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Basal ganglia oscillations: the role of delays and external excitatory nuclei

*†Ihab Haidar, ‡William Pasillas-Lépine, §Elena Panteley, and ¶Antoine Chaillet ||

November 7, 2012

Abstract

Basal ganglia are interconnected deep brain structures involved in movement generation. Their oscillations in the beta band (13-30Hz) is known to be linked to Parkinson's disease motor symptoms. In this paper, we provide conditions under which these oscillations may occur, by explicitly considering the role of the pedunclopontine nucleus (PPN). We analyze the existence of equilibria in the associated firing-rates dynamics, and study their stability by relying on a delayed MIMO frequency analysis. The results are illustrated by simulations.

1 Introduction

Basal ganglia are deep brain structures involved in voluntary motor control as well as cognitive and motivational processes [8, 17]. They have been studied extensively in connection with a variety of pathological observations such as Parkinson's disease [23]. Some evidence suggests that the advance of parkinsonism is highly correlated to the presence of abnormal oscillations in the beta band (13-30 Hz) within the basal ganglia [3]. There exist several hypothesis about the origin of these oscillations. Some of them emphasize the cortical [25] or striatal [16] origin of the phenomenon. But another popular assumption is that these oscillations may originate from the system composed of two excitatory-inhibitory basal ganglia nuclei: the subthalamic nucleus (STN), which is an excitatory nucleus, and the globus pallidus pars externa (GPe), which is an inhibitory nucleus [20]. Since basal ganglia are highly interconnected with the pedunclopontine nucleus (PPN) [4, 9, 21], this nucleus might have an influence on their oscillatory activity. The aim of our paper is to quantify this influence, with the help of control theory tools.

To explore the origin of pathological oscillations in the basal ganglia, several works relying on firing-rate models have been proposed [10, 13, 12, 19]. These models are formulated in terms of an ordinary differential equation that rule the evolution of the number of spikes per time-unit within the considered neuronal population [6]. Other works [22, 11] exploit a microscopic approach in which every neuronal cell is modeled individually. In [10], the authors exploit a spike-rate model of the STN and GPe populations to derive analytical conditions under which beta oscillations occur. These conditions have been improved in [18, 19] to provide tighter conditions for the existence of oscillations. The particular role of PPN within the basal ganglia has been specifically addressed in [15], where the authors study how the PPN responds to physiological and pathological inputs of the basal ganglia.

Here we develop a mathematical model that describes the interaction between three neuronal populations: PPN, STN and GPe (see Section 2). To analyze this model, we extend the approach developed in [18] for two nuclei only. We first study the existence and uniqueness of equilibrium points (see Section 3). 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

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linearized system (see Section 4) to derive explicit conditions on the delays and interconnection gains for the asymptotic stability of the network, and hence the absence of pathological oscillations. The proofs are postponed to the Appendix (see Appendix A), for lightening the presentation. These results are illustrated by numerical simulations (see Section 5).

2 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. The architecture of our model is shown in Figure 1. The STN neurons

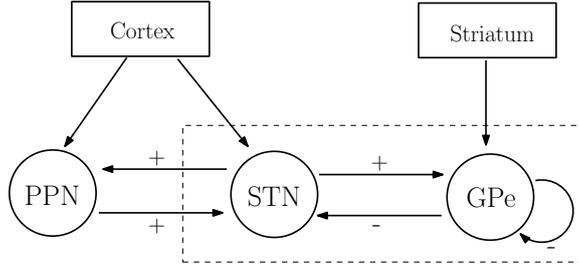


Figure 1: Schematic diagram of three nuclei: STN, GPe and PPN.

project excitatory axons to the GPe [8], while GPe neurons project inhibitory axons to the STN and to other GPe neurons [12]. The STN neurons project also excitatory axons to the PPN [7] which projects back excitatory axons to the STN [21]. Additionally, the STN and PPN nuclei receive inputs from cortex [4, 12, 21] and the GPe nucleus receives input from the striatum [12]. The firing rates model of the STN, GPe and PPN populations respectively, are ruled by the delayed differential equations

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

where x_s, x_g and x_p ¹ represent the firing rates of the STN, GPe and PPN, respectively. The positive gains $c_s^p, c_p^s, c_g^s, c_s^g$ 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 [10, 18], 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 $i \in \{s, g, p\}$.

3 Analysis in the absence of delays

3.1 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 for this system.

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*

$$\sigma_p \sigma_s c_s^p c_p^s \leq 1 \tag{2}$$

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. Moreover, if*

$$\left(\sigma_p c_s^p c_p^s - \frac{1}{\sigma_s}\right) \left(c_g^g + \frac{1}{\sigma_g}\right) > c_s^g c_g^s \tag{3}$$

then, for each constant input u_g^ , there exists a pair of constant inputs (u_s^*, u_p^*) for which the system (1) has at least three distinct equilibria.*

Theorem 1 generalizes the equilibrium study given by [18, Theorem 1] for a two-dimensional system describing the dynamics of two interacting subpopulations of excitatory and inhibitory neurons. It shows, in particular, that under condition (3), the existence of multiple equilibria can occur even for arbitrarily small striatal input.

3.2 Stability of equilibria

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

$$\begin{aligned} \tau_s \dot{e}_s &= \sigma_s^* (c_s^p e_p(t - \delta_s^p) - c_s^g e_g(t - \delta_s^g) + v_s) - e_s \\ \tau_g \dot{e}_g &= \sigma_g^* (c_g^s e_s(t - \delta_g^s) - c_g^g e_g(t - \delta_g^g) + v_g) - e_g \\ \tau_p \dot{e}_p &= \sigma_p^* (c_p^s e_s(t - \delta_p^s) + v_p) - e_p, \end{aligned} \tag{4}$$

where

$$\begin{aligned} \sigma_s^* &:= S'_s(c_s^p x_p^* - c_s^g x_g^* + u_s^*) \\ \sigma_g^* &:= S'_g(c_g^s x_s^* - c_g^g x_g^* + u_g^*) \\ \sigma_p^* &:= S'_p(c_p^s x_s^* + u_p^*). \end{aligned} \tag{5}$$

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*

$$\delta_i^j = 0 \quad \forall \quad i, j \in \{s, g, p\}. \tag{6}$$

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 (5). Then, under Assumption 1, the following holds.*

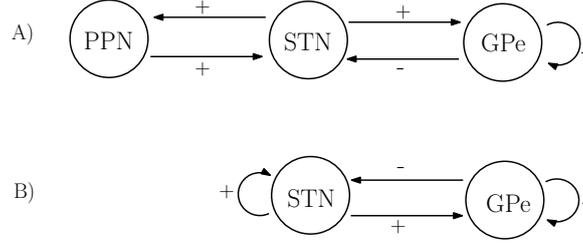


Figure 2: A): three neuron populations. B): two neuron populations.

- If the conditions

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

$$\frac{\sigma_s^*}{\tau_s + \tau_p} \left(\sigma_p^* c_s^p c_p^s - \frac{1}{\sigma_s^*}\right) < \frac{\sigma_g^*}{\tau_g} \left(c_g^g + \frac{1}{\sigma_g^*}\right) \quad (8)$$

are both satisfied, then the equilibrium point x^* is locally exponentially stable for (1).

- If the conditions

$$\sigma_p \sigma_s c_s^p c_p^s < 1 \quad (9)$$

$$\sigma_s (c_s^p + c_s^g) + \sigma_g c_g^s + \sigma_p c_p^s < 2 \quad (10)$$

are both satisfied then x^* is globally asymptotically stable for (1).

Section 4 is devoted to the study of the preservation of these stability properties in the presence of delays. Before that, we close this section by underlining some similarities with the two-nuclei approach developed in [10, 19, 18].

3.3 Comparison with an excitatory-inhibitory model

The PPN-STN interaction being excitatory in both directions, a natural question is whether the three-dimensional system (1) can be analyzed by a two-dimensional system in which the STN feedback to itself in an excitatory manner. Both these situations are depicted by Figure 2. This question creates a natural bridge between this work and [10, 18, 19] in which no explicit influence of PPN is considered. In the situation described by Figure 2B, the evolution of GPe and STN are given by

$$\begin{aligned} \tau_s \dot{x}_s &= S_s (c_s^s x_s(t - \delta_s^s) - c_s^g x_g(t - \delta_g^g) + u_s) - x_s \\ \tau_g \dot{x}_g &= S_g (c_g^s x_s(t - \delta_s^s) - c_g^g x_g(t - \delta_g^g) + u_g) - x_g \end{aligned} \quad (11)$$

where c_s^s defines the STN self-feedback and δ_s^s denotes its transmission delay.

The following result provides conditions under which the networks of Figure 2A and Figure 2B have the same number of equilibria.

Proposition 2 *Under Assumption 1, we have that if*

$$c_s^s \leq \sigma_p c_s^p c_p^s \quad (12)$$

then the equilibrium uniqueness of system (1) implies the equilibrium uniqueness of system (11). Otherwise, the equilibrium uniqueness of system (11) implies the equilibrium uniqueness of system (1).

The following result provides additional conditions under which global asymptotic stability is preserved between systems (1) and (11).

Proposition 3 Under Assumption 1, suppose that $\sigma_s c_s^s < 1$ and $\sigma_p \sigma_s c_s^p c_p^s < 1$. Then we have that if

$$\sigma_s c_s^s \leq \frac{1}{2} (\sigma_s c_s^p + \sigma_p c_p^s) \quad (13)$$

then the global asymptotic stability of (1) implies the global asymptotic stability of (11). Otherwise, the global asymptotic stability of (11) implies the global asymptotic stability of (1).

4 Robustness to delays

In this section, we study the stability properties of the equilibria of (1) by relying on its linearization (4) around an equilibrium point. This system can be described in the frequency domain using the closed-loop transfer functions

$$\begin{aligned} H_s(s) &= \frac{\sigma_s^*}{\tau_s s + 1}, & H_p(s) &= \frac{\sigma_p^*}{\tau_p s + 1} \\ H_g(s) &= \frac{\sigma_g^*}{\tau_g s + 1 + \sigma_g^* c_g^g e^{-\delta_g^g s}}, \end{aligned} \quad (14)$$

by the following system

$$\begin{aligned} \frac{1}{H_s} E_s + c_s^g e^{-\delta_s^g s} E_g - c_p^s e^{-\delta_p^s s} E_p &= V_s \\ \frac{1}{H_g} E_g - c_g^s e^{-\delta_g^s s} E_s &= V_g \\ \frac{1}{H_p} E_p - c_p^s e^{-\delta_p^s s} E_s &= V_p \end{aligned} \quad (15)$$

where $E := (E_s, E_g, E_p)^T$, and $V := (V_s, V_g, V_p)^T$ are the Laplace transforms of e and v . The system defined by (15) can be written as the following feedback system (G, K)

$$\begin{cases} E = GE' + U \\ E' = KE \\ U = GV \end{cases} \quad (16)$$

where the two transfer matrices G and K are given by the following

$$G(s) := \begin{pmatrix} H_s(s) & 0 & 0 \\ 0 & H_g(s) & 0 \\ 0 & 0 & H_p(s) \end{pmatrix}, \quad (17)$$

$$K(s) := \begin{pmatrix} 0 & -c_s^g e^{-\delta_s^g s} & c_p^s e^{-\delta_p^s s} \\ c_g^s e^{-\delta_g^s s} & 0 & 0 \\ c_p^s e^{-\delta_p^s s} & 0 & 0 \end{pmatrix}. \quad (18)$$

In order to study the stability properties of the feedback system (16), 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 for the Callier-Desoer class of scalar irrational transfer functions $\hat{\mathcal{B}}$ (see Appendix B for definitions, see also [5, Definitions 7.1.4 and 7.1.6] for more details). We start by checking the stability of the transfer matrices G and K . Noticing that G and K are irrational transfer matrices, we begin by verifying that each of its components belongs to $\hat{\mathcal{B}}$. This is stated by the following result.

Proposition 4 The entries of the transfer matrices G and K defined in (17)-(18) all belong to the Callier-Desoer class of scalar irrational transfer functions $\hat{\mathcal{B}}$.

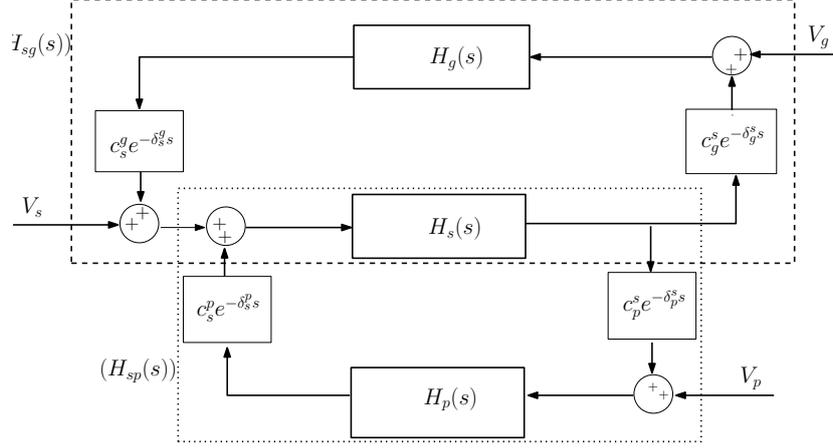


Figure 3: Bloc diagram of the linearized system (4).

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 $\delta_g^g = 0$. [18, Lemma 3], establishes the existence of a delay margin $\Delta(H_g)$ of H_g such that the transfer function H_g is input-output stable if and only if $\delta_g^g < \Delta(H_g)$. We recall that the delay margin of a SISO transmittance² $H \in \hat{\mathcal{B}}$, is defined by

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

To compute the delay margin of H one can associate, at a given frequency ω , its gain $\gamma_H(\omega)$ and phase $\varphi_H(\omega)$ which are defined by the relations

$$\begin{aligned} \gamma_H(\omega) &:= 20 \log_{10} |H(i\omega)| \\ \varphi_H(\omega) &:= \arg(H(i\omega)). \end{aligned} \quad (19)$$

In our approach, the case where the function γ_H is strictly decreasing is of a particular interest. Indeed, in this case, to any strictly proper transfer function H such that $\gamma_H(0) > 0$ we can associate its (gain) crossover frequency ω_H , which is defined as the only frequency such that

$$\gamma_H(\omega_H) = 0. \quad (20)$$

This frequency can be used to define the delay margin $\Delta(H)$ by the relationship

$$\Delta(H) = \frac{\pi - \varphi_H(\omega_H)}{\omega_H}. \quad (21)$$

If γ_H is strictly decreasing but $\gamma_H(0) \leq 0$, and if H is minimum phase (it has neither unstable poles nor unstable zeroes), then we can still define $\Delta(H) = +\infty$.

Since the stability properties of G and K are fully known in open loop, we now turn to study the stability of the feedback system (16). The following result provides a necessary and sufficient condition for the stability of the feedback system (16). Its statement relies on the following two transfer functions

$$\begin{aligned} K_p(s) &:= c_p H_p(s) e^{-\delta_p s} \\ K_g(s) &:= -c_g H_g(s) e^{-\delta_g s} \end{aligned} \quad (22)$$

where the quantities

$$\begin{aligned} c_p &:= c_s^p c_p^s, & c_g &:= c_s^g c_g^s, \\ \delta_p &:= \delta_p^s + \delta_s^p, & \delta_g &:= \delta_g^s + \delta_s^g \end{aligned} \quad (23)$$

²For a formal definition of input-output stability, see Definition 1 in Appendix B, see also [5, Definition 9.1.1].

are defined in order to obtain a lighter notation.

Proposition 5 *Suppose that H_g is input-output stable. The feedback system defined by (16) is input-output stable if and only if*

$$\text{ind}(1 - H_s(K_p + K_g)) = 0, \quad (24)$$

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

The proof of this result is based on standard arguments of the closed-loop stability of delayed MIMO system [5].

The bloc diagram (see Figure 3) comprises two closed-loops, one with external input (V_s, V_g) and the other with external input (V_s, V_p) . Let us introduce the two following transfer functions

$$H_{sp} := \frac{H_s}{1 - H_s K_p} \quad \text{and} \quad H_{sg} := \frac{H_s}{1 - H_s K_g}. \quad (25)$$

H_{sp} and H_{sg} are the closed-loop transfer functions of the rectangles marked in dotted and dashed respectively and which are calculated between V_s and E_s .

The following lemma states that the stability analysis of the full network can be reduced to the study of either $H_{sg}K_p$ or $H_{sp}K_g$.

Lemma 2 *Assume that the transfer functions H_g, H_{sp} and H_{sg} defined in (14) and (25), are input-output stable. Then we have that*

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

According to Lemma 2, if the transfer functions H_g, H_{sp} and H_{sg} are input-output stable, then the stability analysis of the feedback system (16) can be equivalently achieved by studying one of the two feedback systems (H_{sp}, K_g) or (H_{sg}, K_p) . In what follows, we choose to focus on the feedback system (H_{sp}, K_g) to study the stability of the network of Figure 3. This choice is motivated by the following lemma, which provides conditions under which the gain $\gamma_{H_{sp}}$ is monotonically decreasing, thus considerably simplifying the Nyquist plot analysis.

Lemma 3 *Consider the transfer function H_{sp} defined by (25). For each positive δ_p as defined in (23), there exists a positive gain $c_p^*(\delta_p)$ such that the loop gain $\gamma_{H_{sp}}$ is strictly decreasing for every $c_p = c_p^s c_p^g \in (0, c_p^*(\delta_p))$.*

In order to prove the stability of H_{sp} , we can directly invoke [18, Theorem 2]. While the stability of H_{sp} does not depend on the loop delay δ_p , this is not the case for H_{sg} . In particular, when $c_g \sigma_g^* \sigma_s^* > 1 + c_g^g \sigma_g^*$, only a finite upper bound on the delay δ_g can be tolerated. These two observations are formalized by the following statement.

Lemma 4 *For the transfer functions H_{sp} and H_{sg} defined in (25), let*

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

and consider the constants σ_i^* , $i \in \{s, p, g\}$, defined by (5). Then following facts hold:

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

With Proposition 5 and Lemmas 2 and 4 at hand, we are now ready to state the following result, which provides conditions for the local asymptotic stability of the linear system (4).

Theorem 2 Consider the delayed differential equation defined by (4). Let $u^* \in \mathbb{R}^3$ be any input such that, for the equilibrium x^* associated to these inputs, the transfer functions H_g and H_{sp} , defined in (14)-(25), are input-output stable. Define $H := c_g H_g H_{sp}$. Assume that the gain of γ_H is strictly decreasing (which can be verified using Lemma 3 and [18, Lemma 4] together). For every $\delta_p > 0$, x^* is exponentially stable for (4) if and only if $\delta_g < \Delta(H)$.

Using Lemma 3 and the fact that the transfer function H_g can be strictly decreasing [18, Lemma 4], the following result derives directly from Theorem 2.

Corollary 1 Consider the delayed differential equation defined by (4). Let $u^* \in \mathbb{R}^3$ be any input such that, for the equilibrium x^* associated to these inputs, the transfer functions H_g and H_{sp} are input-output stable. Assume that the gain of γ_{H_g} is strictly decreasing. For each $\delta_p > 0$, there exist $c_p^* > 0$ such that for each $c_p < c_p^*$, x^* is exponentially stable for (4) if and only if $\delta_g < \Delta(H)$.

5 Numerical simulations

We now validate our theoretical findings through numerical simulations. As in [18], the activation functions S_s, S_g and S_p are approximated by a normalized sigmoid function of the form

$$S_i(x) = \frac{B_i}{B_i + (M_i - B_i)e^{-4x}}, \quad \forall i \in \{s, g, p\} \quad (26)$$

where B_i and M_i are given in Table 1. These functions satisfy Assumption 1 with $\sigma_i = 1$, for $i \in \{s, g, p\}$. The parameter values of system (1), and precisely the transmission delays, time-constants, and activation functions, are chosen as follows. For the STN and GPe nuclei, these values are the same as those taken in [10, 18] and they are given in Table 1. For the PPN, and since we did not find exact parameters in the literature, the parameters are taken equal to those that correspond to the STN. As in [10, 18] the interconnection gain c_j^i from nucleus i to nucleus j ($i, j \in \{s, g\}$) in the STN-GPe network, is given by

$$c_j^i = c_j^{iH} + k(c_j^{iD} - c_j^{iH}) \quad \forall i, j \in \{s, g\} \quad (27)$$

where k is a parameter that describes the evolution of Parkinson's disease, and c_j^{iH} and c_j^{iD} are, respectively, the interconnection gains for the healthy and diseased states (given in Table 2). Similarly, the external inputs are given by

$$u_i = u_i^H + k(u_i^D - u_i^H) \quad \forall i \in \{s, g, p\} \quad (28)$$

where u_i^H and u_i^D are, respectively, the external inputs for the healthy and diseased states (given in Table 2). The external inputs to the PPN, for the healthy and diseased state, are taken equal to those of STN. The parameter k is fixed to $k = 0.2$, value for which the two-dimensional system STN-GPe is locally asymptotically stable [10, 18, 19]. The evolution of system (1) is carried out in function of the interconnection gains c_p^s and c_p^g , which are taken equal.

One can easily check the dependency on the parameter c_p (defined in (23)) of the delay margin $\Delta(H)$, by plotting $\Delta(H)$ as a function of $c_p \in (0; 1)$ (see Figure 4). It can be observed that the delay margin decreases when c_p increases. In addition, one can see that when $c_p = 0.2$ the linear system (4) is approximately at the bifurcation point. After checking the dependency on c_p of $\Delta(H)$, we set two distinct values of c_p around the bifurcation point: $c_p = 0.1$ and $c_p = 0.3$ (note that for these values the gain $\gamma_{H_{sp}}$ is strictly decreasing). We simulate the evolution of nonlinear system (1) together with Nyquist diagram of its linearization (4) in both cases. The results of our simulations are presented in Figure 5A and 5B. When $c_p = 0.1$, we have $\Delta(H) > \delta_g$, the Nyquist plot does not encircle the critical point, and the nonlinear system (1) is stable. When $c_p = 0.3$, we have $\Delta(H) < \delta_g$, the critical point is encircled, and the nonlinear system (1) is unstable, which predicts the birth of pathological oscillations within the PPN-STN-GPe network.

Table 1: Parameter values needed for simulation.

Parameter	Value	Description
δ_g^s	6 ms	Delay from STN to GPe
δ_s^g	6 ms	Delay from GPe to STN
δ_p^s	6 ms	Delay from STN to PPN
δ_s^p	6 ms	Delay from PPN to STN
δ_g^g	4 ms	Delay from PPN to STN
τ_s	6 ms	Delay from STN to GPe
τ_g	14 ms	Delay from GPe to STN
τ_p	6 ms	Delay from GPe to STN
M_s	300 spk/s	STN Maximal firing rate
B_s	17 spk/s	Firing rate at rest for STN
M_g	400 spk/s	GPe Maximal firing rate
B_g	75 spk/s	Firing rate at rest for GPe
M_p	300 spk/s	PPN Maximal firing rate
B_p	17 spk/s	Firing rate at rest for PPN

Table 2: Parameter values needed for simulation.

Parameter	Healthy state	Diseased state
c_g^s	14.3	15
c_s^g	1.5	14.3
c_g^g	6.6	12.3
u_s	0.2	0.8
u_g	0.1	0.7
u_p	0.2	0.8

Appendix A: Mathematical proofs

Proof of Lemma 1 By Assumption 1, for $i \in \{s, g, p\}$, the activation functions satisfy

$$S_i(x) \geq 0 \text{ and } S_i(x) \leq 1 \text{ for each } x \in [0, 1].$$

Therefore, if $x_i \leq 0$ then $\dot{x}_i \geq 0$ and if $x_i \geq 1$ then $\dot{x}_i \leq 0$. It follows that, for each point on the boundary of D , the vector field that defines the system dynamics points towards D . Hence, this set is positively invariant (independently of the values of the delays and of the external inputs).

Proof of Theorem 1 *First step.* For any constant inputs u_s^*, u_g^* and u_p^* consider the three isoclines

$$\begin{aligned}
N_s &:= \left\{ (x_s, x_g, x_p) \in \mathbb{R}^3 : x_s = S_s(c_s^p x_p - c_s^g x_g + u_s^*) \right\} \\
N_g &:= \left\{ (x_s, x_g, x_p) \in \mathbb{R}^3 : x_g = S_g(c_g^s x_s - c_g^g x_g + u_g^*) \right\} \\
N_p &:= \left\{ (x_s, x_g, x_p) \in \mathbb{R}^3 : x_p = S_p(c_p^s x_s + u_p^*) \right\}.
\end{aligned} \tag{29}$$

All equilibria (x_s^*, x_g^*, x_p^*) of system (1) are located on the set $N_s \cap N_g \cap N_p$. Observe that these sets do not depend on the system's delays. Since

$$N_i \subset \left\{ (x_s, x_g, x_p) \in \mathbb{R}^3 : x_i \in [0, 1] \right\} \text{ for each } i \in \{s, g, p\},$$

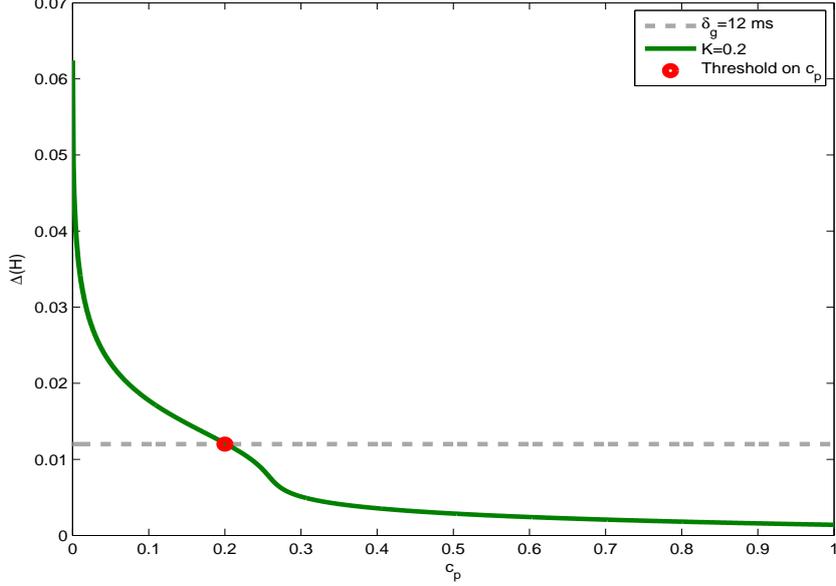


Figure 4: Influence of c_p on the delay margin $\Delta(H)$, for $k = 0.2$.

it follows that all equilibria belong to the unit cube.

Second step. Using the inverse activation functions T_i defined above, the isoclines (29) can be described by

$$\begin{aligned}
 N_s &= \left\{ (x_s, x_g, x_p) \in \mathbb{R}^3 : x_g = \frac{1}{c_s^p} (c_s^p x_p - T_s(x_s) + u_s^*) \right\} \\
 N_g &= \left\{ (x_s, x_g, x_p) \in \mathbb{R}^3 : x_s = \frac{1}{c_s^g} (c_g^g x_g + T_g(x_g) - u_g^*) \right\} \\
 N_p &= \left\{ (x_s, x_g, x_p) \in \mathbb{R}^3 : x_p = S_p(c_p^s x_s + u_p^*) \right\}.
 \end{aligned} \tag{30}$$

The set N_g can always be described as the graph of a strictly increasing function, defined on the interval $[0, 1]$. That is

$$x_s = \varphi(x_g, u_g^*), \quad \forall x_g \in [0, 1].$$

Where the function $\varphi : [0, 1] \rightarrow \mathbb{R}$ is defined as

$$\varphi(x_g, u_g^*) := \frac{1}{c_s^g} (c_g^g x_g + T_g(x_g) - u_g^*).$$

Using the fact that for each u_g^* the function φ is both surjective and strictly increasing on the interval $[0, 1]$, we can define $x_g^0(u_g^*)$ and $x_g^1(u_g^*)$ as the only solutions of the equations

$$\varphi(x_g^0, u_g^*) = 0$$

and

$$\varphi(x_g^1, u_g^*) = 1$$

respectively. Observe that a point (x_s, x_g, x_p) is an equilibrium requires that x_g belongs to the interval $[x_g^0, x_g^1]$ and satisfies the equation

$$x_g = \frac{1}{c_s^g} \left[c_s^p S_p \left(c_p^s \varphi(x_g, u_g^*) + u_p^* \right) - T_s(\varphi(x_g, u_g^*)) + u_s^* \right].$$

Third step. We are now able to define, for each $x \in [x_g^0, x_g^1]$, the function

$$L(x) = \frac{1}{c_s^g} \left[c_s^p S_p \left(c_p^s \varphi(x, u_g^*) + u_p^* \right) - T_s(\varphi(x, u_g^*)) + u_s^* \right] - x.$$

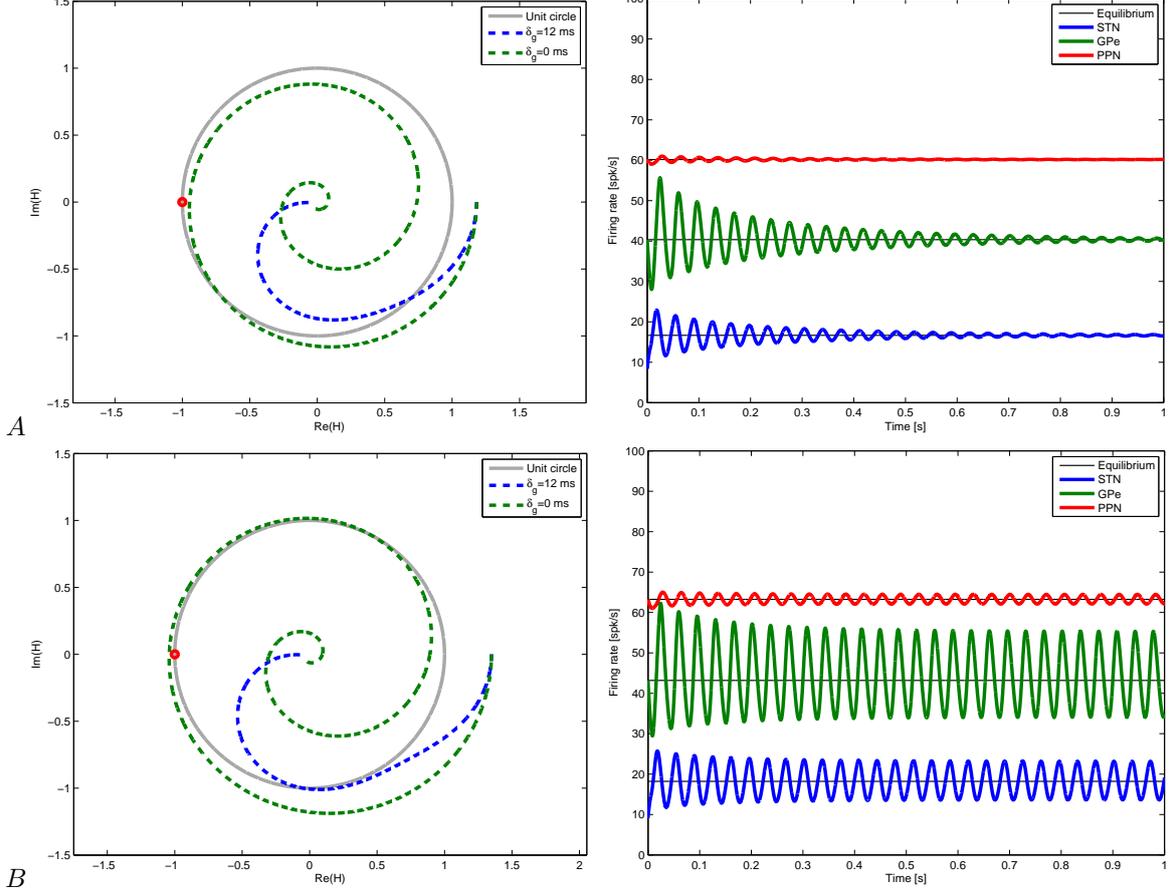


Figure 5: Influence on stability of the interconnection gain c_p^s and c_s^p , for $k = 0.2$. On the left, the open-loop frequency-response is represented in a Nyquist diagram. On the right, the temporal evolution of the system (1) is plotted.

By construction, if (x_s, x_g, x_p) is an equilibrium point of system (1) then we have

$$L(x_g) = 0. \quad (31)$$

Moreover, noticing that $T_s(1) = +\infty$ and $T_s(0) = -\infty$, in any of the three cases described by the theorem, the function L is such that

$$\lim_{x \rightarrow x_g^0+} L(x) = +\infty \quad \text{and} \quad \lim_{x \rightarrow x_g^1-} L(x) = -\infty. \quad (32)$$

Since this function is continuous, the intermediate value theorem guarantees that it must vanish on (x_g^0, x_g^1) . If we omit the dependency of $\varphi(\cdot)$ and $\varphi'(\cdot)$ in u_g^* , the derivative of L can be computed using the chain rule

$$L'(x) = \frac{1}{c_s^g} \left[c_p^s c_p^s \varphi'(x) S_p' \left(c_p^s \varphi(x) + u_p^* \right) - T_s'(\varphi(x)) \varphi'(x) \right] - 1,$$

with

$$\varphi'(x) = \frac{1}{c_s^g} (c_g^g + T_g'(x)).$$

Grouping the factors of $\varphi'(x)$ in $L'(x)$ leads to

$$L'(x) = \frac{S_p'(c_p^s \varphi(x) + u_p^*)}{c_s^g c_s^g} \left(c_p^s c_p^s - (S_p'(c_p^s \varphi(x) + u_p^*))^{-1} T_s'(\varphi(x)) \right) (c_g^g + T_g'(x)) - 1.$$

Using again the chain rule to compute $(S'_p(c_p^s \varphi(x) + u_p^*))^{-1}$ leads to

$$L'(x) = \frac{S'_p(c_p^s \varphi(x) + u_p^*)}{c_g^s c_s^g} \left(c_p^p c_s^s - T'_s(\varphi(x)) T'_p(S_p(c_p^s \varphi(x) + u_p^*)) \right) (c_g^g + T'_g(x)) - 1. \quad (33)$$

By Assumption 1, this function is continuous at each point for which it is defined.

Claim 1 *For a given u_g^* , assume that there exists x_g^* such that $L'(x_g^*) > 0$. Then, for every u_p^* there exists u_s^* such that the system admits at least three distinct equilibria.*

Proof of Claim 1 On the one hand, since $L'(x_g^*) > 0$ and L' is continuous, there exists a strictly positive real number ϵ_0 such that $x_g^* \in (x_g^0 + \epsilon_0, x_g^1 - \epsilon_0)$ and $L'(x) > 0$ for each $x \in (x_g^0 + \epsilon_0, x_g^1 - \epsilon_0)$. Additionally, for every u_p^* we can chose u_s^* such that $L(x_g^*) = 0$. Hence, we can assume that $L(x_g^0 + \epsilon_0) < 0$ and $L(x_g^0 - \epsilon_0) > 0$. But, on the other hand, it follows from (32) that there exist $\epsilon_1 < \epsilon_0$ such that $L(x) > 0$ over $(x_g^0, x_g^0 + \epsilon_1)$ and $L(x) < 0$ over $(x_g^1, x_g^1 - \epsilon_1)$. Therefore, by the continuity of L and by the intermediate value theorem, there exist two points x_1^* and x_2^* such that $x_1^* \in (x_g^0 + \epsilon_1, x_g^0 + \epsilon_0)$ and $x_2^* \in (x_g^1 - \epsilon_0, x_g^1 - \epsilon_1)$, and that satisfy, respectively, the equations $L(x_1^*) = 0$ and $L(x_2^*) = 0$.

Fourth step. Using the previous result, we can continue with the proof of Theorem 1 and treat, one after the other, its three cases.

Item (i). The first case appears when $\sigma_p \sigma_s c_p^s c_s^p \leq 1$. In this case $c_p^s c_s^p - T'_p(S_p(c_p^s \varphi(x) + u_p^*)) T'_s(\varphi(x)) \leq 0$ because that the infimum of the function $T'_p T'_s$ is equal to $1/\sigma_p \sigma_s$. Since $c_g^g + T'_g(x) \geq 1/\sigma_g \geq 0$, we must have in view of (33) $L'(x) < 0$, for each $x \in (x_g^0, x_g^1)$. The uniqueness of the equilibrium point comes from the fact that L is strictly decreasing. Its existence is guaranteed by the intermediate value theorem and by the limits of L at each end of its domain (32).

Item (ii). In this case it must be shown that, when $\sigma_p \sigma_s c_p^s c_s^p > 1$, there always exist u_g^* and a point x^* such that $L'(x^*) > 0$. To this end, for a given u_g^* , we look for a point x^* such that $T'_s(\varphi(x^*)) T'_p(c_p^s \varphi(x^*) + u_p^*) = 1/\sigma_p \sigma_s$. We know from the Assumption 1 That there exist a point y^* where T_s reaches its minimum $1/\sigma_s$. For this y^* and for every u_g^* there exist a point x^* , such that $\varphi(x^*) = y^*$. The existence of x^* comes from the injectivity of φ . In other words, the equation

$$\frac{1}{c_g^s} (c_g^g x + T_g(x) + u_g^*) = y^* \quad (34)$$

always admits a unique solution x^* in (x_g^0, x_g^1) . Furthermore, since the map $x_s \mapsto c_p^s x_s + u_p$ is bijective, then there exists a constant input u_p^* such that $T'_p(c_p^s x_s^* + u_p^*) = 1/\sigma_p$. Moreover, applying S_g to both sides of (34), we obtain

$$\lim_{u_g^* \rightarrow +\infty} x^* = S_g(c_g^s y^* - c_g^g x^* - u_g^*) = 1.$$

Now, combining the equality

$$c_p^p c_s^s - T'_s(\varphi(x^*)) T'_p(c_p^s \varphi(x^*) + u_p^*) = c_p^p c_s^s - 1/\sigma_p \sigma_s$$

with the limit

$$\lim_{u_g^* \rightarrow +\infty} c_g^g + T'_g(x^*) = +\infty,$$

we have, for u_g^* big enough, that

$$\left(c_p^p c_s^s - T'_s(\varphi(x^*)) T'_p(c_p^s \varphi(x^*) + u_p^*) \right) (c_g^g + T'_g(x^*)) > \frac{c_g^s c_s^g}{\sigma_p}.$$

For such an u_g^* , we have $L'(x^*) > 0$. Hence, by Claim 1, there exists u_s^* such that the dynamics (1) has at least three distinct equilibria.

Item (iii). For the third case, observe that the relation $\left(\sigma_p c_p^s c_s^p - \frac{1}{\sigma_s} \right) \left(c_g^g + \frac{1}{\sigma_g} \right) > c_g^s c_s^g$ is satisfied if and only if

$$c_p^s c_s^p > \frac{1}{\sigma_p \sigma_s} + \frac{c_g^s c_s^g}{c_g^g + \frac{1}{\sigma_g}}.$$

Therefore, the condition imposed by this case is more restrictive than that of the previous one. The key point of the proof is to be able to find, for each fixed u_g^* , a point x^* such that $L'(x^*) > 0$. On the one hand, we have

$$c_g^g + T'_g(x) \geq c_g^g + \frac{1}{\sigma_g},$$

for each $x \in (0, 1)$. On the other hand, by Assumption 1, there is always a point on which the function $x \mapsto T'_s(x)T'_p(S_p(c_p^s x + u_p^*))$ reaches its minimum $\sigma_p \sigma_s$. Define y^* to be this point. Now, take the only x^* such that $\varphi(x^*, u_g^*) = y^*$. This is always possible because φ is both surjective and strictly increasing, for each u_i^* . Hence, in view of (33),

$$\begin{aligned} L'(x^*) &= \frac{\sigma_p}{c_g^s c_s^g} \left(c_p^s c_s^p - \frac{1}{\sigma_p \sigma_s} \right) (c_g^g + T'_g(x^*)) - 1 \\ &\geq \frac{\sigma_p}{c_g^s c_s^g} \left(c_p^s c_s^p - \frac{1}{\sigma_p \sigma_s} \right) \left(c_g^g + \frac{1}{\sigma_g} \right) - 1 \\ &> 0 \end{aligned}$$

Since $L'(x^*) > 0$, the proof of this last case of the theorem follows from Claim 1.

Proof of Proposition 1 Item (i). The Jacobian matrix of dynamics 1 at the equilibrium (x_s^*, x_g^*, x_p^*) is given by

$$J(x^*) := \begin{pmatrix} -\frac{1}{\tau_s} & -\frac{c_s^g}{\tau_s} \sigma_s^* & \frac{c_s^p}{\tau_s} \sigma_s^* \\ \frac{c_g^s}{\tau_g} \sigma_g^* & -\frac{1}{\tau_g} - \frac{c_g^g}{\tau_g} \sigma_g^* & 0 \\ \frac{c_p^s}{\tau_p} \sigma_p^* & 0 & -\frac{1}{\tau_p} \end{pmatrix}. \quad (35)$$

Its characteristic polynomial is given by

$$P_J(\lambda) = \lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3.$$

where

$$\begin{aligned} a_1 &= \frac{1}{\tau_s} + \frac{1}{\tau_p} + \frac{1}{\tau_g} (1 + c_g^g \sigma_g^*) \\ a_2 &= \frac{1}{\tau_g} \left(\frac{1}{\tau_s} + \frac{1}{\tau_p} \right) (1 + c_g^g \sigma_g^*) + \frac{1}{\tau_s} \frac{1}{\tau_p} (1 - c_s^p c_p^s \sigma_s^* \sigma_p^*) + \frac{1}{\tau_s} \frac{1}{\tau_g} c_s^g c_g^s \sigma_s^* \sigma_g^* \end{aligned}$$

and

$$a_3 = \frac{1}{\tau_s} \frac{1}{\tau_g} \frac{1}{\tau_p} \left[(1 + c_g^g \sigma_g^*) (1 - c_s^p c_p^s \sigma_s^* \sigma_p^*) + c_s^g c_g^s \sigma_s^* \sigma_g^* \right].$$

According to the Routh-Hurwitz criterion, if $a_1 > 0$, $a_3 > 0$ and $a_1 a_2 - a_3 > 0$, then all the eigenvalues of J have negative real part. We have clearly $a_1 > 0$. Furthermore, we have $a_3 > 0$ if and only if (7) holds. For the sign of $a_1 a_2 - a_3$, we make use of the following notations

$$e_1 = 1 - c_s^p c_p^s \sigma_s^* \sigma_p^*, e_2 = 1 + c_g^g \sigma_g^* \text{ and } e_3 = c_s^g c_g^s \sigma_s^* \sigma_g^*.$$

Using this notations, one obtains

$$\begin{aligned}
a_1 a_2 - a_3 &= \left(\frac{1}{\tau_s} + \frac{1}{\tau_p}\right)^2 \frac{1}{\tau_g} e_2 + \left(\frac{1}{\tau_s} + \frac{1}{\tau_p}\right) \frac{1}{\tau_s} \frac{1}{\tau_p} e_1 + \left(\frac{1}{\tau_s} + \frac{1}{\tau_p}\right) \left(\frac{1}{\tau_g}\right)^2 e_2^2 + \frac{1}{\tau_g} \left(\frac{1}{\tau_s}\right)^2 e_3 + \frac{1}{\tau_s} \left(\frac{1}{\tau_g}\right)^2 e_2 e_3 \\
&= \frac{\tau_s + \tau_p}{\tau_s^2 \tau_p^2} \left(\frac{\tau_s + \tau_p}{\tau_g} e_2 + e_1 + \frac{\tau_s \tau_p}{\tau_g^2} e_2^2 + \frac{\tau_p^2}{\tau_g (\tau_s + \tau_p)} e_3 + \frac{\tau_s \tau_p^2}{\tau_g^2 (\tau_s + \tau_p)} e_2 e_3 \right) \\
&= \frac{\tau_s + \tau_p}{\tau_s^2 \tau_p^2} \left(1 + \frac{\tau_s + \tau_p}{\tau_g} (1 + c_g^g \sigma_g^*) + \frac{\tau_s \tau_p}{\tau_g^2} (1 + c_g^g \sigma_g^*)^2 + \frac{\tau_p^2}{\tau_g (\tau_s + \tau_p)} c_s^g c_g^s \sigma_s^* \sigma_g^* \right. \\
&\quad \left. + \frac{\tau_s \tau_p^2}{\tau_g^2 (\tau_s + \tau_p)} (1 + c_g^g \sigma_g^*) c_s^g c_g^s \sigma_s^* \sigma_g^* - c_p^p c_s^s \sigma_s^* \sigma_p^* \right)
\end{aligned}$$

If (8) holds then we have $a_1 a_2 - a_3 > 0$. Hence, if (7) and (8) holds, the Jacobian matrix (35) is Hurwitz, which establishes that x^* is locally exponentially stable.

Item (ii). With a slight abuse of notation, we define $f_i = (-x_i + S_i)/\tau_i$ for each $i \in \{s, g, p\}$. That is, we omit the arguments of these two functions, which leads to $\dot{x}_i = f_i$. Now, define the function $V : \mathbb{R}^3 \rightarrow \mathbb{R}$ given by

$$V(x) = \frac{1}{2} \sum_{i=s,g,p} \tau_i f_i^2(x). \quad (36)$$

The first part of condition (9) implies, by Theorem 1, the uniqueness of the equilibrium point of system (1), which is then the only point for which

$$V(x^*) = 0.$$

Furthermore, the derivative of V along (1) yield,

$$\begin{aligned}
\dot{V} &= \frac{\partial V}{\partial x_s} f_s + \frac{\partial V}{\partial x_g} f_g + \frac{\partial V}{\partial x_p} f_p \\
&= -f_s^2 - (1 + c_g^g S'_g) f_g^2 - f_p^2 + (c_g^s S'_g - c_s^g S'_s) f_s f_g + (c_p^s S'_p + c_s^p S'_s) f_s f_p \\
&< -f_s^2 - f_g^2 - f_p^2 + (c_g^s S'_g - c_s^g S'_s) f_s f_g + (c_p^s S'_p + c_s^p S'_s) f_s f_p
\end{aligned}$$

using Young's inequality, we obtain

$$\begin{aligned}
\dot{V} &< -f_s^2 - f_g^2 - f_p^2 + \frac{1}{2} (c_g^s S'_g + c_s^g S'_s) (f_s^2 + f_g^2) + \frac{1}{2} (c_p^s S'_p + c_s^p S'_s) (f_s^2 + f_p^2) \\
&\leq -f_s^2 - f_g^2 - f_p^2 + \frac{1}{2} (c_g^s \sigma_g + c_s^g \sigma_s) (f_s^2 + f_g^2) + \frac{1}{2} (c_p^s \sigma_p + c_s^p \sigma_s) (f_s^2 + f_p^2) \\
&< \left(-1 + \frac{1}{2} (c_g^s \sigma_g + c_s^g \sigma_s) + \frac{1}{2} (c_p^s \sigma_p + c_s^p \sigma_s) \right) (f_s^2 + f_g^2 + f_p^2).
\end{aligned}$$

Therefore, when the second part of condition (9) is satisfied, we can always find $\epsilon > 0$ such that

$$\dot{V} \leq -\epsilon (f_s^2 + f_g^2 + f_p^2),$$

and then

$$\dot{V} \leq -kV, \quad (37)$$

where $k = \frac{2\epsilon}{\max_i(\tau_i)}$.

Now, by Theorem 1, the condition (7) implies the uniqueness of the equilibrium point, which is then the only point for which $V(x) = 0$. It follows that V is a Lyapunov function that satisfies the standard conditions for global asymptotic stability [11, Theorem 4.1].

Proof of Proposition 2 Suppose that for every $(u_s^*, u_g^*, u_p^*) \in \mathbb{R}^3$ system (1) has a unique equilibrium point. This implies (from Theorem 1) that (2) holds. If (12) holds then, under Assumption 1 and precisely the fact that $\sigma_s > 0$, we have

$$\sigma_s c_s^s \leq \sigma_p \sigma_s c_s^p c_p^s. \quad (38)$$

Thus, we have

$$\sigma_s c_s^s \leq 1. \quad (39)$$

From [18, Theorem 1], (39) implies the existence and uniqueness of equilibrium to system (11). Suppose now that for every $(u_s^*, u_g^*) \in \mathbb{R}^3$ system (11) has a unique equilibrium point. This implies (from [18, Theorem 1]) that (39) holds. If

$$c_s^s > \sigma_p c_s^p c_p^s$$

then we obtain the following inequalities

$$\sigma_p \sigma_s c_s^p c_p^s < 1$$

which implies (from Theorem 1) the existence and uniqueness of equilibrium to system (1).

Proof of Proposition 3 If $\sigma_s c_s^s < 1$ and $\sigma_p \sigma_s c_s^p c_p^s < 1$ then the system (1) and (11) has a unique equilibrium point in D , respectively. Suppose that the condition (8) is verified, which means that the equilibrium point of (1) is globally asymptotically stable. If (13) holds, then one can easily verify that we have

$$\frac{1}{2} (\sigma_s c_s^g + \sigma_g c_g^s) < 1 - \sigma_s c_s^s. \quad (40)$$

From [18, Proposition 1], (40) implies the global asymptotic stability of the equilibrium point of (11). Suppose now that the condition (40) is verified. If

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

then one can easily verify that we have the second part of (9) which implies together with the fact that $\sigma_p \sigma_s c_s^p c_p^s < 1$ the global asymptotic stability of the equilibrium point of (1).

Proof of Proposition 4 Notice that $e^{-\alpha s} \in \hat{\mathcal{A}}_-$ for any $\alpha > 0$ and so all the components of K are in $\hat{\mathcal{A}}_-$. For the transfer matrix G , the functions H_s and H_p are strictly proper, rational transfer functions with one pole at $s = -1/\tau_s$ and $s = -1/\tau_p$ respectively. Clearly, H_s and $H_p \in \hat{\mathcal{A}}_-$. In fact, H_s and H_p are the Laplace transform of

$$h_s(t) := \frac{\sigma_s^*}{\tau_s} e^{-\frac{1}{\tau_s} t} \quad \text{and} \quad h_p(t) := \frac{\sigma_p^*}{\tau_p} e^{-\frac{1}{\tau_p} t}$$

respectively. Then, one can observe that $e^{\epsilon t} h_s(t)$ and $e^{\epsilon t} h_p(t) \in L_1(0, \infty)$ for every $\epsilon \in (0, \min(1/\tau_s, 1/\tau_p))$. This is not the case of H_g . Indeed, $H_g \in \hat{\mathcal{B}}$. In fact, up to multiplication by a constant, the transfer function H_g has the following form

$$H(s) = \frac{1}{as + b + ce^{-ds}}$$

where a, b, c and $d \in \mathbb{R}$. It is proved that every transfer function having this form ([5], Example 7.1.12, p. 343) is an element of $\hat{\mathcal{B}}$.

Proof of Proposition 5 Under the condition of stability of $\overline{H_g}$ we have clearly that the two transfer matrices G and $K \in \mathcal{M}\hat{\mathcal{A}}_-$ and thus they have no poles in $\overline{\mathbb{C}_0^+}$. then it suffices to prove that GK is strictly proper on $\overline{\mathbb{C}_0^+}$ to conclude the proof. We recall that a transfer matrix M is strictly proper on $\overline{\mathbb{C}_0^+}$ if and only if

$$\lim_{\rho \rightarrow \infty} \sup_{s \in \overline{\mathbb{C}_0^+}, |s| \geq \rho} |M(s)| = 0,$$

where the norm $|\cdot|$ denote a matrix norm of $M(s)$. We have

$$G(s)K(s) = \begin{pmatrix} 0 & -c_g^g e^{-\delta_g^g s} H_s(s) & c_s^p e^{-\delta_s^p s} H_s(s) \\ c_g^s e^{-\delta_g^s s} H_g(s) & 0 & 0 \\ c_p^s e^{-\delta_p^s s} H_p(s) & 0 & 0 \end{pmatrix}.$$

It is obviously that GK is strictly proper on $\overline{\mathbb{C}_0^+}$ since all its components are strictly proper on $\overline{\mathbb{C}_0^+}$. Furthermore, one can easily verify that

$$\det(I - GK) = 1 - H_s(K_p + K_g),$$

and thus we conclude that the feedback system defined by (16) is input-output stable if and only if (24) is hold.

Proof of Lemma 2 We have that the two transfer functions H_s and $K_p \in \hat{\mathcal{A}}_-$, and so they have no poles in $\overline{\mathbb{C}_0^+}$. Otherwise, we know that $H_s K_p$ is strictly proper on $\overline{\mathbb{C}_0^+}$. Then, under the assumption that H_{sp} is input-output stable we have $\text{ind}(1 - H_s K_p) = 0$ (cf. Appendix B (Theorem 3)). And so $1 - H_s K_p$ has no zeros in $\overline{\mathbb{C}_0^+}$. Then $1 - H_s K_p$ is invertible over $\hat{\mathcal{A}}_-$ (cf. Appendix B (property (p_3))). Hence the following equality is well defined in $\hat{\mathcal{A}}_-$

$$1 - H_{sp} K_g = \frac{1 - H_s(K_p + K_g)}{1 - H_s K_p}.$$

Which can be written equivalently in $\hat{\mathcal{A}}_-$ as the following

$$(1 - H_{sp} K_g)(1 - H_s K_p) = 1 - H_s(K_p + K_g).$$

Recall that a scalar complex-valued function g defined and meromorphic on $\mathbb{C}_{-\epsilon}^+$ for some $\epsilon > 0$ has a well defined Nyquist index if it has a nonzero limit at infinity in $\overline{\mathbb{C}_0^+}$. This means that ([5], equation (A.1.6), p. 569)

$$\lim_{\rho \rightarrow \infty} \left[\sup_{s \in \overline{\mathbb{C}_0^+} \mid |s| \geq \rho} |g(s) - g(\infty)| \right] = 0$$

for some nonzero $g(\infty) \in \mathbb{C}$.

Since H_s, K_p and $K_g \in \hat{\mathcal{A}}_-$, we have that $1 - H_s(K_p + K_g) \in \hat{\mathcal{A}}_-$. Hence it is holomorphic on $\mathbb{C}_{-\epsilon}^+$ for some $\epsilon > 0$ ([5], Lemma A.7.47, p. 663). Otherwise, we know that $H_s(K_p + K_g)$ is strictly proper on $\overline{\mathbb{C}_0^+}$, and so $1 - H_s(K_p + K_g)$ has the limit 1 at infinity. Concluding, we have that $1 - H_s(K_p + K_g)$ has a well defined Nyquist index. Similarly, $1 - H_{sp} K_g$ has a well defined Nyquist index. Using a property of the Nyquist index ([5], equation (A.1.9), p. 570) we obtain

$$\text{ind}(1 - H_{sp} K_g) + \text{ind}(1 - H_s K_p) = \text{ind}(1 - H_s(K_p + K_g)),$$

and, together with the fact that $\text{ind}(1 - H_s K_p) = 0$, imply that

$$\text{ind}(1 - H_{sp} K_g) = \text{ind}(1 - H_s(K_p + K_g)).$$

By the same way one can show that we have also

$$\text{ind}(1 - H_{sg} K_p) = \text{ind}(1 - H_s(K_p + K_g)),$$

which ends the proof of Lemma (2).

Proof of Lemma 3 The transfer function H_{sp} is given by

$$H_{sp} = \frac{H_s}{1 - H_s K_p}.$$

By replacing H_s and K_p by their expressions, we obtain

$$H_{sp} = \sigma_s^* \frac{1 + \tau_p s}{(1 + \tau_p s)(1 + \tau_s s) - c_p \sigma_s^* \sigma_p^* e^{-\delta_p s}}.$$

For $s = iw$ ($w \in \mathbb{R}$), the loop gain $\gamma_{H_{sp}}$ is given by

$$\gamma_{H_{sp}}(w) = \sigma_s^* \left(\frac{1 + \tau_p^2 w^2}{(1 - \tau_b w^2 - c_a \cos(\delta_p w))^2 + (\tau_a w + c_a \sin(\delta_p w))^2} \right)^{1/2}$$

where

$$c_a := c_p \sigma_s^* \sigma_p^*, \quad \tau_b := \tau_s \tau_p, \quad \text{and} \quad \tau_a := \tau_s + \tau_p.$$

Let $f(\cdot)$ be the following function

$$f(s) := (\gamma_{H_{sp}}(s)/\sigma_s^*)^2.$$

After developing the denominator of $\gamma_{H_{sp}}$, we obtain

$$f(w) = \frac{1 + \tau_p^2 w^2}{\underbrace{(1 - \tau_b w^2)^2 + \tau_a^2 w^2 + c_a^2}_{F_1(w)} + \underbrace{2c_a \tau_a \sin(\delta_p w) w - 2c_a(1 - \tau_b w^2) \cos(\delta_p w)}_{F_2(w)}}.$$

The derivative of $f(\cdot)$ with respect to w is given by

$$f'(w) = \frac{2\tau_p^2 w(F_1(w) + F_2(w)) - (1 + \tau_p^2 w^2)(F_1'(w) + F_2'(w))}{(F_1(w) + F_2(w))^2}.$$

The derivative of $F_1(w)$ is given by

$$\begin{aligned} F_1'(w) &= -4\tau_b w(1 - \tau_b w^2) + 2\tau_a^2 w \\ &= 4\tau_b^2 w^3 + 2(\tau_s^2 + \tau_p^2)w. \end{aligned}$$

and then, one can verify that we have

$$2\tau_p^2 w F_1(w) - (1 + \tau_p^2 w^2) F_1'(w) = -2\tau_p^2 \tau_b^2 w^5 - 4\tau_b^2 w^3 + 2(c_a^2 \tau_p^2 - \tau_s^2)w.$$

Even, the derivative of $F_2(w)$ is given by

$$\begin{aligned} F_2'(w) &= 4c_a \tau_b \cos(\delta_p w) w + 2c_a(1 - \tau_b w^2) \delta_p \sin(\delta_p w) + 2c_a \tau_a \sin(\delta_p w) + 2c_a \tau_a \delta_p \cos(\delta_p w) w \\ &= 2c_a(2\tau_b + \tau_a \delta_p) \cos(\delta_p w) w + 2c_a(\tau_a + (1 - \tau_b w^2) \delta_p) \sin(\delta_p w). \end{aligned}$$

and then, one can also verify that we have

$$\begin{aligned} 2\tau_p^2 w F_2(w) - (1 + \tau_p^2 w^2) F_2'(w) &= (-4\tau_p^2 c_a - 4\tau_b c_a - 2c_a \tau_a \delta_p (1 + \tau_p^2 w^2)) \cos(\delta_p w) w \\ &\quad + (2\tau_p^2 \tau_a c_a w^2 - 2\tau_a c_a - 2c_a \delta_p (1 + \tau_p^2 w^2)(1 - \tau_b w^2)) \sin(\delta_p w). \end{aligned}$$

Using the fact that for all $w \in \mathbb{R}$, we have the following properties,

$$-1 \leq \cos(w) \leq 1 \quad \text{and} \quad -w \leq \sin(w) \leq w,$$

one can verify that the quantity $2\tau_p^2 w F_2(w) - (1 + \tau_p^2 w^2) F_2'(w)$ is upper bounded as follows

$$\begin{aligned} 2\tau_p^2 w F_2(w) - (1 + \tau_p^2 w^2) F_2'(w) &\leq (4\tau_p^2 c_a + 4\tau_b c_a + 4\tau_a c_a \delta_p + 2c_a \delta_p^2) w \\ &\quad + (4\tau_a \tau_p^2 c_a \delta_p + 2\tau_p^2 c_a \delta_p^2 + 2c_a \tau_b \delta_p^2) w^3 \\ &\quad + 2c_a \tau_b \tau_p^2 \delta_p^2 w^5. \end{aligned}$$

Therefore, by regrouping the terms of $f'(w)$, one obtain the following inequality

$$\frac{(F_1(w) + F_2(w))^2}{2w} f'(w) \leq F_3(w^2),$$

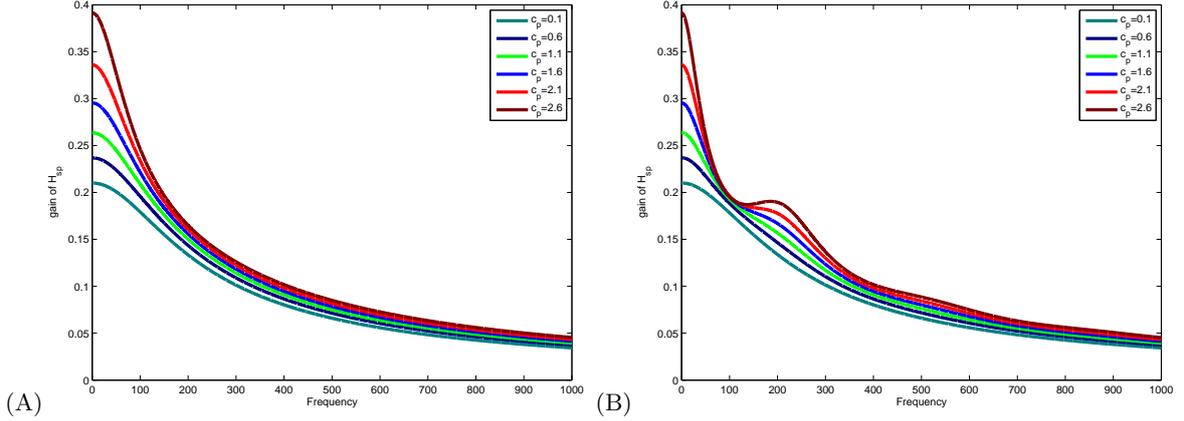


Figure 6: Influence of the connection weight c_p on the monotonicity of the gain of H_{sp} for $K = 0.1$. Figure (A) is plotted for $\delta_p = 2$ ms. In this case we have $c_p^*(\delta_p) \simeq 1.8$. Figure (B) is plotted for $\delta_p = 18$ ms. In this case we have $c_p^*(\delta_p) \simeq 0.55$.

where F_3 is given by the following polynomial expression

$$\begin{aligned}
 F_3(x) &= \underbrace{\tau_b \tau_p^2 (\delta_p^2 c_a - \tau_b)}_{\alpha_1} x^2 \\
 &+ \underbrace{\left(((\tau_p^2 + \tau_b) \delta_p^2 + 2\tau_a \tau_p^2 \delta_p) c_a - 2\tau_b^2 \right)}_{\alpha_2} x \\
 &+ \underbrace{\tau_p^2 c_a^2 + (\delta_p^2 + 2\tau_a \delta_p + 2\tau_p^2 + 2\tau_b) c_a - \tau_s^2}_{\alpha_3}.
 \end{aligned}$$

Remark that if α_1, α_2 and α_3 are strictly less than zero then the quantity $F_3(w^2)$ is negative for every positive real number w . One can easily check that for each fixed $\delta_p > 0$, one can choose $c_p(\delta_p) > 0$ for which α_1, α_2 and α_3 are strictly less than zero. Hence, for each $\delta_p > 0$, there exist $c_p^*(\delta_p) > 0$ for which the loop gain $\gamma_{H_{sp}}$ is strictly decreasing for every $c_p \in (0, c_p^*(\delta_p))$.

Proof of Lemma 4 For item (i), knowing that the two transfer functions H_s and H_p are input-output stable and their gains are strictly decreasing, then by direct application of [18, Theorem 2] we have that H_{sp} is input-output stable if and only if $\delta_p < \Delta(G_{sp})$. When $c_p \sigma_p^* \sigma_s^* < 1$, the stability of H_{sp} results from the small-gain theorem ([5], Theorem 9.1.7) and does not depend on the value of $\delta_p \geq 0$ then in this case we have $\Delta(G_{sp}) = +\infty$. This case is illustrated in Figure 7A. While, when $c_p \sigma_p^* \sigma_s^* \geq 1$, it is easy to show that the Nyquist locus of G_{sp} encircles the critical point when $\delta_p = 0$, and then in this case we have $\Delta(G_{sp}) \leq 0$. This last case is illustrated in Figure 7B.

For item (ii), knowing that the two transfer functions H_s and H_g are input-output stable, then under the condition that H_g is strictly decreasing, like in the case of item (i) we have H_{sg} is input-output stable if and only if $\delta_g < \Delta(G_{sg})$. Like in the case of item (i), when $c_g \sigma_g^* \sigma_s^* < 1 + c_g^g \sigma_g^*$ we have $\Delta(G_{sg}) = +\infty$. This case is illustrated in Figure 7C. While, when $c_g \sigma_g^* \sigma_s^* \geq 1 + c_g^g \sigma_g^*$, the delay margin of the system is well defined, i.e. $\Delta(G_{sg}) > 0$. This last case is illustrated in Figure 7D.

Proof of Theorem 2 We have that H_{sp} and H_g are input-output stable. If γ_H is strictly decreasing then, from Theorem [18, Theorem 2], we have that the delayed feedback system (H_{sp}, H_g) is input-output stable if and only if $\delta_g < \Delta(H)$. And, by Nyquist Theorem, we know that the delayed feedback system (H_{sp}, H_g) is input-output stable if and only if $\text{ind}(1 - H_{sp} K_g) = 0$, which equivalent from Lemma (2) to $\text{ind}(1 - H_s(K_p + K_g)) = 0$. Then, one can conclude with Proposition (5) that the equilibrium point is exponentially stable for (4) if and only if $\delta_g < \Delta(H)$.

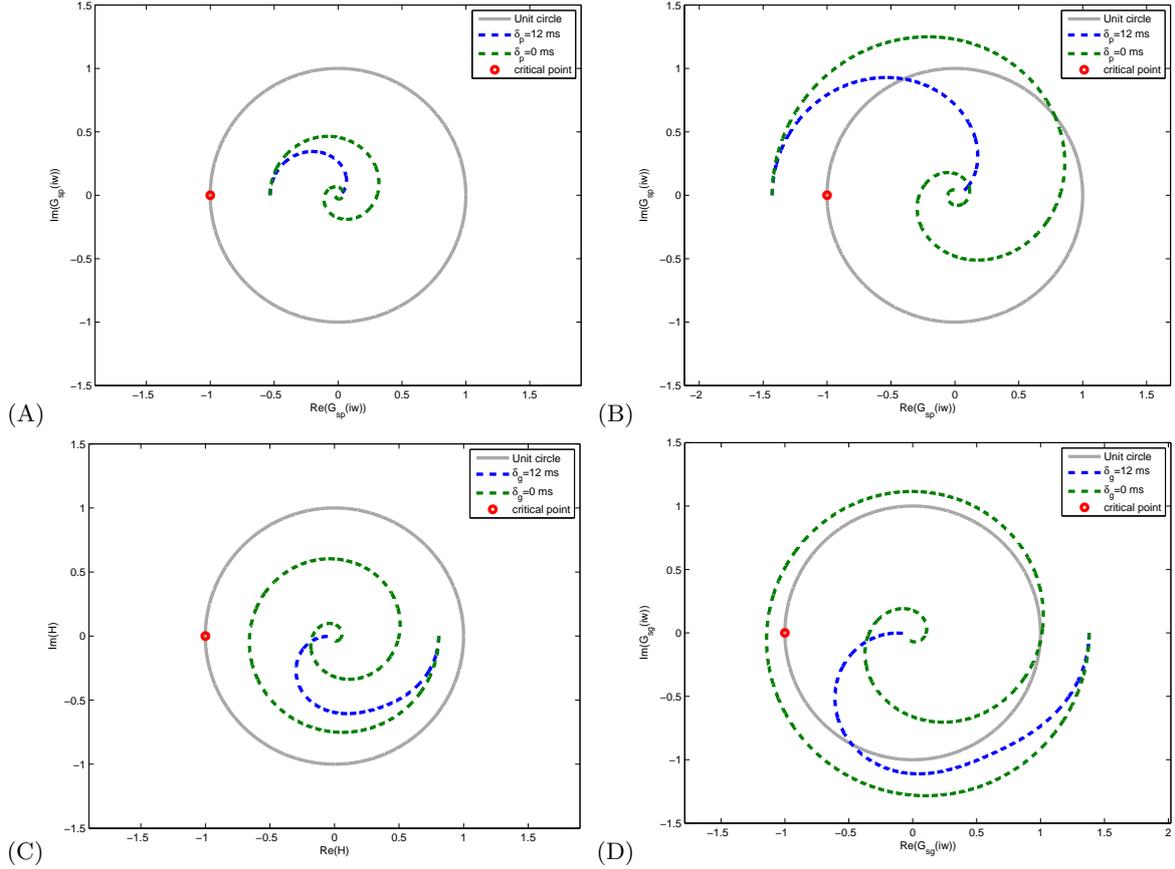


Figure 7: Nyquist diagram associated to four different cases of Lemma 4.

Proof of Corollary 1 We know, from Lemma 3, that for each $\delta_p > 0$ one can find $c_p^* > 0$ such that the gain $\gamma_{H_{sp}}$ is strictly decreasing for every $c_p < c_p^*$. Even, from [18, Lemma 4], one can find, for each set of parameters, a positive real number δ_g^* such that the gain γ_{H_g} is strictly decreasing for every $\delta_g < \delta_g^*$. Therefore, for each $\delta_p > 0$, if γ_{H_g} is strictly decreasing, one can find $c_p^* > 0$ such that the gain γ_H is strictly decreasing. thus, in this case Theorem 2 achieves the proof of the corollary.

Appendix B: Frequency domain methods

Most of the concepts recalled here are taken from [5].

5.1 Convolution algebras

Suppose that β is any real number. We say that $f \in \mathcal{A}(\beta)$ if it has the representation

$$f(t) = \begin{cases} f_a(t) + \sum_{n=1}^{\infty} f_n \delta(t - t_n) & t \geq 0 \\ 0 & t < 0, \end{cases}$$

where $e^{-\beta t} f_a(t) \in L_1(0, \infty)$, $f_n \in \mathbb{C}$, $t_n \in \mathbb{R}; t_1 = 0, t_n > 0$ for $n \geq 2$, $\delta(t - t_n)$ represents the delta distribution centred in t_n and $\sum_{n=1}^{\infty} |f_n| e^{-\beta t_n} < \infty$ ([5], Definition A.7.45, p. 661).

Any function $f \in \mathcal{A}(\beta)$ possesses the Laplace transform $F(\cdot)$ in \mathbb{C}_β^+ given by

$$F(s) = \int_0^{\infty} e^{-st} f_a(t) dt + \sum_{n=1}^{\infty} f_n e^{-t_n s} \quad \text{for } s \in \mathbb{C}_\beta^+$$

Consider the class of Laplace transforms of $\mathcal{A}(\beta)$ given by

$$\hat{\mathcal{A}}(\beta) := \{F : F \in \mathcal{A}(\beta)\}. \quad (41)$$

The set $\hat{\mathcal{A}}(\beta)$ is a commutative Banach algebra with identity under the norm

$$\|F\| := \sup_{s \in \overline{\mathbb{C}_\beta^+}} |F(s)|$$

(see [5], Corollary A.7.48, p. 665).

Let us introduce the two following subsets of $\hat{\mathcal{A}} := \hat{\mathcal{A}}(0)$ given by

$$\hat{\mathcal{A}}_- := \{F : F \in \hat{\mathcal{A}}(-\epsilon) \text{ for some } \epsilon > 0\};$$

and

$$\hat{\mathcal{A}}_\infty := \{F \in \hat{\mathcal{A}}_- : \exists \rho > 0 \text{ such that } \inf_{s \in \overline{\mathbb{C}_0^+} \mid |s| \geq \rho} |F(s)| > 0\}.$$

We note that in ([5], Definition 7.1.4, p. 338) these two sets correspond to $\hat{\mathcal{A}}_-(0)$ and $\hat{\mathcal{A}}_\infty(0)$, respectively.

According to ([5], Lemma 7.1.5, p. 338), both $\hat{\mathcal{A}}_-$ and $\hat{\mathcal{A}}_\infty$ inherit several properties from $\hat{\mathcal{A}}$. In the following we list some of this important properties

- (p₁) $\hat{\mathcal{A}}_-$ is a subalgebra of $\hat{\mathcal{A}}$;
- (p₂) $F \in \hat{\mathcal{A}}_-$ is holomorphic and bounded on $\overline{\mathbb{C}_0^+}$;
- (p₃) $F \in \hat{\mathcal{A}}_-$ is invertible over $\hat{\mathcal{A}}_-$ if and only if $\inf_{s \in \overline{\mathbb{C}_0^+}} |F(s)| > 0$.

From the definition of $\hat{\mathcal{A}}_\infty$, we know that there exists a $\epsilon > 0$ such that $F \in \hat{\mathcal{A}}(-\epsilon)$. Then, from the properties of $\hat{\mathcal{A}}(-\epsilon)$, F is holomorphic over $\mathbb{C}_{-\epsilon}^+$ and so it has only finitely many isolated zeros of finite order in the compact subset $\{s \in \overline{\mathbb{C}_0^+} : |s| \leq \rho\}$ of $\mathbb{C}_{-\epsilon}^+$ ([5], Theorem A.1.4, p. 566). By definition, it cannot have zeros in the subset $\{s \in \overline{\mathbb{C}_0^+} : |s| \geq \rho\}$. Then, an important property of elements belonging to $\hat{\mathcal{A}}_\infty$ is the following

- (p₄) $F \in \hat{\mathcal{A}}_\infty$ has only finitely many zeros of finite order in $\overline{\mathbb{C}_0^+}$.

5.2 Nyquist's Theorem

In this subsection we recall the definition of input-output stability of irrational transfer matrix and then we introduce the Nyquist Theorem in its general form. Firstly, it is necessary to define the class of scalar irrational transfer functions. The quotient algebra $\hat{\mathcal{B}}$ of $\hat{\mathcal{A}}_-$ with respect to $\hat{\mathcal{A}}_\infty$ represents the class of scalar (possibly instable) irrational transfer functions $\hat{\mathcal{B}}$, which is a particular case of the *Callier-Desoer* class ([5], Definition 7.1.6), and that is given by

$$\hat{\mathcal{B}} := \{F = NM^{-1} : N \in \hat{\mathcal{A}}_- \text{ and } M \in \hat{\mathcal{A}}_\infty\}.$$

Observe that, obviously, $\hat{\mathcal{B}} \subset \hat{\mathcal{A}}_-$.

Let $\mathcal{M}\hat{\mathcal{A}}_-$ and $\mathcal{M}\hat{\mathcal{B}}$ denote the set of matrices (of any size) with elements in $\hat{\mathcal{A}}_-$ and $\hat{\mathcal{B}}$ respectively. Using the mathematical structure outlined above, the appropriate stability concepts for transfer matrices is defined by the following definition ([5], Definition 9.1.1, p. 457).

Definition 1 $G \in \mathcal{M}\hat{\mathcal{B}}$ is said to be input-output stable if $G \in \mathcal{M}\hat{\mathcal{A}}_-$.

Furthermore, the connection between the input-output stability of the transfer matrix G and the exponential stability of the semigroup generated by its infinite-dimensional state-space representation is given in ([5], Theorem 7.3.2, p. 364).

Definition 2 ([5], Definition 9.1.1, p. 458) A feedback system (G, K) , where $G, K \in \mathcal{MB}$, is said to be input-output stable if and only if

a. There exists a $\rho > 0$ such that

$$\inf_{s \in \overline{\mathbb{C}_0^+} : |s| \geq \rho} |\det(I - G(s)K(s))| > 0;$$

b. The transfer matrices $S := (I - GK)^{-1}, KS, SG$ and $I + KSG$ are in \mathcal{MA}_- .

We recall that two transfer matrices $M, N \in \mathcal{MA}_-$ are right-coprime over \mathcal{MA}_- , if they have the same number of columns, and there exist $\tilde{X}, \tilde{Y} \in \mathcal{MA}_-$ such that the following *Bezout identity* holds:

$$\tilde{X}M - \tilde{Y}N = I \quad \text{on } \overline{\mathbb{C}_0^+}.$$

We refer to ([5], Definition 7.2.6, p. 352) to the complete definition concerning the left- and right-coprime matrices.

The interesting consequence arising from the use of \mathcal{MB} , to define the class of irrational transfer functions, is that all elements of \mathcal{MB} always possess both left- and right-coprime factorization over \mathcal{MA}_- ([5], Theorem 7.2.8, p. 353). In other words, for each matrix $G \in \mathcal{MB}$, there exist two transfer matrices $M, N \in \mathcal{MA}_-$ such that M and N are left-coprime (right-coprime) over \mathcal{MA}_- , N is a square matrix with $\det(N) \in \hat{\mathcal{A}}_\infty$ and $G = MN^{-1}$ ($G = N^{-1}M$). These factorizations are unique up to a common left (right) multiplication by an invertible element in \mathcal{MA}_- . Seeing that $\det(N) \in \hat{\mathcal{A}}_\infty$, then from the property (p_4), $\det(N)$ has only finitely many zeros of finite order in $\overline{\mathbb{C}_0^+}$. By definition ([5], Definition 7.2.18, p. 359), the poles of G in $\overline{\mathbb{C}_0^+}$ are equal to the zeros of $\det(N)$ in $\overline{\mathbb{C}_0^+}$ and their *McMillan degree* to be the order of the zero.

Theorem 3 *Nyquist Theorem.* ([5], Theorem 9.1.8, p. 463) Suppose that $G, K \in \mathcal{MB}$ have p_G and p_K poles, respectively, in $\overline{\mathbb{C}_0^+}$, counted according to their *McMillan degree*. If GK is strictly proper on $\overline{\mathbb{C}_0^+}$, then the feedback (G, K) is input-output stable if and only if

$$\text{ind}(\det(I - GK)) = -p_K - p_G,$$

where $\text{ind}(\det(I - GK))$ denotes the *Nyquist index* ([5], Definition A.1.15, p. 569) of $\det(I - GK)$.

Corollary 2 *Nyquist Test.* ([5], Corollary 9.1.9, p. 465) Suppose that $G, K \in \mathcal{MB}$ have p_G and p_K poles, respectively, in $\overline{\mathbb{C}_0^+}$, counted according to their *McMillan degree* and neither poles nor zeros on the imaginary axis. If GK is strictly proper on $\overline{\mathbb{C}_0^+}$, then the feedback (G, K) is input-output stable if the plot of $\det(I - GK)(jw)$ as w decreases from ∞ to $-\infty$ encircles the origin $(p_G + p_K)$ times in the clockwise sense.

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