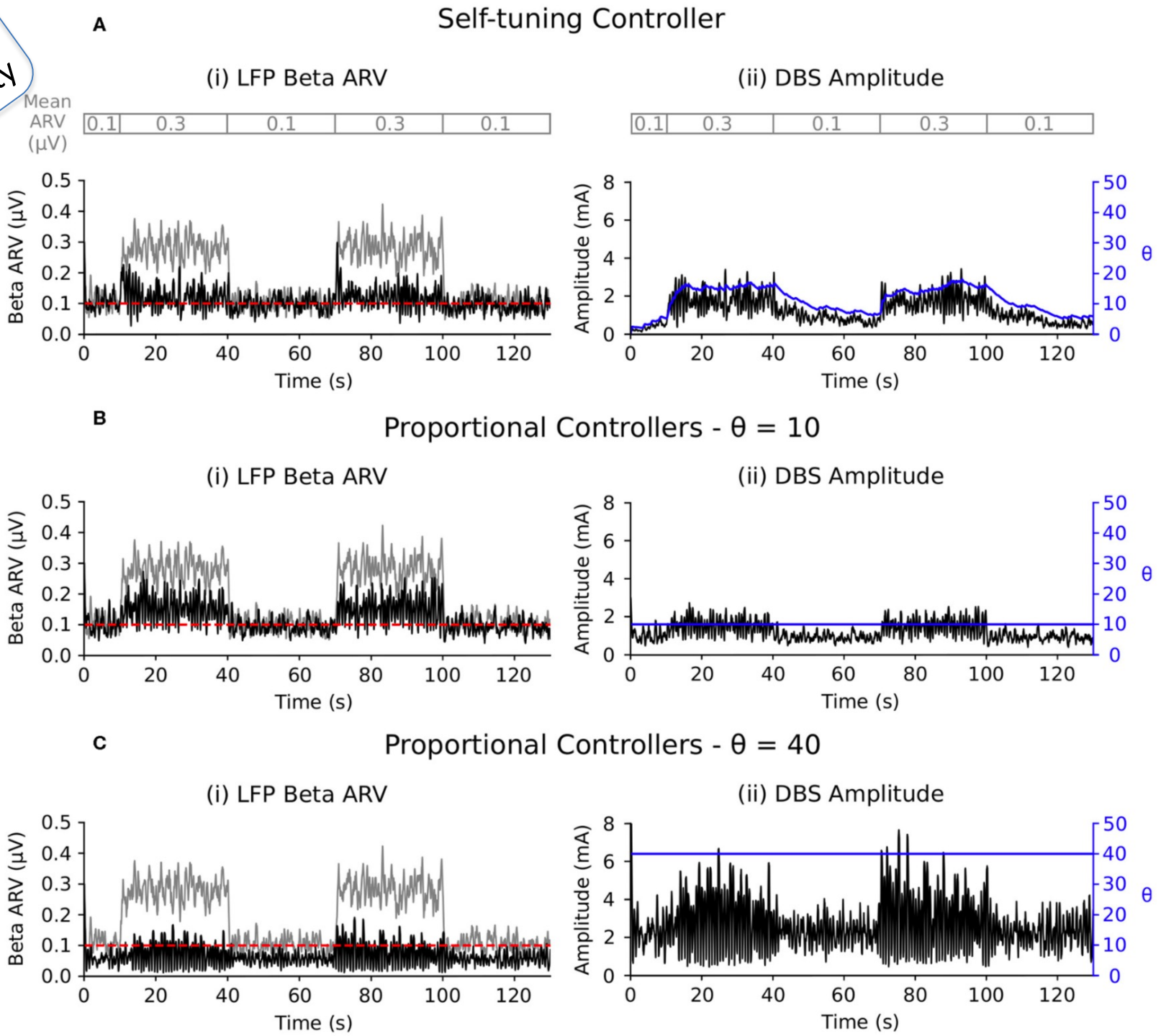
Performance in a numerical model

A more complete model

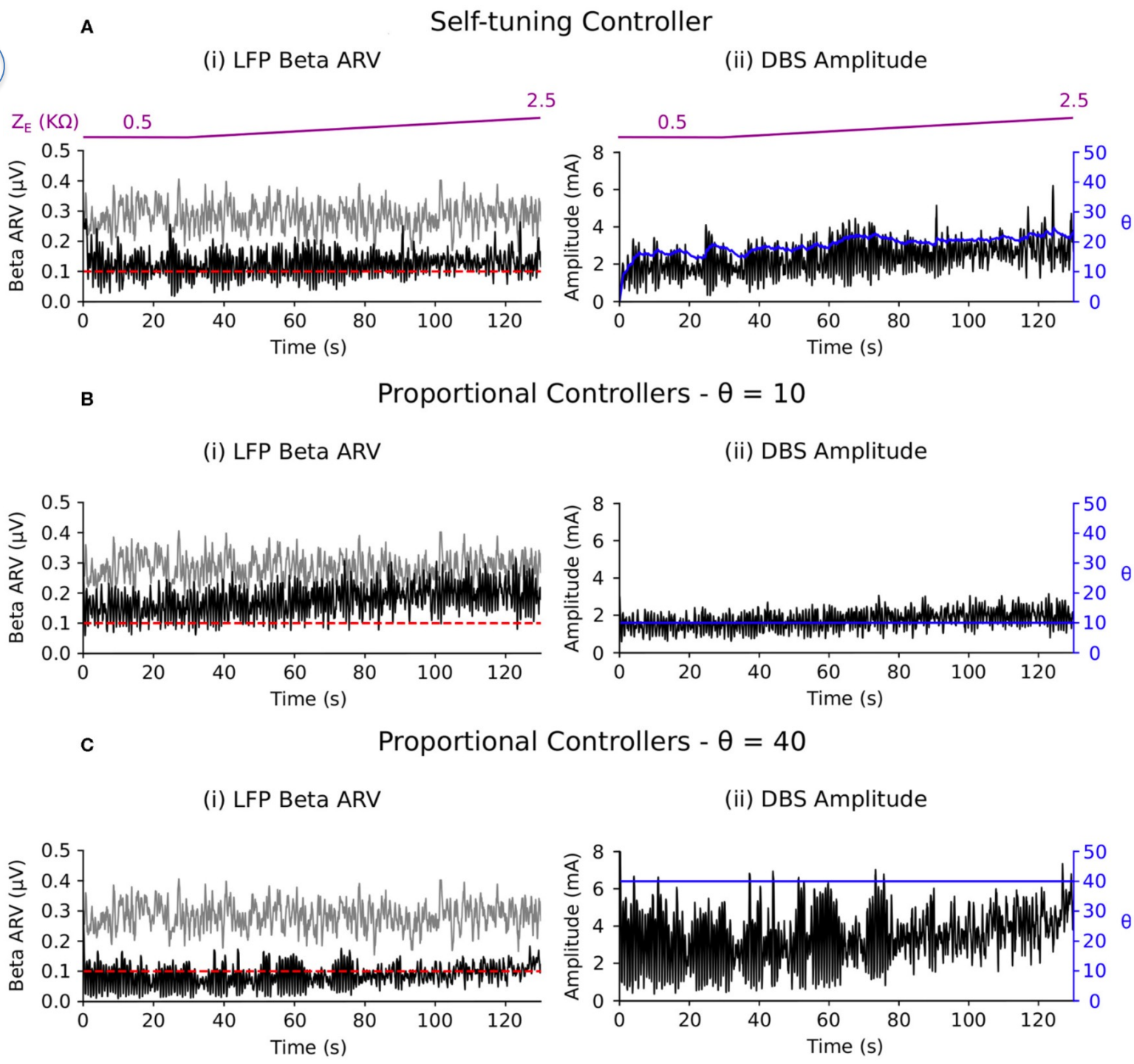


- Each structure composed of 100 neurons
- Each neuron represented by a conductance-based model
- Modeling of synapses
- Consideration of antidromic effect of DBS
- Estimation of local field potential

Robustness to strong variations of cortex activity

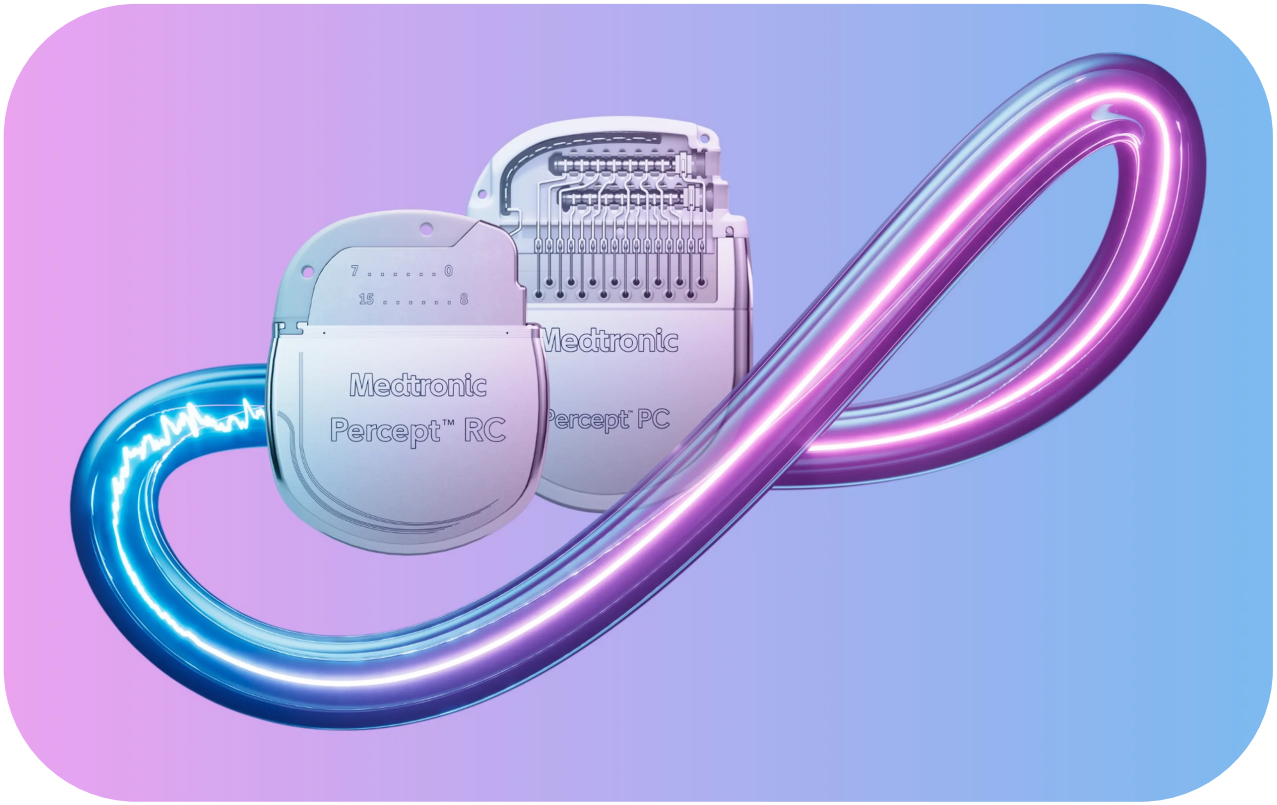


Robustness to variations of electrode impedance



Best symptom biomarker based on patients data

A closed-loop device for patients



- January 2025: CE mark approval for Medtronic’s BrainSense
- Possibility to both record and stimulate
- So far, only ”on-demand” stimulation.

Different symptoms, different waves

Typical LFP frequency bands associated with symptoms in specific disease states.

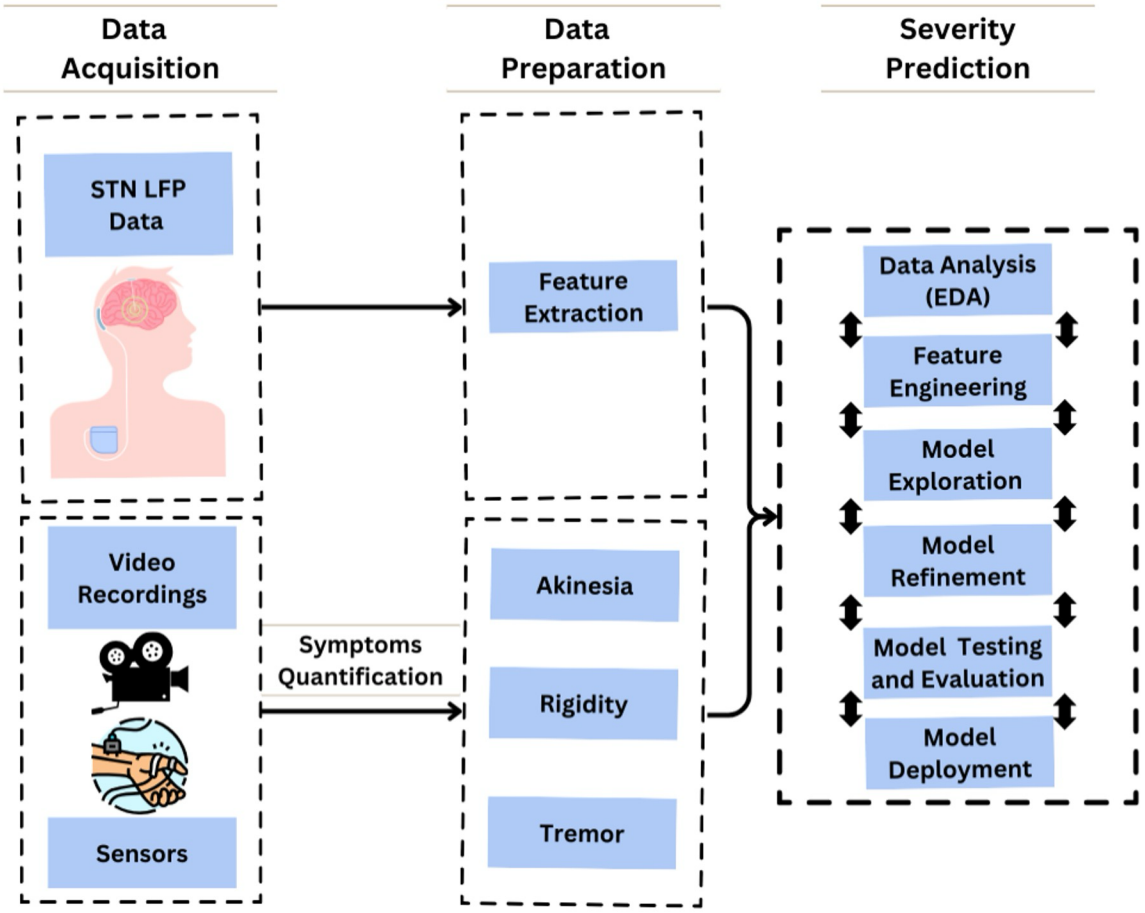
	Delta (0-4 Hz)	Theta/Alpha (4-13 Hz)	Low Beta (13-20 Hz)	High Beta (20-35 Hz)	Gamma (35-250 Hz)
PD: Akinetic-Rigid symptoms			●	○	○
PD: Tremor symptoms		●			●
Essential Tremor		●	○	○	
Dystonia (tonic)	●		○		○ (60-90 Hz)
Dystonia (phasic)		●	○		○ (60-90 Hz)

● likely association of LFP band to disease state (large body of literature supports findings)

○ potential association of LFP band to disease state

- For a given symptom, is there a universal biomarker ?
- If not, can we correlate symptom severity and brain recordings for a given patient ?
- Can we predict symptoms onset in advance ?

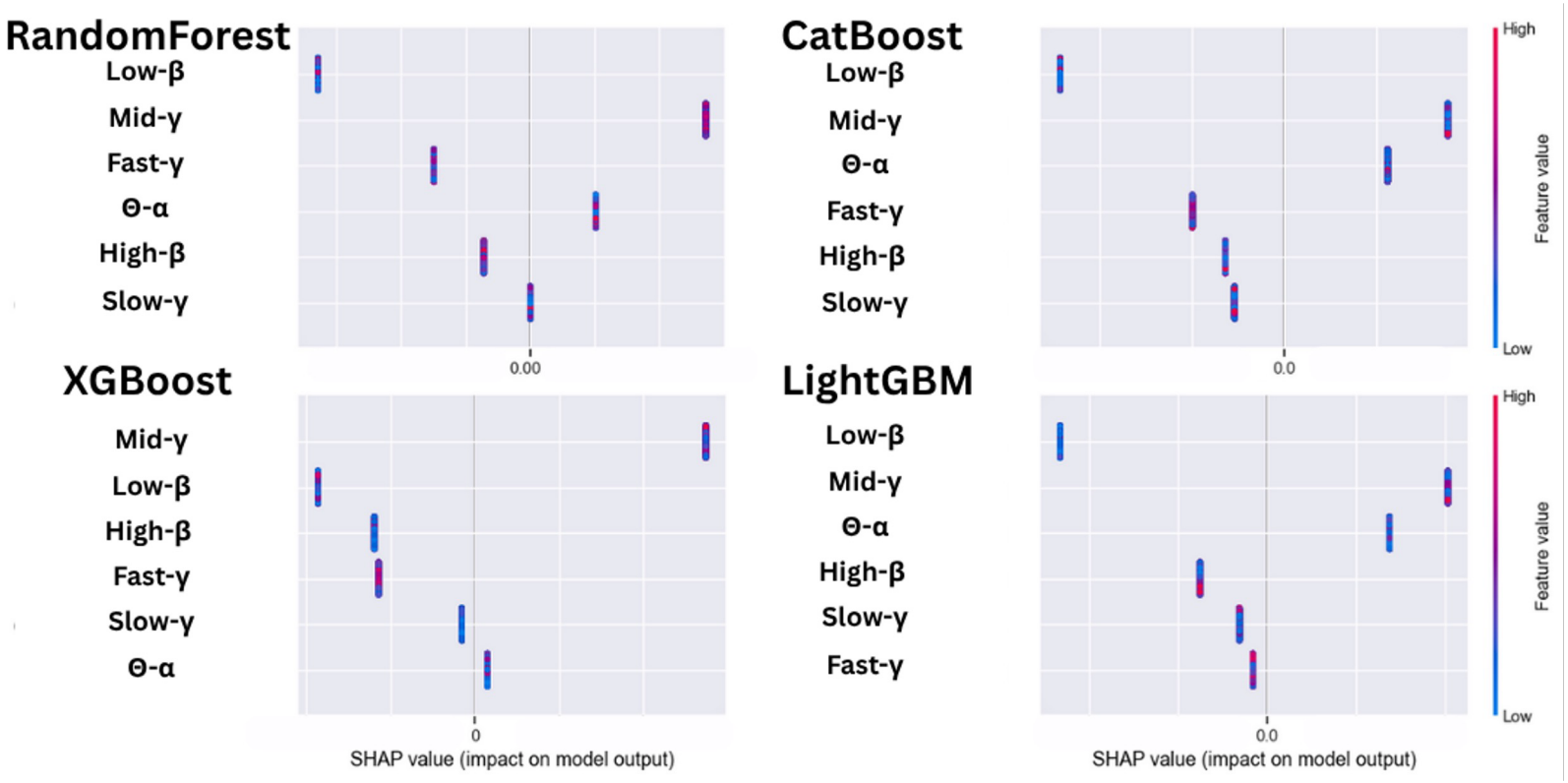
Ongoing work: Nada Zaidouni's PhD thesis



- Brain recordings: LFP data based on BrainSense during motor tasks
- Symptoms recordings: accelerometers, EMG, motion capture, video

Ongoing work: Nada Zaidouni's PhD thesis

- Training on 12 patients, test on 2 other patients
- 80% accuracy in predicting tremor
- Gamma and theta-alpha bands look the most discriminative
- 97% accuracy with patient-specific models.



Conclusion

- Control and neuroscience: a happy marriage!
- Theoretical evidence for advanced closed-loop strategies
- Possibility to predict symptoms severity based on deep brain measurements
- Some remaining challenges:
  - Selective disruption of pathological oscillations
  - Stimulation before symptom appearance.

Control people



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Neurosurgeons



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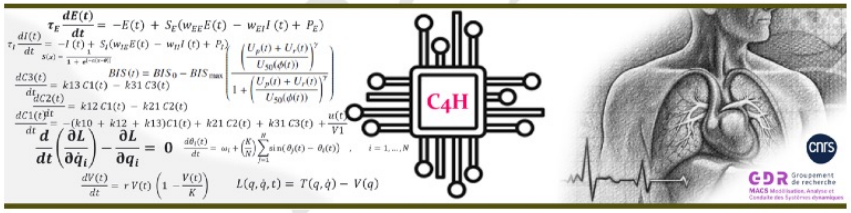
S. Senova
APHP

Jérôme Cieslak*
Antoine Chaillet†
Jean-Julien Aucouturier‡

Control4Health

The emerging French community bridging control sciences and medical researches



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DRAFT

- An overview of « control for health » in France
- Strengths, weaknesses, good practice, recommendations
- Based on a national survey
- Six contributed chapters:
  - Anesthesia
  - Cancerology
  - Cardiorespiratory system
  - Diabetes
  - Medical robotics
  - Neuroscience
- Soon at ISTE, already available on GDR MACS webpage!

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