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Existence of oscillations in basal ganglia: analysis using a control theory approach

Ihab Haidar¹, William Pasillas-Lépine, Elena Panteley and Antoine Chaillet

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Abstract—This work presents recent advances in the formal analysis of the origins of pathological brain oscillations within the basal ganglia. Basal ganglia are deep brain structures involved in voluntary motor control as well as cognitive and emotional functions. Some pathological oscillations in the beta band (meaning 13-30Hz) are known to be strongly linked to motor symptoms in Parkinson disease. The origin of these pathological oscillations are still debated. This work aims at giving some insights on a possible cause of the oscillations generation. More precisely, using tools from control theory, we show that the coupling strength and delays between three basal ganglia (namely, the STN, the GPe and the PPN) determines the generation of such pathological oscillations. In particular, this study sheds some light on the possible role of the PPN within the STN-GPe pacemaker.

I. INTRODUCTION

Basal ganglia are deep brain structures involved in voluntary motor control as well as cognitive and motivational processes [8], [16]. They have been studied extensively in connection with a variety of pathological observations such as Parkinson disease [21]. Some evidence suggests that the advance of Parkinson disease is highly correlated to the presence of abnormal oscillations in the beta band (13-30 Hz) within the basal ganglia [3]. These oscillations may originate from the system composed of two excitatory-inhibitory basal nuclei: the subthalamic nucleus (STN), which is an excitatory nucleus, and the globus pallidus pars externa (GPe), which is an inhibitory nucleus [18], [20]. Another theory gives a cortical origin of these oscillations [23]. More recently, two other explanations have been proposed: in [1] the authors refer to a generation of endogenous bursts in the STN nucleus, while [15] proposes a striatal origin of these oscillations. Since basal ganglia are highly interconnected with the pedunculopontine

nucleus (PPN) [4], [19], the PPN might influence the basal ganglia activity. The aim of our paper is to shed light on the possible role of the PPN within the STN-GPe network in Parkinson's disease symptom, using a control theory approach.

To explore the origin of pathological oscillations in the basal ganglia, many computational models have been proposed [9], [12], [13], [14], [20]. The particular role of PPN within the basal ganglia has been specifically addressed in [14]. All of these studies investigate the conditions under which pathological oscillations are generated. In [9], the authors exploit a spike-rate model of the STN and GPe populations to derive analytical conditions under which beta oscillations occur. This work has been extended in [17], where tighter conditions are provided by using tools from control theory.

By relying on a similar approach, we here develop a mathematical model that describes the interaction between the three neuron populations: PPN, STN and GPe (see Section II). To analyze this model, we extend the approach developed in [17] for two nuclei only. We first study the existence and uniqueness of equilibrium points (see Section III). We derive necessary and sufficient conditions for the existence of multiple equilibria. Additionally, we propose a sufficient condition for global asymptotic stability in the absence of delays. Then, the system is linearized and the MIMO Nyquist stability criterion [5] is applied to the feedback loop of the linearized system (see Section IV) to derive explicit conditions on the delays and interconnection gains for the asymptotic stability of the network, and hence the absence of pathological oscillations.

II. MODEL DESCRIPTION

As we mentioned in the introduction, our objective is to analyze pathological oscillations in the basal ganglia. To characterize the firing rate of neural populations in STN, GPe and PPN, we use the well described firing-rate model [6]. The architecture of our model is shown in Figure 1. The STN neurons project excitatory axons to the GPe [8], while GPe neurons project inhibitory axons to the STN and to other GPe

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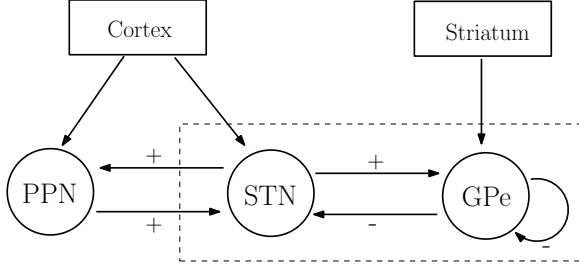


Fig. 1. Schematic diagram of three neuclei: STN, GPe and PPN.

neurons [11]. The STN neurons project also excitatory axons to the PPN [7] which projects back excitatory axons to the STN [19]. Additionally, the STN and PPN nuclei receive inputs from cortex [4], [11], [19] and the GPe nucleus receives input from the striatum [11]. The firing rates model [6] of the STN, GPe and PPN populations respectively, are ruled by the delayed differential equations

$$\begin{aligned}\tau_s \dot{x}_s &= S_s(c_s^p x_p(t - \delta_s^p) - c_s^g x_g(t - \delta_s^g) + u_s) - x_s \\ \tau_g \dot{x}_g &= S_g(c_g^s x_s(t - \delta_g^s) - c_g^g x_g(t - \delta_g^g) + u_g) - x_g \\ \tau_p \dot{x}_p &= S_p(c_p^s x_s(t - \delta_p^s) + u_p) - x_p\end{aligned}\quad (1)$$

where x_s, x_g and x_p ¹ represent the firing rates of the STN, GPe and PPN neurons, respectively. The positive gains $c_s^p, c_p^s, c_s^g, c_g^s$ and c_g^g define the weight of the different synaptic interconnections between these three neuron populations. The variables u_s, u_g and u_p describe the external inputs, from the striatum and cortex, received by these populations. The time constants τ_s, τ_g and τ_p describe how rapidly the three populations react to the inputs. The scalar functions S_s, S_g and S_p define the activation functions of STN, GPe and PPN respectively. We assume that all the delays $\delta_s^p, \delta_p^s, \delta_s^g, \delta_g^s$ and δ_g^g are nonnegative and constant. We also assume the following on the activation functions.

Assumption 1: For each $i \in \{s, g, p\}$, the activation function $S_i : \mathbb{R} \rightarrow (0; 1)$ is continuously differentiable and strictly increasing. Its infimum is equal to 0 and its supremum is equal to 1. In addition, its derivative S'_i is upper-bounded and there exists at least one point at which it reaches its maximum denoted σ_i .

A similar firing-rate model was exploited in [9], [17], to study the generation of pathological oscillations within the STN-GPe network. The remaining is devoted to the influence of PPN in this oscillations generation.

¹By abuse of notation, we omit the dependency of \dot{x}_i and x_i on t , for $i \in \{s, g, p\}$.

III. SYSTEM ANALYSIS IN THE ABSENCE OF DELAYS

A. Existence and uniqueness of equilibrium points

The system (1) is defined everywhere on \mathbb{R}^3 , since the activation functions are defined on \mathbb{R} . Nevertheless, one can check that the unit cube is invariant by this dynamics.

Lemma 1: Under Assumption 1, for any constant inputs u_s, u_g and u_p , the unit cube

$$D := \{(x_s, x_g, x_p) \in \mathbb{R}^3 : x_s, x_g, x_p \in [0, 1]\}.$$

is positively invariant for the delayed system (1).

The following result analyzes the existence and multiplicity of equilibria of the dynamics (1).

Theorem 1: Under Assumption 1, we have that If

$$\sigma_p \sigma_s c_s^p c_p^s \leq 1 \quad (2)$$

then the system (1) has a unique equilibrium point, for each constant vector $(u_s^*, u_g^*, u_p^*) \in \mathbb{R}^3$. Otherwise, there exists a constant vector (u_s^*, u_g^*, u_p^*) for which the system (1) has at least three distinct equilibria.

Theorem 1 generalizes the equilibrium study given by [17, Theorem 1] for a two-dimensional system describing the dynamics of two interacting subpopulations of excitatory and inhibitory neurons.

B. Stability of equilibria

Consider an equilibrium point x^* , associated to a vector of inputs u^* , whose existence is ensured by Lemma 1. Let $e = x - x^*$, and $v = u - u^*$. The linearization of the dynamics (1) around x^* is given by

$$\begin{aligned}\tau_s \dot{e}_s &= \sigma_s^* (c_s^p e_p(t - \delta_s^p) - c_s^g e_g(t - \delta_s^g) + v_s) - e_s \\ \tau_g \dot{e}_g &= \sigma_g^* (c_g^s e_s(t - \delta_g^s) - c_g^g e_g(t - \delta_g^g) + v_g) - e_g \\ \tau_p \dot{e}_p &= \sigma_p^* (c_p^s e_s(t - \delta_p^s) + v_p) - e_p,\end{aligned}\quad (3)$$

where

$$\begin{aligned}\sigma_s^* &:= S'_s(c_s^p x_p^* - c_s^g x_g^* + u_s^*) \\ \sigma_g^* &:= S'_g(c_g^s x_s^* - c_g^g x_g^* + u_g^*) \\ \sigma_p^* &:= S'_p(c_p^s x_s^* + u_p^*).\end{aligned}\quad (4)$$

We next rely on this linearization to study the stability properties of x^* . We start by considering the system (1) in the absence of delays.

Proposition 1: Consider the delayed system (1), and assume that

$$\delta_i^j = 0 \quad \text{for } i, j \in \{s, g, p\}.\quad (5)$$

Fix any input vector $u^* := (u_s^*, u_g^*, u_p^*)^T \in \mathbb{R}^3$, consider an equilibrium $x^* := (x_s^*, x_g^*, x_p^*)^T$ associated to

these input, and let $\sigma_i^*, i \in \{s, g, p\}$ be defined by (4). Then, under Assumption 1, the following holds.

- If the conditions

$$\left(\sigma_p^* c_s^p c_p^s - \frac{1}{\sigma_s^*}\right) \left(c_g^g + \frac{1}{\sigma_g^*}\right) < c_s^g c_g^s \quad (6)$$

$$\frac{\sigma_s^*}{\tau_s + \tau_p} \left(\sigma_p^* c_s^p c_p^s - \frac{1}{\sigma_s^*}\right) < \frac{\sigma_g^*}{\tau_g} \left(c_g^g + \frac{1}{\sigma_g^*}\right) \quad (7)$$

are both satisfied, then the equilibrium point x^* is locally exponentially stable.

- If the conditions

$$\sigma_p \sigma_s c_s^p c_p^s < 1 \quad (8)$$

$$\sigma_s (c_s^p + c_s^g) + \sigma_g c_g^s + \sigma_p c_p^s < 2 \quad (9)$$

are both satisfied then x^* is globally asymptotically stable.

C. Comparison with an excitatory-inhibitory model

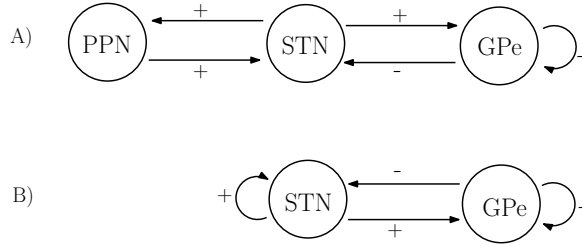


Fig. 2. Two different Schematic diagrams: Diagram A with three neuron populations (two excitatories and one inhibitory) and diagram B with two excitatory-inhibitory neuron populations.

The system (1) describe the evolution of three neuron populations: Two coupled excitatory subpopulations noted by s and p and one inhibitor noted by g . The question is, if we regroup the two excitatory populations in one and split the system into excitatory and inhibitory subpopulations, how this can modify the behavior of our system. In other words, if we decouple the STN-PPN network and suppose that the STN projects excitatory axons to itself (as in Figure 2) how this changes quantitatively and qualitatively the equilibrium points of the new STN-GPe system. In this case the evolution of this two populations of excitatory and inhibitory neurons can be described by the following delayed dynamics [6]

$$\begin{aligned} \tau_s \dot{x}_s &= S_s (c_s^s x_p(t - \delta_s^s) - c_s^g x_g(t - \delta_g^g) + u_s) - x_s \\ \tau_g \dot{x}_g &= S_g (c_g^s x_s(t - \delta_g^s) - c_g^g x_g(t - \delta_g^g) + u_g) - x_g \end{aligned} \quad (10)$$

where c_s^s define the weight of the different synaptic interconnections between the excitatory neurons and δ_s^s the transmission delay between the excitatory neurons.

Proposition 2: Consider the delayed systems (1) and (10).

- If $c_s^s \leq \sigma_p c_s^p c_p^s$ then the uniqueness of equilibrium for the system (1) implies its uniqueness for the system (10).
- If $c_s^s \geq \sigma_p c_s^p c_p^s$ then the uniqueness of equilibrium for the system (10) implies its uniqueness for the system (1).

Proposition 3: Suppose that $\sigma_s c_s^s < 1$ and $\sigma_p \sigma_s c_s^p c_p^s < 1$.

- If

$$\sigma_s c_s^s \leq \frac{1}{2} (\sigma_s c_s^p + \sigma_p c_p^s)$$

then the global stability of the equilibrium point corresponding to system (1) implies the global stability of that corresponding to system (10).

- If

$$\sigma_s c_s^s \geq \frac{1}{2} (\sigma_s c_s^p + \sigma_p c_p^s)$$

then the global stability of the equilibrium point corresponding to system (10) implies the global stability of that corresponding to system (1).

IV. ROBUSTNESS TO DELAYS

In this section, we study the stability properties of the equilibria of (1) by relying on its linearization (3). To that aim, we make use of the Nyquist Theorem [5, Theorem 9.1.8] for MIMO delayed systems. We stress that here the Nyquist Theorem is applied in its general form in the Callier-Desoer class of scalar irrational transfer functions $\hat{\mathcal{B}}$ (See [5, Definitions 7.1.4 and 7.1.6]).

For a delayed feedback system, it is convenient to define the delay margin of stability. For this aim, consider a single-input, single-output plant $G \in \hat{\mathcal{B}}$. Let $\bar{\tau} > 0$, the delay margin is defined by

$$\Delta(G) := \sup\{\bar{\tau} > 0 : \text{the feedback } (G, e^{-\tau s}) \text{ is input-output stable } \forall \tau \in [0, \bar{\tau})\}.$$

For a formal definition of input-output stability, see [5, Definition 9.1.1].

The linearized system (3) associated to an equilibrium point of (1) can be described in the frequency domain using the closed-loop transfer functions

$$\begin{aligned} H_s(s) &= \frac{\sigma_s^*}{\tau_s s + 1}, \quad H_p(s) = \frac{\sigma_p^*}{\tau_p s + 1} \quad \text{and} \\ H_g(s) &= \frac{\sigma_g^*}{\tau_g s + 1 + \sigma_g^* c_g^g e^{-\delta_g^g s}} \end{aligned}$$

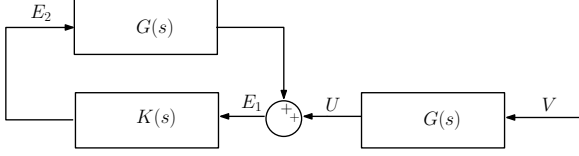


Fig. 3. Bloc diagram of the feedback system (12).

by the following system

$$\begin{aligned} \frac{1}{H_s} E_s + c_s^g e^{-\delta_s^g s} E_g - c_s^p e^{-\delta_s^p s} E_p &= V_s \\ \frac{1}{H_g} E_g - c_g^s e^{-\delta_g^s s} E_s &= V_g \\ \frac{1}{H_p} E_p - c_p^s e^{-\delta_p^s s} E_s &= V_p \end{aligned} \quad (11)$$

where $E = (E_s, E_g, E_p)$, and $V = (V_s, V_g, V_p)$ are the Laplace transform of e and v .

The system defined by (11) can be written as the following feedback system (G, K) represented by Figure 3

$$\begin{cases} E_1 = GE_2 + U \\ E_2 = KE_1 \end{cases} \quad (12)$$

where $E_1 = E$ and the two transfer matrices G and K are given by the following

$$G(s) = \begin{pmatrix} H_s(s) & 0 & 0 \\ 0 & H_g(s) & 0 \\ 0 & 0 & H_p(s) \end{pmatrix}, \quad (13)$$

$$K(s) = \begin{pmatrix} 0 & -c_s^g e^{-\delta_s^g s} & c_s^p e^{-\delta_s^p s} \\ c_g^s e^{-\delta_g^s s} & 0 & 0 \\ c_p^s e^{-\delta_p^s s} & 0 & 0 \end{pmatrix} \quad (14)$$

and

$$U = GV.$$

In order to study the stability of the feedback system (12), we check firstly the stability of the transfer matrices G and K . Seeing that G and K are irrational transfer matrices, we begin by verifying if each of its components belongs to $\hat{\mathcal{B}}$. This point is the main interest of Proposition 4.

Proposition 4: The elements of the transfer matrices G and K defined in (13)-(14) belong to the Callier-Desoer class of scalar irrational transfer functions.

From Proposition 4, the transfer matrix G is not necessarily stable. This comes from the fact that the transfer function H_g is not necessarily stable. However, one can observe that H_g is always stable when $\delta_g^g = 0$. Then, one has to give a marge of delay to δ_g^g

to have the stability of H_g . This point was emphasized in [17, Lemma 3], where they prove the existence of a positif real number δ_g^{g*} such that the transfer function H_g is input-output stable if and only if $\delta_g^g < \delta_g^{g*}$.

Knowing all about the transfer matrices G and K , we turn now to study the stability of the feedback system (12). The aim of the Proposition 5 is to give a necessary and sufficient condition to obtain the stability of the feedback system (12). For this, we define firstly the following two transfer functions

$$K_p(s) = c_p H_p(s) e^{-\delta_p^s s} \text{ and } K_g(s) = -c_g H_g(s) e^{-\delta_g^s s},$$

where the quantities

$$c_p := c_s^p c_p^s, \quad c_g := c_s^g c_g^s,$$

$$\delta_p := \delta_p^s + \delta_s^p, \quad \delta_g := \delta_g^s + \delta_s^g$$

are defined in order to obtain a lighter notation.

Proposition 5: Suppose that H_g is input-output stable. The feedback system defined by (12) is input-output stable if and only if

$$\text{ind}(1 - H_s(K_p + K_g)) = 0, \quad (15)$$

where $\text{ind}(1 - H_s(K_p + K_g))$ denote the Nyquist index [5, Definition A.1.15] of $1 - H_s(K_p + K_g)$.

Even that we know that the feedback system (12) can be input-output stable, at least when the external delays are fixed to zeros, two problems prevent us to define the delay margin of our system. The first reside in the fact of presence of two external delays δ_p and δ_g , that requires at every turn to study the delay margin of the one by keeping the other delay fixed. The second problem occurs from the difficulty to give the necessary conditions for which the gain of the function $H_s(K_p + K_g)$ is strictly decreasing as w decreases from ∞ to $-\infty$.

Regarding this two difficulties, we will try to approach the main problem, given by (12), differently. In fact, the bloc diagram (see Figure 4) comprises two closed-loops, one with external input (V_s, V_g) and the other with external input (V_s, V_p) . Let introduce the two following transfer functions

$$H_{sp} = \frac{H_s}{1 - H_s K_p} \quad \text{and} \quad H_{sg} = \frac{H_s}{1 - H_s K_g},$$

where H_{sp} and H_{sg} replace the closed-loop with external input (V_s, V_p) and (V_s, V_g) respectively and which are calculated between V_s and V_s .

Lemma 2: Assume that the transfer functions H_g, H_{sp} and H_{sg} are input-output stable. We have

$$\begin{aligned} \text{ind}(1 - H_s(K_p + K_g)) &= \text{ind}(1 - H_{sg} K_p) \\ &= \text{ind}(1 - H_{sp} K_g). \end{aligned}$$

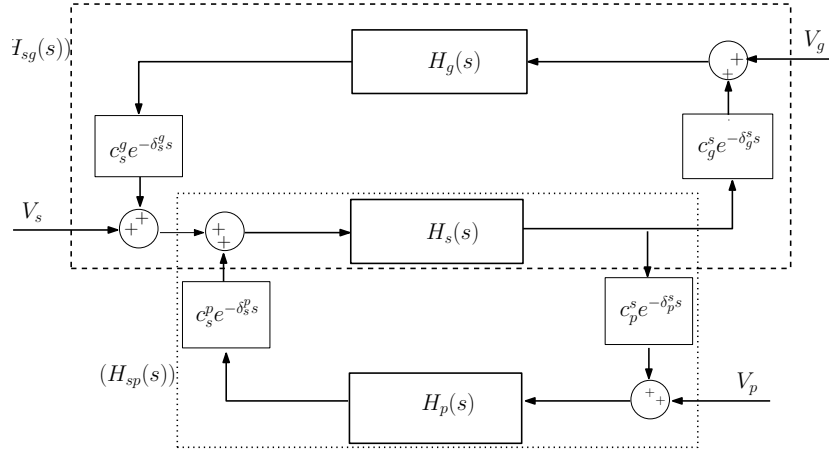


Fig. 4. Bloc diagram of the linearized system (3).

Lemma 2, Proposition 4 and Nyquist Theorem [5, Theorem 9.1.8] shows that under the condition of stability of H_g , H_{sp} and H_{sg} , prove that the feedback system (12) is input-output stable is equivalent to prove that the feedback (H_{sp}, K_g) or (H_{sg}, K_p) is input-output stable.

To prove the stability of H_{sp} and H_{sg} we will apply a direct result given in [17, Theorem 2]. It appears that the stability of H_{sp} does not depend on the delay margin δ_p . this is not the case of H_{sg} . Indeed, when $c_g \sigma_g^* \sigma_s^* > 1 + c_g^g \sigma_g^*$, one has to compute a delay margin of δ_g in order to check the stability of H_{sg} . For the transfer functions H_{sp} and H_{sg} , we introduce the functions G_{sp} and G_{sg} given by the following

$$G_{sp} = c_p H_s H_p \quad \text{and} \quad G_{sg} = -c_g H_s H_g.$$

Lemma 3: We have

- The transfer function H_{sp} is input-output stable if and only if the inequality $\delta_p < \Delta(G_{sp})$. If the inequality $c_p \sigma_p^* \sigma_s^* < 1$ is satisfied then $\Delta(G_{sp}) = +\infty$, otherwise $\Delta(G_{sp}) \leq 0$.
- Assume that the gain γ_{H_g} is strictly decreasing. The transfer function H_{sg} is onput-output stable if and only if $\delta_g < \Delta(G_{sg})$. If the inequality $c_g \sigma_g^* \sigma_s^* < 1 + c_g^g \sigma_g^*$ is satisfied then $\Delta(G_{sg}) = +\infty$, otherwise $\Delta(G_{sg}) > 0$.

According to Lemma 2, if the transfer functions H_g , H_{sp} and H_{sg} are input-output stable, then the study of the feedback system (12) can be achieved (equivalently) by studying one of the two feedback systems (H_{sp}, K_g) or (H_{sg}, K_p) . Furthermore, we have already stressed that the case of transfer functions with a strictly decreasing gain will be important for us. Since it is easier to find the conditions under which we have monotonicity of the loop gain $\gamma_{H_{sp}}$, we focus to prove the stability of the feedback system

(H_{sp}, K_g) . The following Lemma shows the existence of a threshold on the values of c_p for which we have the loop gain $\gamma_{H_{sp}}$ strictly decreasing.

Lemma 4: Consider the transfer function H_{sp} . For each $\delta_p > 0$, there exist $c_p^*(\delta_p) > 0$ such that the loop gain $\gamma_{H_{sp}}$ is strictly decreasing for every $c_p \in (0, c_p^*(\delta_p))$.

Now, with Lemmas 2, 3 and 4, and Proposition 5, we have all the necessary elements to check the local stability of the system (1). Of course we still use the fact that the gain of the transfer function H_g can be strictly decreasing [17, Lemma 4]. The local stability of the system (1) is given by the following result

Theorem 2: Consider the delayed differential equation defined by (3). Fix input u^* such that, for the equilibrium x^* associated to these inputs, the transfer functions H_g and H_{sp} are input-output stable. Define $H = c_g H_{sp} H_g$. Assume that the gain of H_g is strictly decreasing. For each $\delta_p > 0$, there exist $c_p(\delta_p) < 1$ such that the equilibrium point is locally exponentially stable if and only if $\delta_g < \Delta(H)$.

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