Closed-loop disruption of oscillations in a targeted frequency band for a delayed neural field STN-GPe model

{Georgios.Detorakis, Antoine.Chaillet }@lss.supelec.fr

Introduction

Deep brain stimulation (DBS) of subthalamic nucleus (STN) is a successful method of alleviate motor symptoms of Parkinson's Disease (PD). Evidence indicates the crucial role of the network formed by STN and external Globus Pallidus (GPe) in the generation of PD pathological oscillations, which lie in low frequencies (especially the β-band), [1]. In this "pacemaker" hypothesis, oscillations can be seen as endogenous since they are generated by the two strong synaptic coupling between STN and GPe. In our work [5], a closed-loop stimulation has been shown to efficiently disrupt such endogenous oscillations in a delayed neural field model of STN-GPe. Here, we show that this disruption affects only endogenous oscillations, but preserves the spread of exogenous oscillations, possibly arising from cortex or striatum. These exogenous oscillations being unrelated to PD motor symptoms in the pacemaker hypothesis, this indicates that the proposed closed-loop stimulation is an efficient way to counteract pathological oscillations, without affecting healthy ones.

The Delayed Neural Field Model

The model that describes the spatiotemporal dynamics of STN-GPe network is given by the following neural field equations (for a survey of neural fields see [4]):

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

$$\tau_2 \frac{\partial z_2}{\partial t} = -z_2 + S_2 \left(\sum_{j=1}^{2} \int_\Omega w_{ij}(r,r') z_j(r', t - d_j(r,r')) dr' + I_2(r,t) \right). \quad (1b)$$

- Ω is a compact set
- $z_1(r,t)$, $z_2(r,t)$: activity at position $r \in \Omega$ and time $t \geq 0$ of STN and GPe, respectively.
- τ_1 and τ_2: time decay constants.
- $I_1(r,t)$: cortical input.
- $I_2(r,t)$: striatal input.
- w_{ij}: synaptic strength functions.
- d_j: axonal delays described by $d_j(r,r') = \frac{|r-r'|}{c_j}$, where c_i is the axonal conduction velocity of neurons
- S_1 and S_2 : Sigmoid functions given by $S_i(x) = \frac{m_i b_i}{b_i + (m_i - b_i) e^{-4x/m_i}}$, where $m_1 = 300\,\text{spk/s}$, $b_1 = 17\,\text{spk/s}$, $m_2 = 400\,\text{spk/s}$ and $b_2 = 75\,\text{spk/s}$.
- k_c: Feedback gain.
- $\alpha(r)$: Gaussian-like function that defines the portion of neurons that respond to the optogenetic stimulation.
- z_{ref}: Reference signal.

See [2, 3] for a more detailed mathematical description of delayed neural fields. A schematic representation of the closed-loop model is depicted in **Figure 1**.

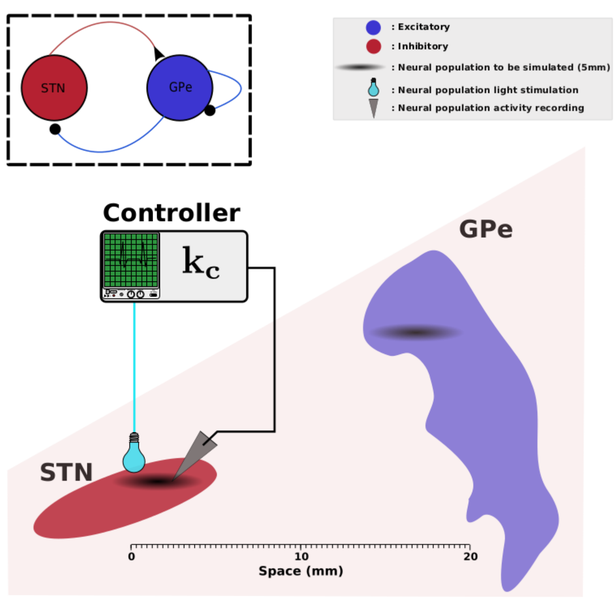

Figure 1

From **Figure 1** it is clear that STN is connected to GPe with excitatory feed-forward connections and GPe is connected to STN in a inhibitory manner. Neurons of GPe are intra-connected and thus GPe receives an excitatory component from STN and an inhibitory one from GPe itself. STN does not contain any intraconnection. Cortex projects with an excitatory component to STN and Striatum projects inhibitory to GPe.

Oscillation Disruption Condition

Theoretical Results:
Consider any admissible target pattern $z_{ref}(r)$. Let the activation functions S_1 and S_2 be bounded, increasing, and with maximum slope ℓ_1 and ℓ_2 respectively. Assume that the lateral synaptic weights in the GPe satisfy

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

and that the photosensitization is efficient over all STN, meaning that $\alpha(r) > 0$ for all $r \in \Omega$. Assume further that the inputs $I_1(r,t)$ and $I_2(r,t)$ from other brain areas are constant in time. Then, for any feedback gain k_c sufficiently large, the neural fields under closed-loop stimulation (1) is stable and, from almost all admissible initial conditions, the STN and GPe activities exponentially converge to constant patterns.

Interpretation: Any pathological oscillation within the STN-GPe network is disruptable by the proposed closed-loop stimulation when the lateral synaptic gains of GPe are not too strong. The synaptic weights of STN-GPe and GPe-STN do not affect the disruption of the pathological oscillations.

Numerical Experiments

All the following simulations are based on [5]. Briefly, each population of the model is discretized in 60 spatial units (neurons) and they are connected as **Figure 1** shows. First we show that proportional closed-loop stimulation disrupts endogenous pathological oscillations in β-band frequencies when no β-band oscillations are present in the exogenous signals (Cortex and Striatum). Then we show that exogenous β-band oscillations (a sinusoidal cortical component of 20Hz) do propagate within the STN-GPe network even in presence of the feedback stimulation.

Pathological Oscillations Disruption

When endogenous pathological oscillations are present, as in the left panel of **Figure 2**, the activation of the feedback stimulation (at t=1s) efficiently disrupts these endogenous oscillations. This is evident also by **Figure 3**, where the left panel shows the frequency spectrum of the firing rates of STN (black) and GPe (red) until 1s and the right panel shows frequencies after the application of the stimulation signal. It is apparent that the frequency in β-band is eliminated. The two peaks at 5Hz and 120Hz result only form the cortical inputs. The middle panel of **Figure 2** depicts the control feedback signal and the right panel shows the spatiotemporal evolution of the model dynamics (again the attenuation of oscillations is apparent).

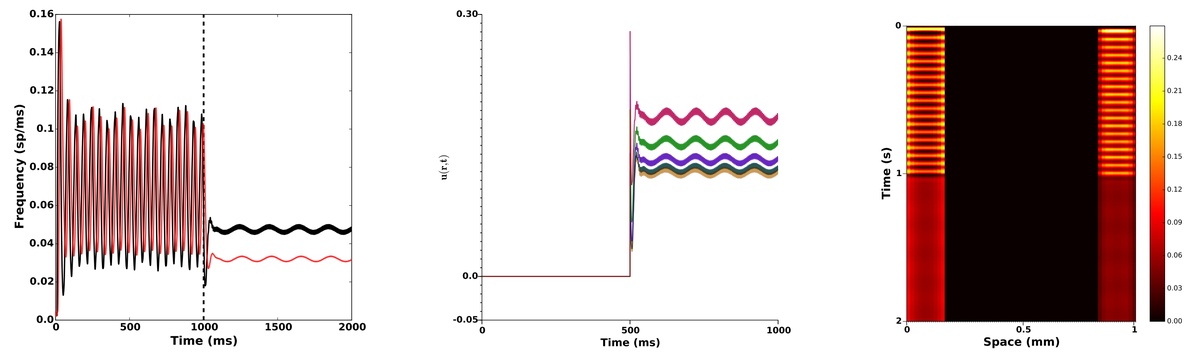

Figure 2

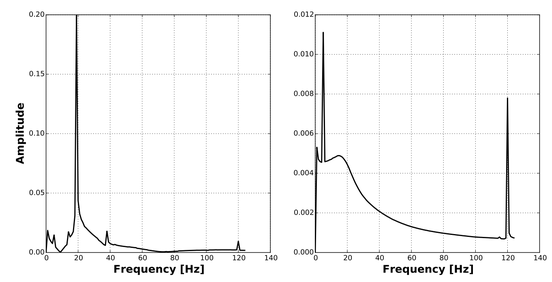

Figure 3

Preservation of non-pathological oscillations

When we add a third cortical input (a sinusoidal signal of 20Hz, so in the β-band) then the closed-loop stimulation eliminates the endogenous pathological oscillations but keep intact the cortical components. This situation is depicted in **Figure 4** (left panel), where the firing rates of STN (black) and GPe (red) indicate that the amplitude within the β-band has been decreased. Left panel of **Figure 5** demonstrates the frequencies of firing rates of STN and GPe until $1s$, and the right panel shows the frequencies after DBS. The cortical component is preserved intact whilst endogenous pathological oscillations have been removed. In addition, the middle panel of **Figure 4** shows the control feedback signal and the right panel displays the spatiotemporal evolution of model dynamics.

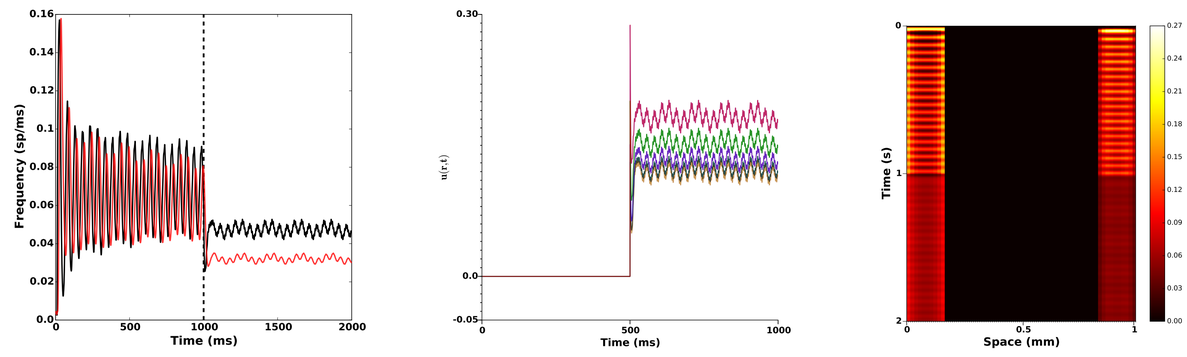

Figure 4

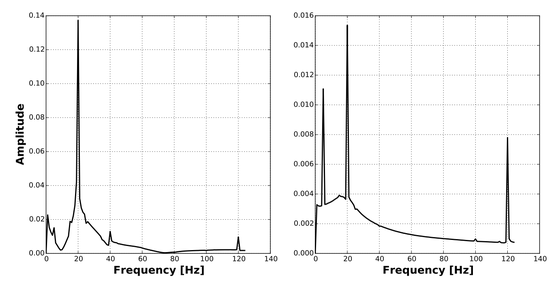

Figure 5

Conclusions

In this work we have shown mainly that when condition (2) holds true then we can attenuate any pathological oscillation within the circuit of STN-GPe described by equations (1). In addition, we have demonstrated by using numerical simulations that when we apply DBS we disrupt pathological oscillations leaving any other physiological oscillatory signal intact. This can be shown analytically by invoking the theory of incremental stability.

References

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