Closed-loop neurostimulation for the treatment of schizophrenia

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Outline

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- 2.2 Model fitting
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Problem

Psychotic transition in schizophrenia is associated with alteration of the EEG

- **increased gamma** activity (25-55Hz)
- **decreased alpha** activity (8-12Hz)

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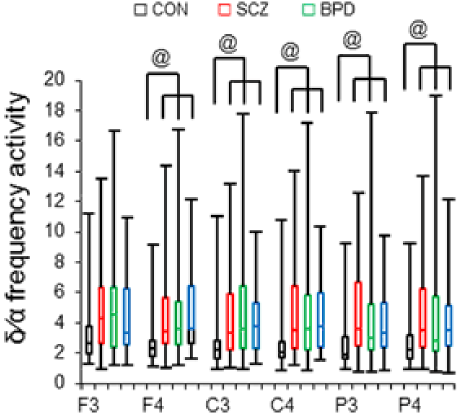
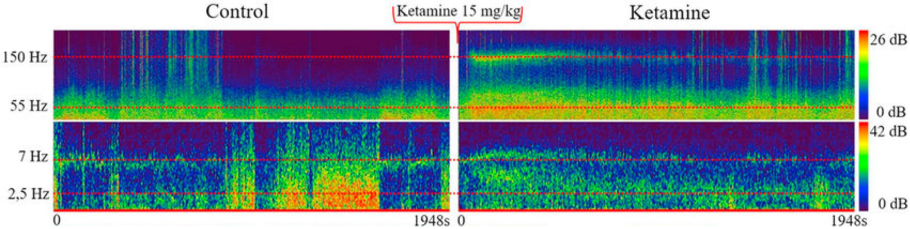
Increased δ- over α-activity ratio [Howells et al., 2018].



- **CON**: control group
- **SCZ**: schizophrenia
- **BPD**: bipolar disorder

Problem

Increased γ-activity in ketamine psychosis models [Fedor et al., 2020].



- 55 Hz and below: γ-activity

Existing solutions

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Drug treatment

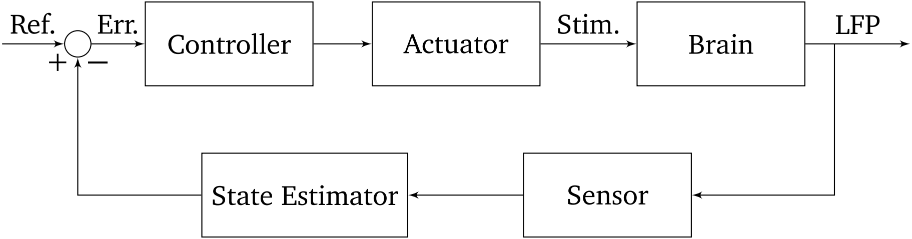
- antipsychotics

Neurostimulation

- open-loop neurostimulation
- closed-loop neurostimulation

Closed-loop neurostimulation

Synthesizes the stimulation signal in **real-time** based on brain state measurements.



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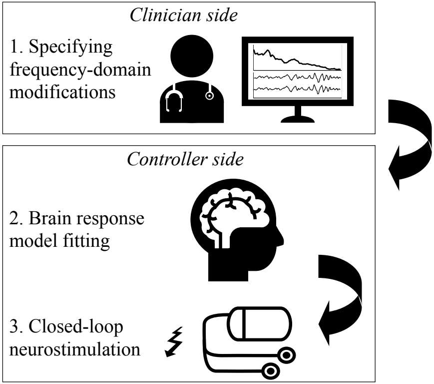
Real-time adaptive closed-loop neurostimulation

- no predefined stimulation signal
- no need to track a predefined reference signal
- signal cancelling/amplifying
- **arbitrary modifications**

Protocol

1. **relative** rather than absolute signal modifications
2. automated **patient-specific model identification**
3. **real-time adaptive** closed-loop neurostimulation



Plant

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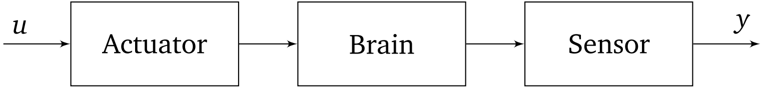
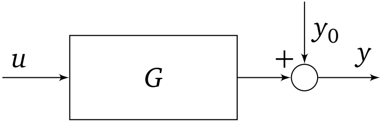
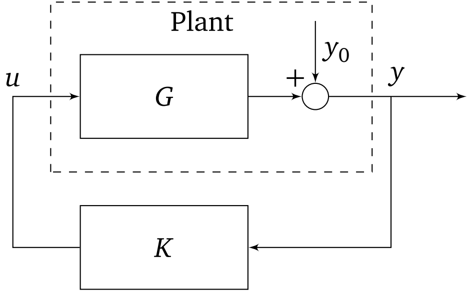


- The **plant** converts the input signal u into the output signal y.
- We cannot distinguish brain dynamics from sensor and actuator dynamics.
- **Direct interactions** between the actuator and the sensor are filtered out.

Plant



- The **plant** can be decomposed into its **resting state** activity signal y_0 and its **input response** system G.
- the **resting state** activity y_0 is **independent from the input signal** u.



- The **controller** K produces the neurostimulation signal u from the measured EEG signal y.

$$\frac{Y(s)}{Y_0(s)} = \frac{1}{1 - G(s)K(s)}$$

Controller synthesis

The **controller**'s **transfer function** is found by solving the following transfer function equation

$$\frac{1}{1 - G(s)K(s)} = 1 + H(s),$$

where H is the transfer function of a **linear filter** encoding the desired **frequency-domain modifications**. Hence we have

$$K(s) = \frac{H(s)}{(1 + H(s))G(s)}.$$

Transfer Function Extraction

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$$y(t) = y_0(t) + g(t) * u(t)$$
$$\hat{y}(\omega) = \hat{y}_0(\omega) + \hat{g}(\omega)\hat{u}(\omega)$$

The **spectral densities** can be expressed based on the **Fourier transforms**:

$$|\hat{y}(\omega)|^2 = |\hat{y}_0(\omega)|^2 + |\hat{g}(\omega)|^2|\hat{u}(\omega)|^2 + 2\mathrm{Re}(\hat{y}_0^*(\omega)\hat{g}(\omega)\hat{u}(\omega))$$
$$S_{yy}(\omega) = S_{y_0y_0}(\omega) + |\hat{g}(\omega)|^2 S_{uu}(\omega).$$

The **magnitude data** can be computed entirely from **spectral densities**:

$$|\hat{g}(\omega)|^2 = \frac{S_{yy}(\omega) - S_{y_0y_0}(\omega)}{S_{uu}(\omega)}.$$

Mininum phase systems

We assume that the plant is a **minimum phase system**.

- **Minimum group delay**: the energy of the response is concentrated at the start
- The phase of the transfer is entirely determined by its magnitude: $\arg(G(i\omega)) = -\mathcal{H}\{\ln(|G(i\omega)|)\}$ where $\mathcal{H}$ is the **Hilbert transform**

Vector fitting algorithm

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Fitting a **pole/residue model** to the data by iteratively relocating the set of poles [Gustavsen and Semlyen, 1999]

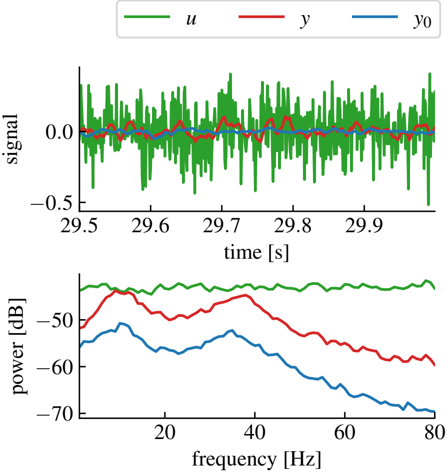
$$G(s) = \sum_{n=1}^{N} \frac{r_n}{s - p_n}.$$

The **magnitude vector fitting algorithm** is a variant that fits a **symmetric pole/residues model** to magnitude data [De Tommasi et al., 2010]

$$|G(i\omega)|^2 = \sum_{n=1}^{N} r_n \left(\frac{1}{i\omega - p_n} - \frac{1}{i\omega + p_n} \right).$$

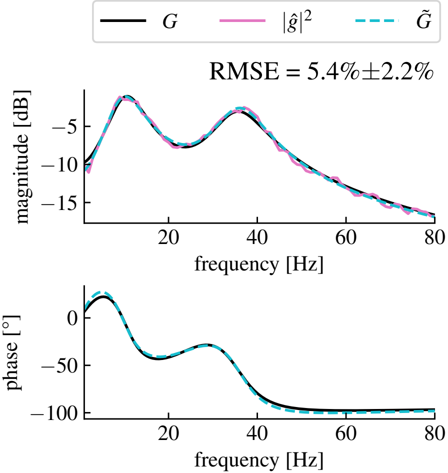
Initial brain state measurement

- **resting-state** activity measurement
- measurement of **stimulated state** with a predefined signal
- **power spectral densities** computation and comparison



Model fitting

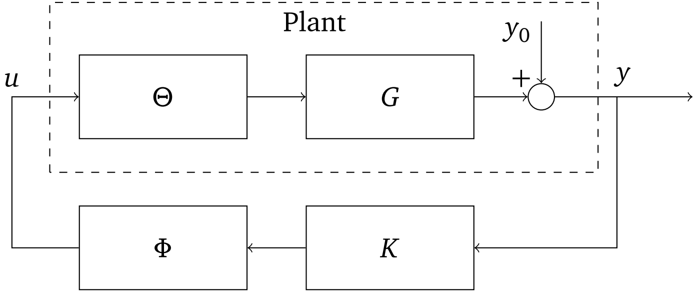
- **plant transfer function** computation from spectral density data
- **linear modal fitting** from computed transfer function data using the **magnitude vector fitting algorithm** [De Tommasi et al., 2010]



The fitted brain model accurately reproduces the **magnitude** and **phase shift** of the original model's transfer function.

Delay compensation

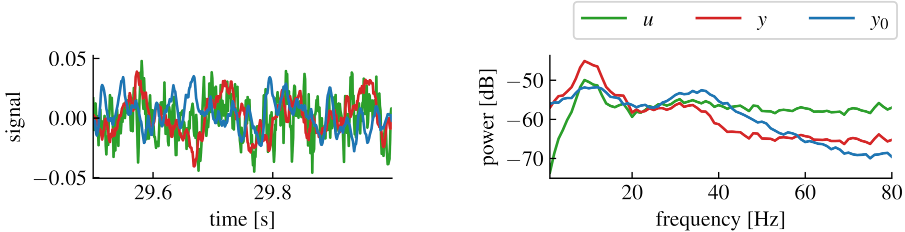
The delay system Θ is **compensated** by adding a **predictor system** Φ at the output of the **controller**.



The predictor minimizes the cost $J = \sum_k (1 - \Theta(i\omega_k)\Phi(i\omega_k))$ for chosen frequency points ω_k.

Numerical simulations

Our method successfully increases α-activity and decreases γ-activity.



- the **order of magnitude** of the stimulation current u is the same as the resting state y_0 and the stimulated state y
- controller is able to **compensate the 5 ms delay** for all frequencies below 60 Hz

Numerical simulations

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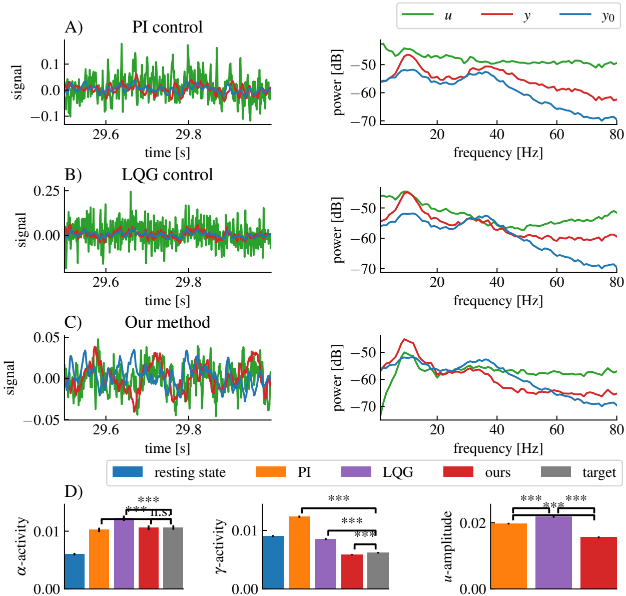

Objective

- increase α
- decrease γ

5 ms delay

- increased output in high frequencies
- increased current in high frequencies

Model fitting & numerical simulations

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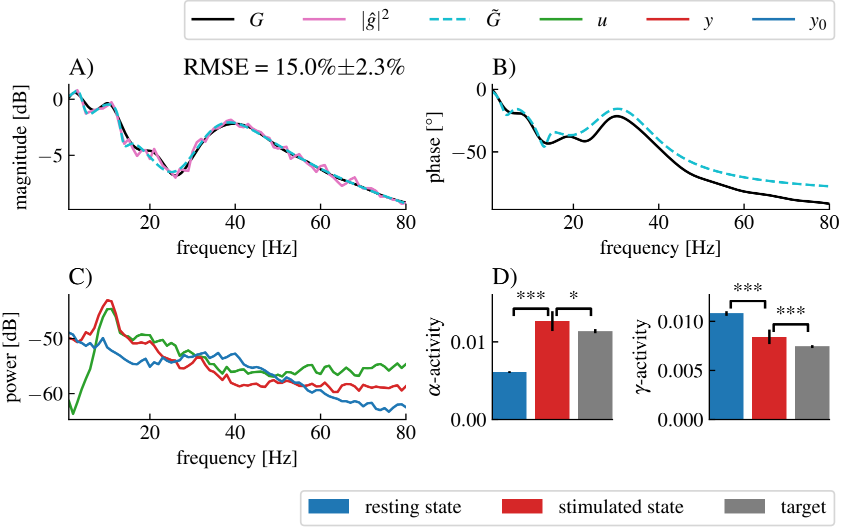
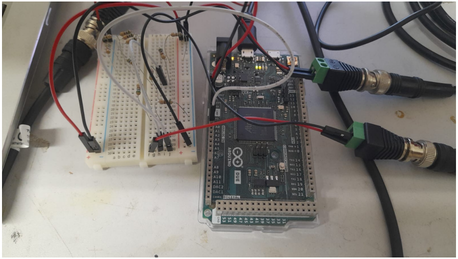
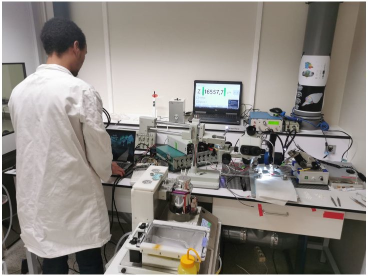
Results hold even for non-linear cortico-thalamic brain model.



In silico implementation





Incorporate long-term neural plasticity effects

- introduce **non-linear** neurostimulation response **dynamics** in our models
- allows to change the **post-stimulation** brain state in a predictable way

References I

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Thank You

for your **attention**.

Do you have any question?