# Recent advances in the analysis and control of spatio-temporal brain oscillations

Antoine Chaillet

L2S - CentraleSupélec - Univ. Paris Sud - Univ. Paris Saclay
Institut Universitaire de France

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1. Context and motivations
2. Spatio-temporal rate model for STN-GPe
3. ISS for delayed spatio-temporal dynamics
4. Stabilization of STN-GPe by proportional feedback
5. Adaptive control for selective disruption
6. Conclusion and perspectives

# Control theory

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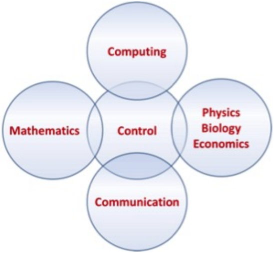

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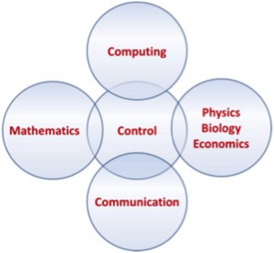
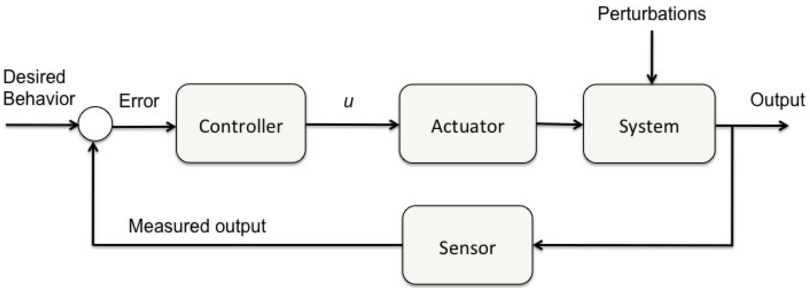
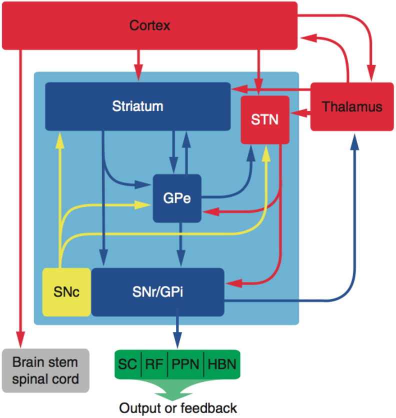
- Traditional applications: mechanical, electrical, chemical systems
- Intrinsically interdisciplinary
- Key notion: the feedback loop.



# Basal ganglia




[Bolam et al. 2009]

- Deep-brain nuclei involved in motor, cognitive, associative and mnemonic functions
  - Striatum (Str)
  - Ext. segment globus pallidus (GPe)
  - Int. segment globus pallidus (GPi)
  - Subthalamic nucleus (STN)
  - Substantia nigra (SN)
- Interact with cortex, thalamus, brain stem and spinal cord, and other structures.

# Parkinson's disease and basal ganglia activity

- Bursting activity of STN and GPe neurons: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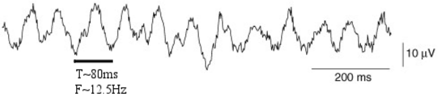
- Prominent $13 - 30Hz$ ($\beta$-band) oscillations in local field potential (LFP) of parkinsonian STN and GPe:
  - In parkinsonian patients:

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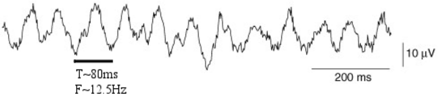


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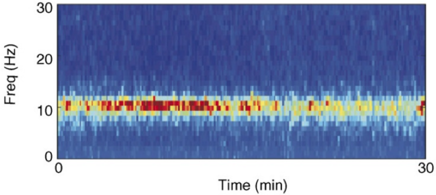
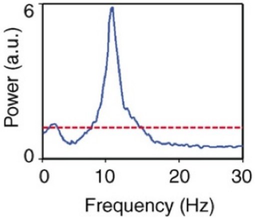
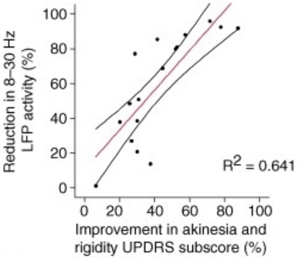
  - In MPTP monkeys:



# Parkinson's disease and basal ganglia activity

- Reduction of $\beta$-oscillations correlates motor symptoms improvement [Hammond et al. 2007, Little et al. 2012]



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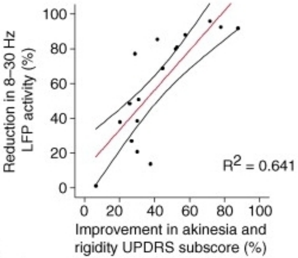
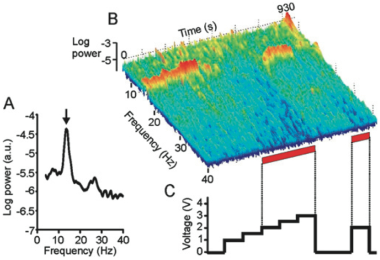



- $\beta$-oscillations may decrease during Deep Brain Stimulation [Eusebio et al. 2013]



# Oscillations onset still debated

Parkinsonian symptoms mechanisms are not fully understood yet:

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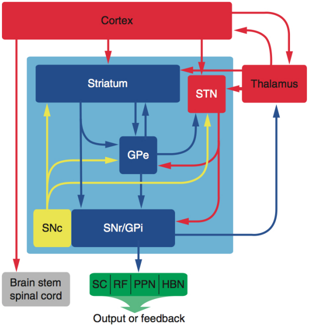
- Cortical endogenous oscillations ?
- Striatal endogenous oscillations ?

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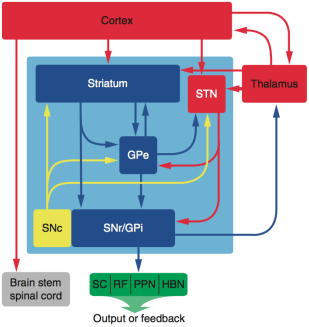


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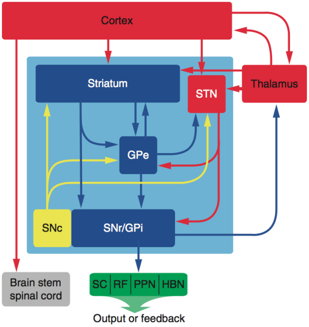


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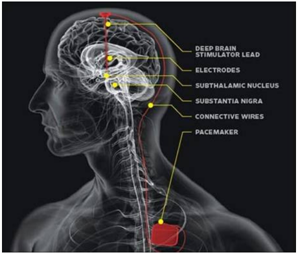
# Disrupting pathological oscillations

## Technological solutions to steer brain populations dynamics

- Deep Brain Stimulation [Benabid et al. 91]:



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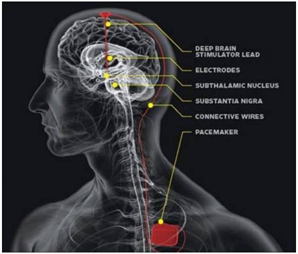
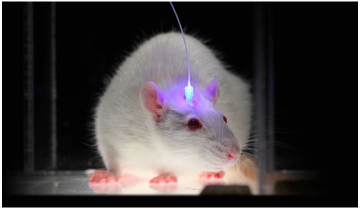



- Optogenetics [Boyden et al. 2005]:



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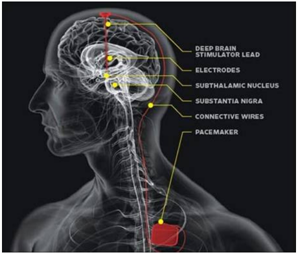


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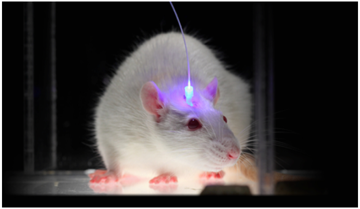

- Acoustic neuromodulation
  [Eggermont & Tass 2015]
- Sonogenetics
  [Ibsen et al. 2015]
- Transcranial current stim.
  [Brittain et al. 2013]
- Transcranial magnetic stim.
  [Strafella et al. 2004]
- Magnetothermal stim.
  [Chen et al. 2015]

# Some attempts towards closed-loop brain stimulation

| Approach | Model | Experimental validation | Analysis tools | Reference |
|---|---|---|---|---|
| ***Adaptive & on-demand*** | | | | |
| On-demand | - | MPTP primates | - | [Rosin et al. 2011] |
| On-demand | - | PD patients | - | [Graupe et al. 2010] |
| On-demand | - | PD patients | - | [Marceglia et al. 2007, Rosa et al.2015] |
| On-demand | - | PD patients | - | [Little et al. 2013, 2015] |
| Adaptive | Conductance-based | - | Artificial neural networks | [Leondopulos 2007] |
| Adaptive | Conductance-based | - | Simulations | [Santaniello et al. 2011] |
| Adaptive | Rubin & Terman | - | Optimization | [Feng & Fei 2002] |
| ***Delayed & multi-site*** | | | | |
| Delayed & multi-site | Conductance-based | MPTP primates in [Tass et al. 2012] | Systems theory in [Pfister & Tass 2010] | [Hauptman et al. 2005] |
| Delayed & multi-site | Phase dynamics | - | Systems theory | [Omel chenko et al. 2008] |
| Multi-site | Phase dynamics | - | Simulations | [Lysyansky et al. 2011] |
| Delayed | Phase dynamics | - | Systems theory | [Rosenblum & Pikovsky 2004] |
| ***Proportional, derivative and integral feedback*** | | | | |
| Proportional and/or multi-site | - | Culture of cortical neurons | - | [Wagenaar et al. 2005] |
| Proportional, PID | Phase dynamics | - | Systems theory | [Zheng et al. 2011; Pyragas et al. 2007] |
| Nonlinear PID | Rulkov model | - | Systems theory | [Tukhlina et al. 2007] |
| Nonlinear PID | Network + volume cond. | - | Systems theory + simu. | [Grant & Lowery 2013] |
| Filtered proportional | Hindmarsh-Rose | - | Simulations | [Luo et al. 2009] |
| Proportional | Phase dynamics | - | Systems theory | [Franci et al. 2011] |
| Filtered proportional | Firing rates dynamics | - | Systems theory | [Pasillas-Lépine et al. 2013] |
| ***Optimal control*** | | | | |
| Optimization | Rubin & Terman | - | Optimization | [Feng & Fei 2002] |
| Optimal control | Conductance-based | - | Phase response curve | [Danzl et al. 2009] |

Survey: [Carron et al. 2013]

# Neuronal populations: rate models

Firing rate: instantaneous number of spikes per time unit

- Mesoscopic models
  - Focus on populations rather than single neurons
  - Allows analytical treatment
  - Well-adapted to experimental constraints
- Rely on Wilson & Cowan model [Wilson & Cowan 1972]
  - Interconnection of an inhibitory and an excitatory populations
  - Too much synaptic strength generates instability
- Simulation analysis: [Gillies et al. 2002, Leblois et al. 2006]
- Analytical conditions for oscillations onset: [Nevado-Holgado et al. 2010, Pavlides et al. 2012, Pasillas-Lépine 2013, Haidar et al. 2014].

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# Neuronal populations: limitations of existing models

- Spatial heterogeneity needs to be considered:
  - Oscillations onset might be related to local neuronal organization [Schwab et al., 2013]
  - Spatial correlation could play a role in parkinsonian symptoms [Cagnan et al., 2015]
  - Possible exploitation of multi-plot electrodes.
- Techniques needed for analytical treatments of:
  - Nonlinearities
  - Position-dependent delays.

# Spatio-temporal model of STN-GPe dynamics

Delayed neural fields:

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

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

- 1: STN population (directly controlled), 2: GPe population (no control)
- $x_i(r,t)$ rate of population $i$ at time $t$ and position $r \in \Omega$
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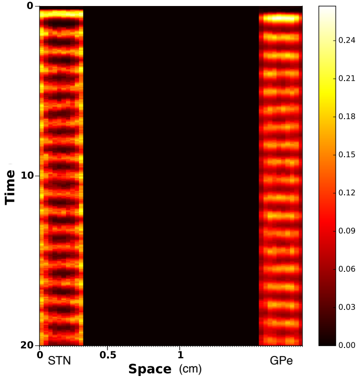
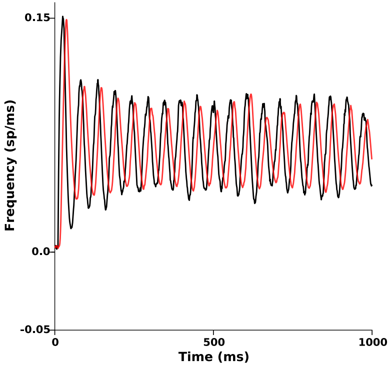
With parameters inspired from [Nevado-Holgado et al. 2010], generation of spatio-temporal $\beta$-oscillations:

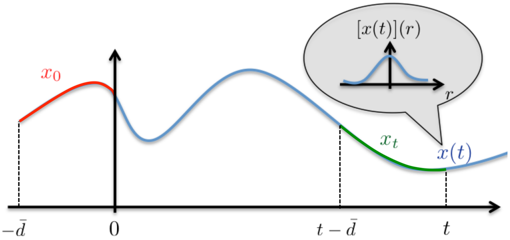


# Mathematical framework

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 segment. 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 $x \in \mathcal{F}$
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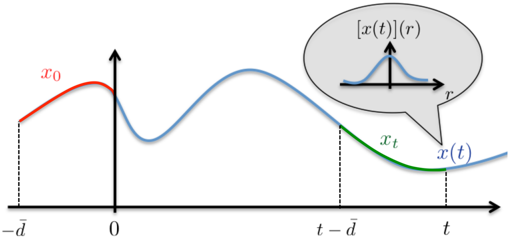


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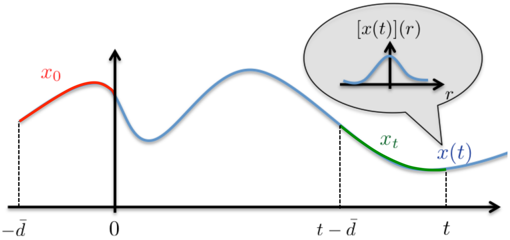


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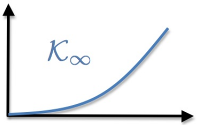
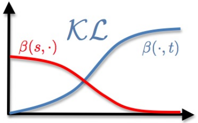
# ISS for delayed spatio-temporal dynamics: definition




**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].

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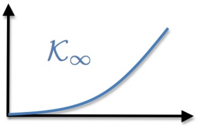


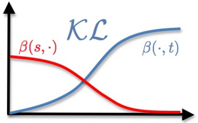


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# Lyapunov-Krasovskii condition for ISS

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

**Theorem: Lyapunov-Krasovskii function for ISS**

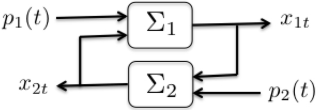
Let $\underline{\alpha}, \overline{\alpha}, \alpha, \gamma \in \mathcal{K}_\infty$ and $V \in C(\mathcal{C}, \mathbb{R}_{\geq 0})$. Assume that, given any $x_0 \in \mathcal{C}$ and any $p \in \mathcal{U}$, solutions of (2) satisfy

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

Then the system (2) is ISS.

Proof similar to Sontag's original result.

# ISS small gain




$$\dot{x}_1(t) = f_1(x_{1t}, x_{2t}, p_1(t)) \tag{3a}$$
$$\dot{x}_2(t) = f_2(x_{2t}, x_{1t}, p_2(t)) \tag{3b}$$

**Theorem: ISS small gain**

Let $\underline{\alpha}_i, \overline{\alpha}_i, \alpha_i, \gamma_i, \chi_i \in \mathcal{K}_\infty$ and $V_i : C(\mathcal{C}, \mathbb{R}_{\geq 0})$. Assume that, given any $x_{i0} \in \mathcal{C}$ and any $p_i \in \mathcal{U}$,

$$\underline{\alpha}_i(\|x_i(t)\|_{\mathcal{F}}) \leq V_i(x_{it}) \leq \overline{\alpha}_i(\|x_{it}\|_{\mathcal{C}})$$

$$V_1 \geq \max\{\chi_1(V_2), \gamma_1(\|p_1(t)\|_{\mathcal{F}})\} \quad \Rightarrow \quad \dot{V}_1|_{(3a)} \leq -\alpha_1(V_1)$$

$$V_2 \geq \max\{\chi_2(V_1), \gamma_2(\|p_2(t)\|_{\mathcal{F}})\} \quad \Rightarrow \quad \dot{V}_2|_{(3b)} \leq -\alpha_2(V_2).$$

Then, under the small-gain condition $\chi_1 \circ \chi_2(s) < s$, for all $s > 0$, the feedback interconnection (3) is ISS.

- Proof similar to [Jiang et al. 1996]
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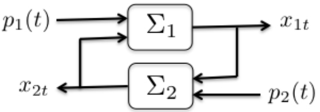


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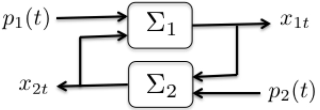


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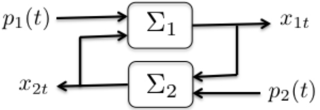


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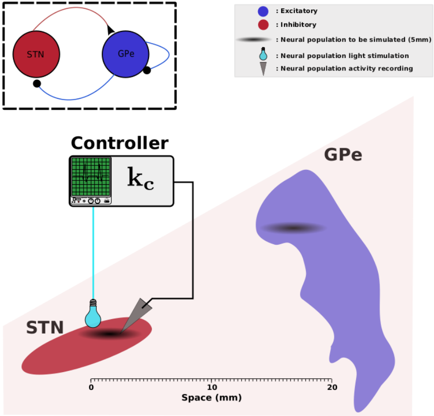
# Proportional feedback on STN




Control input: $u(r,t) = -kx_1(r,t)$:

- Similar control in an averaged model: [Haidar et al. 2016]
- No measurement or control on GPe required.

# Stabilizability by proportional feedback

$$\tau_1 \frac{\partial x_1}{\partial t} = -x_1 + S_1 \left( \sum_{j=1}^{2} \int_\Omega w_{1j}(r,r')x_j(r',t-d_j(r,r'))dr' + \alpha(r)u(r,t) + p_1(r,t) \right)$$
$$\tau_2 \frac{\partial x_2}{\partial t} = -x_2 + S_2 \left( \sum_{j=1}^{2} \int_\Omega w_{2j}(r,r')x_j(r',t-d_j(r,r'))dr' + p_2(r,t) \right).$$

**Theorem: ISS stabilization** [Detorakis et al. 2015]

Assume that $S_i$ are nondecreasing and $\ell_i$-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.

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

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# Stabilizability by proportional feedback

## Sketch of 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.

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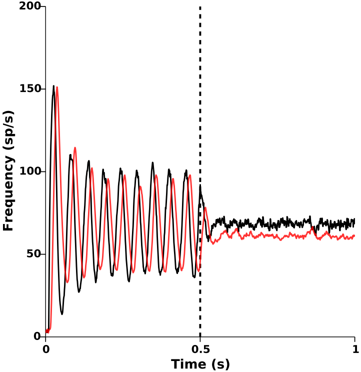
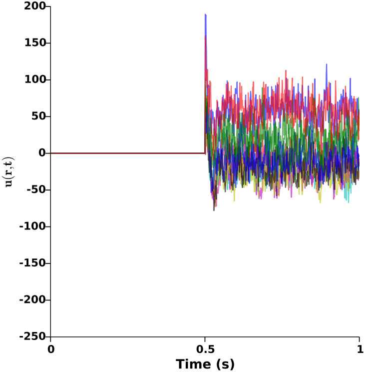
## Simulations




Efficient attenuation of pathological oscillations
using proportional feedback on STN.

# Robustness to feedback 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** [Chaillet et al. 2017]

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. . .
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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 $S_1$
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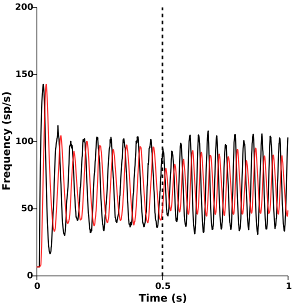


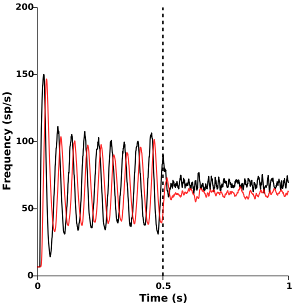


STN and GPe mean activity with acquisition/processing delays of 10ms (left) and 5ms (right).

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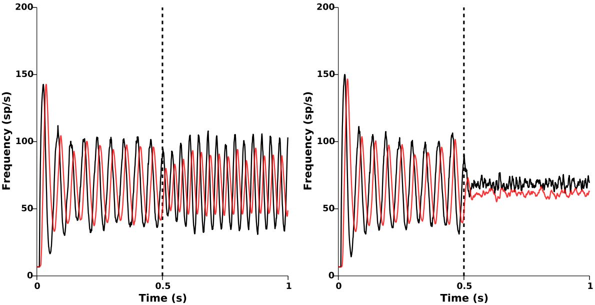


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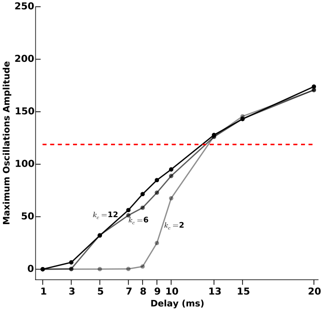


STN oscillations magnitude as a function of acquisition/processing delays.

# Homogeneous control 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: Homogeneous feedback** [Chaillet et al. 2017]

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

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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.

# Homogeneous control signal

## Sketch of 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.

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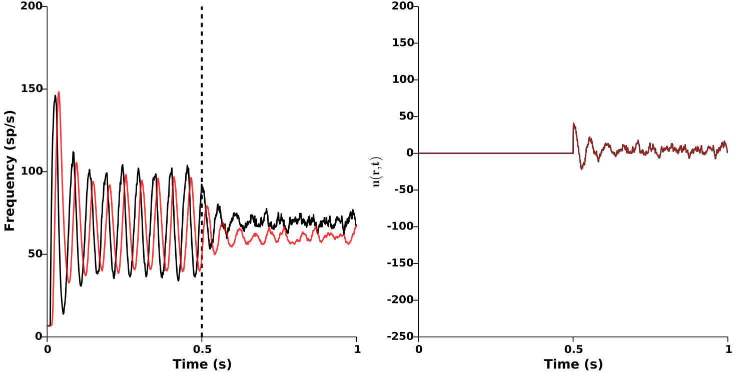
# Homogeneous control signal

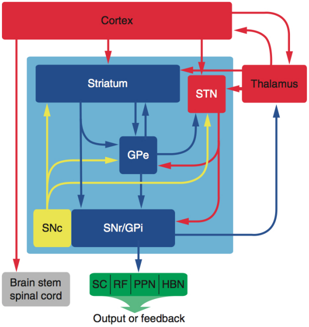
## Simulations




Efficient attenuation of pathological oscillations using homogeneous feedback on STN.

# Selective disruption in a targeted frequency band

- Unlike $\beta$-oscillations, transient $\gamma$-oscillations (30-80Hz) in STN are believed to be pro-kinetic




[Bolam et al. 2009]

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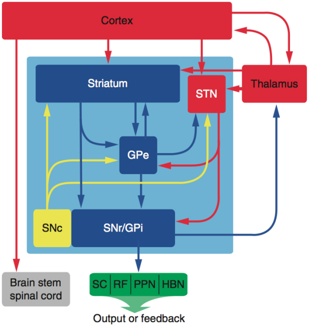
- Unlike $\beta$-oscillations, transient $\gamma$-oscillations (30-80Hz) in STN are believed to be pro-kinetic
- The proportional stimulation attenuates all oscillations, regardless of their frequency

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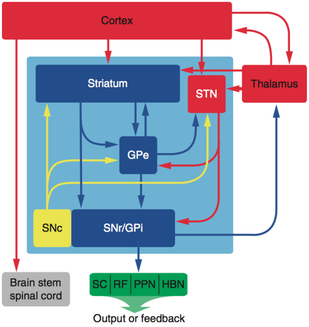
# Selective disruption in a targeted frequency band

- Unlike $\beta$-oscillations, transient $\gamma$-oscillations (30-80Hz) in STN are believed to be pro-kinetic
- The proportional stimulation attenuates all oscillations, regardless of their frequency
- A possible solution: adaptive control.




[Bolam et al. 2009]

# Adaptive control for selective disruption

Modification of the stimulation law:

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

- $z$: intensity of STN activity in the $\beta$-band
- $\varepsilon > 0$: parameter inducing decrease of the gain $k$ when opportune
- $\tau$: time constant defining the response speed to pathological oscillations.

# Adaptive control for selective disruption

Averaged model (no spatial dynamics):

$$\tau_1 \dot{x}_1(t) = -x_1(t) + S_1\Big(c_{11}x_1(t-\delta_{11}) - c_{12}x_2(t-\delta_{12}) + u(t)\Big) \tag{5a}$$

$$\tau_2 \dot{x}_2(t) = -x_2(t) + S_2\Big(c_{21}x_1(t-\delta_{21}) - c_{22}x_2(t-\delta_{22})\Big). \tag{5b}$$

**Theorem: Adaptive control** [Orłowski et al. 2018]

Let $S_i$ be bounded and with maximum slope $\ell_i > 0$ and assume that $c_{22} < 1/\ell_2$. Then there exists $\nu \in \mathcal{K}_\infty$ such that, given any $\varepsilon > 0$, the solutions of (5) in closed loop with the adaptive law $u = -kx_1$ with $\tau\dot{k} = |x_1| - \varepsilon k$ satisfy

$$\limsup_{t\to\infty} |x(t)| \leq \nu(\varepsilon).$$

- Arbitrary reduction of oscillations
- Ongoing work: $\tau\dot{k} = z - \varepsilon k$ and extension to neural fields.

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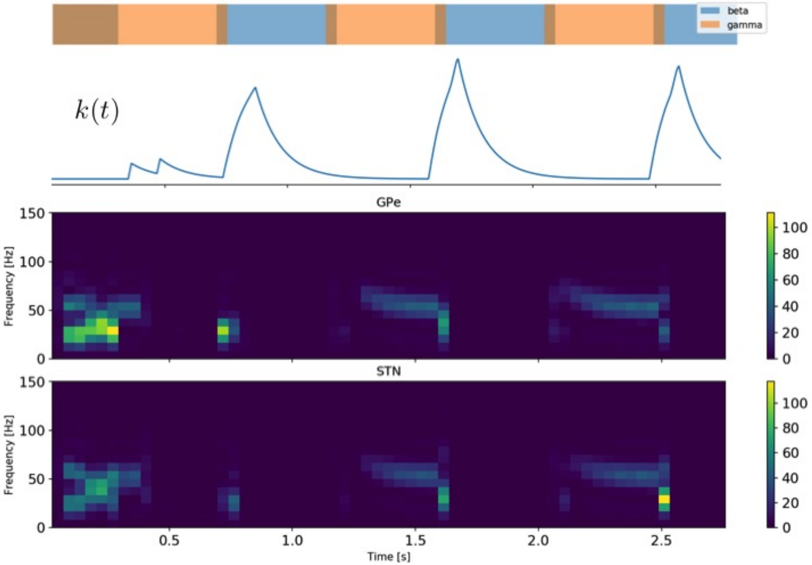
# Adaptive control for selective disruption

## Simulation: delayed neural fields



# Conclusion and perspectives

- What we have so far:
  - A framework for ISS of delayed spatio-temporal dynamics
  - A spatio-temporal model of STN-GPe generating $\beta$-oscillations
  - A condition for robust stabilizability by proportional feedback on STN
  - An adaptive strategy for selective oscillations disruption.
- What remains to be done:
  - Increased robustness to acquisition/processing delays: in the spirit of [Haidar et al. 2016]
  - More precise modeling of actuator dynamics
  - Indirect (cortical) stimulation
  - Experimental validation.

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# Many thanks to my collaborators

- Georgios Detorakis (L2S)
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